Received: 7 April 2022 | Accepted: 29 May 2022

DOI: 10.1002/ppul.26021

ORIGINAL ARTICLE

PEDIATRIC PULMONOLOGY WILEY

Concentrations of nitrogen compounds are related to severe rhinovirus infection in infants. A time-series analysis from the reference area of a pediatric university hospital in Barcelona

Georgina Armero MD[1,2] | Daniel Penela-Sánchez MD[2] | Jordina Belmonte PhD[3] | Diana Gómez-Barroso PhD[4,5] | Amparo Larrauri PhD[4,5] | Desiree Henares MSc[5,6] | Violeta Vallejo[1] | Iolanda Jordan PhD[2,5,6,7] | Carmen Muñoz-Almagro PhD[5,6,8,9] | Pedro Brotons PhD[6,9] | Cristian Launes PhD[1,5,6,7]

[1]Pediatrics Department, Hospital Sant Joan de Déu, Barcelona, Spain

[2]Pediatrics Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain

[3]Botanic Unit of Animal Biology, Vegetal Biology and Ecology Department, Science and Ambiental Technology Institute, Universitat Autònoma de Barcelona, Barcelona, Spain

[4]Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain

[5]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain

[6]Grupo de investigación en enfermedades infecciosas pediátricas, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain

[7]Departament de Cirurgia i Especialitats Medicoquirúrgiques, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain

[8]Molecular Microbiology Department, Hospital Sant Joan de Déu, Barcelona, Spain

[9]Department of Medicine, School of Medicine, Universitat Internacional de Catalunya, Barcelona, Spain

Correspondence

Cristian Launes, Pediatrics Department, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu 2, 08950, Esplugues de Llobregat, Barcelona, Spain.
Email: claunes@sjdhospitalbarcelona.org and claunes@ub.edu

Funding information

Instituto de Salud Carlos III, Grant/Award Numbers: PI17/349, FI17/248

Abstract

Background: There is scarce information focused on the effect of weather conditions and air pollution on specific acute viral respiratory infections, such as rhinovirus (RV), with a wide clinical spectrum of severity.

Objective: The aim of this study was to analyze the association between episodes of severe respiratory tract infection by RV and air pollutant concentrations (NO_x and SO_2) in the reference area of a pediatric university hospital.

Methods: An analysis of temporal series of daily values of NO_x and SO_2, weather variables, circulating pollen and mold spores, and daily number of admissions in the pediatric intensive care unit (PICU) with severe respiratory RV infection (RVi) in children between 6 months and 18 years was performed. Lagged variables for 0–5 days were considered. The study spanned from 2010 to 2018. Patients with comorbidities were excluded.

Results: One hundred and fifty patients were admitted to the PICU. Median age was 19 months old (interquartile range [IQR]: 11–47). No relationship between RV-PICU admissions and temperature, relative humidity, cumulative rainfall, or wind speed was found. Several logistic regression models with one pollutant and two pollutants were constructed but the best model was that which included average daily NO_x concentrations. Average daily NO_x concentrations were related with the presence of PICU admissions 3 days later (odds ratio per IQR-unit increase: 1.64, 95% confidence interval: 1.20–2.25)).

Conclusions: This study has shown a positive correlation between NO_x concentrations at Lag 3 and children's PICU admissions with severe RV respiratory infection. Air pollutant data should be taken into consideration when we try to understand the severity of RVis.

KEYWORDS

air pollutants, intensive care units, respiratory tract disease, rhinovirus, virus infections

1 | INTRODUCTION

Rhinovirus (RV) is one of the main causes of respiratory tract infection in children.[1] RV infection (RVi) ranges from asymptomatic or mild symptomatic infection to being often the only etiological agent in patients requiring advanced life support in intensive care units. Viral and bacterial coinfections have been considered as factors associated with severe disease, but these results are not consistent between series[1,2] and the wide clinical spectrum of RVi has not been clearly explained by a unique element.

On the other hand, exposure to air pollution (i.e., sulfur dioxide [SO_2], ozone [O_3], nitrogen dioxide [NO_2], nitrogen oxides [NO_x], and particulate matter [PM]) has been associated with respiratory exacerbations in asthmatic children and adults.[3] In recent years, the literature collects some studies that show associations between short-term and long-term changes in air pollutants and increased rates of respiratory admissions among young children, especially in those under 4 years old.[4–7]

Overall, there is scarce information focused on the effect of weather conditions and air pollution on specific acute viral respiratory infections, such as RV. RV is a respiratory virus with a poor seasonal pattern of circulation, being detected along all the year seasons in our setting,[8] whereas other respiratory viruses cause epidemic peaks only during winter.

The aim of this study was to analyze the association between episodes of severe respiratory tract infection by RV and air pollution concentrations in a reference area of a university hospital. We hypothesized that either the susceptibility to RVi or its severity could be partially explained by air pollution. Weather variables, circulating pollen grains, and mold spores were also considered. Therefore, this study focuses on elucidating if the air pollutant data should be taken into consideration as another of the variables that may help the scientific community to understand the wide severity range of RVi in children.

2 | MATERIALS AND METHODS

2.1 | Variables

This study analyses a temporal series of daily counts of admissions in a pediatric intensive care unit (PICU) due to severe respiratory RVi, in patients from 6 months to 18 years old, residing in the reference area (Barcelona-South and Baix Llobregat) of a pediatric reference center (Hospital Sant Joan de Déu, Barcelona). This reference area includes a pediatric population of about 300,000 children. Daily weather variables, concentrations of pollen grains, mold spores and air pollutants (NO_x and SO_2) were collected from regional stations. The study spanned from 2010 to 2018.

Daily weather variables (average temperature, average wind speed, and cumulative rainfall) were collected from El Prat Airport Station, Baix Llobregat.[9] Relative humidity was also collected from April 2011 to December 2018 from a station of the same municipality (this data was not available from January 2010 to March 2011).[10] Regarding air pollutants, daily arithmetic mean, as well as the daily maximum peak values of sulfur dioxide (SO_2) and nitrogen oxides (NO_x, which included nitric oxide [NO] and nitrogen dioxide [NO_2]) were monitored from El Prat station (Baix Llobregat). These data were obtained from the Surveillance Network and Air Pollution Forecast from Generalitat of Catalonia.[11] Mean daily pollen and spore concentrations from the station in Barcelona city center were collected from the Aerobiological Network of Catalonia.

2.2 | Definitions

Severe RVi was defined as an acute lower respiratory tract disease (bronchiolitis, bronchitis, or pneumonia) with the need of mechanical ventilation and microbiologically confirmed identification of RV presence in nasopharyngeal aspirates by RNA polymerase chain reaction (PCR) detection. Patients with respiratory (except asthma), cardiac, and neurological chronic diseases were excluded from the count. Addresses of all cases were checked and those who did not live in the reference area (Barcelona-South and Baix Llobregat) were excluded. For reference, 90% of the respiratory admissions in the PICU of this hospital correspond to patients living in this area.

2.3 | Statistical analysis

Continuous non-normal distributed variables were described as median value and interquartile range (IQR). Several logistic regressions with "day with PICU admission (yes/no)" as the outcome variable and income variables were built (generalized linear models). The choice of the optimal degrees of freedom of cubic functions and the choice of the model, which combined the highest goodness of fit and the lowest number of variables was made by minimization of the corrected Akaike Information Criterion (AIC). This strategy also helps to avoid overfitting.

An initial model was created with:

- a natural cubic smooth function of calendar time, with 7 degrees of freedom (df) per year to exclude unmeasured long-term and seasonal trends. Models with 3 and 5 df were also considered, but AIC values were similar among them and several studies in international literature used 7 df per year with the same purpose.[12,13]

- an indicator of the day of the week, as a potential confounder.[3]

- a lagged variable of the daily average temperature (0- to 5-day shifted series), as the risk of RVi had been associated with lower temperatures in several series.[3] A linear function was finally used after exploring a nonlinear effect with 3 df.

To select those variables to be added to the initial model, associations between the number of daily PICU admissions and other main variables were explored. For each variable with a Mann–Whitney U test $p < 0.10$, a model was created. Those variables were introduced using lagged values (0- to 5-day shifted series), which were simultaneously entered in the models ("distributed lag model").[14] Other studies have used similar methodologies.[3,7] Lagged variables were used from 0 to 5 days, because this captures the incubation period of RVi.[15] If more than one variable was associated at some lag-time with the outcome with a $p < 0.10$, a model with >1-pollutant would be considered. A strict p (<0.01) was considered statistically significant to minimize the possibility of chance findings. The corrected AIC was used to compare and to identify the best final model among those with an associated variable with the outcome. Residual autocorrelation was checked in the final model.

Statistical analysis was performed with R software v 4.0.2 and the following packages: dlnm, ggplot2, splines, AICcmodavg.

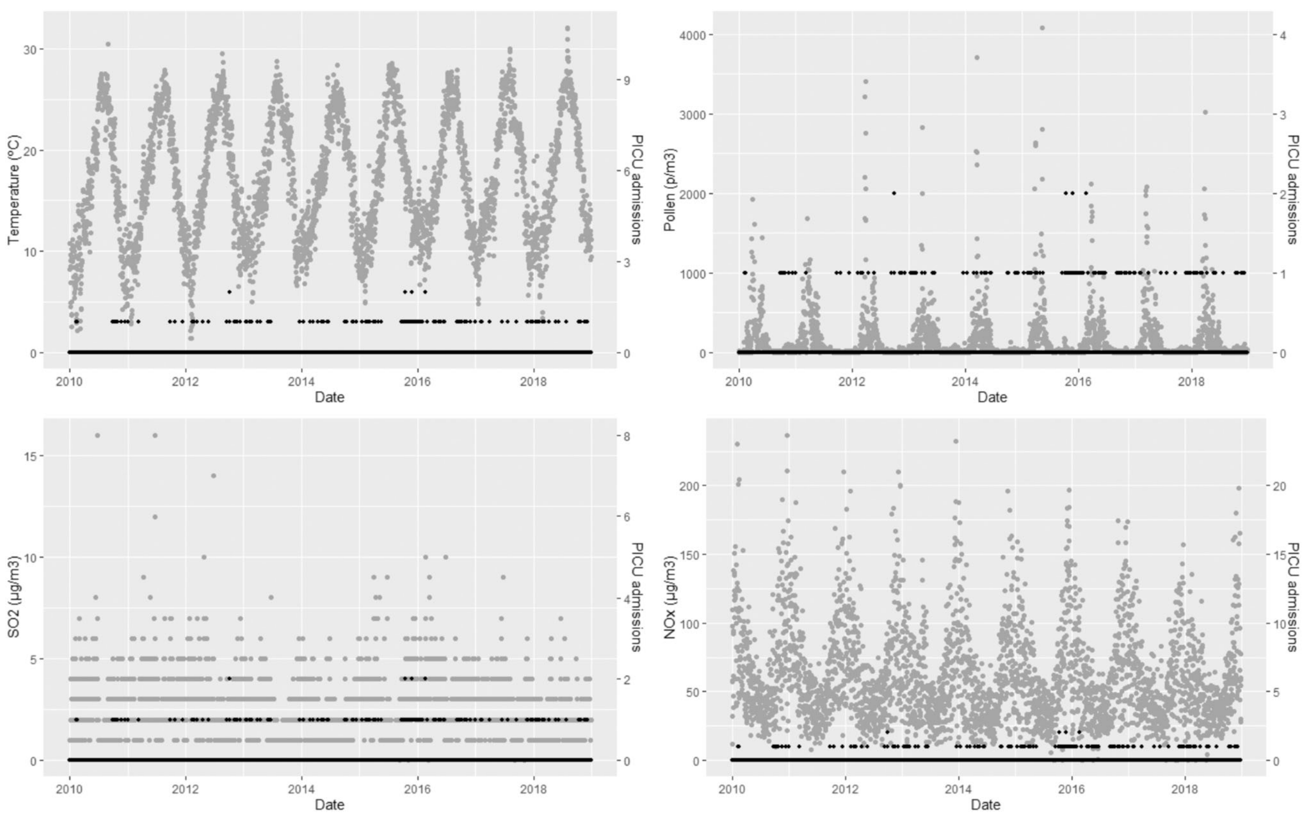

FIGURE 1 Temperature and other variables associated with the number of pediatric intensive care unit (PICU) admissions (SO_2, NO_x, and air pollen concentrations) and number of PICU admissions during the study period.
*Bold spots: number of rhinovirus-related PICU admissions; soft spots: values of weather, pollen or air pollutant variables.

TABLE 1 Weather variables and average daily concentrations of air pollutants, pollen grains, and mold spores of a reference area and number of RV-related PICU admissions of children living in this reference area (2010–2018).

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2010–2018
Max temperature (°C)[a]	20.0 (14.2–25.5)	21.2 (16.4–26.9)	21.0 (16.3–26.7)	20.3 (15.1–25.8)	21.0 (16.6–26.1)	20.7 (16.7–26.2)	20.2 (16.8–26.1)	21.1 (18.9–26.8)	21.6 (16.5–27.2)	20.7 (16.3–26.4)
Min temperature (°C)[a]	11.2 (6.2–18.2)	13.7 (7.4–18.6)	12.7 (7.5–19.1)	12.8 (7.5–18.7)	14.1 (8.9–18.9)	13.4 (7.9–18.8)	12.9 (8.6–18.9)	12.9 (7.8–19.1)	13.9 (8.1–20.3)	13.1 (7.9–18.9)
Average temperature (°C)[a]	15.2 (10.2–21.6)	17.3 (11.9–22.7)	16.7 (11.7–22.9)	16.5 (11.1–22.2)	17.3 (12.4–22.6)	17.1 (12.2–22.6)	16.6 (12.7–22.5)	16.7 (12.3–22.5)	17.8 (12.1–23.9)	16.8 (11.9–22.6)
Relative humidity (%)[a]	–	75 (69–80)	72 (64–79)	72 (66–78)	75 (69–81)	74 (67–79)	73 (66–79)	72 (66–78)	74 (67–81)	73 (67–79)
Cumulative rainfall (mm)[a]	0 (0–0.1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.2)	0 (0–0)
Average wind-speed (km/h)[a]	15.1 (11.9–18.0)	15.1 (12.4–18)	15.1 (11.8–18.3)	23.0 (18.0–28.0)	15.1 (19.7–19.1)	15.1 (12.9–18.0)	15.1 (12.9–19.1)	15.1 (12.9–19.1)	15.1 (12.4–19.1)	15.8 (12.9–20)
Average SO_2 (μg/m^3)[a]	2 (1–3)	3 (2–4)	2 (2–3.2)	2 (1–3)	2 (1–2)	3 (2–4)	3 (2–4)	2 (2–3)	2 (1–2)	2 (1–3)
Average NO_x (μg/m^3)[a]	57.1 (40.3–86.2)	50.1 (36.3–73.4)	54.8 (37.8–80.8)	47.8 (30.4–74.6)	47.8 (30.4–75.8)	53.1 (33.4–78.6)	49.2 (31.7–72.4)	47.4 (33.5–70.2)	47.4 (34.4–62.4)	49.7 (33.5–73.2)
Average pollen grains (g/m^3)[a]	20.3 (7.7–105.5)	24.5 (8.4–165.4)	22.4 (8.4–118.3)	34.3 (10.8–157.- 1)	21.0 (9.1–168.7)	18.9 (8.4–124.6)	24.5 (9.8–140.0)	19.9 (9.8–138.2)	27.3 (9.8–141.4)	23.1 (9.1–140.3)
Average mold spores (n/m^3)[a]	1519 (963–2444)	1671 (955–3528)	1596 (777–3151)	1601 (757–3257)	1243 (700–2596)	1126 (419–2507)	1159 (659–1984)	1080 (622–1900)	1697 (871–9277)	1400 (742–2746)
Number of PICU admissions (*n*)	16	6	15	14	15	28	25	11	20	150

Abbreviations: PICU, pediatric intensive care unit; RV, rhinovirus.

[a]Median and interquartile ranges.

TABLE 2 Spearman ρ matrix correlation between the values of weather variables and airborne concentrations of pollutants, pollen grains, and mold spores, and associations of these variables with the outcome (PICU admissions yes/no).

	Average temperature (°C)	Cumulative rainfall (mm)	Average wind speed (km/h)	Relative humidity (%)	Average daily SO_2 concentrations (µg/m^3)	Average daily NO_x concentrations (µg/m^3)	Daily peak SO_2 (µg/m^3)	Daily peak NO_x (µg/m^3)	Airborne pollen grains (g/m^3)	Average mold spores(n/m^3)
Cumulative rainfall	−0.056[c]									
Average wind speed	0.072[c]	0.016								
Relative humidity	0.001	0.327[c]	−0.199[c]							
Average daily SO_2	−0.200[c]	−0.136[c]	−0.209[c]	−0.017						
Average daily NO_x	−0.464[c]	−0.050[c]	−0.281[c]	0.178[c]	0.492[c]					
Daily peak SO_2	−0.165[c]	−0.149[c]	−0.231[c]	−0.046[b]	0.823[c]	0.488[c]				
Daily peak NO_x	−0.349[c]	−0.068[c]	−0.300[c]	0.178[c]	0.418[c]	0.892[c]	0.478[c]			
Airborne pollen	0.015	−0.102[c]	0.140[c]	−0.192[c]	0.047[c]	−0.204[c]	0.100[c]	−0.170[c]		
Average mold spores	0.404[c]	0.097[c]	0.000	−0.155[c]	−0.101[c]	−0.141[c]	−0.133[c]	−0.166[c]	−0.015	
PICU admissions[a]										
Yes, median (IQR)	14 (11–20)	0 (0–0)	15 (13–20)	73 (67–79)	3 (2–4)	70 (43–100)	6 (4–8)	194 (119–285)	16 (7–99)	1268 (683–2908)
No, median (IQR)	17 (12-23)[c]	0 (0–0)	16 (13–20)	73 (65–80)	2 (1–3)[c]	51 (35–74)[c]	5 (3–7)[c]	147 (86–220)[c]	24 (9–143)[b]	1407 (745–2733)

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit.

[a]Mann–Whitney *U* test was performed to make these comparisons.

[b]$p < 0.10$.

[c]$p < 0.01$.

TABLE 3 Logistic regression models constructed to explain RVi-related PICU admissions

	Univariate models									
	Model with average airborne pollen concentrations (OR per 131 u increase[a])	*p*	Model with average daily SO_2 concentrations (OR per 2 u increase[a])	*p*	Model with average daily NO_x concentrations (OR per 40 u increase[a])	*p*	Model with daily SO_2 peaks (OR per 4 u increase[a])	*p*	Model with daily NO_x peaks (OR per 136 u increase[a])	*p*
Day 0	0.89 (0.73–1.07)	0.209	1.25 (0.89–1.77)	0.198	1.20 (0.90–1.60)	0.207	1.06 (0.94–1.20)	0.352	1.28 (0.96–1.71)	0.091[b]
Day 1	1.09 (0.93–1.29)	0.292	1.03 (0.69–1.53)	0.896	0.92 (0.67–1.27)	0.613	1.04 (0.89–1.22)	0.630	1.07 (0.78–1.46)	0.666
Day 2	1.00 (0.84–1.18)	0.971	0.88 (0.59–1.31)	0.535	0.99 (0.72–1.36)	0.932	0.96 (0.79–1.16)	0.670	1.01 (0.74–1.39)	0.924
Day 3	1.01 (0.85–1.20)	0.936	1.49 (1.01–2.20)	0.045[b]	1.64 (1.20–2.25)	0.002[c]	1.11 (0.95–1.29)	0.183	1.39 (1.03–1.89)	0.033[b]
Day 4	1.07 (0.89–1.28)	0.497	0.84 (0.56–1.26)	0.397	0.88 (0.64–1.22)	0.448	0.90 (0.70–1.16)	0.420	1.09 (0.79–1.48)	0.596
Day 5	0.88 (0.73–1.06)	0.189	1.04 (0.72–1.49)	0.852	0.92 (0.69–1.23)	0.575	0.98 (0.78–1.23)	0.866	0.78 (0.57–1.06)	0.110
cAIC	1097		1123		1108		1132		1123	

Abbreviations: cAIC, corrected Akaike Information Criterion; OR, odds ratio; PICU, pediatric intensive care unit; RVi, rhinovirus infection.

[a]An interquartile range unit increase.

[b]$p < 0.10$.

[c]$p < 0.01$.

2.4 | Ethics approval

This study was approved by the Ethics Committee and Institutional Review Board of the Sant Joan de Déu Hospital (PI179-21) and informed consents from patients' parents were waived.

3 | RESULTS

During the study period, 150 patients (independent observations) were admitted to the PICU with RV detection by PCR in nasopharyngeal aspirate. These patients corresponded to 26 municipalities of Barcelona and the metropolitan area. Mean number of admissions to PICU per day was 0.046 (95% confidence interval [CI]: 0.04–0.05). There were admissions in 146/3285 days (142 days with 1 admission and 4 days with 2). Median age was 19 months old (IQR: 11–47) and 90 (61%) were males (Figure 1).

Regarding contaminants, median of daily average SO_2 was 2 µg/m^3 (IQR: 1–3). Median of the daily peak values of SO_2 was 5 µg/m^3 (IQR: 3–7). The median of daily average NO_x was 49.7 µg/m^3 (IQR: 33.5–73.2) and the median of daily peak values was 149 µg/m^3 (IQR: 87–223). More detailed information about weather conditions and airborne concentrations of contaminants, pollen grains, and mold spores during the study period can be found at Table 1.

SO_2, NO_x, and airborne pollen concentrations were potentially associated with the outcome in the univariate analysis and, therefore, these variables were introduced in the time-series regression models (Table 2).

Five logistic regression models were built, one with each of the following variables added to the initial model: average daily SO_2, average daily NO_x, daily peak value of SO_2, daily peak value of NO_x, and airborne pollen. Models with daily average SO_2 concentrations, the one with daily average NO_x, and the one with the peak values of NO_x had their pollutant values at Lag 3 potentially related to the outcome with a $p < 0.1$ (Table 3). Average daily temperature was not associated with the outcome in any of these models. As NO_x daily average and peak values were strongly correlated between them, two models with two pollutants were built: one with daily average SO_2 and NO_x concentrations, and another one with daily average SO_2 values and peak NO_x concentrations (Table S1). The model including a potential variable related with the outcome with a $p < 0.01$ and with the lowest AIC value was that of NO_x daily average. In this model, NO_x concentration at Lag 3 was associated with PICU admissions with an odds ratio (OR) per IQR increase of 1.64, 95% CI: 1.20–2.25). There was no remaining significant autocorrelation in the deviance residuals.

4 | DISCUSSION

We investigated the association between PICU admissions with RVi and air pollution concentrations in Barcelona South-Baix Llobregat for 9 years. Average daily NO_x concentrations the third day before the PICU admission was related to PICU admissions with RVi. Our observations were made in a metropolitan area with more than 1 million of inhabitants (Barcelona-South and Baix Llobregat). Nitrogen oxides are traffic pollutants from on-road vehicles and Barcelona is the European city with the densest traffic, twice as much as Madrid and three times as dense as London.[16]

Our analysis included a natural cubic smooth function of calendar time with 7 df and, therefore, only short-term effects can be captured. Taking this into consideration, our study showed no relationship of the outcome with changes in temperature, relative humidity, cumulative rainfall, or average wind speed. Other studies carried out in Mediterranean countries[17] support our findings, as they did not find any association between meteorological variables and viral infection caused by RV. On the other hand, respiratory exacerbations caused by other respiratory viruses, such as RSV and influenza, have been related to changes in weather variables.[3,18] Specifically, relative humidity has been positively associated with RSV activity,[19] whereas absolute humidity has been inversely correlated with influenza viruses' circulation,[18,20] being a good predictor of the onset of each influenza season. Other authors who analyzed the incidence of respiratory infections without considering their viral etiologies have not observed any association between these episodes and changes in relative humidity.[21] Many viral infections have non-coincidental seasonal peaks and others, such as RV, are all-year viruses.[22] All these data illustrate that it might be important to discern between viral etiologies when we try to understand the weather effect contribution to respiratory viruses spreading.

With regard to air pollen concentrations, it has been associated with children's respiratory admission cases.[23] Probably, we did not observe this correlation, because most of the patients requiring PICU admission in our series were children under 2 years old and sensitizations to air allergens in this age group are not yet fully developed.[24]

About the association of air pollutant concentrations and respiratory admissions in children, some studies in the international literature have observed similar very-short term effects, most of them in lag periods of up to 5 days.[3,4,25] Moreover, Fusco et al.[26] observed that same-day levels of NO_2 were associated with an increase of 4% in admissions due to respiratory infections in children.

It is known that exposure to air pollutants (NO_2, NO_x, and PM < 10 µm) decreases lung function[7,27] and induces oxidative stress, resulting in the production of free radicals, which may damage the respiratory system, reducing the resistance to viral infections.[28] Wong et al.[29] described a significant association between the level of NO_2 and admissions with pneumonia and influenza, indicating that exposure to NO_2 increases the susceptibility to influenza virus infection. Spannhake et al.[30] investigated the effects of NO_2 exposure and RVi in human nasal and bronchial epithelial cells in vitro. They found that exposure to NO_2 after RVi increases the production of interleukin-8 greater than only NO_2 exposure, making it evident that a direct additional effect of NO_2 exposure over the RVi exists.[30] In the same way, Greve et al.[31] showed that NO_2 exposure enhances the expression of intercellular adhesion molecule 1. This molecule is a receptor for the RVs and this could be a potential mechanism explaining the observed increased susceptibility to RVi by NO_2 exposure in other settings.[32] Moreover, assessing the associations between severity of RVi and NO_x in children aged between 8 and 11 years, Chauhan et al.[33] described that a high exposure to NO_x during the week before starting a respiratory viral infection by RV or respiratory syncytial virus was associated with an increase in the severity of asthma exacerbations caused by these viruses. These results are in agreement with our findings about the involvement of nitrogenous compounds in RVi severity.

The main limitation of this study is the low number of admissions with severe RVi. However, as far as we know, this is one of the largest series exploring the associations between admissions with severe RVi requiring intensive care and air pollutants. Second, despite using a strict cutoff *p*, chance findings are still possible due to the many variables analyzed. Finally, our time-series analysis relies on data from only one fixed-site monitoring station. Thus, we want to remark that our findings are the result of an exploratory study and further multicenter research with more outcomes and with data from other settings are needed.

In conclusion, this study shows a positive association between average daily NO_x concentrations and children's PICU admissions with severe RV respiratory infection 3 days later. Therefore, the wide range of clinical severity of RVi could partially be explained by air pollutants concentrations (nitrogen compounds). These results could be helpful to adopt policies that mitigate environmental pollution and the burden of this common viral infection in young children.

AUTHOR CONTRIBUTIONS

Georgina Armero: Conceptualization; methodology; investigation; data curation; formal analysis; writing—original draft. **Daniel Penela-Sánchez**: Data curation; investigation; writing—original draft; methodology; formal analysis. **Jordina Belmonte**: Data curation; investigation; writing—review and editing. **Diana Gómez-Barroso**: Investigation; methodology; validation; formal analysis; writing—review and editing. **Amparo Larrauri**: Investigation; methodology; validation; formal analysis; writing—review and editing; supervision. **Desiree Henares**: Conceptualization; investigation; writing—original draft. **Violeta Vallejo**: Writing—review and editing; investigation; data curation; validation. **Iolanda Jordan**: Writing—review and editing; conceptualization; investigation; supervision. **Carmen Muñoz-Almagro**: Validation; visualization; conceptualization; investigation; data curation; writing—original draft; writing—review and editing. **Pedro Brotons**: Funding acquisition; writing—review and editing; writing—original draft; conceptualization; methodology; formal analysis; investigation. **Cristian Launes**: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; writing—review and editing; formal analysis.

ACKNOWLEDGMENTS

Thanks to all the clinical, laboratory, and diagnostic imaging personnel who took care of these patients. We are also grateful to the editors and peer reviewers for their thoughtful comments that helped us improve the quality of this manuscript. Finally, we are thankful to all the children and their parents who have participated in this study within the project 17/349, which is supported by the Spanish National Health Institute Carlos III. This project was partially supported by the Spanish National Health Institute Carlos III (Grant id. PI17/349). Desiree Henares received a grant for predoctoral training in research into Health by the Spanish National Health Institute Carlos III (project number: FI17/00248). The funders have not influenced the design or analysis, nor have they had any role in preparing the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available upon reasonable request to the corresponding author.

ORCID

Daniel Penela-Sánchez http://orcid.org/0000-0002-5289-6609
Jordina Belmonte http://orcid.org/0000-0002-6419-9595
Diana Gómez-Barroso http://orcid.org/0000-0001-7388-1767
Amparo Larrauri http://orcid.org/0000-0002-1704-2245
Desiree Henares http://orcid.org/0000-0003-2631-2718
Iolanda Jordan http://orcid.org/0000-0002-2041-4425
Carmen Muñoz-Almagro http://orcid.org/0000-0001-5586-404X
Pedro Brotons http://orcid.org/0000-0002-2399-7320
Cristian Launes http://orcid.org/0000-0002-0913-9303

REFERENCES

1. Louie JK, Roy-Burman A, Guardia-Labar L, et al. Rhinovirus associated with severe lower respiratory tract infections in children. *Pediatr Infect Dis J*. 2009;28:337-339.
2. Penela-Sánchez D, González-de-Audicana J, Armero G, et al. Lower respiratory tract infection and genus enterovirus in children requiring intensive care: clinical manifestations and impact of viral co-infections. *Viruses*. 2021;13:2059.
3. Nhung NTT, Schindler C, Dien TM, Probst-Hensch N, Perez L, Künzli N. Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: an eight-year time series study. *Environ Int*. 2018;110:139-148.
4. Darrow LA, Klein M, Flanders WD, Mulholland JA, Tolbert PE, Strickland MJ. Air pollution and acute respiratory infections among children 0-4 years of age: an 18-year time-series study. *Am J Epidemiol*. 2014;180:968-977.
5. MacIntyre EA, Gehring U, Mölter A, et al. Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE project. *Environ Health Perspect*. 2014;122:107-113.
6. Mehta S, Shin H, Burnett R, North T, Cohen AJ. Ambient particulate air pollution and acute lower respiratory infections: a systematic review and implications for estimating the global burden of disease. *Air Qual Atmos Health*. 2013;6:69-83.
7. Le TG, Ngo L, Metha S, et al. Effects of short-term exposure to air pollution on hospital admissions of young children for acute lower respiratory infections in Ho Chi Minh City, Vietnam. *Res Rep Health Eff Inst*. 2012;169:73-83.
8. Andrés C, Peremiquel-Trillas P, Gimferrer L, et al. Genetic diversity of rhinoviruses detected at a tertiary hospital in Catalonia (Spain) during the 2014–2017 seasons. *Future Microbiol*. 2018;13: 1565-1573.
9. Gobierno de España. 2022. Ministerio para la transición ecológica y el reto demográfico. Agencia Española de Meteorología. Accessed May 1, 2022. https://datosclima.es/
10. Generalitat de Catalunya, Departament d'Acció Climàtica, Alimentació i Agenda Rural. 2022. Servei Meteorològic de Catalunya. Accessed May 1, 2022. https://analisi.transparenciacatalunya.cat/Medi-Ambient/Dades-meteorol-giques-de-la-XEMA/nzvn-apee/data
11. Generalitat de Catalunya, Departament d'Acció Climàtica, Alimentació i Agenda Rural. 2022. Xarxa de Vigilància i Previsió de la Contaminació Atmosfèrica. Accessed May 1, 2022. https://mediambient.gencat.cat/ca/05_ambits_dactuacio/atmosfera/qualitat_de_laire/vols-saber-que-respires/descarrega-de-dades/descarrega-dades-automatiques/
12. Pan R, Wang X, Yi W, et al. Interactions between climate factors and air quality index for improved childhood asthma self-management. *Sci Total Environ*. 2020;723:137804.
13. Samet JM, Zeger SL, Dominici F, et al. The national morbidity, mortality, and air pollution study. Part II: morbidity and mortality from air pollution in the United States. *Res Rep Health Eff Inst*. 2000;94(5-70; discussion):71-79.
14. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol*. 2013;42:1187-1195.
15. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis*. 2009;9:291-300.
16. Ajuntament de Barcelona. 2022. Did you know that Barcelona is the city with the highest vehicle density in Europe? [Internet]. Accessed April 02, 2022. https://ajuntament.barcelona.cat/qualitataire/en/noticia/did-you-know-that-barcelona-is-the-city-with-the-highest-vehicle-density-in-europe_405934
17. Nenna R, Evangelisti M, Frassanito A, et al. Respiratory syncytial virus bronchiolitis, weather conditions and air pollution in an Italian urban area: an observational study. *Environ Res*. 2017;158:188-193.
18. Gomez-Barroso D, León-Gómez I, Delgado-Sanz C, Larrauri A. Climatic factors and influenza transmission, Spain, 2010-2015. *Int J Environ Res Public Health*. 2017;14:1469.
19. Meerhoff TJ, Paget JW, Kimpen JL, Schellevis F. Variation of respiratory syncytial virus and the relation with meteorological factors in different winter seasons. *Pediatr Infect Dis J*. 2009;28: 860-866.
20. Shaman J, Pitzer VE, Viboud C, Grenfell BT, Lipsitch M. Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biol*. 2010;8:e1000316.
21. Amarillo AC, Carreras HA. The effect of airborne particles and weather conditions on pediatric respiratory infections in Cordoba, Argentine. *Environ Pollut*. 2012;170:217-221.
22. Price RHM, Graham C, Ramalingam S. Association between viral seasonality and meteorological factors. *Sci Rep*. 2019;9:929.
23. Marqués-Mejías MA, Tomás-Pérez M, Hernández I, López I, Quirce S. Asthma exacerbations in the pediatric emergency department at a tertiary hospital: relationship with environmental factors. *J Investig Allergol Clin Immunol*. 2019;29:365-370.
24. Kim HY, Shin YH, Han MY. Determinants of sensitization to allergen in infants and young children. *Korean J Pediatr*. 2014;57: 205-210.
25. Barnett AG, Williams GM, Schwartz J, et al. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am J Respir Crit Care Med*. 2005;171: 1272-1278.

26. Fusco D, Forastiere F, Michelozzi P, et al. Air pollution and hospital admissions for respiratory conditions in Rome, Italy. *Eur Respir J*. 2001;17:1143-1150.
27. Gehring U, Gruzieva O, Agius RM, et al. Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect*. 2013;121:1357-1364.
28. Domingo JL, Rovira J. Effects of air pollutants on the transmission and severity of respiratory viral infections. *Environ Res*. 2020;187(00):187.
29. Wong TW, Lau T, Yu TS, et al. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med*. 1999;56:679-683.
30. Spannhake EW, Reddy SPM, Jacoby DB, Yu XY, Saatian B, Tian J. Synergism between rhinovirus infection and oxidant pollutant exposure enhances airway epithelial cell cytokine production. *Environ Health Perspect*. 2002;110:665-670.
31. Greve JM, Davis G, Meyer AM, et al. The major human rhinovirus receptor is ICAM-1. *Cell*. 1989;10(56):839-847.
32. Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol*. 2007;19:1135-1146.
33. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. *Lancet*. 2003;361:1939-1944.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Armero G, Penela-Sánchez D, Belmonte J, et al. Concentrations of nitrogen compounds are related to severe rhinovirus infection in infants. A time-series analysis from the reference area of a pediatric university hospital in Barcelona *Pediatric Pulmonology*. 2022;1-9. doi:10.1002/ppul.26021