Are Meteorological Parameters Associated with Acute Respiratory Tract Infections?

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Background. Information on the onset of epidemics of acute respiratory tract infections (ARIs) is useful in timing preventive strategies (eg, the passive immunization of high-risk infants against respiratory syncytial virus [RSV]). Aiming at better predictions of the seasonal activity of ARI pathogens, we investigated the influence of climate on hospitalizations for ARIs.

Methods. Samples obtained from 3044 children hospitalized with ARIs in Mainz, Germany, were tested for pathogens with a multiplex reverse-transcriptase polymerase chain reaction enzyme-linked immunosorbent assay from 2001 through 2006. Hospitalizations for ARIs were correlated with meteorological parameters recorded at the University of Mainz. The frequency of hospitalization for RSV infection was predicted on the basis of multiple time series analysis.

Results. Influenza A, RSV, and adenovirus were correlated with temperature and rhinovirus to relative humidity. In a time series model that included seasonal and climatic conditions, RSV-associated hospitalizations were predictable.

Conclusions. Seasonality of certain ARI pathogens can be explained by meteorological influences. The model presented herein is a first step toward predicting annual RSV epidemics using weather forecast data.

Acute respiratory tract infections (ARIs) are the most common illnesses in humans [1]. On a global scale, ARI-associated pneumonia is the main cause of childhood mortality, primarily for ARIs in children aged <5 years in developing countries [2, 3]. The offending respiratory pathogens are similar for developing and developed countries and include a large variety of colonizing and usually noncolonizing bacteria and viruses. Some—but, remarkably, not all—known ARI viruses cause epidemics during the cold season (ie, every winter in the northern and southern hemispheres but year round in tropical climates). This is reflected in the fact that many languages designate ARI as a *cold* to express the genuine experience that low temperature is the cause of ARIs.

Interestingly, in the early 1930s, ARIs occurred on the islands of Spitsbergen in the Arctic Sea during summertime [4]. When outdoor temperature increased, ships made it through the arctic ice to reach the small population after many months of isolation. Ship crews likely then introduced ARI viruses into the Spitsbergen population; after recovery, patients and finally the whole small community were immune to the respective pathogen, and the epidemic was over. These data provide epidemiological evidence that microorganisms are a necessary prerequisite for ARI. Although low outdoor temperatures may be associated with ARI outbreaks, they are not the *causa.* Low temperatures or other climatic factors may, however, influence the interaction among the host, pathogen, and environment, increasing the probability of exposure, susceptibility, and infection.

In 1996, a multiplex reverse-transcriptase polymerase chain reaction (RT-PCR) was developed to detect initially 9 and finally 19 noncolonizing ARI pathogens [5].

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This test was systematically used to detect ARI pathogens in children hospitalized with ARI in 3 areas in the German Pediatric Infectious Diseases Network on Acute Respiratory Tract Infections (PID-ARI.net; see http://www.pid-ari.net). Distinct 1- and 2-year patterns of occurrence for some ARI pathogens, particularly respiratory syncytial virus (RSV), were identified, allowing predictions on epidemics to some degree [6, 7]. The goals of this study were to find out whether climatic factors are associated with ARI epidemics among children and whether such factors are useful to predict epidemics with higher precision.

METHODS

Study design. A retrospective study was conducted to investigate the relationship between meteorological parameters and the frequency of ARI-associated hospitalization of children.

Meteorological data. Temperature, relative humidity, wind velocity, and relative atmospheric pressure were routinely measured in intervals of 10 min at the meteorological station of the Institute for Atmosphere Physics at the University of Mainz. These data were available for the period from March 2001 through December 2006, with the exception of wind velocity, which was measured from June 2001 through December 2006 only.

Data of hospitalizations of children with ARIs. Within PID-ARI.net, all children aged <16 years hospitalized with an ARI at the Department of Paediatrics, University of Mainz, Germany, were eligible for participation in the study. This is the only children's hospital in the city of Mainz. The participation rate was ∼75%. Results from 3044 samples tested by PCR were available for statistical analysis from the study database from March 2001 through December 2006. For the description of the 4 most common ARI pathogens, we only took into consideration the 2012 samples of the period from July 2003 through December 2006, when all 19 ARI pathogens were tested in PID-ARI.net. Detailed hospitalization rates associated with different respiratory pathogens have been published recently [8, 9].

Multiplex RT-PCR. Nasopharyngeal aspirates were obtained from children according to a standard protocol and were tested for 9 pathogens until October 2002, for 16 pathogens until April 2003, and for 19 pathogens thereafter. Therefore, data on RSV, influenza A, and adenovirus hospitalizations were available for the whole study period. Details of the method have been previously described [5]. Validation of the method (for 9 pathogens, including RSV, influenza, and adenovirus) was published earlier [10], and the validity of the extended method for these pathogens is comparable, with a sensitivity of 90%–100% and a specificity of ∼99%. Rhinovirus infections were tested from October 2002 only with the extended method. Validity of the method to detect picornavirus (including rhinovirus and enterovirus) was good, and the correct differentiation between enterovirus and rhinovirus within the specimens tested for validation was verified by sequence analysis (unpublished data).

Statistical analysis. For the description of the percentage of the different ARI pathogens the period from July 2003 through December 2006 was compromised only, when all 19 ARI pathogens were detected by multiplex RT-PCR. The number of hospitalizations of children with ARI and the averages of the meteorological parameters were calculated for intervals of 14 days, which is the predictive period of current weather forecasts. Description was performed by time series diagrams. Inferential statistics included Spearman rank correlations, partial correlations, and multiple time series analysis. The number of children hospitalized with ARI was the dependent variable. The independent variables were the meteorological data and a seasonal component.

Associations between ARI hospitalization frequency and meteorological parameters were explored by Spearman rank correlations. With partial correlations the strength of the association between meteorological parameters and ARI hospitalizations were analyzed after adjusting for the correlations among meteorological parameters. Spearman correlations were calculated for 12 common ARI pathogens. Partial correlations were calculated for hospitalizations due to the 4 most common pathogens and for all hospitalizations with an identified pathogen only.

With the final goal of prediction of occurrence of RSV infection on the basis of meteorological data, an autoregressive integrated moving average (ARIMA) model was developed. ARIMA models (Box and Jenkins models) have the flexibility to control for the autocorrelation of time series data. The Box-Ljung test was used to prove the null hypothesis that the autocorrelations of the residual time series are equal to zero.

The ARIMA model was built in the period between the 47th calendar week of 2001 and the 30th calendar week of 2004 (estimation period). It was evaluated by comparing predicted versus observed frequencies of hospitalization due to RSV infection in the period between the 31st calendar week of 2004 and the 52nd calendar week of 2006 (evaluation period). The R^2 autoregression coefficient was calculated for the model. For influenza A, adenovirus, and rhinovirus, the time dependence of the association with meteorological parameters was proved by multiple time series analysis.

All statistical tests were 2-tailed, and P values <.05 were considered to be statistically significant in terms of an explorative data analysis. The α level was not adjusted for multiple testing procedures because of the explorative study design. For statistical analysis we used SPSS software, version 15 (SPSS).

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RESULTS

Description. In 1350 (66.9%) of the 2017 nasopharyngeal samples tested for ARI from July 2003 through December 2006, at least 1 ARI pathogen was detected. Altogether 1712 pathogens were detected by multiplex RT-PCR. Human rhinovirus (574 [33.5%] of 1712), RSV (326 [19.0%]), adenovirus (223 [13.0%]), and influenza A virus (138 [8.1%]) were the most common respiratory pathogens detected in these samples (Figure 1). This was comparable to the order and frequency of pathogens detected in the PID-ARI.net from October 2002 through May 2007 [8].

Human rhinovirus, enterovirus, and adenovirus were detected all year round, whereas RSV, influenza A virus, and human metapneumovirus showed distinctive winter peaks (Figures 1 and 2). In the graphs showing the outside temperature and the respective hospitalization rates due to 1 of the 4 most common pathogens detected over time (Figure 2*A*–2*D*), an increased activity of ARI pathogens with lower temperatures can be seen for all 4.

Bivariate analysis. Mean temperature, relative humidity, and wind velocity were significantly correlated with the overall number of ARI hospitalizations only. RSV was most strongly inversely correlated with temperature, followed by influenza A virus, rhinovirus, and adenovirus. We found statistically significant but weaker correlations for the association between relative humidity and wind velocity and these 4 pathogens, with the exception of human rhinovirus and wind velocity (Table 1).

Because different meteorological parameters may also be correlated with each other (winters in Mainz tend to be cold and humid and may have an increased wind velocity), we analyzed the relationship among those parameters. In fact, temperature was inversely correlated with relative humidity ($r_s = -0.63$; $P < .001$) and wind velocity ($r_s = -0.50$; $P < .001$), whereas the latter ones were not correlated with each other. Atmospheric pressure showed no relevant correlations with other meteorological parameters and was not further considered in the advanced analysis.

Accounting for these intercorrelations, associations between meteorological factors and ARI hospitalization rates were then analyzed using partial correlations: detection of any of the 19 pathogens was inversely related to mean temperature only. In contrast, rhinovirus was correlated with increased humidity, and RSV activity was associated with lower temperatures and higher wind velocity. Influenza A virus and adenovirus were associated with low temperatures only (Table 2).

Multiple analyses. In an ARIMA model with second-order autoregression, initially a seasonal component, mean temperature, and wind velocity were included. The model was then stepwise fitted for significant covariates associated with the frequency of RSV hospitalization. Temperature was the only independent covariate that was significantly associated with the frequency of RSV hospitalization in the multiple time series analysis (Table 3). The R^2 was 0.65 for the fitted ARIMA model. The β coefficient for the parameter temperature was negative in the multiple analyses, indicating increasing RSV frequency with decreasing temperature.

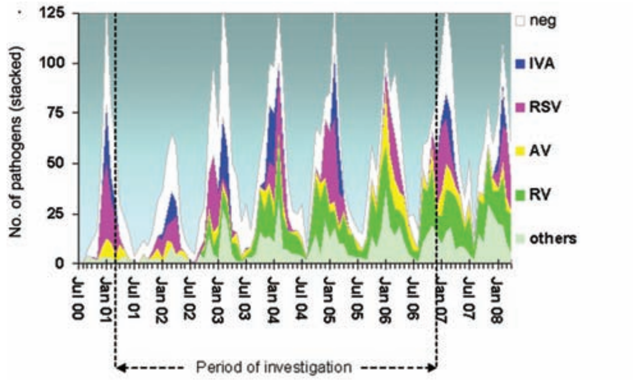

Figure 1. Detection of acute respiratory tract infection (ARI) pathogens in hospitalized children in Mainz, Germany. The 4 most frequent pathogens leading to hospitalization of children aged ⩽16 years with a diagnosis of ARI in Mainz from 2000 through 2008 were, in order, rhinovirus (RV), respiratory syncytial virus (RSV), influenza virus A (IVA), and adenovirus (AV).

RSV infection–associated hospitalizations were then predicted with this ARIMA model on the basis of a model building period from March 2001 through June 2004 and a forecast (evaluation) period from July 2004 through December 2006 (Figure 3).

Multiple time series analysis was also performed for the influence of meteorological parameters on the hospitalization frequency due to adenovirus, influenza A virus, and human rhinovirus infections. For all 3 an ARIMA model with a first-order autoregression fit best, and by a stepwise adjustment the same meteorological parameters as in the partial analysis proved to be significant: temperature for adenovirus ($\beta = -.089$; $P < .001$) and influenza A virus ($\beta = -.215$; $P = .002$) and relative humidity for human rhinovirus ($\beta = .218$; $P = .002$).

DISCUSSION

This is the first study, to our knowledge, to analyze the relationship between the most common known ARI pathogens in children and different meteorological parameters for >5 years. Earlier investigations were limited in the number of ARI pathogens detected, the method used for testing ARI viruses, and the observation period. To our knowledge, it is also the first study to model prediction of RSV infection-associated hos-

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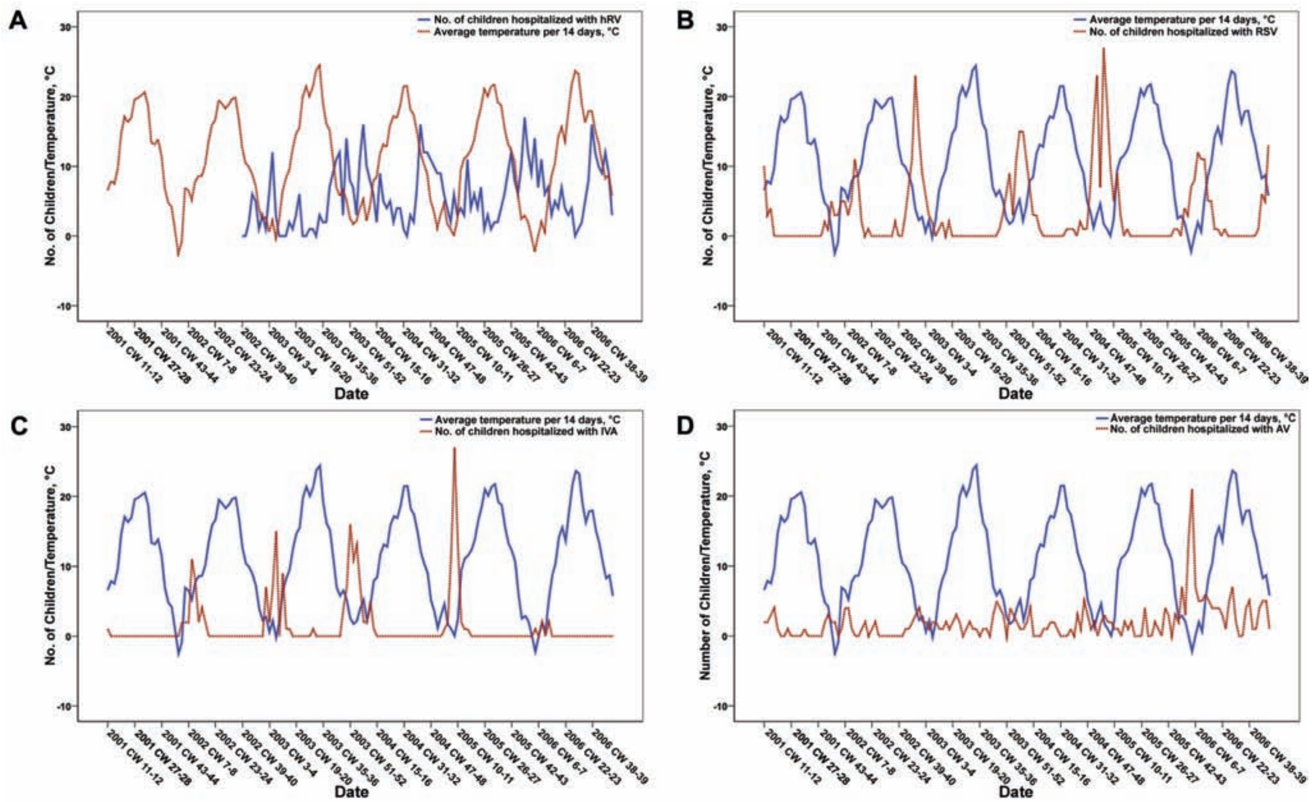

Figure 2. Mean temperature and hospitalizations due to human rhinovirus (hRV; *A*), respiratory syncytial virus (RSV; *B*), influenza virus A (IVA; *C*), and adenovirus (AV; *D*). An alternate course is seen between temperature and RSV and IVA, but this was less distinct for RV and AV. CW, calendar week.

pitalizations on the basis of weather variables in an ARIMA model.

We found that some pathogens of ARIs, such as RSV and influenza virus, show specific patterns of annual or biannual rhythmicity (Figure 1). We also found that some pathogens are significantly associated with meteorological parameters (eg, RSV with temperature or rhinovirus with relative humidity) (Tables 1–3). In addition, within certain limits, the occurrence of RSV infections was predictable on the basis of its own rhythmicity and on the influence of meteorological parameters (Figure 3).

Our findings are in agreement with an investigation performed in Buenos Aires, Argentina, in 1998 through 2002 [11]. In 32.8% of the 18,561 children younger than 5 years who were hospitalized with respiratory symptoms in this study, a common ARI virus was identified, compared with 66.9% in our study. Temperature was highly inversely correlated with RSV, influenza A, and adenovirus frequency. As in our investigation, rhinovirus was also associated with relative humidity. The congruence of these results with ours is remarkable. The significant correlation between relative humidity and rhinovirus frequency is consistent with the observation that rhinoviruses cannot survive in a dry environment [12]. Rhinovirus can cause infections the whole year round, with peak occurrence during late autumn and late winter or in early spring [6, 8, 13].

From our database it cannot be excluded that ARI incidence was constant over time and that chilliness would contribute to a higher hospitalization rate in cold seasons. Results from earlier studies make this assumption improbable [14–16]. In one study that included community-based data and hospitalization rates for children with respiratory diseases, both the community incidence and hospitalization rates peaked during wintertime and decreased during springtime [14]. This is in agreement with the present findings and demonstrates that outpatient and hospital respiratory infections show parallel patterns over time. Data of the national surveillance for RSV in the United States involving 74 laboratories for >5 years described winter peaks all over the country [15]. In another investigation decreasing temperatures were associated with an increasing incidence of common colds in family members of all ages as in the present study [16]. The authors concluded that the reason could be "reflex cooling" of the nasal mucosa because this has been observed during anxiety-induced stress, which is also associated with higher common cold frequency.

The specific rhythmicity of certain ARI pathogens has been described earlier; in particular, the 2-year rhythm of RSV, hu-

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Table 1. Spearman Rank Correlation Coefficients for the Associations between Meteorological Parameters and Hospitalizations of Children with Respiratory Pathogens

	Mean temperature		Mean relative humidity		Mean wind velocity		Mean atmospheric pressure	
ARI pathogens	r_s	P	r_s	P	r_s	P	r_s	P
All 19 ARI pathogens	−0.71	<.001	0.51	<.001	0.45	<.001	0.06	.476
Human rhinovirus	−0.42	<.001	0.56	<.001	0.13	.162	−0.05	.628
Respiratory syncytial virus	−0.76	<.001	0.42	<.001	0.56	<.001	0.01	.871
Influenza A virus	−0.53	<.001	0.17	<.001	0.42	<.001	0.02	.769
Adenovirus	−0.42	<.001	0.25	<.001	0.28	<.001	0.00	.983
Metapneumovirus	−0.54	<.001	0.32	.001	0.28	.003	0.09	.345
Enterovirus	−0.07	.385	0.17	.039	0.00	.987	−0.01	.889
Mycoplasma pneumoniae	−0.19	.022	0.30	<.001	−0.05	.540	0.07	.390
Parainfluenza type 1	−0.05	.507	0.21	.009	−0.20	.016	0.14	.089
Parainfluenza type 3	−0.17	.037	0.01	.887	−0.29	<.001	−0.11	.200
Influenza B virus	−0.33	<.001	−0.04	.597	0.38	<.001	−0.15	.073
Coronavirus	−0.61	<.001	0.28	.007	0.42	<.001	0.21	.050
Chlamydophila pneumoniae	−0.03	.749	0.12	.156	0.07	.382	−0.13	.114

NOTE. ARI, acute respiratory tract infection.

man metapneumovirus, and parainfluenza virus epidemics is well known [6–8]. Predictions of the onset of RSV disease can be useful in timely immunization with specific RSV antibodies in infants, which is an effective, albeit expensive, prophylaxis. The influence of meteorological parameters on the time course of RSV was investigated in more detail. Average outdoor temperatures were identified to be significantly associated with the onset and course of this pathogen. Taking into account its own rhythm and the temperature course, onset and course of RSV infection were predicted on the basis of an ARIMA model. Within certain limits the predicted and observed time course of RSV infection–associated hospitalization was in good agreement. Our model can be a next step to allow better predictions of RSV and other ARI waves using weather forecast data.

In temperate climates the winter peak of certain ARIs is well described [11, 16–20]. This explains the expression *common cold*. The seasonality of common ARIs in tropical regions is less distinct [21]. Here, ARI pathogens appear to be active all year round, the incidence peaks are less prominent, and the association of ARI with meteorological factors, such as temperature, seems to be less clear. In Singapore, RSV infection was associated with higher temperatures but also with a higher temperature variation [22]. Higher RSV infection–associated hospitalization rates in this investigation could therefore have been associated with a relative decrease in temperature. In Israel [23] an increasing occurrence of RSV infection was associated with decreasing temperatures, comparable to our results. In Guinea [19] and Hawaii [24], RSV infections were more often observed during rainy seasons. Both a coincidence of lower temperatures and a higher number of rainy days were associated with increasing frequencies of RSV infection in Malaysia [25] and Santiago de Chile [26]. Such a seasonal trend has also been observed for Hong Kong and Singapore, with different times for the peak incidence [22, 27]. In studies from the Indian

Table 2. Partial Correlations between Meteorological Parameters and Hospitalizations of Children aged ≤16 years Due to Infections with Respiratory Pathogens for the Adjustment of Correlations among Meteorological Parameters

	Mean relative humidity		Mean temperature		Mean wind velocity	
Pathogen	Correlation	P	Correlation	P	Correlation	P
All 19 ARI pathogens	0.16	.058	−0.48	<.001	0.13	.139
Human rhinovirus	0.41	<.001	−0.07	.457	0.03	.737
Respiratory syncytial virus	0.01	.951	−0.41	<.001	0.18	.038
Influenza A virus	−0.12	.165	−0.35	<.001	0.04	.618
Adenovirus	−0.00	.965	−0.25	.002	0.00	.997

NOTE. ARI, acute respiratory tract infection.

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Table 3. Multiple Adjusted Regression Analysis for Respiratory Syncytial Virus Infection–Associated Hospitalizations of Children Based on the Autoregressive Integrated Moving Average Model

Factor	Lag time, weeks	$\beta \pm$ SE	t	P
Constant	…	6.157 ± 1.380	4.461	<.001
Autoregression	1	0.855 ± 0.111	7.727	<.001
Autoregression	2	−0.214 ± 0.108	−1.981	.05
Mean temperature	0	−0.290 ± 0.102	−2.831	.006

NOTE. SE, standard error.

subcontinent, one part showed higher RSV frequency during the cold season and the other during the rainy season [28]. In The Gambia, higher RSV activity was observed in the rainy season only [28]. As for RSV, the annual influenza season in temperate climates is less clear-cut in tropical climates [29].

The association between meteorological parameters and the activity of ARI pathogens could, on the one hand, be explained by an enhanced probability for infection of children staying at home longer on cold or rainy days, resulting in closer contact and higher transmission rates among household members. On the other hand, virus transmission under certain climatic conditions could play a role. In an experimental study using guinea pigs, the infection rate followed by the aerosol spread of influenza virus depended on ambient relative humidity and temperature [30]. Cold and dry conditions favored transmission. This is in agreement with the present findings. However, according to our data, it cannot be excluded that the relationship among temperature, relative humidity, and influenza frequency results from an association with vapor pressure, which might be a reason for influenza seasonality [31].

The reasons for the seasonality of influenza are not known, and it has been assumed that a combination of immunological, epidemiological, and virological factors may explain this phenomenon [29]. A recent study found that influenza viruses coat themselves in fatty material that hardens and protects the organism in colder temperatures [32]. Besides host- and virus-specific factors, climate could also contribute to the seasonality of influenza epidemics.

Generally speaking, reasons for the seasonality of certain ARI pathogens may include (1) the effects of climatic factors on the survival and spread of infectious pathogen in the environment [30, 32, 33]; (2) the changing population susceptibility to ARIs, depending on physiological reactions of the host to certain climatic conditions [34–36]; and (3) the changing probability of transmission of ARI pathogens through changing host behavior under certain climatic conditions.

The relationship between cold exposure and the development of common colds has also been investigated in an experiment on volunteers. Exposure to chilliness appeared to trigger the onset of the common cold [37]. The major shortcoming of this study is the lack of detection of ARI pathogens. The observed respiratory symptoms may have been due to a sterile inflammatory response induced by cold injury. Thus, although low outdoor temperatures alone cannot cause an infection, they may cause respiratory symptoms. In contrast to this assumption, another study of volunteers demonstrated that the exposure to cold alone without contact with infectious material

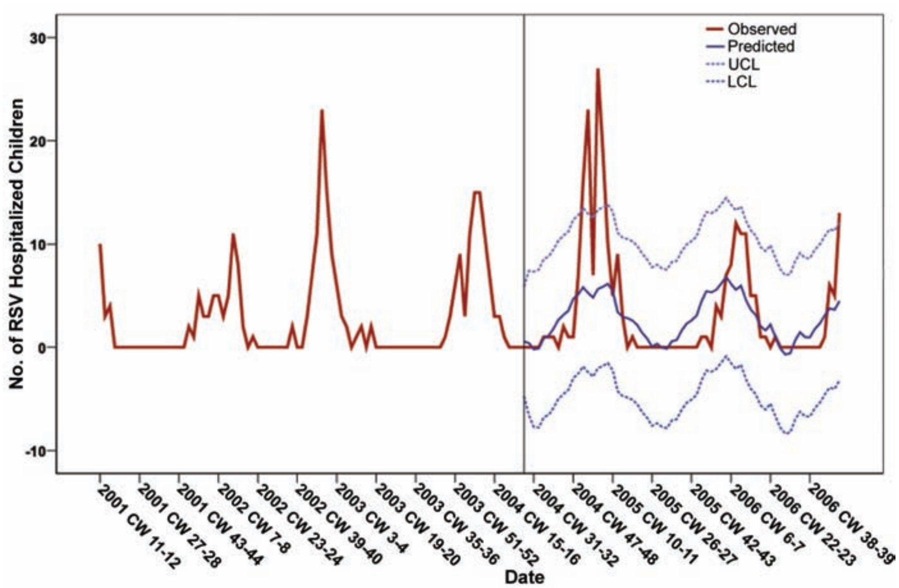

Figure 3. Prediction of respiratory syncytial virus (RSV) hospitalizations on the basis of an autoregressive integrated moving average model (2, 0, 0), with mean temperature as the covariate. Good agreement was found between observed and predicted RSV infection–associated hospitalizations. CW, calendar week; LCL, lower confidence interval; UCL, upper confidence interval.

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from patients with a common cold was insufficient to cause symptoms of a common cold [38]. However, in both groups exposed to infectious agents with or without cold exposure some individuals developed respiratory symptoms. Taking all evidence into account, in large populations low temperatures might enhance (1) the likelihood of exposure to an ARI pathogen, (2) the spread of ARIs, and (3) the susceptibility to true ARIs.

Our study was able to show that with appropriate ARI surveillance in place, the epidemic occurrence of at least some specific ARI pathogens can be predicted on the basis of pathogen-specific seasonal rhythm and weather forecast data within certain limits. According to these findings, respiratory pathogens have a different affinity to certain climatic conditions. Rhinovirus preferred a humid climate, whereas many other respiratory pathogens, such as RSV and influenza A, favored low temperatures. For the latter, this observation might explain the peak incidence in cold seasons, at least in temperate climates. In a time series model RSV was predicted on the basis of the influence of temperature and its own rhythm.

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