Association between environmental factors and hospital visits among allergic patients: A retrospective study

Jie Chen,1 Li Peng,2 Shan He,1 Youjin Li1 and Zhe Mu2

Summary

Objective: This study investigated correlations between meteorological and environmental factors (MEFs) and allergic rhinitis in childhood (ARC).

Methods: Children who received treatment for AR and meteorological data that might have influenced AR in the same time period were included in this study. Daily average maximum values of sulfur dioxide (SO2), nitrogen dioxide (NO2), and particulate matter (PM10) at 3 a.m. and 8 a.m. were provided by the Shanghai Environmental Bureau for statistical analysis using a generalized additive model (GAM).

Results: Outpatient visits for ARC were higher, with a bimodal shape, for daily average temperatures of about 11°C and 21°C. However, increasing humidity was associated with a downward trend in outpatient visits for ARC, suggesting that high humidity had a protective effect on AR. When levels of air pollutants such as O3, SO2, and PM10 increased by 10 μg/m³, AR outpatient visits increased by 1.95%, 1.19% and 0.33%, respectively, suggesting that air pollution might increase the risk of AR episodes.

Conclusions: MEFs were significantly correlated with the incidence of ARC. (Asian Pac J Allergy Immunol 2016;34:21-9)

Keywords: allergic rhinitis, meteorological factors, environmental factors, childhood, prevention and treatment

Introduction

Allergic rhinitis (AR) typically presents as nasal itching, sneezing, congestion, and discharge; this major nasal disease affects the health, academic performance, and quality of life of children, and may also induce bronchial asthma, nasal sinusitis, nasal polyps, otitis media, allergic conjunctivitis, etc. Both its prevalence and social impacts are high. In recent years, the International Study of Asthma and Allergies in Childhood (ISAAC) reported that the global prevalence of AR, asthma, and atopic eczema showed an overall upward trend.1 AR incidence accounted for 5%-50% of the total worldwide population,2 and the incidence rate was 37.74% in China.3 With the continuous development of society, living environments have undergone tremendous changes, particularly in developing countries, and environmental pollution risen, leading directly to increasing annual incidence of AR. Evidence has shown that meteorological and environmental pollution factors are closely related to the incidence of AR4-6 and that outdoor air pollution could increase the chances of allergic rhinitis in childhood (ARC).7,8 Industrial pollutants (sulfur dioxide [SO2], total suspended particles, and dust sedimentation) have been shown to be predisposing factors for upper respiratory tract infections, and diesel exhaust particles (DEP) and nitrogen dioxide (NO2) emitted by diesel engines could increase the sensitivity to and incidence of allergic reactions.9, 10 Exposure to air pollutants including suspended particulate matters with particle size less than 10 and 2.5 μm (PM10 and PM2.5, respectively), nitric oxide (NO), NO2, ozone (O3), and pollens, produce chronic effects in the nasal cavity, trachea, and lungs, including increased respiratory symptoms, AR, acute asthma, and other respiratory illnesses.11,12 Exposure to PM10 results in direct injury to the human respiratory tract.13 Many
countries have established health warning systems to quickly convey accurate meteorological and environmental information to the public, and remind the public to take appropriate preventive measures to reduce the likelihood of disease progression.14 The large Chinese population with high AR prevalence, long treatment periods, and large family and social economic burdens result in increased social impacts that should be considered by social and medical personnel. Therefore, in this study, we hoped to provide children with AR timely and appropriate risk warning and prevention guidelines based on the established Shanghai ARC-meteorological and environmental factors (MEFs) prediction model and warning system. Corresponding 5-year meteorological and environmental data were analyzed, and time-sequence analytical methods were used to establish a warning data model to forecast levels associated with AR onset, including the meteorological and environmental factors useful for forecasting trends in incidence. AR can seriously affect the health and life quality of diseased children; treatment costs are expensive and the course long, and some children require lifelong treatment. AR is a social as well as a medical problem. The purpose of this study was to investigate the impacts of MEFs on ARC onset. This preliminary study will form the basis for a future one-year prospective study to verify these findings; further studies will perform appropriate interventions and observe their results. The results of this study provide a reliable theoretical basis for ARC prevention and treatment, guide parents and children to improve their living habits to minimize the impacts of risk factors, and reduce the incidence of respiratory allergic diseases in childhood.

Methods

Outpatient data

Data from outpatient ARC at our hospital were selected among outpatient visits seen by the department of otorhinolaryngology from January 1, 2007 to December 31, 2011; return visits and medication prescriptions were excluded, and data including date of birth, date of visit, and gender were collected. A total of 19,370 patients presenting with AR were included (13,014 men and 6,356 women), aged 2 to 15 years. All enrolled children were diagnosed with AR by four experienced physicians based on their clinical manifestations, topical nasal examinations, and results of allergen testing. Peripheral blood samples were collected from the children. The serum concentrations of total immunoglobulin E (IgE) and allergen-specific IgE (sIgE) antibodies were measured using an AllergyScreen system from Mediwiss Analytic GmbH (Germany) according to manufacturer directions. Serum concentrations of sIgE antibodies for ten common inhalant allergens were measured, including Dermatophagoides pteronyssinus (Dp), house dust, mulberry, cat dander, dog dander, cockroach, Amaranthus retroflexus, mixed grass pollen (mugwort, ragweed, Humulus japonicus, and grey quinoa), mixed tree pollen (oak, Firmiana simplex, and willow), and mixed mold (Penicillium notatum, branch spore mold, Alternaria alternata, Aspergillus fumigatus, and Aspergillus niger). In addition, nine common food allergens were measured, including egg white, milk, shrimp, beef, mussel, crab, mango, cashew nut, and pineapple. Serum concentrations of total IgE less than 100 IU/mL were considered normal, and sIgE greater levels than or equal to 0.35 IU/mL were considered positive. The quantitative test results of sIgE were divided into six levels according to concentrations: 0: <0.35 IU/mL; 1: 0.35–0.69 IU/mL; 2: 0.7–3.49 IU/mL; 3: 3.50–17.49 IU/mL; 4: 17.50–49.99 IU/mL; 5: 50.00–100.00 IU/mL; and 6: >100.00 IU/mL.

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shanghai Jiaotong University. Written informed consent was obtained from all participants.

Meteorological and atmospheric data

Meteorological data that might affect AR were collected from January 1, 2007 to December 31, 2011 by the Shanghai Meteorological Center as previously described; these analytical factors included the daily average temperature (temperature), relative humidity (humidity), wind speed (wind), and rainfall in Shanghai. Atmospheric levels of SO2, NO2 and PM10 were provided by the Shanghai Environmental Bureau (covering six observation sites in Shanghai), and the average maximum values at 3 a.m. and 8 a.m. among the six sites (Xujia, Baoshan, Chongming, Dongtan, Pudong and Jinshan) were used for analysis.

Statistical analysis

A generalized additive model (GAM), an extension of the generalized linear model (GLM),
allowed various parts of GAM’s hypothetic functions to be added; this model could handle the complex nonlinear relationships among outcome variables and numerous explanatory variables and it thus was suitable for complex environmental factors-health time-sequence studies. Therefore, this study used GAM as the basic statistical method. In addition, generally under the same environment, the outpatient numbers on the same day would approximately obey the Poisson distribution, so this study used Poisson distribution as the family distribution of regression model. Many similar studies in China and abroad also assumed that the daily numbers of death, outpatient visits, or hospitalizations approximately obeyed the Poisson distribution.

\[
\log \mu_1 = \alpha + \beta \chi_{t-1} + \eta z_1 + s(t, \lambda) + \varepsilon_1
\]

In the above equation, \( \chi_{t-1} \) was the atmospheric composition, \( z_1 \) was the meteorological factor, \( s(t, \lambda) \) was the confounding of other unmeasured factors, and this confounding was assumed to be smooth over time, and could be controlled by the smooth function.

In addition, because the daily outpatient data were time-sequence data, and might be non-independent among observation sites, diagnosis by the fitting model also considered the relevance problem of residual errors; the obtained GAM model was then subjected to residual error analysis, and a residual error-autocorrelogram of each model was then drawn to determine if the residual errors were the randomly stationary. If the values of residual errors’ auto-correlated functions were less than 0.1, the residual errors were basically uncorrelated; in other words, they would basically have no effect on the statistical inference of model parameters, but absolute values greater than 0.1 indicated that correlations among the residual errors should be considered. The following GAM + AR (P) calibration model was used for the statistical inference:

\[
\log \mu_1 = \alpha + \beta \chi_{t-1} + \eta z_1 + s(t, \lambda) + \varepsilon_1, \\
\varepsilon_1 = \gamma_1 \varepsilon_{t-1} + \gamma_2 \varepsilon_{t-2} + \gamma_3 \varepsilon_{t-3}
\]

The model’s degree of freedom was selected based on the main purpose of this study, which was to estimate the effective value rather than the predictive value of each factor, combined with the value of generalized cross validation (GCV). The punishment splines were used to judge the model’s goodness of fit and to select the degree of freedom for each spline function. Because air pollution and meteorological indicators might have delayed effects on the number of hospital emergency cases, this study also set the delayed effect item (retention period effect) as the analytical indicator; the meteorological factors had the largest non-linear correlation coefficient, and the delayed period was included, which had the highest correlation coefficient among the meteorological factors and outpatient visits, into the model. The selection of atmospheric pollutants informed the delay period based on the maximal effect value of each pollutant under controlled weather conditions. \( P < 0.05 \) were considered statistically significant.

**Results**

**Correlation between seasonal factors and AR incidence**

Table 1 shows the basic distribution of ARC and meteorological and environmental factors from 2007 to 2011. In order to understand the fluctuations of meteorological and atmospheric pollutant indicators within this time period, we compared the time-sequence diagram of Shanghai meteorological indicators and atmospheric pollutants from 2007 to 2011 to daily outpatient visits for ARC, which

<table>
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<th>Variables</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>P25</th>
<th>Median</th>
<th>P75</th>
<th>Max</th>
<th>MISSING</th>
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<td>1</td>
<td>22.00</td>
<td>30.00</td>
<td>38.00</td>
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<td>9.050</td>
<td>-3</td>
<td>9.60</td>
<td>18.30</td>
<td>25.20</td>
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<td>Average daily relative humidity</td>
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<td>12.768</td>
<td>20</td>
<td>60.00</td>
<td>70.00</td>
<td>70.00</td>
<td>90</td>
<td>0</td>
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<td>Average daily wind speed</td>
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<td>2.20</td>
<td>2.80</td>
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<td>7</td>
<td>20.00</td>
<td>33.00</td>
<td>52.00</td>
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<td>31</td>
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<td>NO2</td>
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<td>21.231</td>
<td>11</td>
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<td>50.00</td>
<td>65.00</td>
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<td>19.717</td>
<td>2</td>
<td>56.80</td>
<td>78.70</td>
<td>107.63</td>
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<td>57.99</td>
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<td>46.00</td>
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Table 1. Basic distributions of ARC and meteorological environments
increased slightly each year. The long-term MEF trends were not obvious, but the temperature and levels of O₃, PM, SO₂, and NO₂ showed a seasonal distribution. Interestingly, the seasonal distributions of O₃ and temperature were similar, suggesting a possible correlation between these factors (Figures 1-2). In addition, the average number of monthly ARC emergency visits peaked in spring (April-May) and autumn (October and November). Therefore, the statistical analysis included seasonal factors and long-term trends in the model as confounding factors.

**Correlation of meteorological and atmospheric environmental factors**

Spearman correlation analysis (Table 2) revealed a strong correlation with atmospheric concentrations; correlation coefficients were greater than 0.5 for NO₂ and SO₂, PM10 and NO₂, and PM10 and NO₂, indicating a moderate correlation; the correlation between O₃ and temperature was also high (r = 0.486), consistent with previous reports. NO₂ was moderately negatively correlated with wind (r > 0.5), for high wind speeds and relatively low pollutant concentrations, suggesting correlations among meteorological and atmospheric variables that were not independent.

**Delayed effects**

The delay periods were determined by calculating Spearman correlation coefficients between MEFs and outpatient-emergency ARC visits; the final results showed that the temperature on the exact day had the highest correlation coefficient with the outpatient-emergency visits of ARC. The correlation coefficients of 2-day delayed humidity, 3-day delayed wind, and rainfall amount on the exact day had maximal correlation coefficients. O₃, NO₂, and SO₂ levels on the exact day and 6-day delayed PM10 had maximal correlation coefficients (Table 3). Finally, temperature; humidity; and levels of O₃, SO₂, and PM10 were statistically significant (P < 0.05). The results showed that, after controlling for time-related trends, week effects, and other factors, outpatient

![Figure 1](http://www.apjai-journal.org)

**Figure 1.** Time sequences of temperature, humidity, wind power and O₃ within 2007-2011.  
visits for ARC were higher for average daily temperatures of 11°C and 21°C, which exhibited a bimodal distribution. However, with increasing humidity, outpatient visits for ARC decreased, indicating that high humidity had a protective effect on AR. When the air pollutants O₃, SO₂, and PM₁₀ increased by 10 μg/m³, outpatient visits for ARC increased by 1.95%, 1.19% and 0.33%, respectively (Table 3, Figure 3), suggesting that air pollution might increase the risk of AR onset.

**Discussion**

With increased worldwide industrialization, AR-asthma has become a serious allergic disease, affecting patient work, learning, and living.⁵-⁶, ¹¹ Epidemiological studies have reported that AR incidence accounts for 5%-50% of the total world population;² the incidence rate in China was about 37.74%.³ The AR incidence in children 6-7 and 13-14 years of age was 8.5%, and 14.6%, respectively;¹ early childhood living conditions such as the mother’s gestational age, multiple pregnancies, low birth weight, family history of allergic diseases, and race, as well as the surrounding smoking environment, urban living, nutritional status, and air pollution, were all considered risk factors of AR onset.⁷,⁸,¹⁵ In the current study, the daily number of outpatient ARC cases slightly increased each year. Based on the time-sequence diagram from Shanghai meteorological indicators and atmospheric pollutants from 2007 to 2011, long-term MEFs trends were not obvious, but temperature and levels of O₃, PM, SO₂,

and NO₂ showed seasonal distribution (Figures 1-2). Spearman correlation analysis (Table 2) revealed strong correlations among atmospheric pollutant concentrations; correlation coefficients between NO₂ and SO₂, PM10 and NO₂, and PM10 and NO₂, were greater than 0.5 (moderate correlation), and the correlation between O₃ and temperature was also high (r = 0.486), consistent with previous findings. NO₂ was moderately negatively correlated with wind strength (r > 0.5): when the wind was strong, pollutant concentrations were relatively low, indicating a correlation between meteorological and atmospheric variables, and these factors were not independently associated with the average monthly number of emergency visits for ARC. The numbers of emergency visits in spring (April-May) and autumn (October and November) were slightly higher than in other months. Because this study mainly evaluated the relationship between meteorological environmental factors and ARC, seasonal factors were not considered; instead, this study mainly considered the non-pollen stage, and the statistical analysis controlled for seasonal factors and long-term trends included in the model as confounding factors. Correspondingly, analysis of the controlled time trend, week effects, and other factors, revealed that outpatient visits for ARC were higher when the average daily temperatures were 11°C and 21°C, which exhibited a bimodal shape.

Recent studies have reported that outdoor air pollution increases the risk of ARC. Industrial pollution such as SO₂, total suspended particles, and dust sedimentation were predisposing factors for upper respiratory tract infections. SO₂ could cause decreased activities of the mucociliary epithelium in the respiratory system, diminished cilia movement, resulting in an inability to remove local allergens, thus increasing the chances of mucous membranes contacting with the antigens and enhancing the sensitization effects. SO₂ could also be adsorbed as a gas sol by the nasal epithelium, thus stimulating an immune response in the nasal mucosa and inducing allergic diseases such as AR, asthma, and others. In addition, SO₂ can promote lipid peroxidation, resulting in damage to the nasal epithelium and exposed nerve endings, which leads to nasal hyper-responsiveness when the nerves are stimulated by allergens. DEP and NO₂ emitted by automotive

Table 3. Analytical results of multivariate model parameters of AR-MEFs

|                          | Estimate  | Std. Error | T value | Pr(>|t|) |
|--------------------------|-----------|------------|---------|---------|
| (Intercept)              | 1.115150  | 0.1697266  | 6.57    | 5.02E-11*** |
| Ns(temp, 7)1             | 0.2719054 | 0.0666801  | 4.078   | 4.55E-05*** |
| Ns(temp, 7)2             | 0.1172234 | 0.0831776  | 1.409   | 0.158742  |
| Ns(temp, 7)3             | 0.1725149 | 0.0782247  | 2.205   | 0.027428*  |
| Ns(temp, 7)4             | 0.1160396 | 0.0835551  | 1.389   | 0.1649    |
| Ns(temp, 7)5             | 0.0739482 | 0.0675786  | 1.094   | 0.273843 |
| Ns(temp, 7)6             | 0.0832075 | 0.1593722  | 0.522   | 0.601604  |
| Ns(temp, 7)7             | -0.0214815| 0.0800651  | -0.372  | 0.748165  |
| Ns(2humi, 4)1            | -0.1703828| 0.0603897  | -2.821  | 0.004782** |
| Ns(2humi, 4)2            | -0.223784 | 0.044808   | -4.994  | 5.91E-07*** |
| Ns(2humi, 4)3            | -0.4057343| 0.1409381  | -2.879  | 0.003992** |
| Ns(2humi, 4)4            | -0.1779216| 0.0395086  | -4.503  | 6.69E-06*** |
| As.factor(week)1         | 2.3557959 | 0.0503923  | 46.749  | < 2e-16 *** |
| As.factor(week)2         | 2.1768428 | 0.0506506  | 42.978  | < 2e-16 *** |
| As.factor(week)3         | 2.0901416 | 0.0507562  | 41.18   | < 2e-16 *** |
| As.factor(week)4         | 2.0449764 | 0.0508186  | 40.241  | < 2e-16 *** |
| As.factor(week)5         | 2.1924193 | 0.0506103  | 43.32   | < 2e-16 *** |
| As.factor(week)6         | 2.2099222 | 0.0506162  | 43.483  | < 2e-16 *** |
| Ns(date, 42)1            | -0.5816783| 0.1175663  | -4.948  | 7.51E-07 *** |
| Ns(date, 42)2            | 0.0577884 | 0.0666456  | 0.867   | 0.385887  |
| O₃                       | 0.0193459 | 0.0024634  | 7.853   | 4.05E-15 *** |
| SO₂                      | 0.0118577 | 0.0024728  | 4.795   | 1.63E-06 *** |
| PM10                     | 0.0032521 | 0.0008599  | 3.782   | 0.000156 *** |

*, P<0.05, **, P<0.01, ***, P<0.001
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diesel engines could increase sensitivity and incidence of allergic diseases.\textsuperscript{9,18,19} PM10 has direct effects on injury in the human respiratory tract.\textsuperscript{10} Research in past decades has substantially increased understanding of the pathogenesis of allergic diseases, including the underlying mechanism involving a Th2-dominant immune response that leads to tissue inflammation and remodeling. Recently, new evidence has also been presented to support the importance of innate immunity at the level of dendritic and epithelial cell response for disease expression; additional types of T-cell responses also likely contribute to disease progression\textsuperscript{20,21}. There is now a wealth of evidence linking exposure to outdoor and indoor air pollution, especially airborne PMs, to adverse effects on allergic diseases, where PM’s surface materials may target immune regulatory and pulmonary resident cells.\textsuperscript{22,23} Several reviews have discussed the potential mechanisms of each individual component associated with PMs; for example, the functional impact of air pollutant gases such as O$_3$, NO$_2$, and CO has been extensively studied and several recent reviews\textsuperscript{24,25} have proposed a series of mechanistic events resulting from PM exposure; their surface chemical and metal components have been used to establish the exposure-disease mechanistic relationship and explain the relationship between particulate air pollutants and allergic diseases. This study showed that levels of atmospheric pollutants O$_3$, SO$_2$, and PM10 increased by 10 μg/m$^3$, the number of patient visits would increased by 1.95%, 1.19% and 0.33%, respectively (Table 3, Figure 3), suggesting that air pollution might increase risk of AR onset. Research in the United Kingdom showed that short-term acute exposure to environmental O$_3$ and SO$_2$ was closely correlated with AR onset.\textsuperscript{13} In recent years, the concentration of NO$_2$, a traffic-related pollutant, has increased every year. NO$_2$ can increase respiratory tract sensitivity: in 2006, a report from Taiwan found that continuous exposure to environmental NO$_2$, CO, and SO$_2$ might increase AR incidence in schoolchildren.\textsuperscript{26-28} However, in this study, NO$_2$ was moderately correlated with the number of ARC patient visits, although the difference was not statistically significant. This study also suggested a less significant correlation between MEFs and NO$_2$.

A study in Jinan, China reported that increased PM10 and NO$_2$ concentrations immediately resulted in increased patient visits for AR; however, there was a 3-day delayed effect when SO$_2$ concentrations increased.\textsuperscript{29} In this study, Spearman correlation coefficients of MEFs and outpatient-emergency ARC visits were calculated to determine the delay period; analysis showed that the temperature on the exact day had the maximal correlation coefficient with ARC outpatient-emergency numbers. Low temperatures may cause nasal mucosa irritation, resulting in systolic and diastolic dysfunctions, especially in children. The correlation coefficients were highest for 2-day delayed humidity, 3-day delayed wind, and rain amount on the exact day. Levels of O$_3$, NO$_2$, and SO$_2$ on the exact day and 6-day delayed PM10 had the maximal correlation coefficients, different from findings in Jinan. Moisture may increase aerosolization of pollutant particles, but rainwash could reduce their airborne concentrations air, so the combined action of these two factors, with increasing humidity, likely resulted

![Figure 3. Exposure-response relationships of relative risk degrees of O$_3$, SO$_2$ and PM10 with the number of AR patient visits, respectively. A: Exposure-response relationships of O$_3$ and relative risk degree of AR clinical visits; B: Exposure-response relationships of SO$_2$ and relative risk degree of AR clinical visits; C: Exposure-response relationships of PM10 and relative risk degree of AR clinical visits.](http://www.apjai-journal.org)
in reduced AR patient visits, suggesting that the high humidity had a protective effect on AR.

AR results in dysfunction of peripheral immune tolerance, which generates deviated and over-reactive immune reactions towards some "harmless" allergens due to both genetic and environmental factors.\cite{10,11} This study found that MEFs were closely correlated with ARC incidence, but it remains unclear whether increased environmental pollution could lead to the occurrence and development or severity and risk of allergic diseases in subsets of populations with genetic susceptibilities. Additional research on the interactions between genetic and environmental factors could provide important information; however, this research is currently scarce. Future studies will explore the impact of MEFs on ARC, as well as interactive factors such as genetic single nucleic acid polymorphisms and environmental factors, thus providing a reliable theoretical basis for ARC prevention and treatment, increasing the dissemination of related knowledge and guiding parents and children to improve their living habits to reduce exposure to risk factors and incidence of ARC.

Conflict of interest

All authors have no conflict of interest regarding this paper.

References


5. Kennedy DW. The contribution of environmental pollution in the development of allergic rhinitis (AR) and asthma has been previously studied and documented. Introduction. Int Forum Allergy Rhinol. 2014;4:91-2.


