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ORIGINAL ARTICLE

Many respiratory viruses have temporal association with meningococcal disease

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KEYWORDS
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Abstract
Background: Previous ecological studies have shown a temporal and spatial association between influenza epidemics and meningococcal disease (MNG); however, none have examined more than two respiratory viruses.
Methods: Data were obtained in Chile between 2000 and 2005 on confirmed cases of MNG and all confirmed cases of respiratory viruses (influenza A and B; parainfluenza; adenovirus; and respiratory syncytial virus [RSV]). Both variables were divided by epidemiological weeks, age range, and regions. Models of transference functions were run for rates of MNG.
Results: In this period, 1022 reported cases of MNG and 34,737 cases of respiratory virus were identified (25,137 RSV; 4300 parainfluenza; 2527 influenza-A; 356 influenza-B; and 2417 adenovirus). RSV was the major independent virus temporally associated to MNG (it appears one week before MNG), followed by parainfluenza, influenza-B, adenovirus, and influenza-A.
Conclusions: The rate of MNG in Chile is temporally associated to all of the respiratory viruses studied, but with variability according age range, and regions.

What is already known about the topic?

- Ecological studies worldwide show a temporal and spatial association between influenza and respiratory syncytial virus (RSV) epidemics.

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What this paper adds

- This is the first study to consider laboratory confirmation of many respiratory virus in all age ranges. We found that the rate of meningococcal disease in Chile is temporally related to all the respiratory viruses tested (RSV, parainfluenza, influenza A and B, and adenovirus), but varied according to the combination of specific age group and region e.g. climate and latitude.

Introduction

Meningococcal disease (MNG) refers to several highly lethal presentations (occult bacteraemia, meningitis, fulminate sepsis) caused by *Neisseria meningitidis*. Moreover, *N. meningitidis* is the main cause of meningitis worldwide. It is well known that around 10% of the general population become nasopharyngeal carriers of *N. meningitidis*. Humans are the only reservoir of *N. meningitidis* and transmission is by direct contact with nasopharyngeal secretion. MNG in Chile is under surveillance notifying all suspected cases to the Epidemiological Unit of The Ministry of Health and by sending *N. meningitidis* isolated from clinical samples in any microbiology laboratory to our National reference Laboratory. During the period of 2000–2005, MNG cases in Chile were: 41% meningitis, 40% meningococcaemia, 16% meningitis plus meningococcaemia, and 2% others (including Waterhouse–Friderichsen syndrome); no cases of bacteraemia were reported.[1] Half of the MNG cases were children under the age of five.[1] MNG has a universal distribution and presents itself in Chile mainly during the winter season. Since 1993, the incidence of MNG in Chile has been stable and in 2005 it was 1.3/100,000 population, with a mortality rate of 0.2–0.3/100,000 population.[1]

Viral respiratory tract infections also predominate in Chile during winter.[1] These viruses, together with *N. meningitidis*, live in upper respiratory tract mucose.[2] Ecological studies in Denmark,[2] the UK/Wales,[3] France,[4] and Spain[5] show a temporal and spatial association between influenza epidemics and MNG, with an increased number of MNG cases following (approximately two weeks after) influenza cases.[3,4] The explanation might be alterations in the immune response of the host and/or damage to the respiratory epithelium caused by the virus.[2] However, these studies used ''influenza-like clinical cases'' without requiring viral confirmation.[2–5] Two small case–control studies with identified respiratory viruses yielded contradictory results.[6,7] While Makras et al.[6] reported that only influenza type A, and not type B, was a risk factor for MNG during an outbreak among 55 recruits in Greece; Dunlop et al.[7] showed no association of confirmed common respiratory viruses (rhinovirus, adenovirus, parainfluenza, influenza type A, and respiratory syncytial virus [RSV]) and MNG among 104 children in the UK. Other ecological,[8,9] and case–control[10] studies have reported a lack of association between RSV and MNG.

There is also a lack of information in Latin America regarding the potential association between MNG and influenza or other respiratory viruses. Considering that epidemiological and laboratory surveillance of MNG and respiratory tract infections has existed in Chile for many years, we explored the hypothesis that different types of respiratory viruses (influenza, parainfluenza, adenovirus, and RSV) were associated with MNG in different age groups in Chile. Our hypothesis considers that more than one respiratory virus could be temporally associated with MNG according to different regions (climate).

Methods

Between January 2000 and December 2005, data of confirmed MNG cases were obtained weekly from the Epidemiology Department of the Chilean Ministry of Health. For this same period of time, data of confirmed cases of respiratory virus: identified by nasopharyngeal aspirated for influenza (A and B), parainfluenza (1,2,3), adenovirus, and RSV by indirect immunofluorescence, from the Public Health Laboratory of the Chilean Ministry of Health as a part of the National Respiratory Virus Surveillance were obtained weekly. This surveillance was carried out in pre-established sentinel health centres throughout the country.

Both MNG and respiratory viruses cases were divided by epidemiological weeks during this period (2000–2005), by age range group (<1 y or infants, 1–14 y or children and >14 y of age or adolescents/adults) and by seven regions or geographical areas most representative of Chile (regions II and IV in the north, region V and the metropolitan region in the centre and regions VIII, X and XI in the south). Mean temperature, precipitation, latitude and sea level characteristics of each region are presented in Table 1. We used rates of MNG and rates of each of the respiratory viruses (number of cases per 10,000 population for each age group and each region). Population data were taken from the Chilean National Institute of Statistics.

Statistical analysis

Models of transference functions for the rates of MNG by each epidemiological week and age range in each region had the following general formula:

$$\begin{aligned}
&(1-B^{12})^{\beta}(MNG_t-\alpha MNG_{t-1})\\
&\quad=\mu+\sum_{i=1}^{5}\sum_{g=1}^{3}\frac{(w_g^{o,i}-w_g^{1,i}B-w_g^{2,i}B^2)}{(1-\delta_g^{1,i}B-\delta_g^{2,i}B^2)}(X_{t-s_g}^{i,g}-\alpha_g^{i}X_{t-s_g}^{i,g})\\
&\qquad+\frac{1-\theta_1^{g}B-\theta_2^{g}B^2-\cdots-\theta_q^{g}B^q}{(1-\varphi_1^{g}B-\varphi_2^{g}B^2-\cdots-\varphi_p^{g})(1-\Phi_1^{g}B-\Phi_2^{g}B^2-\cdots-\Phi_P^{g}B^P)}\varepsilon_t
\end{aligned}$$

where $g=1,2,3$ is the three age groups (infants, children and adolescents/adults); $i=1,2,3,4,5$ corresponds to the five respiratory viruses considered (RSV, adenovirus, parainfluenza, influenza A and influenza B). B is the backward operator; $BX_t=X_{t-1}$ β is 1 or 0, depending whether stationary differentiation is applied or not to the weekly MNG rates of the regional and age groups. α is 1 or 0, depending whether we model the original series of MNG or the differential series of the regional and age groups. μ is a specific constant for each region and age group. $\alpha_{g,r}^{i}$ is 1 or 0, depending whether it is necessary to differentiate the ith predictor of age group g $w_g^{s,i}$ and $\delta_g^{s,i}$ (with $s=0,1,2$) correspond to the coefficients of the numerator and denominator, respectively, of the transference function to the ith