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# Respiratory syncytial virus infection and meningococcal disease

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## SUMMARY

Although viral respiratory tract infections may predispose to meningococcal disease, strong evidence that they do so exists only for influenza. Data on laboratory reported cases of respiratory syncytial virus (RSV) infections and meningococcal disease in England and Wales from mid-1989 to mid-1994 were analysed. Although the rise in RSV cases preceded the rise in meningococcal disease cases each winter, the interval between the rise and fall of the two diseases was inconsistent, no association was found between time series after removal of the seasonal component, and there was no evidence that more cases of meningococcal disease occurred in winters with more RSV disease. RSV may have less effect on the two most likely mechanisms whereby influenza predisposes to meningococcal disease, namely lowered immunity and impaired pharyngeal defences.

## INTRODUCTION

Viral respiratory tract infections may predispose to meningococcal disease [1]. Evidence is strongest for influenza [2–4] which probably increases susceptibility to meningococcal disease by transient reduction in immune function and/or pharyngeal defences. This evidence is provided by comparisons of time trends of the two diseases, documented outbreaks of meningococcal disease following outbreaks of influenza, and an analytical epidemiological study demonstrating increased odds of recent influenza infection in cases of meningococcal disease.

The finding that meningococci have an increased affinity for RSV-infected HEp2 cells in vitro [5] prompted us to review the epidemiological evidence for an association between RSV and meningococcal disease. A preliminary comparison of laboratory reported cases of these two diseases in England and Wales confirmed that both have winter peaks and high attack rates in infancy. We explored the hypothesis that RSV predisposes to meningococcal disease by a retrospective study of reported cases in England and Wales from mid-1989 to mid-1994.

## METHODS

### RSV case ascertainment

Data on RSV infections reported by laboratories in England and Wales to the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC) between mid-1989 and mid-1994 were analysed by date of specimen.

### Meningococcal case ascertainment

Data on meningococcal case isolates from mid-1989 to mid-1994 were obtained from the Meningococcal Reference Unit (MRU), Manchester Public Health Laboratory, classified by date of receipt at the MRU. Notifications of meningococcal meningitis and septicaemia to the Office of Population Censuses and

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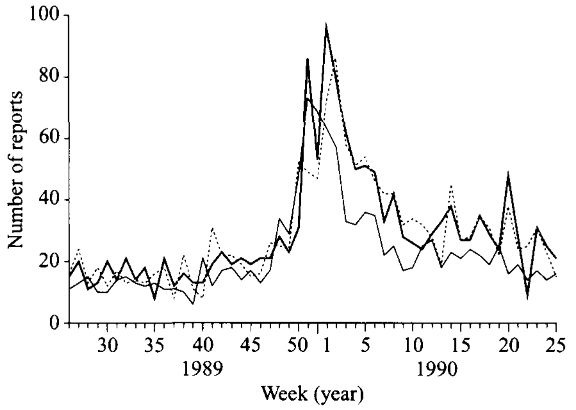


**Fig. 1.** Incidence of meningococcal disease 1989/90, by CDSC date of specimen, OPCS date of notification and MRU date isolate received: ——, CDSC; ······, OPCS; ——, MRU.

Surveys (OPCS) were examined for the same period, as well as reports from laboratories to CDSC according to date of specimen. The trends of all three sources of meningococcal disease incidence data were similar. Both MRU and OPCS data lagged by a mean interval of one week behind CDSC date of specimen data (example of one year's data in Fig. 1). As the number of identified cases was highest in the MRU data set, this source of laboratory confirmed cases was selected for comparison with the RSV date of specimen data. Dates of isolates received at the MRU were brought back by one week in all calculations and figures to allow for the time lag.

### Time trends

Time trends were compared using time series analysis in the statistical package MINITAB [6]. Logarithms of the weekly number of cases were used to stabilize the variance and produce a more symmetrical distribution. Cross correlations were calculated to measure the difference in seasonal trends at time lags from −26 to +26 weeks. The time series were smoothed to identify and then remove the cyclic (probably seasonal) component and residuals were adjusted for autocorrelation using ARIMA models [6]. Cross correlations between the time trends of the residuals from the smoothed series for the two diseases were then calculated.

### Season and age variation

Reported cases of RSV and meningococcal diseases cases in the five winters (weeks 42–15) were ranked and compared by rank correlation [7]. The age distribution of cases was compared in summer (weeks 16–41) and winter.

## RESULTS

### Time trends

The rise in RSV infections preceded the rise in meningococcal disease in all winters, but the intervals between the rise and fall of the two diseases was not consistent (Figs 2–6) Cross correlation between the time series was highest when RSV preceded meningococcal disease by an interval of 1–4 weeks (Fig. 7). After removal of the seasonal component, the analysis of residuals did not show any statistically significant correlation at any time lag between numbers of RSV and meningococcal cases. Using CDSC date of specimen data for meningococcal cases instead of MRU data did not change this result.

### Season and age variation

There was no evidence that more cases of meningococcal disease occurred in winters with more cases of RSV (Table 1). The rank correlation was negative (−0·6) although this was not statistically significant ($P = 0{\cdot}15$). During the period of analysis 97·3% (46895/48180) of RSV cases occurred during the winter months compared with 65·0% (4305/6619) of meningococcal cases. Where age was stated, 87·1% (39716/45575) of RSV isolates were from children < 1 year compared to 23·7% (1506/6350) for meningococcal disease. The proportion of reported cases of meningococcal disease in infants did not differ significantly between winter and summer (23·1% *vs.* 24·9% respectively, $P = 0{\cdot}11$).

## DISCUSSION

Most viral respiratory tract infections peak in the winter months [8] as does meningococcal disease, so that temporal associations may be due to independent external factors. In contrast to the evidence for a causal link between influenza and meningococcal disease [2–4], the evidence from this study does not support the hypothesis that RSV predisposes to meningococcal disease.

This descriptive epidemiological study cannot exclude the possibility of some effect of RSV on meningococcal disease, especially as the seasonal rise

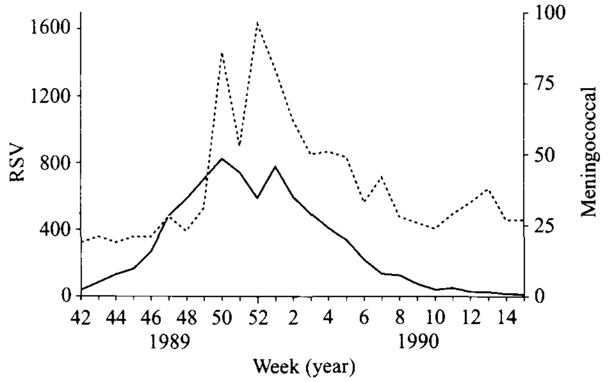


**Fig. 2.** Incidence of RSV and meningococcal disease 1989/90: ——, RSV; ······, meningococcal disease.

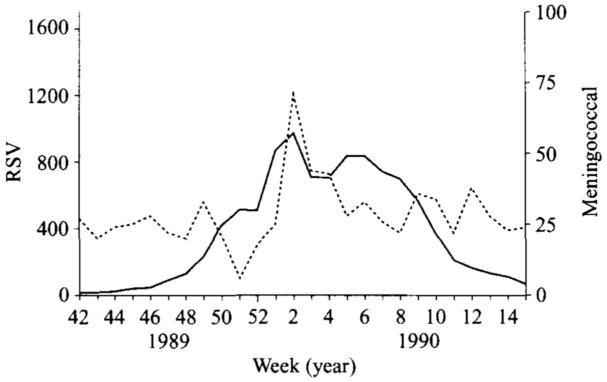


**Fig. 5.** Incidence of RSV and meningococcal disease 1992/93: ——, RSV; ······, meningococcal disease.

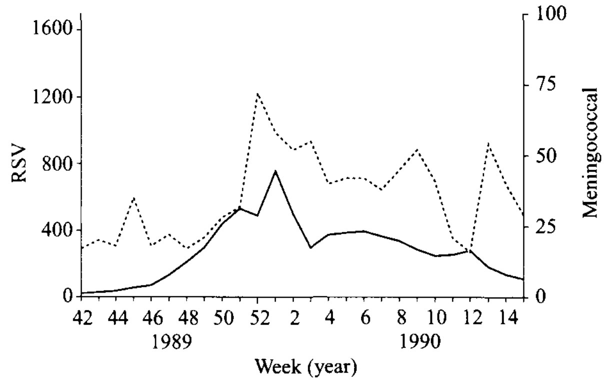


**Fig. 3.** Incidence of RSV and meningococcal disease 1990/91: ——, RSV; ······, meningococcal disease.

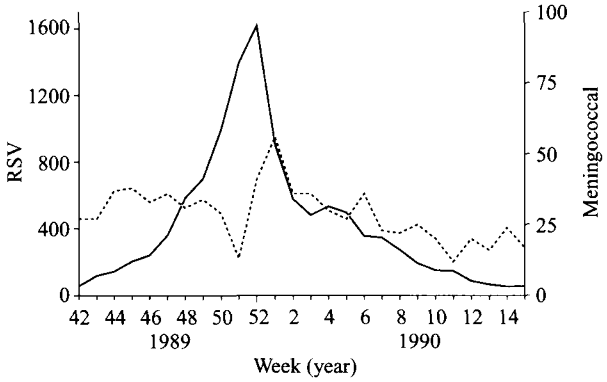


**Fig. 6.** Incidence of RSV and meningococcal disease 1993/94: ——, RSV; ······, meningococcal disease.

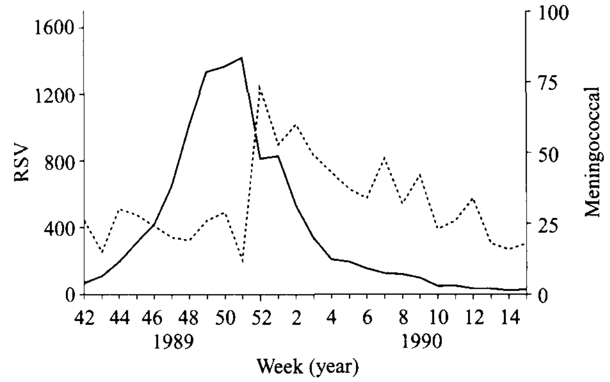


**Fig. 4.** Incidence of RSV and meningococcal disease 1991/92: ——, RSV, ······, meningococcal disease.

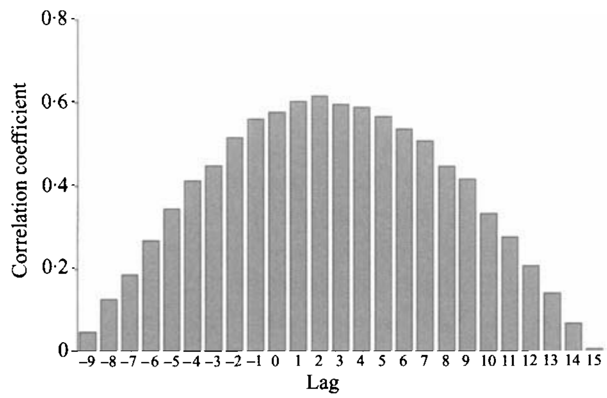


**Fig. 7.** Cross correlation function (CCF). RSV versus meningococcal disease mid 1989 to mid 1994.

in RSV preceded the rise in meningococcal disease each year. However, the interval between the rise and fall of the two diseases was inconsistent, there was no correlation between winters with proportionally more cases of RSV and winters with proportionally more cases of meningococcal disease, and analysis of time series after removal of the seasonal component did not show any association. Analysis of time series for influenza and meningococcal disease has shown a statistically significant association using the same methodology (J. Watson, personal communication). Ideally an analytical study (e.g. case control study) should be conducted, as in one investigation of the association between influenza and meningococcal

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Table 1. *Comparison of reported RSV and meningococcal case numbers in England and Wales in the winters from 1989/90 to 1993/94*

| | RSV | | | Meningococcal disease | | |
|---|---|---|---|---|---|---|
| Winter | Number | Percent | Rank | Number | Percent | Rank |
| 89/90 | 7957 | 16·9 | 4 | 1031 | 23·6 | 1 |
| 90/91 | 7114 | 15·2 | 5 | 925 | 21·6 | 2 |
| 91/92 | 10556 | 22·5 | 2 | 834 | 19·5 | 3 |
| 92/93 | 10111 | 21·6 | 3 | 760 | 17·7 | 4 |
| 93/94 | 11157 | 23·8 | 1 | 755 | 17·6 | 5 |
| Total | 46895 | 100 | — | 4305 | 100 | — |

disease [2]. However, RSV can only be isolated transiently during the acute phase of illness, and current serological tests cannot reliably distinguish recent from past infection (P. Openshaw, personal communication), so that it would not be possible to determine recent RSV infection with accuracy in cases of meningococcal disease or their controls.

Reported RSV disease predominantly affected infants. An increased proportion of meningococcal disease among infants was not observed during the winter months when 97% of RSV disease occurred. However, unrecognized RSV infection is frequent in older children and adults at the same time as disease is apparent in the young [9], so that an age shift would not necessarily be expected if RSV infection increased susceptibility to meningococcal disease.

Viral infection may predispose meningococcal disease by lowering of immunity, damaging pharyngeal defences or increasing rates of meningococcal transmission [2]. There is considerable body of evidence to show that influenza lowers immunity [10]; no similar evidence exists for RSV although the effects of RSV on immune function are not yet fully known [10, 11]. Viral pharyngitis may increase vulnerability to meningococcal invasion [1]. However, the main clinical features of RSV infection in children are of lower respiratory tract disease, commonly bronchiolitis or pneumonia [12], and RSV infection in adults is usually dominated by nasal congestion and cough; sore throat and pharyngeal injection are uncommon [13]. Viral respiratory tract infections could increase transmission of meningococci through coughing. Cough is an important feature of RSV illness in older children and young adults who are likely to have high meningococcal carriage rates [14]. If increased prevalence of coughing leads to increased meningococcal acquisition rates, a rise in RSV disease should be accompanied by a coincident rise in the incidence of meningococcal disease. We found no evidence for such an effect. Perhaps surprisingly, coughing may not be an important factor in increasing meningococcal transmission rates; other studies have shown that meningococcal carriage and acquisition rates are not increased during seasons when respiratory tract infections are common [15, 16].

RSV infection probably has less effect than influenza on immune suppression and damage to pharyngeal defences, the two most likely mechanisms by which influenza predisposes to meningococcal disease. The role of other viral infections in the epidemiology of meningococcal disease needs further clarification.

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