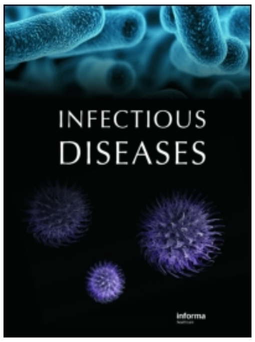

Infectious Diseases

ISSN: 2374-4235 (Print) 2374-4243 (Online) Journal homepage: http://www.tandfonline.com/loi/infd20

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To cite this article: Igor C. Borges, Dafne C. Andrade, Maria-Regina A. Cardoso, Andreas Meinke, Aldina Barral, Helena Käyhty, Olli Ruuskanen & Cristina M. Nascimento-Carvalho (2016): Seasonal patterns and association of meteorological factors with infection caused by Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in childhood community-acquired pneumonia in a tropical region, Infectious Diseases, DOI: 10.1080/23744235.2016.1212170

To link to this article: http://dx.doi.org/10.1080/23744235.2016.1212170

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INFECTIOUS DISEASES, 2016
http://dx.doi.org/10.1080/23744235.2016.1212170

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LETTER TO THE EDITOR

Seasonal patterns and association of meteorological factors with infection caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in childhood community-acquired pneumonia in a tropical region

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Sir,

We read with interest the recent article in the present journal [1] on the effect of bacterial colonization in children with bronchiolitis during autumn and winter in China. Taking into account that bacterial pathogens are frequent causative agents of respiratory infections, the identification of temporal patterns of bacterial infection in children with respiratory diseases may allow planning of preventive strategies and may guide empirical therapies. Thus, we aimed to investigate the seasonal distribution and the association of meteorological factors with the frequency of infection caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in children with community-acquired pneumonia (CAP) in a tropical region.

The study sample was drawn from a clinical trial, evaluating the efficacy of amoxicillin given twice or thrice for the outpatient treatment of children aged 2–59 months with non-severe CAP.[2] The study was held in the Emergency Department of the Federal University of Bahia Hospital, in Salvador, northeastern Brazil, from November 2006 to April 2011. This emergency department is accessible for anyone and is free of charge. Inclusion criteria comprized respiratory complaints, lower respiratory findings, and presence of pulmonary infiltrate/consolidation on the chest radiograph taken on admission and read by the paediatrician on duty. Out of the 820 children from that study, 130 patients were excluded from the present investigation due to severe malnutrition (Z-score for weight-for-age under −3.00 – checked using 'Anthro' software [Geneva, Switzerland]; $n = 1$), previous vaccination with pneumococcal vaccines ($n = 48$), or absence of acute or convalescent serum sample ($n = 81$). Therefore, 690 patients were included in the present study. Data about age distribution, sampling interval, duration of disease, antibody level in acute phase samples, and frequency of increase in antibody levels in paired serum samples from this study group have been previously published.[3]

Written informed consent was obtained from legal guardians before patient enrolment. The study protocol was approved by the Ethics Committee of the Federal University of Bahia.

Acute and convalescent serum samples were assayed with a multiplexed bead-based serological test measuring IgG antibodies against eight recombinant pneumococcal protein antigens (Ply, CbpA, PspA 1, PspA 2, PcpA, PhtD, StkP-C, and PcsB-N), three *H. influenzae* recombinant protein antigens (Protein D, NTHi0371-1, and NTHi0830), and five *M. catarrhalis* recombinant protein antigens (outer membrane protein CD, MC_RH4_2506, MC_RH4_1701, MC_RH4_3729-1, and MC_RH4_4730). Ply, CbpA, PcpA, PhtD, StkP-C, and PcsB-N were conjugated in one-bead region each. PspA 1 and PspA 2 were conjugated in the same bead region, and all *H. influenzae* and all *M. catarrhalis* antigens were conjugated onto one-bead region per bacterium. Acute and convalescent serum samples were tested on the same plate and true duplicates were used throughout the procedures. Further details of the serology protocol have been published elsewhere.[4]

Infection caused by *S. pneumoniae* was indicated by ≥1.5-fold rise in antibody levels against PcpA or ≥2-fold rise in antibody levels against Ply, CbpA, PspA, PhtD, StkP-C, or PcsB-N. Infection caused by *H. influenzae* or *M. catarrhalis* was established by detection of ≥2-fold rise in antibody levels against antigens of each of these two bacteria.

Meteorological data were provided by the Institute of Environment and Water Resources (INMET) in the State of Bahia (former Institute of Water Monitoring [INGA]) from a meteorological station located ∼2 km away from the Emergency Department of the Federal University of Bahia Hospital. Rainfall was measured as daily precipitation in millimetres and was analyzed as the total quantity of the month. Data about relative humidity (%) and air temperature (°C) were measured three times daily and were monthly averaged. Hours of sunshine were measured as daily duration of sunshine, in hours, and were calculated as total monthly hours of sunshine. Summer was considered as the period from January to March, fall from April to June, winter from July to September, and spring from October to December.

Categorical variables were presented as absolute number (percentage) and continuous variables as median (interquartile range [IQR]). Medians between two groups were compared using Mann–Whitney *U* test. Time series analysis using Prais–Winsten generalized linear regression was used for identification of seasonality and association of the logarithmic transformation of monthly bacterial detection count and monthly values of meteorological factors. Seasonal distribution was identified when the coefficients correspondent to sine (b2) or cosine (b3) terms of the linear regression equation with seasonal component ($Y(i) = b0 + b1*X(i) + b2*\sin[2\pi X(i)/L] + b3*\cos[2\pi X(i)/L]$) was statistically different from zero in the hypothesis tests. Meteorological factors were evaluated separately using data of the current month and the lag of the preceding month. Statistical tests were two-tailed, with a significance level of 0.05. The software Stata version 13 (StataCorp, College Station, TX) was used for analyses.

There were 351 (50.9%) boys and the median age of the study population was 26.7 (14.5–41) months. Among the

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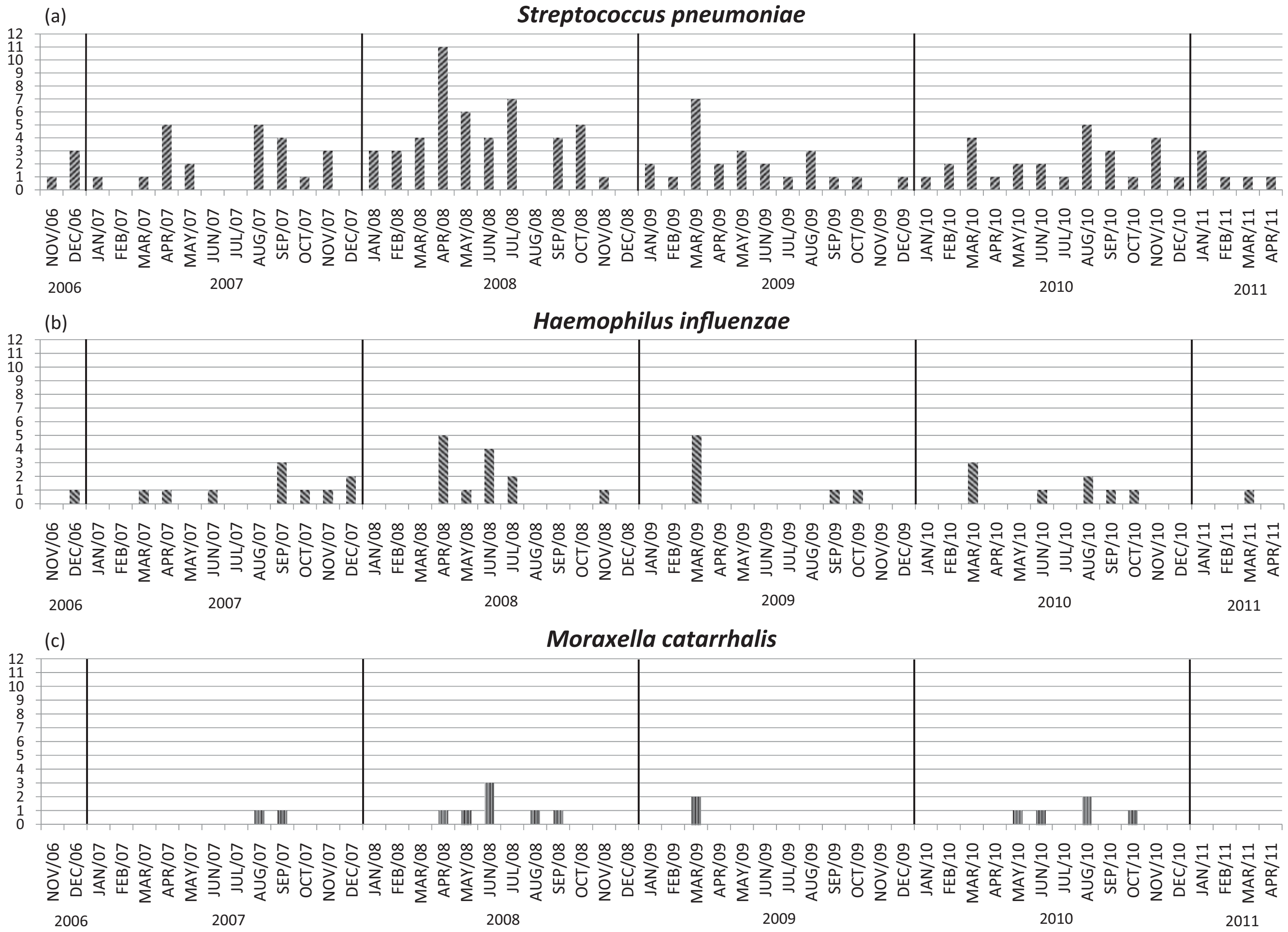

Figure 1. Distribution of the monthly count (absolute number) of cases with infection caused by *Streptococcus pneumoniae* (a), *Haemophilus influenzae* (b), or *Moraxella catarrhalis* (c) during a 54-month period in Salvador, northeastern Brazil, among children with non-severe community-acquired pneumonia.

690 CAP cases, 131 (19%) had pneumococcal infection, 40 (5.8%) had *H. influenza* infection, and 16 (2.3%) had *M. catarrhalis* infection.

During the study period, 18 months had only one case of pneumococcal infection per month, seven months had only two cases per month, and 22 months had ≥ 3 cases per month; for *H. influenzae*, 14 months had only one case per month, three months had only two cases per month, and five months had ≥ 3 cases per month; for *M. catarrhalis*, nine months had only one case per month, two months had only two cases per month, and one month had ≥ 3 cases per month.

Infections caused by *M. catarrhalis* demonstrated seasonal distribution ($b2 = -0.3$; $p = 0.003$) and the median monthly count was higher during fall-winter, compared to spring-summer (median [IQR] monthly count: 0 [0–1] *vs.* 0 [0–0]; $p = 0.005$). Thirteen (81.3%) out of the 16 cases of *M. catarrhalis* infection were detected during fall-winter. The monthly count of CAP cases and of *S. pneumoniae* or *H. influenzae* infection did not show seasonal variation. Figure 1 shows the monthly distribution of infection caused by each one of these three bacteria.

All meteorological factors demonstrated seasonal distribution (data not shown). Fall-winter was the period with higher rainfall and air humidity, and lower sunlight and air temperature (Figure 2).

There was a positive association between monthly count of *M. catarrhalis* infection and relative humidity of the preceding month ($\text{coefficient} = 0.05$; $p = 0.02$). There was a negative association between monthly count of *M. catarrhalis* infection and air temperature of the current ($\text{coefficient} = -0.1$; $p = 0.01$) and preceding month ($\text{coefficient} = -0.1$; $p = 0.03$), and with sunshine of the preceding month ($\text{coefficient} = -0.003$; $p = 0.047$). There were no associations between the monthly count of *S. pneumoniae* or *H. influenzae* infection and meteorological factors.

The present study demonstrates that *M. catarrhalis* infections are more frequent during fall-winter in children with non-severe CAP in a tropical city. Furthermore, it demonstrates that the frequency of *M. catarrhalis* infection is positively associated with relative humidity and negatively associated with air temperature and sunshine. The frequency of *S. pneumoniae* or *H. influenzae* infection do neither show a seasonal pattern nor is associated with meteorological factors.

The seasonal pattern of *M. catarrhalis* infections herein demonstrated is probably due to the association of infections caused by this bacterium and meteorological factors. Interestingly, *M. catarrhalis* infections were associated with

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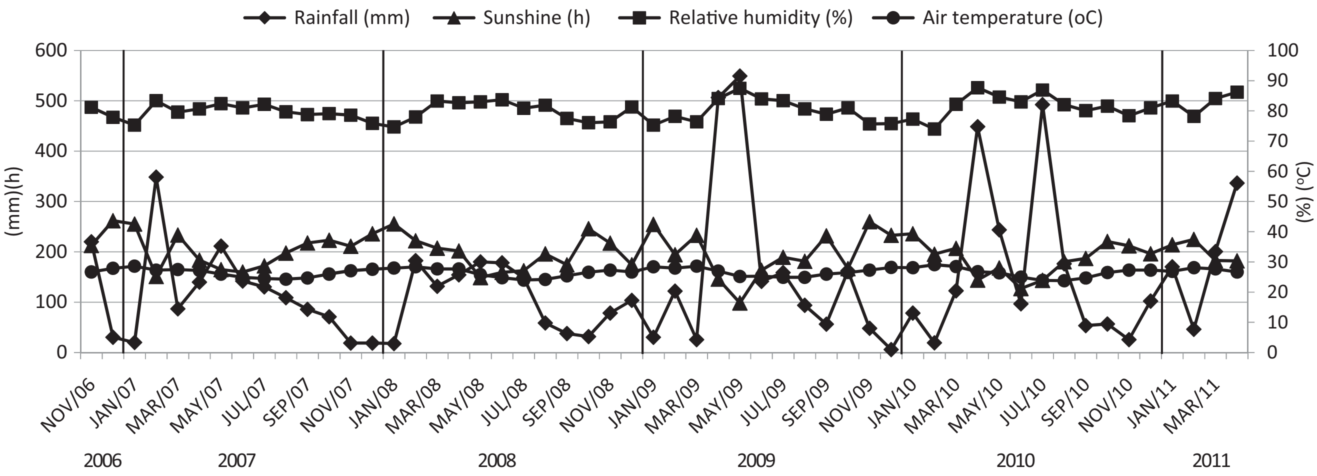

Figure 2. Distribution of total monthly rainfall and sunshine and average monthly relative humidity and air temperature during a 54-month period (from November 2006 to April 2011) in Salvador, northeastern Brazil.

three meteorological parameters of the preceding month and were associated with only one meteorological parameter of the current month of the disease. These findings might be related to the mechanisms of pathogen transmission or disease development in children. Perhaps, meteorological factors interact with conditions that predispose children to *M. catarrhalis* pneumonia, such as bacterial carriage.

Few previous studies evaluated the role of *M. catarrhalis* in children with CAP. For instance, Nascimento-Carvalho et al. evaluated the detection of antibody responses against whole-cell *M. catarrhalis* antigens in hospitalized children with CAP in the same city where the present investigation was carried out. They failed to demonstrate association between response to this bacterium and meteorological factors.[5] This difference is probably related to the distinct antigen and patient characteristics of the studies and also the duration of patient recruitment (that study recruited hospitalized patients in a 21-month period). In this context, the present study helps to better understand the pattern of *M. catarrhalis* detection in children with CAP. This information may be useful for the development of preventive and therapeutic strategies for CAP management in children.

Unexpectedly, we did not find a seasonal pattern of pneumococcal infection and there was no association between pneumococcal infections and meteorological factors. Jain et al. showed that pneumococcal infection incidence increased during winter in hospitalized children with pneumonia in the United States.[6] In addition, Weinberger et al. demonstrated that bacteremic pneumococcal pneumonia also peaked during winter time in children from the Navajo reservation in the United States.[7] Furthermore, Iroh Tam et al. and White et al. demonstrated that invasive pneumococcal disease peaked in the winter in the United States.[8,9] The differences between the present and the previous studies can be due to distinct patient characteristics (hospitalized *vs.* non-hospitalized pneumonia or invasive *vs.* non-invasive pneumococcal disease), method of pneumococcal identification (microbe culture *vs.* antibody response), and climate conditions (temperate *vs.* tropical). Regarding the association between *S. pneumoniae* and meteorological factors, Nascimento-Carvalho et al. showed negative correlation between the frequency of antibody responses against Ply and air temperature in children with CAP hospitalized in the same city of the present study.[5] Additionally, Numminen et al. demonstrated that pneumococcal nasopharyngeal carriage transmission is higher during the periods of lower temperature and lower rainfall rates in the Thailand-Myanmar border.[10] The differences between the results from these two studies compared to ours could be explained by the distinct types of pneumococcal infection evaluated (nasopharyngeal carriage *vs.* severe CAP *vs.* non-severe CAP). It seems that conclusions regarding pneumococcal infection seasonality are strictly related to the type of infection and the climate conditions.

Our study has some limitations. The uncertainty of the optimal threshold fold-increases in antibody levels against *H. influenzae* and *M. catarrhalis* antigens that are associated with infections caused by these agents' limits the interpretation of antibody responses. In addition, there is little variation in meteorological factors in tropical regions. Thus, future studies should evaluate meteorological and seasonal patterns of infection caused by these bacteria in children with CAP in different climate conditions in order to better understand the association between these variables. Finally, the low rate of *M. catarrhalis* and *H. influenzae* detection may impair statistical analysis using these data. However, we did identify statistically significant differences in our investigation with regard to *M. catarrhalis* infection.

In conclusion, *M. catarrhalis* infections are more frequent during fall-winter in children with non-severe CAP in a tropical region. Additionally, the frequency of infection caused by this bacterium is positively associated with relative humidity and negatively associated with air temperature and sunshine. Seasonality and meteorological factors do not seem to play a role in the frequency of *S. pneumoniae* and *H. influenzae* infections in children with non-severe CAP in a tropical region.

Acknowledgments

We thank Sanofi Pasteur (Lyon, France) for supplying PcpA and PhtD; Prof. Elaine Tuomanen at St. Judes Children's Research Hospital (Memphis) for supplying Ply, CbpA, PspA 1; Profs. Susan Hollingshead, David Briles, and Pat Coan at University of Alabama (Birmingham) for supplying PspA 2; and Valneva Austria GmbH (Vienna, Austria) for supplying SP1732-3, SP2216-1, NTHi Protein D, NTHi0371-1, NTHi0830, MC Omp CD, MC_RH4_2506, MC_RH4_1701, MC_RH4_3729-1, and MC_RH4_4730. We also thank Camilla Virta and Leena Saarinen for their help in the laboratory.

Disclosure statement

Andreas Meinke is an employee of Valneva Austria GmbH. Profs. Aldina Barral, Maria Regina A. Cardoso, and Cristiana M. Nascimento-Carvalho are investigators at CNPq.

Funding

This work was supported by: Bahia State Agency for Research Funding (FAPESB), Brazil; Brazilian Council for Scientific and Technological Development (CNPq), Brazil; and in part by National Institute for Health and Welfare, Finland.

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Received 19 June 2016; revised 1 July 2016; accepted 5 July 2016

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