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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 (NO_x, 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 (PM_{10}), 2.5 μm ($PM_{2.5}$) and 1 μm (PM_1). 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,

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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		
O_3	−0.08 (−0.115– −0.044)	<0.0001		
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	0.025 (0.002–0.048)	0.04
NO_2	0.208 (0.152–0.265)	<0.0001		
PM_1	−0.146 (−0.247– −0.045)	0.005		
$PM_{2.5}$	−0.122 (−0.2– −0.044)	0.002		
PM_{10}	−0.121 (−0.201– −0.04)	0.004		
Relative humidity	−0.119 (−0.189– −0.05)	0.001		
Temperature	−0.456 (−0.546– −0.367)	<0.0001	−0.073 (−0.108– −0.038)	<0.0001
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		
NO	0.139 (0.065–0.212)	0.0003		

PM_x: particles with a 50% cut-off aerodynamic diameter of x µm.

$PM_{2.5}$, 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.

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, O_3 illustrates the interaction between air pollutants and atmospheric conditions. Although it has a well-known detrimental effect on the respiratory tract, O_3 was associated with lower levels of pneumococcal disease. A possible explanation is that ground level O_3 is produced by solar radiation, reaching its peak during spring and summer, while NO_x and O_3 are inextricably linked such that high levels of O_3 are accompanied by low levels of NO_x [14]. As such, high levels of O_3 are associated with high levels of a protector (solar radiation) and low levels of noxious gases (NO_x).

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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