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Impact of outdoor air pollution on the incidence of pertussis in China: a time-series study

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Abstract

Background The increasing number of pertussis cases worldwide over the past two decades has challenged healthcare workers, and the role of environmental factors and climate change cannot be ignored. The incidence of pertussis has increased dramatically in mainland China since 2015, developing into a serious public health problem. The association of meteorological factors on pertussis has attracted attention, but few studies have examined the impact of air pollutants on this respiratory disease.

Methods In this study, we analyzed the relationship between outdoor air pollution and the pertussis incidence. The study period was from January 2013 to December 2018, and monthly air pollutant data and the monthly incidence of patients in 31 provinces of China were collected. Distributed lag nonlinear model (DLNM) analysis was used to estimate the associations between six air pollutants and monthly pertussis incidence in China.

Results We found a correlation between elevated pertussis incidence and short-term high monthly CO_2 and O_3 exposure, with a 10 µg/m³ increase in NO₂ and O_3 being significantly associated with increased pertussis incidence, with RR values of 1.78 (95% Cl: 1.29-2.46) and 1.51 (95% Cl: 1.16-1.97) at a lag of 0 months, respectively. Moreover, PM_{2.5} and SO₂ also played key roles in the risk of pertussis surged. These associations remain significant after adjusting for long-term trend, seasonality and collinearity.

Conclusions Overall, these data reinforce the evidence of a link between incidence and climate identified in regional and local studies. These findings also further support the hypothesis that air pollution is responsible for the global resurgence of pertussis. Based on this we suggest that public health workers should be encouraged to consider the risks of the environment when focusing on pertussis prevention and control.

Keywords Air pollution, Distributed lag non-linear model, Pertussis, Risk, Resurgence, Time-series

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Introduction

Pertussis has been resurging worldwide in the past two decades. Pertussis epidemics have been reported increasingly in East Asia (ie, mainland China, India), Europe (ie, United Kingdom), North America (ie, America and Canada), and Oceania (ie, Australia) since 2008 [1–4]. One study indicated that in 2012, the rate of pertussis in the U.S. was higher than in any previous year since the vaccine was first implemented [2]. A burst of pertussis incidence also appeared in China in recent years and has lasted till today.

Pertussis is a highly contagious respiratory disease caused by the bacterium Bordetella pertussis [5]. After an incubation period of about 1 to 3 weeks (usually 7 to 10 days), patients develop apparent symptoms, from a runny dry cough to a progressive spasmodic cough, the latter lasting for up to 2 months [6]. The pathophysiologic mechanism involves inflammation and spasm of the respiratory tract. The pathogen adheres to the respiratory epithelium and releases toxins causing an inflammatory response that leads to swelling of the respiratory mucosa, increased secretions and decreased mucus membrane secretion. This eventually causes narrowing and obstruction of the respiratory muscle spasm will exacerbate this phenomenon and prolong the onset [7–9].

The epidemiology of pertussis appears to be the result of a combination of factors such as un-vaccination, reduced vaccine efficacy, gene mutation in Bordetella pertussis, environmental factor, and climate change [10, 11]. Air pollution has been recognized as a pervasive public health threat [12]. Previous studies have reported the relationship between weather parameters and pertussis [6, 13, 14]. Through regression tree models and DLNMs, Zhang et al. revealed that temperature change, high temperature, and relative humidity increased pertussis risk, temperature found to be a key driver of pertussis infection. Interestingly, the association between pertussis infection and meteorological factors was stronger in people over 10 years old [14]. By studying the relationship between meteorological parameters and the risk of pertussis in Chongqing, China from 2004 to 2018, Wang et al., have shown that for each unit increase in monthly average temperature, the number of monthly pertussis cases increased by 19.496% (95%CI 2.368-39.490%), and meteorological factors such as air pressure and precipitation were also linked to pertussis [6]. However, the small size of the target population, or the assessment of the effect of a single meteorological parameter on pertussis in these studies, was not sufficient to compare the changes of disease incidence and show the long-term role of climate change in the spread of pertussis. What is more, very few studies have explored the impact of air pollutants on this respiratory disease. Therefore, it is necessary to conduct a study that also considered common air pollutants such as ($PM_{2.5}$, PM_{10} , SO_2 , CO, NO_2 , and O_3), to comprehensively elucidate the long-term quantitative association between atmospheric pollutants and pertussis incidence to address the growing threat posed by pertussis to public health.

In this observational study, we aimed to assess changes in pertussis epidemiology, using DLNM models, to explain the complex causes of pertussis surges and the associations between six air pollutants and pertussis, and discuss how to manage these factors to prevent future epidemics and provide early warning information and reference for pertussis epidemic.

Materials and methods

Data collection

We obtained pertussis cases data from the China Public Health Science Data Center (https://www.phscienced ata.cn/Share/en/index.jsp.). Population data of the corresponding periods were obtained from the National Bureau of Statistics of the People's Republic of China (http://data. stats.gov.cn). All notified cases were diagnosed according to detailed instructions issued by the National Health Commission in 2007 (http://www.nhc.gov.cn/wjw/s9491/ 201410/52040bc16d3b4eecae56ec28b3358666.shtml). The monthly average air pollutant concentrations ($PM_{2.5}$, PM₁₀, SO₂, CO, NO₂, and O₃) and meteorological data (sunshine, mean wind speed, precipitation, relative humidity, and mean temperature) of 31 provinces in China from 2013 to 2018 were obtained from 393 National Air Quality Monitoring Stations (https://www.epmap.org/) and 839 meteorological monitoring stations (https://data.cma.cn/), respectively (Fig. 1).

Statistical analysis

We analyzed the association between monthly trends in atmospheric pollutants and monthly incidence of pertussis. Since meteorological conditions can affect the concentration of air pollutants, we incorporated five common meteorological conditions into the DLNM model to improve the accuracy of the results. The effects of air pollutants on pertussis were evaluated using DLNM models.

DLNM were based on traditional model ideas such as generalized additive models and distributed lag linear models [15]. The main idea was to add a lag dimension



Fig. 1 Geographical location of air quality monitoring stations (during 2013-2018) and meteorological monitoring stations (2004-2018) in China. Air quality monitoring stations (*N*=393); meteorological monitoring stations (*N*=839)

to the exposure-response relationship through a cross basis function. In this way, the change distribution of its effect in the independent variable dimension and the lag dimension was described at the same time.

Both single-pollutant and multi-pollutant models were used to analyze the effect of air pollutant variables on pertussis incidence. The single-pollutant model considered not only air pollutants, but also long-term trend, meteorological conditions, quartiles of average incidence, and incidence in the previous month. The final model looked like this:

Model 1 : Log
$$[E(Yt)] = \beta + cb (Kt, 2, \beta 1) + S1 (x) + S2 (z)$$

+ S3 (m) + S5 (Region) + S6 (Season)

Where t is the observation month; [E(Yt)] is the observed pertussis cases in year Yt, and β is the intercept of the whole model; cb (Kt, 2, and β 1) is the cross basis of K, and β 1 is an estimate of the effect of K in a given lag month t, with the maximum delay month set to 2; K is one of the four air pollutants. S1-3 are "average sunlight", "average temperature", and "average wind speed" representing meteorological factors associated with pertussis incidence; "Region" and "Season" represents the covariates; month is the ordinal variable of January in a year; and S() is the penalized spline function. In this study, we used cubic spline functions S1-3 to adjust for confounders in the model, and S5 (Region) and S6 (Season) to adjust for monthly confounders.

The multi-pollutant model took air pollutants and meteorological conditions (sunshine, wind speed, and mean temperature) associated with pertussis incidence into account, other adjustment variables in the model were long-term trend, seasonal trend, quartile arrays of mean incidence, and the incidence in the previous month. The final model looked like this:

Model : Log
$$[E(Yt)] = \beta + cb(Kt, 2, \beta 1) + S1(x) + S2(z) + S3(m)$$

+ S5(Region) + S6(Season) + S7(lag.value1)

where t is the observation month; [E(Yt)] is the observed pertussis cases in year Yt, and β is the intercept of the whole model; cb (Kt, 2, and β 1) is the cross basis of K, and β 1 is the estimated impact of K at a specific lag month t, with the maximum delay month set to 2; K is the sum of the four air pollutants. S1-3 are "average sunshine," "average temperature," and "average wind speed," representing meteorological factors associated with pertussis incidence; "region", "season" and "lag.value1" covariates; "lag.value1" represents the average incidence in the previous month; and S() is a penalized spline function. In this study, we used cubic spline functions S1-3 to adjust for confounders in the model, and S5 (Region) and s6 (Season) to adjust for monthly confounders.

The construction of the basis function used the crossbasis () function in the "dlnm" package. The exposure-response dimension fitting was performed using natural cubic splines with node positions set at the 10_{th}, 75_{th} and 90_{th} percentiles. The exposure-lag dimension fitting also used the natural cubic spline function, the lag period was selected to be seven months, and the node positions were set using the logarithmic equal spacing method provided by the package "dlnm" (version 4.1.3, https://cran.r-project.org/web/package/dlnm/index.html) [16]. Second, according to the AIC+BIC criterion we selected the degree of freedom, and chose the degree of freedom with the smallest AIC+BIC value to build the final model.

Variables	Mean	SD	Min.	P25	P50	P75	Max.	China Class II Limit
No. of cases	692	689	93	276	494	869	3635	/
PM _{2.5} (μg/m ³)	50.65	28.91	6.29	30.72	43.98	63.36	216.84	35
PM ₁₀ (μg/m³)	87.67	42.99	16.57	56.8	77.52	110.04	319.58	70
SO ₂ (μg/m ³)	24.5	21.71	2.2	11.57	17.85	28.86	195.29	60
NO ₂ (μg/m³)	33.19	13.19	7.86	23.45	31.21	41	94.55	40
O ₃ (μg/m ³)	84.36	31.08	12.06	60.86	81.98	106.5	184	160
CO (mg/m ³)	0.98	0.43	0	0.74	0.92	1.11	4.29	4

/: Not available, SD Standard deviation, min minimum, P25 25_{th} Percentile, P50 Median, P75 75_{th} Percentile, max maximum, PM_{2.5} Particulate matter of <2.5 μm, PM₁₀ Particulate matter of <10 μm, SO₂ Sulfur dioxide, NO₂ Nitrogen dioxide, O₃ Ozone, CO Carbon monoxide



Fig. 2 Contour plots of exposure-response relationships between pertussis incidence and four air pollutants in the single-pollutant model. **A-D** Four air pollutants associated with ($PM_{2.5}$, SO_2 , NO_2 and O_3) pertussis incidence from 2013 to 2018. The reference level was set to the median value of the corresponding variable. The Y-axis represents the lag period from 0 to 2 months. The e-axis represents the range of observations for each variable. RR stands for relative risk, red stands for RR>1, white stands for RR=1, and blue stands for RR<1



Fig. 3 Contour plots of exposure-response relationships between pertussis incidence and four air pollutants in the multi-pollutant model. **A-D** Four air pollutants associated with ($NO_{2^{\prime}}O_{3^{\prime}}$, $PM_{2.5}$ and SO_{2}) pertussis incidence from 2013 to 2018. The reference level was set to the median value of the corresponding variable. The Y-axis represents the lag period from 0 to 2 months. The X-axis represents the range of observations for each variable. RR stands for relative risk, red stands for RR>1, white stands for RR=1, and blue stands for RR<1

Results

Descriptive analysis

From 2013 to 2018, 79 757 cases were reported in China. On average, the monthly mean concentration of PM_{2.5}, PM₁₀, SO₂, NO₂, O₃ and CO were 50.65 μ g/m³, 87.67 μ g/m³, 24.5 μ g/m³, 33.19 μ g/m³, 84.36 μ g/m³, and 0.98 mg/m³, respectively (Table 1).

DLNM model

Single-pollutant models showed that four air pollutants (PM_{2.5}, SO₂, NO₂, and O₃) were associated with pertussis incidence from 2013 to 2018 (Fig. 2), with relative risks ranging from 0.59-1.27 for PM_{2.5}, 0.46-1.79 for SO₂, 0.57-3.72 for NO₂, and 0.98-2.61 for O₃. In the multi-pollutant models (Fig. 3), the relative risk of PM_{2.5} was 0.43-1.38, SO₂ was 0.21-3.82, NO₂ was 0.33-2.97, and O₃ was 0.85-1.99. The maximum RR for PM_{2.5} was 1.38 with exposure to 10 μ g/m³ PM_{2.5} at lag 2 months. The maximum RR for SO₂ was 3.82 with exposure to 195 μ g/m³ SO₂ at lag 1 months. The maximum RR for NO₂ was 2.97 with exposure to 8 μ g/m³ NO₂ at lag 0 months. The maximum RR

for O_3 was 1.99 with exposure to 15 μ g/m³ O_3 at lag 1.6 months.

The lag relationship between air pollutants and the incidence of pertussis

The results of DLNMs were shown in DLNMs, we used median $PM_{2.5}$, median SO_2 , median NO_2 , and median O_3 as references, and then RR of pertussis incidence with lag 0-2 months was calculated with the extremely low (2.5_{th}), 25_{th}, 75_{th} and extremely high (97.5_{th}) percentile of $PM_{2.5}$, SO₂, NO₂, and O₃, respectively.

The 3-D plots for multiple pollutants show that the RR values would increase when the NO₂ and SO₂ concentrations increase at a lag of 1 and 0 months (Fig. 4). Furthermore, single-pollutant plots presented in Fig. 5 showed that under the 75_{th} quantile of NO₂, RR for lag 0 months (RR = 1.15, 95% CI: 1.03-1.28) and RR for 2 months (RR = 1.12, 95% CI: 1.01-1.24) were significantly high. However, under extremely low (2.5_{th}) ,25_{th} and high (97.5_{th}) NO₂, no statistical significance in RR was observed; Under the 2.5_{th} quantile of O₃, the RR for lag



Fig. 4 3-D plot of relative risk of pertussis onset (RR) versus lag time for exposure to four air pollutants. **A-D** Four air pollutants associated with (NO_2 , O_3 , $PM_{2.5}$ and SO_2) pertussis incidence from 2013 to 2018. The X-axis represents the exposure concentration of the four pollutants, the Y-axis represents the lag period from 0 to 2 months, the Z-axis represents the relative risk of each variable (NO_2 , O_3 , $PM_{2.5}$ and SO_2)

0 months (RR = 1.37, 95% CI: 1.02-1.83) and the RR for lag 2 months (RR = 1.69, 95% CI: 1.32-2.17) were significantly high. In addition, Under the 97.5_{th} quantile of O₃, the RR for lag 0 months (RR = 1.21, 95% CI: 1.00-1.44) and the RR for lag 2 months (RR = 1.32, 95% CI: 1.10-1.58) were significantly high. And under the 25_{th} and 75_{th} percentile of O₃, no statistical significance in RR was observed. Under the 2.5_{th}, 25_{th}, and 75_{th} percentile of PM_{2.5}, no statistical significance in RR was observed; under the 2.5_{th}, 25_{th} quantile of SO₂, RR for lag 0 months (RR = 1.60, 95% CI: 1.10-2.33), RR for lag 0 months (RR = 1.10, 95% CI: 1.00-1.21), were significantly high, respectively. Under the 75_{th} percentile of SO₂, no statistical significance in RR was observed.

Multi-pollutant plots presented in Fig. 6 showed at the 2.5_{th} , 25_{th} , 75_{th} and 97.5_{th} percentile of NO₂, the RR for lag 2 months (RR = 1.45, 95% CI: 1.07-1.98), RR for

lag 2 months (RR = 1.26, 95% CI: 1.07-1.48), RR for lag 2 months (RR = 1.15, 95% CI: 1.04-1.27), and RR for 2 months (RR = 1.43, 95% CI: 1.09-1.89) were significantly high, respectively. In addition, under extremely low (2.5_{th}) NO₂, the risk was greatest at a lag of 0 months (RR = 1.78, 95% CI: 1.29-2.46). Under the 2.5_{th} , 75_{th} and 97.5_{th} quantile of O_3 , the RR for lag 2 months (RR = 1.45, 95% CI: 1.17-1.80), RR for lag 2 months (RR = 1.13, 95% CI: 1.05-1.22) and the RR for lag 2 months (RR = 1.32, 95% CI: 1.22-1.57) were significantly high, respectively. Additionally, under extremely low (2.5_{th}) O_3 , the risk was greatest at a lag of 1 months (RR = 1.51, 95% CI: 1.16-1.97). Under the 25_{th} percentile of O₃, no statistical significance was observed for RR. Lastly, Under the 2.5_{th} , 25_{th} , 75_{th} and 97.5_{th} percentile of $\mathrm{PM}_{2.5}$ and the $2.5_{\mathrm{th}},\,25_{\mathrm{th}}$ and 75_{th} percentile of SO_2, no statistical significance was observed for RR.



Fig. 5 Summary of relative risk curves for different lags between air pollutants and pertussis incidence in single-pollutant models from 2013 to 2018. The Y-axis represents the relative risk of each variable (NO_2 , O_3 , $PM_{2.5}$ and SO_2), the X-axis represents the lag period from 0 to 2 months. Lines represent means estimated using the DLNM single-pollutant model, shaded areas represent 95% confidence intervals

Discussion

Our study mainly analyzed the association between monthly air pollution and monthly pertussis incidence in 31 provinces and regions in China from 2013 to 2018. Estimates of the percent change in pertussis cases with a 10-unit increase in air pollutants were based on a large dataset. Through the indicator, the epidemic trend of pertussis can be predicted, targeted prevention and control measures can be taken in advance, and health education and public health interventions for susceptible populations can be carried out.

Over the past 71 years, the pertussis epidemic in China has gone through four stages: high incidence, decline, low incidence, and resurgence. In addition, the incidence of some respiratory infectious diseases has increased over the past decade. Finally, because of the strong link between climate change and respiratory infectious diseases, we believe that climate has played an important role in the resurgence of pertussis. The research focused on the association between air pollutants and pertussis incidence. A novel discovery of this research was the exposure-response relationship between the cumulative risk of NO₂, O₃, PM_{2.5} and SO₂ and the incidence of pertussis. Considering there was no much literature reporting the association between air pollutants and pertussis, we compared the results of our study with other respiratory infectious diseases.

Environmental particulate matter may play an important role in the occurrence and development of respiratory diseases. Our research results revealed that NO_2 increased the risk of pertussis and this was consistent with recent discovery. One possible mechanism of NO_2 and other air pollutants was that, regardless of the duration of exposure, high levels of NO_2 can irritate airways and increase susceptibility to respiratory infections [17, 18]. Compared with adults, children are at a higher risk because they breathe at higher rates and spend more time outdoors and their lungs and immune systems are immature.



Fig. 6 Summary of relative risk curves for different lags between air pollutants and pertussis incidence in multi-pollutant models from 2013 to 2018. The Y-axis represents the relative risk of each variable (NO₂, O₃, PM_{2.5} and SO₂), the X-axis represents the lag period from 0 to 2 months. Lines represent means estimated using the DLNM multi-pollutant model, shaded areas represent 95% confidence intervals

Previous studies have shown that exposure to O_3 in early life can impair lung function and growth [19–21]. In infant rhesus monkeys, sustained exposure to O_3 caused structural abnormalities in bronchioles and increased susceptibility to antigen-induced airway remodeling [22]. We found significant evidence of spatial heterogeneity in the associations between air pollutants and morbidity across provinces and regions. Many factors may contribute to this variability, including different geographic distributions, long-term air pollution levels, population susceptibility, environmental policy and planning, and different study period lengths.

Our study found that short-term (0-15 lag days) exposure to high concentrations of $PM_{2.5}$ increased the risk of pertussis infection, and some studies reported that short-term exposure to outdoor particulate matter (PM_{10} or $PM_{2.5}$) have been found to reduce lung function and increase hospitalization rates [23–26]. A recent study assessed the association between ambient particulate matter exposure and chronic obstructive pulmonary disease, using logistic regression analyses and multiple linear regression models. The results provided evidence that exposure to higher PM_{10} or $PM_{2.5}$ concentrations increased the risk of developing COPD and decreased the respiratory function [27]. Mortality rates from respiratory diseases have gradually decreased as air pollutant levels have improved [28, 29]. However, studies have shown that even lower levels of ambient air pollutants can have harmful effects on the respiratory system and lungs, suggesting that even at lower concentrations of pollutants, there is still a risk of disease [30].

As a potent lung irritant that can reduce lung function, SO_2 has been identified as a cause of respiratory symptoms including cough and reduced lung function. Exposure to high levels of SO_2 can cause severe airway damage. A study examined the relationship between nitrogen dioxide and sulfur dioxide concentrations and children's lung function in Greece showed that long-term exposure to higher concentrations of air pollutants was associated with subclinical airway narrowing and slower increase of percent forced vital capacity (FVC%) in 8-10-year-old children [31]. Our results also suggest that higher concentrations of SO_2 increase the risk of pertussis infection during the lag period of 0-30 days.

Over the past 30 years, the Chinese government has implemented policies to improve air quality and ameliorate the adverse effects of air pollutants on public health. Since 2013, air quality has been continuing to improve in most regions. However, this study showed that NO_2 , O_3 , $PM_{2.5}$ and SO_2 concentrations and their lagged effects were associated with the risk of pertussis, which indicated that high baseline levels of pollution and its impact on pertussis cases would persist.

Using air pollutants and case data from 2013 to 2018, We found a non-negligible association between shortterm pollutant exposure and the development of pertussis. Our previous study analyzed the risk of pertussis after long-term (0-15 lag months) exposure to these major air pollutants. However, considering that it has an incubation period of 1-2 weeks, and even the duration of the disease lasts only 4-6 weeks, we adjusted the lag time to 0-2 lag months in the current study. Generally speaking, these findings further support the hypothesis that air pollution is responsible for the global resurgence of pertussis. Finally, we recommend encouraging public health workers to consider NO₂ and O₃ risks in response to the pertussis resurgence.

This study has several limitations. First, we could not obtain the data of air pollutants before 2013 because the national air quality monitoring network was only established at 2013. Second, on the basis of only monthly data we were unable to work out the acute effects of air pollutants on pertussis. Third, we were unable to extrapolate the effect of individual exposure levels on pertussis risk from air pollution across provinces. This study focused on the relationship between six air pollutants and pertussis incidence in China from the perspective of time lag effect. We need to further investigated the potential role of air pollutants in accelerating pertussis transmission in the future.

Abbreviation

DLNM Distributed lag nonlinear model

Supplementary Information

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Additional file 1: Fig. S1. AIC+BIC parameters for selecting the main model.

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Authors' contributions

Y.X., Y.L., L.A., C.Z. and W.T. Conceptualize and design the study, Y.X., Y.L., H.L., Y.W., D.N., N.Y., D.H and J.Q. analyze and interpret the data, C.L. and G.W. draft the manuscript and W.T. and J.W. collect the data. All authors reviewed the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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