Seasonal association between viral etiologies of hospitalized acute lower respiratory infections and meteorological factors in China

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Research in context

Evidence before this study

We searched Web of science, Google Scholar, and China National Knowledge Infrastructure using broad search terms associated with “ALRI”, “respiratory”, “influenza OR respiratory syncytial virus OR RSV OR parainfluenza OR PIV OR metapneumovirus OR MPV OR adenovirus OR ADV OR coronavirus OR hCoV OR human bocavirus OR hBoV” with no date or language restrictions. Our search yielded more than 200 studies, and more than 50 studies were related to the association between meteorological factors and ALRI or common respiratory viruses, with most focusing on RSV and FLU in some local regions. Some evidence suggested that cold environmental temperature and relative humidity were associated with RSV and FLU epidemics in temperate regions and rainfall in tropical regions. However, most previous studies have lacked a systematic analysis especially for objectively comparing other meteorological factors on other respiratory viruses (PIV, ADV, hMPV, hBoV and hCoV, etc.) with an overall scale. There is a need for studies based on long-term and larger spatial scale data.

Added value of this study

This is the first systematic analysis of the quantitative contributions of different meteorological factors and their interactions to the seasonality of most common respiratory viruses in both temperate (north) and subtropical (south) climate
regions in China. Furthermore, we also expound the mechanisms of how meteorological factors act on respiratory viruses, including four aspects, namely the virus’s survival, infection, transmission and human immune responses. The seasonality of RSV, FLU and hMPV is obvious with peaks in winter in the north, and some summer peaks in the south, other viruses don’t exhibit clear annual seasonality. We find that temperature, atmospheric pressure, vapor pressure and rainfall have strong explanations in both northern and southern China, relative humidity is dominant in the north while has no significant explanation in the south. Hours of sunlight has only explanation for RSV, FLU in the north, while has great explanations for most viruses in the south (except hCoV and ADV). Moreover, it is of note that the single contributions of these factors are difficult to disentangle because their interaction powers are nonlinearly or bivariately enhanced.

**Implications of all the available evidence**

The evidences of this study should be used to predict the seasonal patterns of these common respiratory viruses and interpret the mechanism of how meteorological factors act on them. More understanding of the meteorological effects on the activity of these viruses would also be helpful in guide government planning, such as public health interventions, good hygiene, infection control practice and timing of passive immunoprophylaxis, may facilitate the development of future vaccine strategies.
Abstract

Background: Acute lower respiratory infections (ALRIs) caused by respiratory viruses are common and persistent infectious diseases worldwide and in China, which present pronounced seasonal patterns. Meteorological factors are determinant factors of the seasonality of some major viruses, especially respiratory syncytial virus (RSV) and influenza virus (FLU). Our aim is to identify the dominant meteorological factors and to model their effects on the common respiratory viruses in different regions of China.

Methods: We analyzed monthly respiratory virus data from 81 sentinel hospitals in 22 provinces in mainland China from January 2009 to September 2013. Meteorological data of the same period were used to analyze their relationships. Geographical detector was used to quantify the explanatory power of each meteorological factor and their interaction effects on respiratory viruses.

Findings: Altogether, seven viruses from 28 369 hospitalized ALRI patients (cases) were tested. Overall, 10 387 cases (36·6%) were positive for at least one virus, among them were RSV (4 091, 31·98%), FLU (2 665, 20·83%), PIV (2 185, 17·06%), ADV (1 478, 11·55%), hBoV (1 120, 8·76%), hCoV (637, 4·98%), and hMPV (615, 4·81%). RSV and FLU had annual peak in the north and semi-annual peak in the south. PIV and hBoV had higher positive rates in spring-summer. ADV and hCoV exhibited no clear annual seasonality, hMPV had annual peak in winter-spring especially in the north. Temperature, atmospheric
pressure, vapor pressure and rainfall had most explanatory power on most respiratory viruses in each region, relative humidity was only dominant in the north, but had no significant explanation for most viruses in the south. Hours of sunlight had only significant explanations for RSV and FLU in the north, and had significant explanations for most viruses in the south. Wind speed was only the dominant explanatory power for hCoV. Besides, the interacted explanations of any two of the paired factors got enhanced bivariately or nonlinearly.

**Conclusions:** Our results described the different explanation power of different meteorological variables on different viruses in different major climate regions of China. The spatiotemporal heterogeneity of most viruses was also detected in this study. Moreover, the interactions of each pair of meteorological factors were also enhanced. These findings may be helpful to guide government planning, such as public health interventions, good hygiene, infection control practice and timing of passive immunoprophylaxis, may facilitate the development of future vaccine strategies.

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Introduction

Acute lower respiratory tract infections (ALRIs) are a major public health problem in both developed and developing countries, causing nearly 2·38 million deaths globally in 2016, making them the fifth leading cause of death overall and the leading infectious cause of death in all age deaths during the past three decades. Moreover, most ALRI fatalities occur in developing countries, 40% are reported in Africa, and 30% in southeast Asia.

Many pathogens are responsible for ALRIs including bacteria, viruses, and fungi. Most respiratory viruses have been detected in recent years, such as respiratory syncytial virus (RSV), Influenza virus (FLU), Human parainfluenza virus (PIV), Adenovirus (ADV), Human metapneumovirus (hMPV), human rhinovirus (HRV), human coronavirus (hCoV), human bocavirus (hBoV). Among these viruses, RSV is the most predominant viral cause of hospitalization, especially in infants, being responsible for almost 65% of hospitalized cases. As the second most common virus, FLU can cause widespread morbidity and mortality among human populations worldwide. The infection mechanism of PIV is similar to that of RSV infection in children, serological surveys indicated that nearly every child would likely be infected at least once with RSV or PIV before 5 years of age.

The seasonality of ALRIs is varied among different study periods and regions in different countries, recently a global seasonal pattern of some common viruses
has been described in detail.\textsuperscript{12} A clear understanding of the relationship between seasonality of different viruses and meteorological factors is critical to the successful implementation of prevention and control program. In recent years, substantial studies have focused on how weather patterns influence the seasonality and transmission of RSV and FLU in some local regions.\textsuperscript{13-17} However, most previous studies lacked a comprehensive evaluation on weather factors on other common respiratory viruses with an overall scale.

China is a geographically and climatologically diverse country with a temperate climate in the north, subtropical climate in the south, and a tropical climate in Hainan and some cities in Guangdong. In this study, using the viral etiologies of hospitalized ALRI data covering five consecutive years in most representative regions in China, we provide insight into the explanatory powers of different meteorological factors on different common respiratory viruses in different major climate regions comprehensively. Furthermore, with the explanatory powers of these weather factors, the seasonality and transmission of these viruses in different environments would be better understood, which can help in the prediction of future outbreaks and government planning.

**Methods**

**Viral etiologies of hospitalized ALRI data**

In this study, active surveillance for all-age hospitalized ALRI patients in 108 sentinel hospitals in 24 provinces of China was initiated from January 2009 to
September 2013. All these sentinel hospitals were chosen after carefully considering capacities of surveillance and laboratory testing, and for geographical representativeness. Specimens from the first two or five ALRI patients weekly or monthly in each sentinel hospital were tested for RSV, FLU, PIV, ADV, hCoV, hBoV and HMPV (cases were screened weekly in 49 hospitals and monthly in the other 59 hospitals). A brief verbal consent was recorded from patients or their parents/guardians during their enrollment. Detailed data regarding patient demographics and clinical characteristics including signs and symptoms and laboratory test results were collected. The ALRI case was defined by a national surveillance protocol developed by the Chinese Centre for Disease Control and Prevention (China CDC, Beijing) and regional reference laboratories. After excluding 27 sentinel hospitals which had only sparse patients fewer than 40 in total, we eventually enrolled a total of 28,369 hospitalized ALRI patients from 81 sentinel hospitals in 22 provinces in China for final analysis (Figure 1). Considering the current surveillance and research situation, China is divided into northern and southern parts by conventional geographic divisions, following the Qinling Mountain range to the west and the Huai River to the east.
Outcome Measures

The monthly positive rates of seven common viruses were calculated for the study period to represent the seasonal activity of each virus infection in each region. The calculation formula is as follows:

\[ X_{ij} = \frac{\text{Monthly number of positive tests}}{\text{Monthly number of ALRI patients}} \]

\( i = 1, 2, \ldots, 12 \) (from January to December);

\( j = 1, 2, \ldots, 5 \) (from 2009 to 2013);

\( X \) represents FLU, RSV, PIV, ADV, hMPV, hCoV, and hBoV.

Meteorological Data

In this study, a total of 24 daily meteorological parameters were collected from
the China Meteorological Data Sharing Service System (http://data.cma.gov.cn) in 756 ground weather stations nationwide from 1 Jan 2009 to 31 Sep 2013. Considering the multicollinearity in some meteorological parameters, for example, maximum, minimum and mean atmospheric pressure have a strong correlation of 0.99, only seven average parameters were involved in this article, including mean temperature, mean atmospheric pressure, vapor pressure, rainfall, hours of sunlight, mean relative humidity, and mean wind speed. The results of other meteorological parameters were omitted. Monthly level meteorological data were calculated by averaging the daily value of each meteorological variable in each month except rainfall and hours of sunlight, which were calculated by summation. The city-level monthly meteorological indicators for the study area were interpolated by the inverse distance weighted interpolation method (IDW). Eventually, the monthly meteorological data for the whole of China were acquired by averaging these 36 study cities, and the monthly meteorological data for northern and southern China were calculated by averaging those cities in the north or the south respectively.

**Statistical analysis**

In this study, an initial descriptive analysis was performed firstly by plotting the time-series of each respiratory virus-positive rates and each meteorological factor in both northern and southern China. The effects of individual meteorological factors and their interactive effects were evaluated by the
geographical detector method. Geographical detector, proposed by Wang,\textsuperscript{20,21} is a novel spatial variance analysis method firstly designed as a test of spatial stratified heterogeneity and now widely used to explore the determinant power of driving factors responsible for heterogeneity. Spatial stratified heterogeneity is a widely existing phenomenon that describes that within strata variance is less than between strata variance classification.\textsuperscript{22} If this phenomenon is dominated by some risk factors, the spatial and temporal distribution of this risk factor will be coupled to this phenomenon, which is the key underlying assumption used in geographical detector. Compared to traditional linear models, geographical detector is not restricted by the assumption of linearity and immunity to the collinearity multivariable. In this article, the \( q \)-statistic in geographical detector is used to express explanations of each meteorological factor on virus variation.\textsuperscript{20}

The mathematical formulation of \( q \)-statistic is expressed as follows:\textsuperscript{22,23}

\[
q = 1 - \frac{\sum_{h=1}^{L} N_h \sigma_h^2}{N \sigma^2} = 1 - \frac{SSW}{SST}
\]

\[
SST = N \sigma^2, \quad SSW = \sum_{h=1}^{L} N_h \sigma_h^2
\]

\( q \in [0,1] \)

where \( N \) and \( \sigma^2 \) represent the total number of samples and the variance of \( Y \) in the whole study area respectively; \( h=1, 2, \ldots, L \) is the number of strata of factors \( X \); \( N_h \) and \( \sigma_h^2 \) mean the number of samples and the local variance of \( Y \) in strata \( h \), respectively. Besides, \( SSW \) and \( SST \) are the within sum of squares and the total sum of squares, respectively. The range of \( q \)-statistic is from 0 to 1; the
larger the $q$ value is, the stronger the influence of variable $X$ is on $Y$. If the $q$ value approaches 1, the value of $\sigma^2_h$ is close to 0, $X$ has the same distribution as $Y$.

In addition, the interaction detector can be used to reveal the interactive effects of every two different factors ($X_1$, $X_2$). The $q$-statistic of factors $X_1$ and $X_2$ calculated can be marked as $q (X_1)$ and $q (X_2)$. By overlaying factors $X_1$ and $X_2$, we can calculate the $q$-statistic value marked as $q (X_1 \cap X_2)$. The interactive result can be weaken, enhance, or independent. If $q(X_1 \cap X_2) > q(X_1)$ or $q(X_2)$, the factors enhance with each other; if $q(X_1 \cap X_2) > q(X_1)$ and $q(X_2)$, the factors bivariate enhance with each other; if $q(X_1 \cap X_2) > q(X_1) + q(X_2)$, the factors nonlinearly enhance with each other; if $q(X_1 \cap X_2) = q(X_1) + q(X_2)$, then they are independent of each other; if $q(X_1 \cap X_2) < q(X_1)$ or $q(X_2)$, they are univariate weak with each other; if $q(X_1 \cap X_2) < q(X_1)$ and $q(X_2)$, they are nonlinearly weak with each other; if $q(X_1 \cap X_2) < q(X_1) + q(X_2)$, they are weak with each other.

In this article, all statistical analyses were conducted using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided $p$-value of less than 0.05 was considered statistically significant. The geographical detector method was implemented here using R packages and software downloaded from www.geodetector.org.

**Role of the funding source**

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

**Results**

| Virus | Family | Structure | Climate influences | References |
|-------|--------|-----------|--------------------|------------|
| RSV   | Paramyxoviridae | Non-segmented negative sense single-stranded RNA virus | low temperature, relative humidity | 13,14,16,24,25 |
| FLU   | Orthomyxoviruses | Lipid-enveloped, single-stranded, pleomorphic RNA virus | low temperature, low relative humidity | 13,15,17,26 |
| PIV   | Paramyxoviridae | Enveloped, single-stranded negative sense RNA virus | Temperature, relative humidity, wind speed | 24,27,28 |
| ADV   | Mastadenovirus genus in the family Adenoviridae | Non-enveloped, double-stranded, icosahedral DNA virus | Temperature | 27,29 |
| hBoV  | Bocavirus of the family Paroviridae, subfamily Parvovirinae. Members of the genus | Non-enveloped, single-stranded DNA virus | Low temperature, wind speed | 24 |
| hCoV  | the family Coronaviridae and the order Nidovirales | Enveloped, positive-sense, single-stranded RNA virus | Temperature | 24,27 |
| hMPV  | Mononegavirales, the genus Metapneumovirus, the subfamily Pneumovirinae | Enveloped, nonsegmented negative-strand RNA viruses or mononegaviruses | Low temperature, wind speed | 24,30 |

RSV: Respiratory Syncytial Virus, FLU: Influenza virus, PIV: Human parainfluenza virus, ADV: Adenovirus, hBoV: Human bocavirus, hCoV: Human Coronaviruses, hMPV: Human Metapneumovirus.

*Table 1:* Summary of respiratory viruses and the potential climate influence factors from other literatures.
Table 1 summarized the structure of these respiratory viruses and the possible climate influence factors from other literatures. Figure 2 summarized the mechanisms that how meteorological factors act on the seasonal characteristics of these viruses. The demographic characteristics of the patients included in this study were shown in Supplementary appendix S1. Out of the 28,369 specimens tested, 17,127 (60.4%) were below 5 years of age. There were more male ALRI patients than female, so did each virus being detected. Moreover, 10,387 (36.6%) patients were positive for at least one respiratory virus (mono-infection and co-detection). The most frequently detected virus was RSV, which was found in 4,091 (32%) positive samples, followed by FLU (2,665, 20.8%), PIV (2,185, 17%), ADV (1,478, 11.6%). Other viruses like hBoV (1,120, 8.8%), hCoV (637, 5%) and hMPV (615, 4.8%) occupied small percentage. Supplementary appendix S2 showed the number of each virus in Northern and Southern China. The
differences between these virus-positive tests in the north and south were also significant \( (p<0.001) \). Supplementary appendix S3 showed the statistical descriptions of seven respiratory virus and meteorological variables. There was no significant difference in monthly positive rates of seven respiratory viruses in two regions.

Supplementary appendix S4-5 exhibited the monthly positive rates of each virus and meteorological factors in different regions of China. For total viruses detected in whole China, the average monthly positive rate was 45%, peaking from November to the following March; only December-2012 was declined and the epidemic period was postponed for two months. The seasonality in the south was similar to the whole of China, while in the north, the difference between the epidemic period and non-epidemic period was more obvious. Besides, almost all viruses could be detected year-round, and the most dominating viruses were RSV, FLU and PIV.

For RSV-associated hospitalizations, there was a clear seasonal variation with peaks in the winter months of November through March and very low positive rates during the summer months of June through September. In the summer of 2009 and 2011, there was a small peak in the south, and the epidemic period was postponed for two months in 2010 in both the north and south. FLU had annual peak in cold months in winter in the north and semi-annual peak in summer and winter in the south. On the contrary, PIV and hBoV positive rates were higher in
spring-summer in most research years. ADV and hCoV exhibited no clear annual seasonality. Although the seasonality was not obvious for hMPV, there still existed an annual peak in winter-spring (Jan-May), especially in the north.

| Age group | Tem  | AP   | VP   | Rain | Sun  | RH   | WS   |
|-----------|------|------|------|------|------|------|------|
| Overall   | 0.552** | 0.439** | 0.601** | 0.531** | 0.525** | 0.373* | 0.216 |
| 0-5       | 0.395 | 0.328' | 0.460 | 0.433 | 0.431 | 0.352 | 0.154 |
| 5-64      | 0.498' | 0.489'' | 0.554' | 0.540' | 0.422 | 0.374 | 0.148 |
| >65       | 0.208 | 0.233 | 0.192 | 0.162 | 0.193 | 0.132 | 0.146 |
| North     | 0.632** | 0.478'' | 0.639'' | 0.615'' | 0.268' | 0.415'' | 0.151 |
| 0-5       | 0.503'' | 0.434'' | 0.557'' | 0.407 | 0.398'' | 0.395' | 0.175 |
| 5-64      | 0.428' | 0.453'' | 0.401 | 0.493' | 0.364 | 0.378 | 0.149 |
| >65       | 0.274 | 0.317 | 0.367 | 0.282' | 0.407 | 0.330' | 0.279 |
| South     | 0.476'' | 0.453'' | 0.495'' | 0.382'' | 0.325' | 0.092 | 0.108 |
| 0-5       | 0.323 | 0.287 | 0.326 | 0.353 | 0.330 | 0.333 | 0.312 |
| 5-64      | 0.481' | 0.325 | 0.555'' | 0.417' | 0.404' | 0.412'' | 0.176 |
| >65       | 0.326 | 0.174 | 0.129 | 0.261 | 0.202 | 0.109 | 0.056 |

**, significant at the 0·01 level; *, significant at the 0·05 level.

Table 2: Explanatory power of meteorological factors on total respiratory viruses in different age groups in different regions of China.
Table 2 showed the explanatory power of these meteorological factors on total virus positive rates in different age-groups. Almost all factors except hours of sunlight in the north had higher explanations than the south. Vapor pressure was the most dominant factor in each region. The results were quite different in different age-groups and genders (Supplementary appendix S6). Overall, the
explanatory power of each meteorological factor of the males outperformed the females in each age group. The associations between most meteorological factors and total virus in the age group older than 65 were only significant in the north. Figure 3 showed the significant explanatory power \( p<0.05 \) on each respiratory virus, the results for different age-groups and genders were showed in Supplementary appendix S7. In the whole of China (Figure 3A), all meteorological factors had significant explanations on RSV and hMPV, and the most one for RSV was temperature \( q=0.654 \), followed by vapor pressure and atmospheric pressure with \( q \) values of 0.622 and 0.575 respectively. Relative humidity \( q=0.407 \) was the most dominant factor for hMPV. Atmospheric pressure, vapor pressure, temperature, rainfall and hours of sunlight had significant explanations for FLU, PIV and hBoV, while wind speed and relative humidity were significantly associated with ADV and hCoV. Besides, rainfall was another dominant power for ADV.

In northern China (Figure 3B), all factors except wind speed could significantly explain the variation of RSV, and the dominant one was rainfall \( q=0.723 \). Temperature was the most dominant factor \( q=0.416 \) for FLU, other factors could also significantly explain over 25% of its variation except for relative humidity. No significant explanation was found for PIV. Relative humidity was the most dominant factor for ADV, hBoV, with \( q \) values of 0.333 and 0.322, respectively. For hMPV, all factors except hours of sunlight had great
explanations. However, hCoV was associated only with vapor pressure and wind speed.

In southern China (Figure 3C), there was no significant explanation power for relative humidity. RSV, PIV and hBoV were significantly associated with temperature, atmospheric pressure, vapor pressure, rainfall and hours of sunlight. Temperature, vapor pressure, and hours of sunlight had significant influences on FLU. ADV was significantly associated with vapor pressure and rainfall. Only wind speed could significantly explain 39% of the variation of hCoV. The most dominant factor for hMPV was vapor pressure, with the $q$ value of 0.358. Supplementary appendix S8-15 showed variation trend of each and total virus positive rates on the dominant meteorological factor in each region.

Figure 4 showed the interactive effects of each paired meteorological factors on total respiratory viruses in different regions (see Supplementary appendix S16-22 for each virus). The dominant interaction with their largest $q$ values in different regions was shown in Supplementary appendix S23. Overall, the explanatory power of any two independent factors got enhanced after interaction, bivariately or nonlinearly. In the whole of China, the dominant interaction for each virus was different. For example, the interactive effect of wind speed and atmospheric pressure for RSV could be greater than the sum of each individual effect, with the largest $q$ value of 0.84, while the dominant interactive effect for FLU was vapor pressure and hours of sunlight. In the north, relative humidity
played a great role in the interaction effect. The dominant interactive power was relative humidity interacting with others for most viruses except ADV. Although the independent explanation power of wind speed was not significant for most viruses, the interactive effect with others could be the dominant one, especially in the south.

**Discussion**

To our knowledge, this study was the first to quantitatively demonstrate the explanations of different meteorological factors and their interactions on common respiratory viruses causing ALRIs based on a large sample size across the temperate climate and subtropical climate in China simultaneously. The current study highlighted the different seasonality of common respiratory viruses and the different explanatory powers of different meteorological variables on these respiratory viruses in different major climate regions of China. Our findings about the different influences of meteorological factors could explain most seasonal variations of these viruses to some extent.

Overall, our findings on epidemic cycles of respiratory viruses in different
regions of China were consistent with previous studies in other temperate and subtropical regions. A recent global review by You Li concluded that four main respiratory viruses had distinct seasonal patterns, and hypothesized that temperature, humidity, precipitation and solar radiation were the possible seasonal stimuli. In our study, we found RSV and FLU had clear seasonal epidemic in winter months in the north and semi-annual epidemic in the south. PIV and hBoV epidemics were found mostly in spring and early summer. hMPV had annual peak in winter-spring, especially in the north. ADV and hCoV did not exhibit clear annual seasonality. Our findings were consistent with You Li's conclusions. A study in US also found that RSV had strong seasonality with annual epidemics in winter, and vapor pressure had the highest explanatory power for the seasonality. Another study in Sweden (temperate climates) found that RSV, FLU, hCoV, and hMPV all had strong seasonal patterns in winter. A Malaysia study also found clear seasonality of main respiratory viruses.

Our study found that the most dominant factor for total respiratory viruses was vapor pressure (north: 64%, south: 50%), other factors such as temperature, rainfall, atmospheric pressure and hours of sunlight also played important role in both temperate (north) and subtropical (south) regions in China. Relative humidity only had significant explanations in the north but not in the south. An explanatory hypothesis of vapor pressure proposed by Daniel was that low vapor pressure can increase the possibility of airborne virus spread by favoring rapid
evaporation of the infectious droplets.\textsuperscript{16}

To date, various theories behind the association between meteorological factors and respiratory viruses have been proposed.\textsuperscript{17,33} Together, as shown in Figure 2, the mechanisms of how meteorological factors act on respiratory viruses include mainly four aspects, namely the virus’s survival, infection, transmission and human immune responses. Firstly, meteorological factors can change viral stability, viability, activity, pathogenesis or virulence, and prolong or shorten virus’ survival time.\textsuperscript{34} Laboratory studies concluded that most viruses tend to survive longer in lower temperatures and lower relative humidity.\textsuperscript{35} Some aerosol viability experiments present that ADV was more stable at high relative humidity, by contrast, PIV was more stable at low relative humidity, while RSV got bimodal peak stability at 20\% or 40–60\% relative humidity and instability at 30\%. FLU was also generally more stable at lower relative humidity.\textsuperscript{35,36}

Secondly, infections are more likely to happen in certain weather conditions. For example, in cold weather, the decrease of temperature would lower physical protection barrier of the human body by decreasing the secretion function of respiratory mucosa membrane and weaken the body’s immune function by decreasing erythrocyte sedimentation rate in blood, which would lead to the occurrence of infection. Thirdly, weather conditions can affect different transmission routes of different respiratory viruses in a dissimilar way, like changing human behavior (e.g. crowding in rainy days),\textsuperscript{37} changing respiratory
droplet size and deposition, airflow and recirculation, making them difficult to investigate experimentally. After being infected by these viruses, the human immune system would respond by changing the host’s respiratory resistance, respiratory secretion production and viscosity, seasonal nutritional deficiencies and so on. Weather could also change human’s lifestyles, such as making more crowded conditions by staying indoors in cold weather and promoting circulation by going outside when the weather became warmer and drier. Lastly, weather can alter host defense mechanisms, such as cooling of the nasal airway, stimulating vitamin D metabolism, impairing mucociliary clearance and reducing the phagocytic activity of leukocytes with inhalation of cold, dry air. Our findings on the associations between meteorological factors and each individual virus could be explained by these aspects. RSV was transmitted by large particle aerosols or by direct or indirect contact in human secretions. In winter, cold weather in temperate climates (north) with low temperature and relative humidity would facilitate its survival and transmission. Experimental studies demonstrated that RSV inactivation required a longer time when the temperature decreased. Although low relative humidity was identified to contribute transmission and survival of the influenza virus previously, no significant explanation of relative humidity was found in our study (p>0.05). The transmission of FLU via airborne routes in the north, like most temperate regions, might be affected by ambient humidity, which was expressed by temperature and
atmospheric pressure, affecting its stability and respiratory droplet size.\textsuperscript{35} In the south, fewer hours of sunlight reduce levels of UVB radiation, which could enhance FLU survival, because solar radiation is well known to be an effective sterilizing agent for most infectious agents.\textsuperscript{14} Also, reduced sun exposure could lead to vitamin D levels dropping, which might down-regulate the expression of antimicrobial peptides, and further reduce immune-system functionality and increase susceptibility to seasonal viruses.\textsuperscript{41}

We inferred that PIV was less dependent on weather in the north. In the south, except relative humidity and wind speed, other climate factors had significant explanations. An analysis over 11 years in Suzhou, a subtropical city of China, suggested that temperature had a positive correlation with PIV activity,\textsuperscript{29} while another article written by Sundell found a weaker correlation between PIV and vapor pressure.\textsuperscript{24} Several studies found that rainfall was positively correlated with ADV activity in many regions, including Europe, Africa and Asia,\textsuperscript{29,42} comparable results were obtained in our study in the south, while relative humidity was the most dominant power in the north. Vapor pressure was the dominant factor for hMPV in both north and south China. Other factors also had significant explanations to some extent. This finding agreed with a Swedish study that hMPV was associated with low temperature and vapor pressure,\textsuperscript{24} although another French study found that low temperature and wind speed were the main drivers of hMPV seasonality in temperate regions.\textsuperscript{30} For hBoV,
atmospheric pressure and relative humidity were two dominant factors in the north. In the south, almost all factors had great explanations except relative humidity. Our results for hCoV were in agreement with Sundell’s study\(^{24}\), wind speed played important role in each region. There also existed some hypotheses. First, strong wind can accelerate the spread of hCoV by increasing air flow. Second, strong wind would cool body surface temperature, which would cause vasoconstriction in the respiratory tract mucosa and suppression of immune responses, leading to increased susceptibility to infections.

Our study also provided the explanatory powers of meteorological factors on ALRI viruses in different genders and different age groups in both north and south regions. The effects of climate factors on these viruses were considerably different. This may be due to the different responses of different age groups to climate changes. Children are more susceptible to infections because they prefer to stay outside and play with others, they are more sensitive to meteorological factor. Older people with poor health and low immunity are more willing to stay at home. Hence, the influences of meteorological factors on older people were not very significant.

Furthermore, the interaction roles of these factors on respiratory viruses were also discussed here. Generally, the dominant interaction of different viruses in different regions were varied. This is because respiratory viruses displayed a great deal of variety not only in their virion structure and genome composition
but also in their modes of transmission among humans. Taken together, the
enhanced interaction between any two variables implied that the seasonal
prevalence of these viruses was not determined by a single factor. Relative
humidity was the most dominant interaction factor after interacting with others
in the north for most viruses. In the south, wind speed also presented great
interaction role, although it was not the main single factor for most viruses. In
general, meteorological factors are not independent of each other, thus the
epidemic cycles of respiratory viruses could be the result of the combined
environmental parameters rather than the action of any single factor. Our
findings about the dominant interaction of meteorological factors further
revealed the importance of their joint effects.

This paper, like most previous studies, just investigated the influences of climate
factors relied on outdoor meteorological variables, while people may spend more
time indoors.\textsuperscript{43} It is likely that outdoor environmental conditions are not the real
environment for the viability and transmission of viruses.\textsuperscript{44} Considering that
indoor data are not widely available, outdoor climate factors were used as
surrogate markers of indoor climates in this study. Meteorological factors are
more linked to change human behaviour and living environment to indirectly
influence the spread of viruses. In temperate regions, indoor crowding was
speculated as one main reason for influenza/RSV peaks in cold season by many
studies.\textsuperscript{45,46} In subtropical regions, wet and hot air in summer forces people to
stay in crowded, air-conditioned environment, which favors the easy transmission of viruses.\textsuperscript{47} Besides, the usage rate of air conditioning is determined by income and wealth. There is also a need to further study the relationship between economic conditions and viruses.

There were also some important limitations to consider. Firstly, the spatial representation of sentinel hospitals in this study was conducted by a national surveillance protocol\textsuperscript{18}. Specimens were tested in different laboratories, the time and amount of specimen collection and the testing capacity were varied in different hospitals, which might lead to some statistical differences. Secondly, our present dataset was not sufficient to support the study at the city or hospital level because specimens were collected from the first two or five ALRI patients weekly or monthly in each sentinel hospital, which would lead to some limitations to reveal the relationships about local situations or individual exposures. Thirdly, virus (sub) typing was not performed systematically and (sub) typing data were not collected here, which might provide a more comprehensive picture in various regions.\textsuperscript{48} Fourthly, we had only statistically explored the relationship between meteorological factors and the seasonal characteristics of these viruses, the findings were just statistically extrapolated, the truly mechanism of the influence of meteorological factors on these viruses might be very complex. Lastly, the association between meteorological factors and these viruses could be influenced by many confounding factors. Considering the fact
that people prefer to stay indoors during cold or rainy days, indoor climate, humidity in particular, was suggested as an important factor in respiratory virus transmission, future studies should consider both the role of the outdoor and indoor climate on respiratory virus infections.

**Conclusion**

This study systematically and quantitatively described the different explanatory power of different meteorological variables on different viruses in both temperate (north) and subtropical (south) climate regions in China. The spatiotemporal heterogeneity of most viruses was also detected in this study. The dominant factor was varied for different viruses in different age groups in different regions. Our results highlighted that temperature, vapor pressure, atmospheric pressure, rainfall and sunlight were dominant factors for most viruses in both northern and southern China, relative humidity had great explanatory power for some viruses in the northern China (temperate climate) while it did not have significant role in the south (subtropical climate). Moreover, the interaction of each pair of meteorological factors on different viruses was also detected enhanced. More understanding of the meteorological effects on the seasonality of these viruses would be helpful in guiding government planning, such as through public health interventions, good hygiene and infection control practice, timing of passive immunoprophylaxis and facilitating the development of future vaccine strategies.
Supporting Information

Supplementary appendix S1: Demographic and clinical characteristics of enrolled hospitalized ALRI patients and laboratory-confirmed viral etiologies in China.

Supplementary appendix S2: Number of each virus detected in hospitalized ALRI patients in different regions of China.

Supplementary appendix S3: Statistical descriptions of seven respiratory viruses and meteorological variables (mean ± standard deviation) in different regions of China.

Supplementary appendix S4: Monthly positive rates of seven respiratory viruses in different regions of China.

Supplementary appendix S5: Monthly meteorological factors in different regions of China.

Supplementary appendix S6: Explanatory power of meteorological factors on total respiratory viruses by age group and gender in different regions of China.

Supplementary appendix S7: Explanatory power of meteorological factors on each respiratory virus by age group and gender in different regions of China.

Supplementary appendix S8: Average total virus positive rates of different levels on vapor pressure in different regions of China.
Supplementary appendix S9: Average RSV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S10: Average FLU positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S11: Average PIV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S12: Average ADV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S13: Average hBoV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S14: Average hCoV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S15: Average hMPV positive rates of different levels on dominant factors in different regions of China.

Supplementary appendix S16: Interactive effects of each paired factors on RSV positive rates in different regions of China.

Supplementary appendix S17: Interactive effects of each paired factors on FLU positive rates in different regions of China.

Supplementary appendix S18: Interactive effects of each paired factors on PIV positive rates in different regions of China.

Supplementary appendix S19: Interactive effects of each paired factors on
ADV positive rates in different regions of China.

Supplementary appendix S20: Interactive effects of each paired factors on hBoV positive rates in different regions of China.

Supplementary appendix S21: Interactive effects of each paired factors on hCoV positive rates in different regions of China.

Supplementary appendix S22: Interactive effects of each paired factors on hMPV positive rates in different regions of China.

Supplementary appendix S23: Factor interaction with maximum q value for each virus in different regions of China.

Contributions

BX and ZL contributed equally in this study. JW and WY received and contributed to the conception and design of the study. BX and JY contributed to literature review. SL, ZL, and LW contributed to the ALRI data collection and data quality control. BX, JY and CX collected the meteorological data. BX, JY, YL, MH and CX cleaned, analysed, and visualised the data. JW and WY supervised the analysis and generating of results. BX and JW drafted and finalised the paper. All authors contributed to data interpretation, and reviewed and approved the final version manuscript. WY had full access to all the data in the study, JW and WY had final responsibility for the decision to submit for publication.
Declaration of interests

The authors declare no competing interests.

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