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Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990

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SUMMARY

The effects of influenza A and B and RSV on mortality in England and Wales were assessed by regression analysis for the period 1975–90. Morbidity data from sentinel practices were used to calculate 4-weekly rates of aggregated upper respiratory tract infections (URTI); PHLS laboratory reports were used as indices of infection, and 4-weekly death rates from all causes, excluding childbirths, were used to study relationships with mortality. Deaths correlated strongly with influenza A and B reports, temperature, and interactions between aggregated URTI and temperature, and RSV outbreaks and temperature. Estimates of 'seasonal' 4-weekly mortality associated with URTI were made by substituting into primary regression models the mean of annual trough consultation rates for aggregated URTI and baseline values for RSV and influenza. Peak 4-weekly mortality associated with URTIs was estimated at *c.* 24000 and *c.* 28000 during combined influenza and RSV epidemics of 1975–6 and 1989–90 respectively. Secondary regression analysis was carried out with the estimated 'seasonal' 4-weekly deaths associated with URTI as dependant variable and laboratory data as regressors. Estimated excess mortality associated with influenza was considerable even during years without major epidemics. Overall during the 15 winters the estimated mortality associated with RSV was 60–80% more than that associated with influenza. The modelling permits only a crude estimate of RSV associated mortality. None the less it suggests that RSV is an important cause of winter mortality.

INTRODUCTION

Since the earliest days of death registrations there have been relatively more deaths in winter than during the rest of the year. In the Registrar General's Report in 1841 it was noted that the number of deaths in London rose when the temperature at night fell below freezing, and rose more markedly when the mean day and night temperature dropped below 0 °C. The rise in mortality was immediate but the effects continued over a 30–40 day period after the extreme cold had passed.

Besides the decrease in temperature, the winter months see increased viral respiratory infections including respiratory syncytial virus and influenza A and B. In 1847 William Farr [1] estimated the impact of 'influenza' in London by subtracting the number of deaths recorded in an 'influenza-free' winter from the number recorded during an epidemic. Influenza was associated with increased numbers of deaths, not only from the infection itself but also from other conditions. Subsequent observations have confirmed associations between influenza and excess deaths from cerebrovascular disease, diabetes and respiratory diseases [2–5], but the contribution of influenza to these deaths is often not recognized in individuals when they die. A further problem in assessing the impact of influenza is that it often occurs concurrently with RSV and other respiratory viruses. Moreover there has been a secular reduction in death rates, and

the severity of winter, as measured by ambient temperature varies from year to year.

Although the disease burden of RSV is concentrated in infants and young children, several severe outbreaks have been noted in elderly patients in hospitals and nursing homes, suggesting that RSV may be a more frequent cause of respiratory illness and pneumonia among the elderly than hitherto recognized. One outbreak in a psychogeriatric hospital in the English West Midlands affected 17 of 40 (42·5%) residents, of whom 1 gradually deteriorated and died 1 month later [6]. Two of 24 patients in a psychogeriatric unit died during an outbreak reported to the PHLS Communicable Disease Surveillance Centre, and in a geriatric hospital 15 patients were affected, 8 of whom died [7]. In a fourth outbreak in Devon at least 20 of 50 (40%) residents of an old peoples' home were affected and 4 patients died within a week of onset of illness [8].

In Missouri, USA, an outbreak in a nursing home affected 15 of 77 (19%) residents, 7 of whom (47%) developed pneumonia [9]. In Rochester, New York, Mathur and colleagues [10] investigated 71 cases of upper respiratory illness in institutionalized elderly people during a community outbreak of RSV and influenza A Texas/77 infections; 7 of 32 patients with an aetiologic diagnosis had RSV, 24 had influenza, and 1 had both. A comparison of the clinical features revealed no significant differences in the respiratory or systemic signs and symptoms, except coryza which was commoner with RSV. None of the patients died, but 2 of those with RSV infection developed pneumonia. Morales and coworkers [11] reported 12 RSV infections with 2 deaths among 159 respiratory episodes during a 6-month study of respiratory infections in geriatric wards in Edinburgh, and Sorvillo and colleagues [12] describe an outbreak in a Los Angeles County nursing home in which 40 of 101 (40%) residents were affected, 22 (55%) of whom had pneumonia and 8 (20%) died.

Nicholson and colleagues [13] identified 9 RSV infections among 179 respiratory infections in residential homes in Leicester, U.K. Three of the 9 infections were associated with lower respiratory tract complications and 2 other patients died on days 5 and 8 of illness coinciding with RSV in the home. RSV infections occurred at the same time as influenza, rhinovirus, coronavirus and adenovirus infections, and the episodes caused by these viruses were clinically indistinguishable. Overall RSV was implicated in 9 of 41 (22%) infections for which a pathogen was identified, but represented only 5% of the total infections. In Rochester, New York, nursing homes, 13 of 126 people (*c.* 10%) had serological evidence of RSV infection [14]. In four studies involving the elderly in homes or hospitals to which RSV and influenza serology were undertaken the ratio of influenza to RSV infection was 3:1 [10, 11, 13, 14].

Besides affecting the young and frail elderly RSV is found in healthy adults and the ambulant elderly. In Tecumseh, Monto and Carvallaro [15] found that more than 20% of the RSV isolations were made from adults. In adults overall there were twice as many influenza A and B infections as RSV infections. In the United Kingdom data are collected weekly on mortality, GP consultations and virus isolates. Using these data this paper reports the use of multiple linear regression to explore the possibility that RSV, like influenza, is associated with excess mortality.

SOURCE OF DATA AND METHODS

Death registrations

Four-weekly registrations of deaths in England and Wales from all causes for the years 1975–90 inclusive were obtained from weekly reports published by the Office of Population Censuses and Surveys (OPCS). The weekly registrations for weeks ending on Fridays were converted into 4-weekly death rates per 100000 population using OPCS population statistics. The mortality statistics relate to death registrations rather than the actual occurrence of deaths, but as there is seldom a delay of more than 2–3 days between these events, the distinction between the weekly numbers of occurrences and registrations can usually be ignored [16]. However, this is not the case at times of public holidays, when the numbers registered in a particular week may fall considerably short of the numbers actually occurring.

Acute upper respiratory tract infections

OPCS data on the rates of 'epidemic influenza', 'influenza-like illness', 'sore throat and tonsillitis', 'colds', and 'laryngitis and tracheitis' were collected by the Birmingham Unit of the Royal College of General Practitioners (RCGP) and are based on returns from 40–62 practices throughout England and Wales covering a population of 200000 to 445000. These practices record and index all new illnesses as they occur and report every week to the Birmingham Research Unit where they are analysed to provide

incidence data presented as new episodes per 100000 individuals. The monitoring system operates with no imposed diagnostic criteria and without laboratory backup. The necessity of practitioners to assign a diagnostic label to all new episodes prevents selective exclusion of episodes in which the diagnosis is less certain.

Laboratory surveillance

Laboratory reports of influenza A, B, *Mycoplasma pneumoniae*, and RSV, by week ending on Friday, were obtained from the PHLS Communicable Disease Reports.

Analysis

Data for the 15 winters from 1975–6 to 1989–90 were studied by simple and multiple regression analysis. The data were aggregated for 4-weekly periods since the multiple regression method is not suitable for monitoring activity from week to week. The method depends upon elimination of serial correlation from the residuals, which would not be possible if weekly data were used. As in previous models [17–19], 4-weekly periods were chosen as the shortest intervals suitable for this method. The variables used in the primary analyses were as follows.

Mortality data used as dependent variable

y_1 = total 4-weekly deaths/100000, all causes excluding stillbirths.

Regressor variables

Each of the following were significantly associated with y_1 deaths/100000, in a simple regression analysis and the most significant variables were entered into a forward stepwise regression to select a model.

Clinical data

x_1 = RCGP consultation rate for clinical 'epidemic influenza',

x_2 = RCGP consultation rate for clinical 'influenza-like illness',

x_3 = RCGP consultation rate for 'sore-throat and tonsillitis',

x_4 = RCGP consultation rate for 'colds',

x_5 = RCGP consultation rate for 'laryngitis and tracheitis',

$x_6 = x_1 + x_2$,

$x_7 = \log_{10}(x_1 + x_2)$,

$x_8 = x_1 + x_2 + x_3 + x_4 + x_5$ (consultation rate for aggregated acute upper respiratory tract infections).

Variables to describe long-term trend

x_9 = Year (1975 = 0, 1976 = 1, etc.),

x_{10} = Month number: 4-weekly periods from January 1975 through December 1990 were numbered consecutively.

Laboratory data

x_{11} = 4-weekly influenza A reports,

x_{12} = 4-weekly influenza B reports,

x_{13} = 4-weekly influenza A + B reports,

x_{14} = 4-weekly RSV reports,

x_{15} = 4-weekly RSV reports as a percentage of the total for the 'winter'. Because of increasing numbers of RSV reports during the study period, analysis was focused on the timing rather than the absolute number of isolations by converting the number of reports for each 4-weekly period during each winter, i.e., during the last 26 weeks of one calendar year and the first 26 weeks of the next, to a percentage of the total for the period. This conversion eliminated from the analysis any differences in the numbers of virus isolations that resulted from improved diagnosis, increased awareness, or the number of reporting laboratories during the study,

$x_{16} = \log_{10} x_{15}$ Since $\log_{10}$ transformation of zero is infinity, 'zero' was calculated as 0·03, which is equal to the lowest percentage value for RSV during the study period,

x_{17} = Four-weekly mycoplasma reports.

Temperature recordings

x_{18} = Mean 4-weekly temperature (°F) recorded at London Heathrow Airport.

Interactions

$x_{19} = x_7 \div x_{18}$, the interaction between consultation rates for aggregated acute upper respiratory tract infections and mean 4-weekly temperature,

$x_{20} = x_8 \div x_{18}$, the interaction between consultation rates for aggregated acute upper respiratory tract infections and mean 4-weekly temperature (°F),

$x_{21} = x_{16} \div x_{18}$, the interaction between $\log_{10}$ trans-

formed 4-weekly RSV reports as a percentage of the 'winter' total and mean 4-weekly temperature (°F).

Dummy variables to described seasonal pattern

x_{22} = 1 for observations in weeks 41–44, otherwise 0,
x_{23} = 1 for observations in weeks 45–48, otherwise 0,
x_{24} = 1 for observations in weeks 49–52, otherwise 0,
x_{25} = 1 for observations in weeks 1–4, otherwise 0,
x_{26} = 1 for observations in weeks 5–8, otherwise 0,
x_{27} = 1 for observations in weeks 9–12, otherwise 0.
Weeks 13–40 inclusive are uniquely defined by $x_{22} = x_{23} = x_{24} = x_{25} = x_{26} = x_{27} = 0$. The six dummy variables were forced into relevant regression equations to described seasonal pattern.

Predicted excess deaths used as dependent variable

To estimate expected mortality in the absence of seasonal acute upper respiratory tract infections including RSV and influenza, the mean of the lowest RCGP consultation rates for aggregated acute upper respiratory tract infections for each of the 16 years under study was employed as a baseline value in the regression equations identified above. There were only isolated reports of influenza during the baseline periods so the virological variable influenza A and B was excluded from analysis. The regressor variable for RSV in the modelling involved an interaction between temperature and $\log_{10}$ transformed RSV%. Accordingly 'zero' RSV% was calculated as 0·03 (which was the lowest 4-weekly percentage value for RSV during the study) for $\log_{10}$ transformation of baseline RSV. The other variables were left at their observed values. An expected number of deaths, in the absence of seasonal acute upper respiratory tract infections including RSV and influenza, was then identified using the primary regression model and subtracted from the observed number of deaths for each 4-weekly period to provide an estimated excess related to seasonal acute 'upper' respiratory tract infections.

y_2 = 4-weekly estimated excess deaths related to seasonal acute upper respiratory tract infections including RSV and influenza and possibly other pathogens.

Regressor variables

Each of the following were significantly associated with y_2, estimated excess deaths related to seasonal acute upper respiratory tract infections, by simple regression analysis and were used in the secondary regression analysis to estimate the contribution of influenza, RSV, and *Mycoplasma pneumoniae* to the estimated excess mortality.

Laboratory data

x_{11} = 4-weekly influenza A reports,
x_{12} = 4-weekly influenza B reports,
x_{13} = 4-weekly influenza A + B reports,
x_{15} = 4-weekly RSV reports as a percentage of the total for the 'winter',
x_{17} = 4-weekly mycoplasma reports.

RESULTS

Inspection of the raw data revealed temporal associations between 4-weekly peaks of mortality and peak reporting of influenza A and B and RSV. Peak influenza and A and B reporting occurred mostly 1 or 2 months after peak mortality (Fig. 1*a*), and peak RSV reporting occurred mostly concurrently with peak mortality, or 1 month later (Fig. 1*b*). The mean 4-weekly temperature troughs either coincided with the peaks of mortality or occurred 4 weeks later (Fig. 1*c*). The virological peaks and temperature troughs shifted slightly from year to year and also varied in amplitude. Inspection of the raw data did not reveal a predominant relationship between influenza, RSV, or temperature with mortality. Accordingly their relationship with mortality was examined further by regression analysis.

Table 1 shows the results of separately regressing y_1 total 4-weekly deaths/100000 on each of the variables subsequently selected by forward stepwise regression into the models. As outlined in the Methods, in addition to the explanatory variables in Table 1, other variables were significantly associated with mortality by simple regression analysis. Table 1 shows that the interaction between temperature and aggregated consultation rates for acute respiratory infections accounted for 84·6% of the total variance in y_1 total 4-weekly deaths per 100000. The mean 4-weekly temperature (°F), and the interaction between $\log_{10}$ 4-weekly RSV reports expressed as a percentage of the winter total and mean 4-weekly temperature (°F), both accounted for ~ 68% of the variance. Both RSV and influenza A and B reports were significantly ($P < 0·001$) associated with mortality, but the R^2 values of 0·55 for RSV%, and 0·36 for influenza A and B, indicate that much of the variability in death rates can not be explained by these pathogens alone.

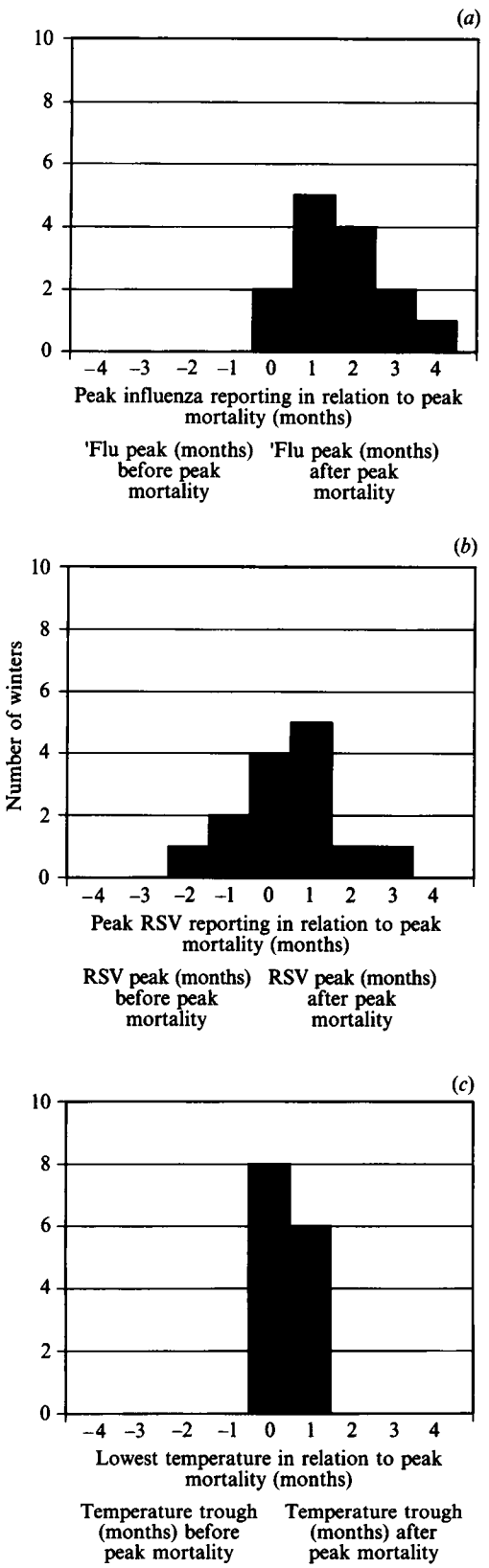

Fig. 1 (*a–c*). Relationship between annual 4-weekly periods with highest mortality with: (*a*) annual peak 4-weekly reporting of influenza A and B, (*b*) annual peak 4-weekly reporting of RSV, and (*c*) the annual 4-weekly period with the lowest mean temperature. At months labelled 'zero', peak influenza and RSV reports and trough temperatures coincide with peak 4-weekly mortality.

Figure 2*a* shows that the death rates increase approximately 20% for a decrease in temperature of 20 °F (6·7 °C). The R^2 value for this regression was 0·69, but at temperature above 50 °F there was less variation in death rate (coefficient of variation = 4·85) than at lower temperatures (coefficient of variation = 9·63), suggesting that seasonal factors other than temperature are relevant. Two models, one with and one without dummy variables, were developed to examine the possibility that during regular winter epidemics of RSV, excess deaths due to RSV could be accounted for in part by dummy variables which describe seasonal pattern. One included the six variables describing seasonal pattern, and both included consultation rates, virological data, and the variables x_{10} describing long-term trend.

Primary regression without forced variables

The regression model for y_1, 4-weekly deaths/100000 as the dependent variable included x_{10}, the 4-weekly period numbered consecutively (Fig. 2*b*); x_{13}, PHLS influenza A and B reports (Fig. 2*c*); x_{18}, mean 4-weekly temperature (°F) (Fig. 2*a*); x_{20}, RCGP consultation rates for aggregated acute upper respiratory tract infections ÷ temperature (°F) (Fig. 2*d*); and x_{21}, the interaction between $\log_{10}$ 4-weekly RSV reports as a percentage of the 'winter' total ÷ mean 4-weekly temperature (°F) (Fig. 2*e*). Table 2 shows the regression coefficients, standard errors, *t*, and *P*-values for the explanatory variables selected into the model as estimated by multiple regression analysis. The PHLS reports for influenza A and B, and the interactions between $\log_{10}$ RSV% and temperature, and aggregated acute upper respiratory infections and temperature were significant at least the 0·001% level. The variable x_{10}, describing long-term trend, and x_{18}, temperature (°F), were also selected into the model, but had lower *p*-values. Correlation of y_1 4-weekly deaths/100000, with the variables selected into the model was strong with an *F*-value of 284·1 with 181 + 5 D.F. and a S.E. of 3·75. The square of the multiple correlation coefficient (R^2), which measures the proportion of variation in y_1 explained by the regression equation, i.e., the fit between the observed mortality and that predicted by the regression equation, was 88·7%, and the Durbin–Watson statistic was 1·94.

Table 1. *Explanatory variables selected into the primary multiple regression models, showing regression coefficients, standard error,* P *and* R^2 *values for simple regression of* y_1, *total 4-weekly deaths/100000, all causes excluding stillbirths*

Explanatory variable	Regression coefficient	S.E.	*P*	R^2
x_{10}, 4-weekly number	−0·0297	0·0126	0·019	0·029
x_{13}, PHLS influenza A + B reports	0·0255	0·0025	< 0·001	0·3589
x_{18}, Mean 4-weekly temperature (°F)	−0·9828	0·0485	< 0·001	0·6880
x_{20}, RCGP consultation rates for aggregated acute respiratory infections ÷ temperature (°F)	2·5633	0·0800	< 0·001	0·8465
x_{21}, $\log_{10}$ RSV% ÷ temperature (°F)	524·2058	26·3343	< 0·001	0·6817

To estimate expected mortality in the absence of influenza and RSV the mean of the lowest RCGP consultation rates for aggregated acute upper respiratory infections during the 16-year period was employed as baseline value in the regression equation; the variable influenza A + B was excluded from analysis; 'zero' RSV% was calculated as 0·03 (which was the lowest percentage value for RSV during the study) for $\log_{10}$ transformation of baseline RSV; and the other variables were left at observed values. The difference between the 4-weekly estimates and observed mortality was taken as the 4-weekly excess mortality associated with acute upper respiratory infections, including influenza and RSV. Figure 3*a* shows the actual weekly death registrations (upper plot) and the estimated 4-weekly excess mortality associated with respiratory infections (lower plot). The validity of the modelling is indicated by Fig. 3*a* which shows that peak 4-weekly death registrations during epidemics in 1989–90 (67082 registered deaths), 1975–6 (63758 deaths), 1985–5 (56409), and 1977–8 (55636) were closely associated with peak predicted excess mortality related to acute upper respiratory infections of 28441 for 1989–90, 24335 for 1975–6, 16179 for 1985–6, and 15980 for 1977–8. The shape of the 4-weekly plots of observed mortality and predicted excess mortality related to acute upper respiratory infections illness in Fig. 3*a* are similar, suggesting that much of the variation in winter mortality is accounted for by respiratory infections and their interaction with temperature.

Primary regression with forced variables

The regression model included the six forced variables describing seasonal pattern ($x_{22} - x_{27}$ inclusive) regardless of the significance of the individual variables (Table 2). Only two of the seasonal variables (for weeks 45–48, and 1–4) achieved statistical significance. Correlation of y_1 4-weekly deaths/100000 with x_{10} (the variable describing long-term trend), x_{13} influenza A and B reports, x_{18} (temperature, °F), and x_{20} and x_{21} (interactions between temperature and consultation rates for aggregated upper respiratory tract infections and RSV reports) was again strong with an F-value of 169·9 with 175 + 11 D.F. and S.E. of 3·32. The square of the correlation coefficient (R^2) was 91·4%, and the Durbin–Watson statistic was 1·92.

As in the model without forced variables the validity of the modelling is indicated by Fig. 3*b* which shows that the peak 4-weekly mortality during epidemics in 1989–90 (67082 registered deaths), 1975–6 (63758), 1985–6 (56409), and 1977–8 (55636) (upper plots) were closely associated with peak predicted excess mortality related to acute upper respiratory infections of 27262 for 1989–90, 24104 for 1975–6, 15104 for 1985–6, and 15487 for 1977–8 (lower plots). As before the shape of the weekly plots for observed mortality and predicted excess mortality related to 'influenzal' illness (Fig. 3*b*) are similar.

Secondary regression to estimate the number of deaths caused by influenza and RSV

Simple regression of x_{13} (4-weekly influenza A and B reports) and x_{15} (4-weekly RSV reports expressed as a percentage of the 'winter' total) revealed an association between deaths and laboratory reports for these viruses. The multiple regression modelling (Table 2) further shows that y_1 4-weekly deaths/100000 are influenced significantly by consultation rates for aggregated acute upper respiratory infections, temperature and a secular trend, thus precluding the use of models in Table 2 to estimate mortality due to RSV and influenza. An estimate of the mortality caused by these viruses can be obtained from the regression of y_2, the 4-weekly estimated excess deaths

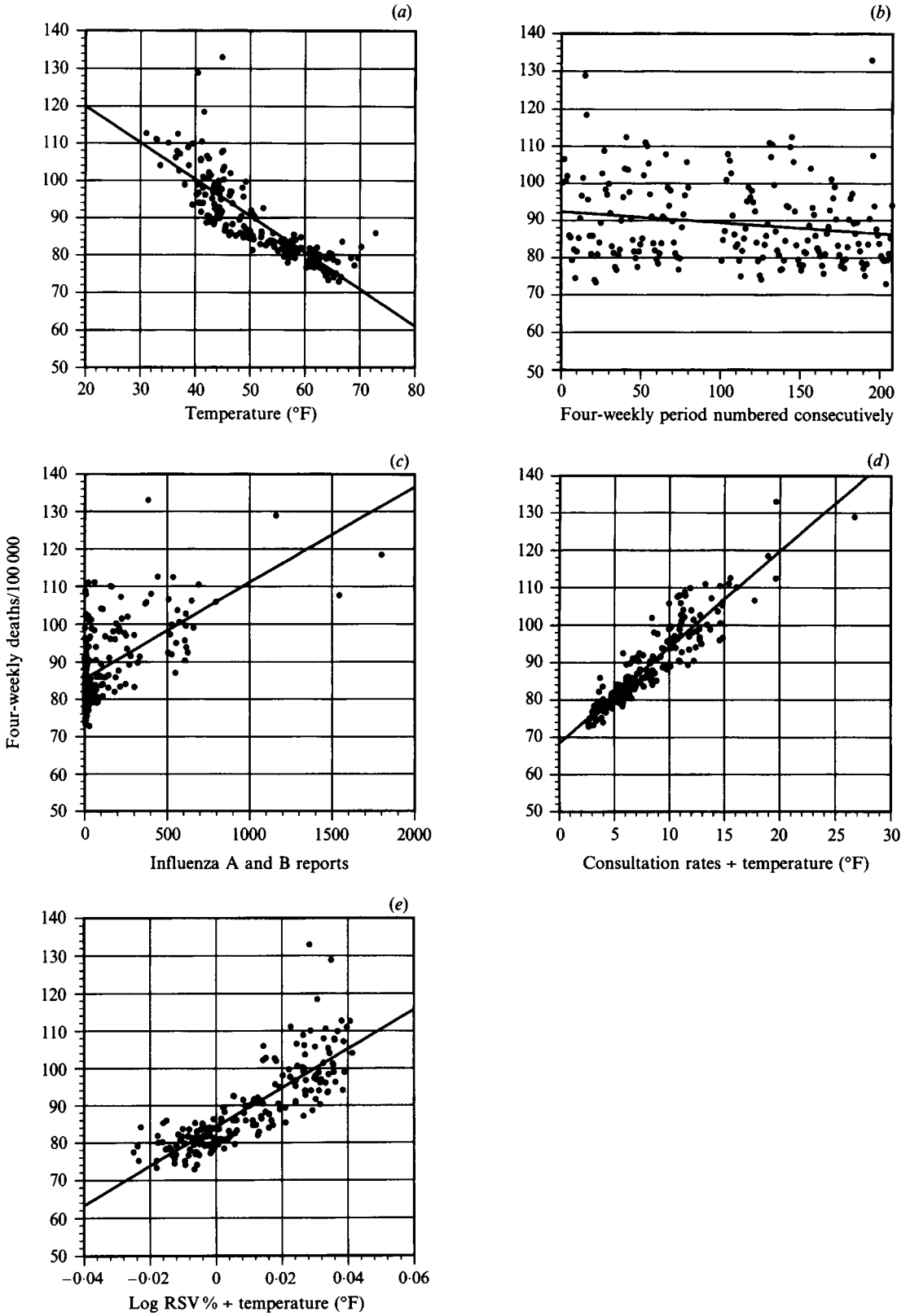

Fig. 2(*a–e*). Simple regression of y_1, total 4-weekly deaths/100000, all causes excluding stillbirths, in England and Wales with: (*a*) x_{18}, weekly mean temperature (°F) recorded at London, Heathrow, (*b*) x_{10}, 4-weekly period numbered consecutively, (*c*) x_{13}, influenza A and B reports combined, (*d*) $x_{20} = x_8 \div x_{18}$, the interaction between consultation rates for aggregated acute upper respiratory tract infections and mean weekly temperature, (*e*) $x_{21} = x_{16} \div x_{18}$, the interaction between $\log_{10}$ transformed 4-weekly RSV reports as a percentage of the total for the 'winter' and mean 4-weekly temperature (°F).

Table 2. *Multiple regression models of* y_1, *total 4-weekly deaths/100000, all causes excluding stillbirths, showing the regression coefficients* S.E. *error,* t *and* P*-values*

Explanatory variable*	Regression coefficient	S.E.	*t*	*P*
Model excluding variables describing seasonal pattern				
Constant	83·5139	4·4196	18·8961	< 0·001
x_{10}, 4-weekly number	−0·0118	0·0045	−2·6084	0·01
x_{13}, PHLS influenza A + B reports	0·0070	0·0013	5·3691	< 0·001
x_{18}, Mean 4-weekly temperature (°F)	−0·1509	0·0675	−2·2358	0·027
x_{20}, RCGP consultation rates for aggregated acute respiratory infections ÷ temperature (°F)	1·5368	0·1554	9·8919	< 0·001
x_{21}, $\log_{10}$ RSV % ÷ temperature (°F)	126·53	32·6162	3·8794	< 0·001
Model including variables describing seasonal pattern				
Constant	84·4323	4·2070	20·0696	< 0·001
x_{10}, 4-weekly number	−0·0090	0·0041	−2·2059	0·029
x_{13}, PHLS influenza A + B reports	0·0062	0·0014	4·5220	< 0·001
x_{18}, Mean 4-weekly temperature (°F)	−0·1864	0·0650	−2·8674	0·005
x_{20}, RCGP consultation rates for aggregated acute respiratory infections ÷ temperature (°F)	1·7422	0·1586	10·9819	< 0·001
x_{21}, $\log_{10}$ RSV % ÷ temperature (°F)	69·9758	32·2391	2·1705	0·031
x_{22}, (weeks 41–44 = 1)	−1·8359	1·0181	−1·8033	0·073
x_{23}, (weeks 45–48 = 1)	−3·5599	1·1922	−2·9861	0·003
x_{24}, (weeks 49–52 = 1)	−0·4601	1·3862	−0·3319	0·740
x_{25}, (weeks 1–4 = 1)	4·7744	1·3681	3·4897	0·001
x_{26}, (weeks 5–8 = 1)	−2·3052	1·4756	−1·5622	0·120
x_{27}, (weeks 9–12 = 1)	−1·6900	1·2753	−1·3252	0·187

* See text, pp. 53–54.

related to seasonal acute upper respiratory infections with x_{13} (4-weekly influenza A and B reports) and x_{15} (4-weekly RSV reports expressed as a percentage of the 'winter' total). Although this has the disadvantage of deriving one estimate from another, the estimates for influenza related deaths can be compared to those obtained by other investigators using different methods.

Regression of y_2, the 4-weekly estimated excess deaths related to seasonal acute upper respiratory infections, was first carried out using estimated excess deaths related to these infections as derived from the modelling for y_1, but excluding the forced variables describing seasonal pattern. Table 3 shows the regression coefficients, S.E., *t*, and *P* values for the explanatory variables selected into the model. Correlation of y_2 with influenza A and B reports, 4-weekly RSV reports as a percentage of the 'winter' total, and *Mycoplasma pneumoniae* reports was strong with an *F*-value of 117·3 and 181 + 3 D.F.. The square of the correlation coefficient (R^2) was 66·0% indicating that two-thirds of the variation in y_2 was explained by the regression. Estimates of the winter excess mortality due to influenza A and B were made by multiplying the β-coefficient for influenza A and B with the total number of influenza A and B reports for each winter (Table 4). The model predicted a total of 207888 influenza A- and B-related deaths over 15 winters, the winters of 1975–6 and 1989–90 being especially severe with 29945 (±6882, 95% confidence limits) and 23278 (±5350) predicted deaths respectively. The model predicted 25573 (±4458) RSV-related excess deaths each winter. For the 15 years overall the modelling predicted *c.* 1·8 RSV related deaths for every one related to influenza. The model also revealed an association between *Mycoplasma pneumoniae* and mortality. During the 15-winter study period there were three *M. pneumoniae* epidemics. Plotting the number of laboratory reports of mycoplasma over time did not reveal a secular trend in reporting, in contrast to RSV. The epidemic curve of the first epidemic was similar to those occurring later. For this first epidemic the model predicted *c.* 24885 mycoplasma-related deaths over four years, but the 95% confidence limits were wide (±24218) and the *P*-value was low.

Regression of y_2, the four-weekly estimated excess deaths related to seasonal acute upper respiratory

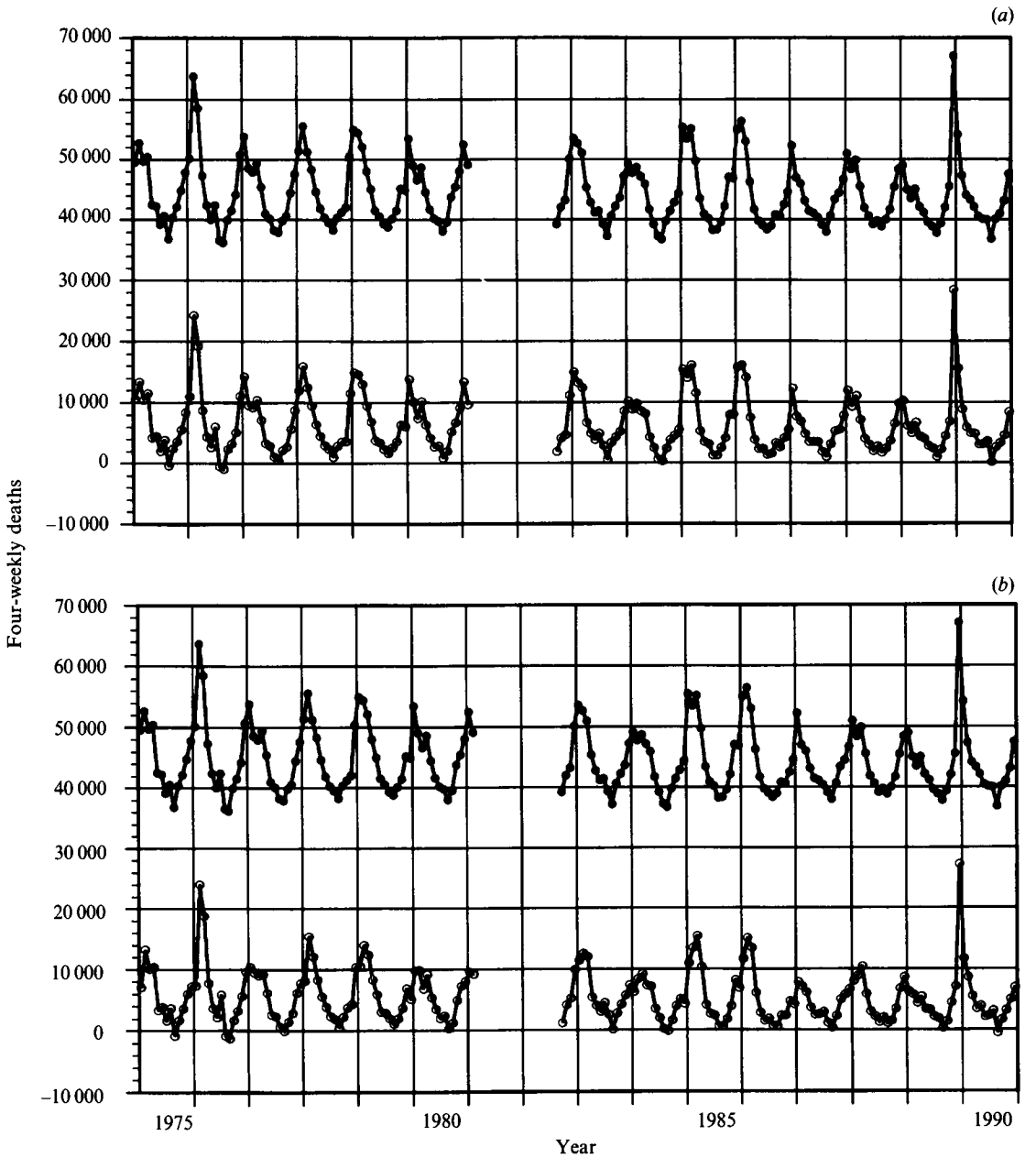

Fig. 3(*a–b*). Four-weekly deaths and predicted mortality related to acute upper respiratory tract infections as estimated by multiple regression: (*a*) without dummy variables. Data for 1981–2 missing due to strike action by the Registrars of Births, Marriages and Deaths, (*b*) with dummy variables.

infections, was also carried out using estimated excess deaths related to these infections as derived from the modelling for y_1 including the forced variables describing seasonal pattern. Correlation of y_2 with influenza A and B reports and four-weekly RSV reports expressed as a percentage of the 'winter' total was similar to the previous model with an F-value of 147·1 and 184+2 D.F. The square of the correlation coefficient (R^2) was 61·5%. Estimates of the winter excess mortality due to influenza A and B were again made by multiplying the β-coefficient for influenza A and B with the total number for each winter (Table 4). The model predicted a total of 205813 influenza A- and B-related deaths over 15 winters, the winters of 1975–6 and 1989–90 being especially severe with 29646 (±6723, 95% confidence limits) and 23046 (±5226) predicted deaths respectively. This model also predicted 22022 (±4270) RSV-related excess deaths each winter. For the 15 years overall the modelling predicted *c.* 1·5 RSV related deaths for every one related to influenza. Using data derived from the model for y_1 with forced variables, forward

Table 3. *Multiple regression models of* y_2, *the weekly estimated excess deaths related to seasonal acute upper respiratory infections, showing the regression coefficients, standard error,* t *and* P-values

Explanatory variable	Regression coefficient	S.E.	*t*	*P*
Data for Y_2 *from primary model excluding variables describing seasonal pattern, no dummy variables in secondary regression*				
Constant	2745·2646	352·5838	7·7861	< 0·001
x_{13}, PHLS influenza A + B reports	7·3340	0·8600	8·5276	< 0·001
x_{15}, RSV %	255·7255	22·7455	11·2429	< 0·001
x_{17}, *M. pneumoniae*	6·0211	2·9896	2·0140	0·045
Data for Y_2 *from primary model including variables describing seasonal pattern, no dummy variables in secondary regression*				
Constant	2736·3645	258·2442	10·5960	< 0·001
x_{13}, PHLS influenza A + B reports	7·2608	0·8401	8·6428	< 0·001
x_{15}, RSV %	220·2158	21·7863	10·1080	< 0·001

Table 4. *Estimated number of excess deaths associated with influenza A and B for the winters of 1975/6 to 1989/90*

Winter	Influenza A + B identifications	Estimated no. of influenza-related deaths (95% confidence limits; from secondary regression only)	
		No dummy variables in primary regression	Dummy variables in primary regression
1975/76	4083	29945 (±6882)	29646 (±6723)
1976/77	1574	11544 (±2653)	11428 (±2592)
1977/78	1523	11170 (±2567)	11058 (±2508)
1978/79	1097	8045 (±1849)	7965 (±1806)
1979/80	780	5720 (±1315)	5663 (±1284)
1980/81	1105	8104 (±1863)	8023 (±1819)
1981/82	2413	17697 (±4067)	17520 (±3973)
1982/83	2202	16149 (±3712)	15988 (±3626)
1983/84	1591	11668 (±2682)	11552 (±2620)
1984/85	2315	16978 (±3902)	16809 (±3812)
1985/86	2355	17272 (±3969)	17099 (±3878)
1986/87	860	6307 (±1450)	6244 (±1416)
1987/88	1894	13890 (±3192)	13752 (±3119)
1988/89	1380	10121 (±2326)	10020 (±2272)
1989/90	3174	23278 (±5350)	23046 (±5226)

stepwise modelling for y_2 failed to selected *Mycoplasma pneumoniae* into the model.

DISCUSSION

Estimates of mortality associated with influenza have been made previously by subtracting from the number of deaths in an 'influenza winter' those in one or more adjacent winters, or by use of multiple regression statistical methods. The first approach provides an assessment of mortality which fails to consider the severity of winter, secular trends in mortality, or the effect of other viruses such as RSV. Moreover influenza surveillance has demonstrated the regular appearance of influenza A virus of both H1N1 and H3N2 subtypes and influenza B [20]. Hence assessments of excess mortality during an influenza epidemic will be underestimated when compared to mortality during an adjacent year. Theoretically the multiple regression method can circumvent problems such as the severity of winter, secular trends in mortality and co-circulation of RSV and influenza, and it has been used with various regressor variables to calculate the impact of influenza on mortality in the United Kingdom [16–18, 21, 22], United States [23] and Holland [24].

Until recently RSV was considered to cause little adult morbidity and the association between RSV outbreaks and excess winter mortality attracted little attention. RSV outbreaks occur each winter and although the outbreak week and week of peak activity of RSV vary somewhat from year to year, estimates of RSV-associated mortality from comparisons of years 'with' and 'without' RSV are not feasible. In 1990 Anderson and colleagues [25] revealed a strong correlation between RSV isolations in the United States with peaks of national respiratory deaths of infants and young children. Recently Fleming and Cross [26] compared consultation rates for acute respiratory disease, death registrations and the timing of influenza and RSV isolations in England and Wales from 1989/90 through 1992/3. Fleming and Cross were unable to quantify influenza and RSV-associated mortality, nonetheless they concluded that RSV is as important as influenza virus in causing morbidity and excess mortality among elderly people.

In this study I used multiple regression models to examined further the relationship between mortality and outbreaks of RSV and influenza. As in studies of influenza mortality, I included RCGP consultation rates, ambient temperature, dummy variables to described seasonal pattern, and a variable to describe long-term trend [17, 21, 22]. The greater than ninefold increase in RSV laboratory reports from 1975 through 1990 suggested that the increase was related more to improved awareness and diagnosis of RSV than to increasingly large epidemics. Accordingly the regressor variable for RSV focused on the timing of RSV rather than the absolute number of RSV reports and, as generally seems to occur in the United States [27], the model assumes that the magnitude of RSV outbreaks remains constant.

In contrast, influenza epidemics are known to vary in timing and magnitude. The peaks of mortality during 1975/6 and 1989/90 were followed by peak influenza laboratory confirmations and simple regression revealed a significant association between influenza A and B reports and weekly deaths per 100000. Laboratory reports of influenza have not been used in previous publications suggesting that they may provide a poor quantitative index of influenzal mortality. However, influenza and RSV are clinically indistinguishable in the elderly [10, 13] and inclusion of laboratory data is essential in modelling exercises which examine the relative impact of influenza and RSV. Both influenza A and B reports and the interaction between RSV and temperature were selected into the modelling ($P \leqslant 0{\cdot}001$) in addition to RCGP diagnostic indices, indicating that they are of value in estimating mortality.

The modelling in this report assumes that the laboratory reporting of influenza and *M. pneumoniae* reflects the prevalence of these pathogens rather than variations in awareness and diagnostic testing over time. It further assumes that the different influenza and RSV strains are equally pathogenic, and the consultation behaviour of the general population remained constant throughout the study. None of these assumptions are necessarily true and the data should therefore be interpreted appropriately. Despite these reservations the regression data confirm and extend previous observations.

In the multiple regression models described here, mortality was significantly associated with temperature, but temperature also influenced mortality through interactions with consultation rates for aggregated acute upper respiratory tract infections and RSV laboratory reports. Bull and Morton [28] established a relationship between temperature changes and pneumonia and bronchitis deaths. These investigators found the relationship to be more pronounced in the elderly, who succumbed more than 5 days after a temperature change. It is conjectural whether a temperature decrease affects immunity in the frail elderly or more readily facilitates virus transmission.

Using multiple regression Curwen and Devis [16] showed that each degree celsius by which a 17-week winter period is colder than the average was associated with about 8000 excess deaths as compared with the average for the summer and autumn. However, Curwen and Devis did not consider confounding illnesses and their possible interaction with temperature. In this study the modelling suggests that a change in temperature of 1 °C is associated with *c.* 3150 deaths over a 17-week period when the consultation rates and other variables remain constant. The difference between this estimate and the 8000 predicted by Curwen and Devis [16] raises the possibility that at least half of the normal winter excess mortality is related to 'upper' respiratory infections and their interaction with temperature, rather than hypothermia and the other effects of temperature.

The models presented here confirm the existence of a relationship between rates of aggregated acute upper respiratory infections and deaths [19]. The models also provide an estimate of deaths linked to acute

upper respiratory tract infections, which was used as the dependant variable in the secondary regression. The secondary regression has the drawback of deriving one estimate from another, thereby increasing the confidence limits, but there seems to be no other means of estimating RSV deaths and the influenza-related deaths can at least be compared with those identified in previous models. During the 1975–6 the models predicted *c.* 29600–29900 excess deaths associated with influenza, which is comparable to the 22300 deaths predicted by Tillett and colleagues [18]. Similarly for 1989–90 the models predicted *c.* 23000 influenza deaths which compares with 'over 20000' [5], 25185 [16], 26080 [22], 24877 [29], and 15000 [30] estimated by other investigators.

'Severe' influenza outbreaks, with mortality clearly in excess of that in adjacent years, occur infrequently. None the less the PHLS confirms the presence of influenza in the community each year, and it is to be expected that even the less severe outbreaks increase mortality. The data presented here support this view and predict a minimum of several thousand influenza deaths each winter.

In the elderly RSV can produce a 'flu-like syndrome indistinguishable from influenza and is known to cause a high incidence of pneumonia and death [6–14]. The estimates provided by the present analysis indicate that RSV gives rise to considerable mortality in England and Wales causing 60–80% more deaths than influenza, i.e., a predicted 22000–23000 deaths each winter. Although RSV outbreaks occur annually, inspection of the raw data revealed slight shifts in the time of appearance of RSV and peak virological reporting. The modelling included dummy variables describing the winter pattern of deaths, and with the regular winter epidemics of RSV it is conceivable that the dummy variables may describe part of the RSV excess mortality. To explore this possibility models with and without forced variables were developed and mortality predicted from both models were compared. The forced variables achieved statistical significance in two of the six 4-weekly periods and the number of deaths predicted by models with and without the dummy variables was virtually identical.

The modelling indicates that pathogens other than influenza A and B and RSV are involved in 'winter' excess mortality. *M. pneumoniae* just achieved statistical significance in models without dummy variables, but was no longer significant when the dummy variables were used in the modelling. Conceivably other respiratory pathogens, such as rhinoviruses and coronaviruses, cause deaths in the frail elderly, not only during the winter months but also during months of the year with the lowest consultation rates for acute upper respiratory tract infections.

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