Influence of environmental conditions and pollution on the incidence of *Streptococcus pneumoniae* infections

To the Editor:

*Streptococcus pneumoniae* colonizes a large percentage of the population and while it can cause mild respiratory infections it is also responsible for more severe illnesses, such as invasive pneumococcal disease. Patient co-morbidities, concomitant viral infection, low temperature and environmental pollutants all have a synergistic effect that predisposes to pneumococcal infection, exerting deleterious effects on respiratory epithelium and local immune system, diminishing bacterial clearance and favouring infection [1].

The objective of this study was to analyse the influence of environmental factors on the incidence of pneumococcal infection. For this purpose we designed a retrospective study where data on all cases of *S. pneumoniae* at the University and Polytechnic Hospital La Fe (located in the city of Valencia which has a population density of about 6000 inhabitants·km$^{-2}$ [2]) during a 2-year period (2011–2012) was gathered and grouped by week. A case was considered confirmed when a consistent clinical syndrome occurred in association with the isolation of *S. pneumoniae* or the detection of pneumococcal antigen in urine (BinaxNOW® *Streptococcus pneumoniae* Antigen Card, Alere, Scarborough, ME, USA). Invasive pneumococcal infection was defined as the isolation of *S. pneumoniae* from a normally sterile site (i.e. blood, cerebrospinal fluid or pleural fluid).

Meteorological data including temperature (°C), relative humidity (%) and atmospheric pressure (mb) for the period from 2011 to 2012 was obtained from weather stations located in the health area of the hospital. Information pertaining to air quality during the years of interest included the concentrations of nitrogen oxides (NOx, NO, NO$_2$; µg·m$^{-3}$), ozone (O$_3$; µg·m$^{-3}$), sulfur dioxide (SO$_2$; µg·m$^{-3}$), carbon monoxide (CO; mg·m$^{-3}$), solar radiation (W·m$^{-2}$) and particles with a 50% cut-off aerodynamic diameter of 10 µm (PM10), 2.5 µm (PM2.5) and 1 µm (PM1). The arithmetic weekly means of the air quality values were used as exposure variables.

The relationship between the weekly cases of *S. pneumoniae* and the environmental factors was studied by logistic linear regression using SPSS Statistics 15.0 (IBM, Armonk, NY, USA). Initially a univariate analysis was carried out, followed by a multivariate analysis of the factors significantly associated with the number of infections caused by *S. pneumoniae*. Different models were tried, with different combinations of factors that could affect *S. pneumoniae* incidence, and the model that best fitted the data was chosen.

A total of 619 pneumococcal infections were included (58.8% men, 41.2% women) of which 117 (18.9%) were invasive pneumococcal infections (59.2% men, 40.8% women). Age presented a bimodal distribution with two local maxima at 0 years and 65 years. In adult patients, co-morbid conditions were chronic obstructive pulmonary disease (COPD; 33.9%), chronic cardiovascular disease (22.0%), chronic renal failure (11.7%), diabetes (21.8%), cirrhosis (2.3%) and chronic neurological disease (25.5%), while a number of patients were smokers (9.6%) and alcohol abusers (2.5%).

A seasonal pattern was observed with the highest incidence of disease in winter, when temperatures drop and more fossil fuel is consumed, and the lowest incidence in summer (ANOVA test, p<0.001). It was found that SO$_2$, NO$_x$, NO$_2$, NO and CO showed a significant positive relationship with the number of pneumococcal infections in univariate analysis, whereas temperature, solar radiation, relative humidity,
PM$_{2.5}$, PM$_{1}$, PM$_{10}$ and O$_3$ had a negative relationship (table 1). As for invasive pneumococcal infections, only SO$_2$, NO$_x$ and NO showed a significant positive relationship, whereas temperature and solar radiation presented a negative relationship.

The multivariate model which best fitted the data for pneumococcal infection included temperature, SO$_2$, NO and relative humidity, and was able to explain 61% of the variation observed ($R^2$ 0.61; F statistic $p<0.001$). For invasive infection only temperature and SO$_2$ were included ($R^2$ 0.17; F statistic $p<0.001$) (table 1). It is worth mentioning that although the model for invasive infection was significant, SO$_2$ had a 95% confidence interval that barely passed above zero, probably due to the paucity of data.

Univariate analysis found many possible factors related to the occurrence of *S. pneumoniae* infection but, by multivariate analysis, it was possible to build a solid model with just four variables. This reduction can be explained by the interrelationship between atmospheric factors. Using univariate analysis, Kim et al. [1] found the same associations of SO$_2$ and O$_3$ with pneumococcal infection; however, they used SO$_2$ as a marker for other air pollutants, whereas in our study we tested each of them individually.

In our models, gaseous air pollutants characteristic of fossil fuel combustion processes positively influenced the appearance of *S. pneumoniae* and this effect can be explained by the local damage which occurs in the respiratory mucosa. In fact, SO$_2$ and NO$_x$ impair mucociliary activity by decreasing ciliary beating and altering cellular metabolism and morphology [3–6].

Surprisingly, our data showed that particulate matter had a protective effect with respect to pneumococcal disease. A recently published paper [7] linked particulate matter exposure to higher risk of admission for pneumonia, especially in older patients or patients with cardiovascular disease, although no specific aetiological agent was studied. Interestingly, PM$_{2.5}$ enhances macrophage *S. pneumoniae* binding but decreases internalization and phagocytosis [8]. This binding may render bacteria unable to establish infection. In any case, associations with *S. pneumoniae* and other pathogens should be further studied.

As described in other studies [1, 9, 10], solar radiation, higher temperatures and high humidity levels reduce the number of cases. Cold stress has a local immunomodulatory effect on respiratory mucosa but may also influence microbiota composition. This effect has been described by Bogaert et al. [11] who found seasonal variability in the nasopharyngeal microbiota of children, with a less-balanced microbiota being observed during autumn and winter. However, pneumococcal disease does not necessarily increase in colder regions and population density may play an important role as well [12]. Likewise, low humidity levels affect mucus, which is rich in water, altering its function and composition. Overall, cold stress and low air humidity levels may favour infection.

### TABLE 1 Univariate and multivariate models

| Model            | Pneumococcal infection | Invasive pneumococcal infection |
|------------------|------------------------|---------------------------------|
|                  | Coefficient (95% CI)   | p-value                         | Coefficient (95% CI)   | p-value                         |
| **Univariate**   |                        |                                 |                        |                                 |
| SO$_2$           | 1.411 [0.94–1.881]     | <0.0001                         | 0.243 [0.088–0.398]    | 0.002                           |
| CO               | 9.303 [0.956–17.651]   | 0.03                            | 0.009 [0.0003–0.018]   | 0.04                            |
| O$_3$            | −0.08 [−0.115–−0.044]  | <0.0001                         | 0.025 [0.002–0.048]    | 0.04                            |
| NO$_x$           | 0.103 [0.078–0.127]    | <0.0001                         | 0.009 [0.0003–0.018]   | 0.04                            |
| NO               | 0.261 [0.198–0.323]    | <0.0001                         | 0.009 [0.0003–0.018]   | 0.04                            |
| NO$_2$           | 0.208 [0.152–0.265]    | <0.0001                         | 0.009 [0.0003–0.018]   | 0.04                            |
| PM$_1$           | −0.146 [−0.247–−0.045] | 0.005                           | −0.073 [−0.108–−0.038] | <0.0001                         |
| PM$_{1.5}$       | −0.122 [−0.2–−0.044]   | 0.002                           | −0.004 [−0.008–−0.001] | 0.008                           |
| PM$_{10}$        | −0.121 [−0.201–−0.04]  | 0.004                           | −0.004 [−0.008–−0.001] | 0.008                           |
| Relative humidity| −0.119 [−0.189–−0.05]  | 0.001                           | −0.073 [−0.108–−0.038] | <0.0001                         |
| Temperature      | −0.456 [−0.546–−0.367] | <0.0001                         | −0.004 [−0.008–−0.001] | 0.008                           |
| Solar radiation  | −0.029 [−0.039–−0.019] | <0.0001                         | −0.004 [−0.008–−0.001] | 0.008                           |
| **Multivariate** |                        |                                 |                        |                                 |
| SO$_2$           | 0.732 [0.342–1.121]    | 0.0003                          | 0.158 [0.005–0.322]    | 0.058                           |
| Temperature      | −0.196 [−0.326–−0.065] | 0.003                           | −0.052 [−0.090–−0.014] | 0.008                           |
| Relative humidity| −0.054 [−0.105–−0.002] | 0.04                            | −0.052 [−0.090–−0.014] | 0.008                           |
| NO               | 0.139 [0.065–0.212]    | 0.0003                          | −0.052 [−0.090–−0.014] | 0.008                           |

PM$_x$: particles with a 50% cut-off aerodynamic diameter of $x$ $\mu$m.
Finally, chronic exposure to different pollutants and the interactions between them need to be studied to completely understand their effects on the respiratory tract. Beyond local and immediate damage, De Jong et al. [13] have found that chronic exposure to air pollutants is associated with restrictive ventilatory patterns, favouring pulmonary disease and infection. Within this context, O₃ illustrates the interaction between air pollutants and atmospheric conditions. Although it has a well-known detrimental effect on the respiratory tract, O₃ was associated with lower levels of pneumococcal disease. A possible explanation is that ground level O₃ is produced by solar radiation, reaching its peak during spring and summer, while NOₓ and O₃ are inextricably linked such that high levels of O₃ are accompanied by low levels of NOₓ [14]. As such, high levels of O₃ are associated with high levels of a protector (solar radiation) and low levels of noxious gases (NOₓ).

To conclude, our paper studies the interactions between pneumococcal infection and environmental conditions using a global approach and makes evident how relevant they are, although more studies are needed to better define relations and causality. Lastly, not all cases of pneumococcal infection are explained by environmental conditions. Indeed, factors specific to the individual and concomitant infections have an undeniable weight in the predisposition to this disease, especially for invasive pneumococcal infection.

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Received: Feb 06 2017 | Accepted after revision: Oct 05 2017

Conflict of interest: None declared.

Acknowledgements: The authors would like to express their gratitude to José Luis Pisón and Ana Viciano Pastor from the Acoustic Pollution Service of the city of Valencia for providing environmental data.

References
1. Kim PE, Mushet DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996; 22: 100–106.
2. Statistics Office of Valencia City Council. Population density by district, 2001-2016. www.valencia.es/ayuntamiento/catalogo.nsf/IndiceAnuario/readForm&lang=1&capitulo=2&tema=1&bdOrigen=ayuntamiento/estadistica.nsf&iDApoyo=59BF3C7A3D6E414C1257DD40057BE6C. Date last accessed: August 2017.
3. Wolff RK. Effects of airborne pollutants on mucociliary clearance. Environ Health Perspect 1986; 66: 223–237.
4. Bailey KL, Robinson JE, Sisson JH, et al. Alcohol decreases RhoA activity through a nitric oxide (NO)/cyclic GMP (cGMP)/protein kinase G (PKG)-dependent pathway in the airway epithelium. Alcohol Clin Exp Res 2011; 35: 1277–1281.
5. Kienast K, Riechelmann H, Knaust M, et al. Combined exposures of human ciliated cells to different concentrations of sulfur dioxide and nitrogen dioxide. Eur J Med Res 1996; 1: 533–536.
6. Riechelmann H, Maurer J, Kienast K, et al. Respiratory epithelium exposed to sulfur dioxide–functional and ultrastructural alterations. Laryngoscope 1995; 295–299.
7. Vodonos A, Kloog I, Boehm L, et al. The impact of exposure to particulate air pollution from non-anthropogenic sources on hospital admissions due to pneumonia. Eur Respir J 2016; 48: 1791–1794.
8. Zhou H, Kozbik L. Effect of concentrated ambient particles on macrophage phagocytosis and killing of Streptococcus pneumoniae. Am J Respir Cell Mol Biol 2007; 36: 460–465.
9. Ciruela P, Bronser S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006–2012). BMC Public Health; 2016; 16: 400.
10. Liu Y, Liu J, Chen F, et al. Impact of meteorological factors on lower respiratory tract infections in children. J Int Med Res 2016; 44: 30–41.
11. Bogaert D, Keijser B, Huse S, et al. Variability and diversity of nasopharyngeal microbiota in children: A metagenomic analysis. PLoS One 2011; 6: e17035.
12. Feemster KA, Li Y, Localio AR, et al. Risk of invasive pneumococcal disease varies by neighbourhood characteristics: implications for prevention policies. Epidemiol Infect 2013; 141: 1679–1689.
13. De Jong K, Vonk JM, Zijlema WL, et al. Air pollution exposure is associated with restrictive ventilatory patterns. Eur Respir J 2016; 48: 1221–1224.
14. Clapp LJ, Jenkin ME. Analysis of the relationship between ambient levels of O₃, NO₂ and NO as a function of NOX in the UK. Atmos Environ 2001; 35: 6391–6405.