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APPLICATION OF MULTIPLE TIME SERIES ANALYSIS TO THE ESTIMATION OF PNEUMONIA AND INFLUENZA MORTALITY BY AGE 1962–1983

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SUMMARY

We employed multiple time series analysis to estimate the impact of influenza on mortality in different age groups, using a procedure for updating estimates as current data become available from national mortality data collected from 1962 to 1983. We compared mortality estimates that resulted from a multivariate model for epidemic forecasting with those obtained from univariate models. We found more accurate prediction of deaths from all age groups using the multivariate model. While the univariate models show an adequate fit to the data, the multivariate model often enables earlier detection of epidemics. Additionally, the multivariate approach provides insight into relationships among different age groups at different points in time. For both models, the largest excess mortality due to pneumonia and influenza during influenza epidemics occurred among those 65 years of age and older. Although multiple time series models appear useful in epidemiologic analysis, the complexity of the modelling process may limit routine application.

KEY WORDS Forecasting Time series Multivariate analysis Pneumonia and influenza

INTRODUCTION

The method used by the Centers for Disease Control (CDC) to estimate excess mortality associated with influenza epidemics evolved from a 1935 study by Collins who defined the expected number of weekly deaths from pneumonia and influenza, or from all causes, as the median number of deaths for a given week during non-epidemic years.[1] Excess deaths from pneumonia and influenza, or from all causes, were defined as the difference between the observed and the conditional expected numbers, a one-period-ahead forecast based on some model. Because the number of deaths attributed to causes other than influenza and pneumonia also increases during epidemic periods, one measures the impact of an influenza epidemic on mortality by excess mortality due both to pneumonia and influenza and to all causes.[1–4]

In the 1960's, Serfling fitted a regression equation to the weekly pneumonia and influenza mortality data determined in a sample of U.S. cities to estimate the expected number of deaths.[2] Serfling deleted the deaths for past epidemic periods because epidemic activity was unpredictable, and, in a biological sense, exceptional. In addition, since the expected number of deaths presumes no epidemic, it is appropriate to estimate this number with data from previous non-epidemic periods. In 1979, CDC adopted a new method to estimate expected deaths with the fit of a seasonal autoregressive moving average model to all available data.[3–5] This method did not delete data from epidemic periods, but rather replaced them with the numbers of expected deaths had there

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been no epidemic. More recently, CDC has proposed a sinusoidal regression model to estimate expected mortality.[6]

Previous estimates of excess age-specific mortality associated with influenza have entailed separate estimates for each age group.[7,8] We introduce a new method to analyse influenza mortality data based on a multiple time-series model, an extension of previous applications of the univariate model. A time series is a sequence of data collected over time, for example, influenza deaths within a specific age group. Our model uses multiple series occurring simultaneously to forecast the expected numbers for each age group but, in addition, takes into account statistical associations among the different age groups that might explain differences in age-specific patterns.[9] For example, during periods when the expected number of deaths increases in the elderly, the number may decrease in young children. Use of the multiple time-series model enables the incorporation of this association into the forecast of expected numbers for these two component series.

In this investigation, we use an interative method for updating models. Modelling of influenza surveillance data is done in real time (that is, with new data arriving after a model has been accepted). Such models must be updated iteratively to incorporate the new data so as to account for resultant changes in the model form. This iterative process improves both the fit of the model and the forecast based on the model. Classical time series modelling strategies operate on the entire series at once and may validate the model by applying it to data other than that used for fitting. The iterative method we employ here, on the other hand, validates the model at each successive time period and may require model adaption at some time during the process.[3]

This investigation has three goals. First, we use national mortality data to construct a time series model for multiple age groups as well as separate univariate models to forecast deaths by age both for pneumonia and influenza and for all causes. Second, we compare these two approaches with regard to the fit of the model to the data. Third, we compare results from a multivariate model (with use of deaths from all age groups in the prediction) with a simpler univariate approach that looks only at past history of that age group. To this end, we compare periods of excess mortality as determined by the statistical model with epidemic periods defined epidemiologically, including morbidity indices and viral activity as well as mortality data.

METHODS

We derived multivariate and univariate models for influenza and all-causes mortality with use of monthly data for five age groups: less than 1 year (infants); 1–14 (children); 15–44 (young adults); 45–64 (adults); 65+ (elderly). For either the multivariate or the univariate models, the updating algorithm prescribes the following procedure. First, using an initial set of data, we fit a model. We accepted a model when it met two criteria:

1. All parameters in the model were significant. We assessed significance of individual parameters by use of a t statistic and a significance level less than 0·05.
2. We assessed fit using the autocorrelation and the partial autocorrelation functions, discussed below. If these functions were not significant, we accepted the model.

Second, we applied this model to the initial set of data to obtain a one-period-ahead forecast of mortality (called the conditional expectation) and upper and lower limits of a 95 per cent confidence interval for this forecast. For the multivariate case, we obtained the conditional expectation from a simultaneous forecast for the five age groups.[3,4] If the number of actual deaths exceeds the upper 95 per cent limit for the forecast, then we declare deaths to be in excess. A statistical excess period included any months with excess deaths. CDC defined an epidemic period

to include any months with reports of widespread influenza-like morbidity and marked increase in influenza virus isolates as reported to CDC (references available on request).

Next, we replaced data for a month with statistical excess in mortality by the upper 95 per cent confidence limit for the forecast. Generally, the method for dealing with extreme data points has been to delete them before fitting.[10,11] We adopt the method of replacement rather than deletion because the expected number of deaths presumes no epidemic and it is appropriate to estimate this number using data from previous non-epidemic periods. Choi and Thacker[3-5] showed that the replacement of the value with the conditional expectation both produced a model with better fit and achieved a more accurate forecast. We use the 95 per cent limit as the replacement value so that the model will produce more consistent forecasts. The conventional method of prefiltering the series to account for exceptional points is not appropriate or practical in this updating context, since addition of new data to the series could alter the form of the prefiltering function.

Statistical models for time series analysis

The multivariate model developed in this research is an extension of a univariate class of stochastic models called AutoRegressive Integrated Moving Average (ARIMA) models of Box and Jenkins.[12-14] The process of model fitting consists of identification, estimation, and diagnostic validation. One then evaluates competing models on the basis of the fit of the models to the observed data and the accuracy of the forecasts.

In regard to the identification of the model building process, we must first consider the integrated, autoregressive, and moving average components of time series modelling. Suppose that Y_t is the number of pneumonia and influenza deaths in month t. We define trend as any systematic change in the level of a time series. We can represent a time series without trend as

$$Y_t = b_0 + a_t. \tag{1}$$

The parameter b_0 is the average value or level of the process, and a_t is a random variable having zero expectation and a common variance with the property that at times t and t', a_t and $a_{t'}$ are statistically independent. (We need the assumption that a_t has a Gaussian distribution for tests of hypotheses regarding measures of association.)

The first step in an analysis of a time series is the removal of any trend present in the data, so that one can analyse other patterns of variation more easily. The *integrated* component of the ARIMA model removes the trend to create a stationary (that is, trendless) process. In this investigation, we modelled the trend and any non-monotonic drift in the data with difference equations.[14] A first order difference equation for the series Y_t is given by z_t, the difference between points in the series 1 unit apart, calculated as

$$z_t = Y_t - Y_{t-1}. \tag{2}$$

We may also write z_t as

$$z_t = (1 - B) Y_t \tag{3}$$

where we define B as the backward shift operator which yields the value of the data one time period back, that is,

$$B(Y_t) = Y_{t-1}. \tag{4}$$

Similarly, we can compute dth order differencing with

$$B^d(Y_t) = Y_{t-d}.$$

For a series evolving in time, the *autocorrelation* measures the relationship between two data

points that are a number, say k, time units apart in the same sense that a correlation coefficient measures a relationship between two variables at a single point in time. For a series Y_t the autocorrelation function (ACF), for each value of k greater than 0, is the ratio of the covariance of Y_t with Y_{t-k} to the variance of Y_t. For a given lag k (that is, unit of time difference), if Y_t equals Y_{t-k}, then the ACF = 1.

To remove the effect of seasonality, we select the ACF of various differenced series to approach zero fairly quickly. For non-seasonal data, first order differencing usually suffices. We then use the differenced data to model other components. We model seasonality, important in epidemiologic analyses, separately through differencing. Because over-differencing can result in biased estimates,[14] we use the smallest appropriate value of the difference. In subsequent discussions, we assume that one applies methods to the suitably differenced series z_t.

An *autoregressive model of length p* reflects the characteristic that the number of deaths in month t, Y_t, depends to some extent on the numbers of deaths in the p previous months (that is, Y_{t-1}, $Y_{t-2}, \cdots, Y_{t-p}$). We write this model as

$$Y_t = \phi_1 Y_{t-1} + \phi_2 Y_{t-2} + \cdots + \phi_p Y_{t-p} + a_t \tag{5}$$

where ϕ_t are the weights assigned to the p most recent past values of the series, referred to as the partial autoregressive coefficients (PARC), and a_t is a random disturbance. Although not required by this definition, frequently, the weights assigned to the previous months' number of pneumonia and influenza deaths decrease with time from month t. This is an appropriate assumption for epidemiologic modelling, since influenza activity is more closely related to biologically more similar strains that had been circulating in the previous season and less to biologically less similar strains that had circulated in earlier years.[15] Alternatively, we might use the backward shift operator defined in equation (4) and write

$$(1 - \phi_1 B - \phi_2 B^2 - \cdots - \phi_p B^p) Y_t = a_t. \tag{6}$$

The *moving average* component of the ARIMA model characterizes forces with a finite persistence of length q, that is

$$Y_t = (1 - \theta_1 B - \theta_2 B^2 - \cdots - \theta_q B^q) a_t. \tag{7}$$

where θ_t are weights applied to residuals from previous months to adjust for errors in earlier forecasts. This models a situation where the random disturbance enters the system at time $t-q$ and persists until time t, when it leaves the system. One might use this to model response to an influenza strain that persists for a limited time in the population before its replacement by a different strain.

The processes described separately above may occur jointly in real data. For example, influenza activity has components of seasonality (repeated increase of deaths in winter months), long-term trend (number of deaths systematically decreases over time, on average), autoregression (the number of deaths in a given month relates to the numbers of deaths in previous months), and moving average (finite persistence of specific strains of influenza). Hence, we can describe their combined effect as an ARIMA (p, d, q) process in which three effects occur jointly. Here p represents the number of preceeding months that affects the current month's value, d is the lag in the differencing operation to eliminate trend and stabilize variance (achieve stationarity), and q is the number of terms included in the moving average.

In addition to the ACF, we use another identification statistic, the partial autocorrelation function (PACF), to distinguish models. The lag $-k$ PACF measures the dependence between the value of the series at time t and time $t-k$, with adjustment for intermediate values at $t-1$, $t-2, \cdots, t-k$. This adjustment is analogous to the control for confounders in other types of

epidemiologic analyses; that is, this gives the relationship between deaths at month t and deaths at month $t-k$, with values at intermediate months held constant. The lag$-k$ PACF is the correlation between the PARC's.

Data sources

We obtained monthly mortality data on all deaths as well as deaths due to pneumonia and influenza from the National Center for Health Statistics (NCHS) for the 20-year period 1962–1983. We defined deaths due to pneumonia and influenza as those with influenza or pneumonia recorded as the underlying cause on death certificates with use of ICD7-ICD9 codes where appropriate. We stratified deaths into five age groups: under 1 year; 1–14 years; 15–44 years; 45–64 years; and 65 years or older. We obtained population data (mid-year estimates) from the U.S. Bureau of the Census.[16,17]

Building the univariate model

For each age group, we used the following procedure to fit a univariate model to the series (3). We smoothed the starting series of 36 months with use of sinusoidal smoothing:

$$Y_t = C_1 \sin\frac{2\pi t}{N} + C_2 \sin\frac{4\pi t}{N} + d_1 \cos\frac{2\pi t}{N} + d_2 \cos\frac{4\pi t}{N} \tag{8}$$

where Y_t is the number of pneumonia and influenza deaths in month t, and N is the number of data points (for example, 11 in the first application of the model). We used this model for initial data entry into the ARIMA model until sufficient data were avialable for the ARIMA approach. We performed the initial smoothing with 36, 48, and 72 months of data, with no change in the ARIMA results.

Then, we replaced the pneumonia and influenza deaths for the excess months by the expected pneumonia and influenza deaths forecast from the smoothed series. We made the replaced series stationary by differencing:

$$z_t = Y_t - Y_{t-d}. \tag{9}$$

We fit autoregressive, moving average terms to the stationary series,

$$\phi(B)z_t = c + \theta(B)a_t, \tag{10}$$

where z_t is an observation of the stationary time series at time t, c is a constant to be determined from the data, the random disturbance $[a_t]$ is defined above (see equation (1)), and

$$\phi(B) = 1 - \phi_1 B - \cdots - \phi_p B^p \tag{11}$$

and

$$\theta(B) = 1 - \theta_1 B - \cdots - \theta_q B^q \tag{12}$$

are polynomials in the backshift operator B. One can replace either $\phi(B)$ or $\theta(B)$ by polynomial factors (for example, $\phi(B) = \phi_1(B)\phi_2(B) \cdots \phi_k(B)$). In each instance, we added parameters to the model as long as all parameters were significant. We assessed significance by use of a t statistic and significance probability less than 0·05.

We assessed model fit by a process called diagnostic checking that uses the residuals from the fitted model (residual = data − model). Residuals from an appropriate model should have values for ACF, PACF, and PARCs that do not differ significantly from zero, with standard error constant over the range of the analysis. We altered the model form at the point in time at which residuals indicated lack of fit. Changing model form is an indication that the correction needed to

achieve stationarity in the series has changed (that is, the order of the appropriate differencing operation is different). Consideration of different model forms is recommended for sufficiently long time series.[18] This is one method to account for a perturbation to the system at equilibrium, such as the introduction into the population of a new drift variant.

After we established the adequacy of the models by examination of the residuals, we used the series to forecast the data and compared actual data with the forecast value to compute a percentage error for each month. For our data, estimation variability in the parameters did not affect the forecasts.[19]

Multivariate models

The multiple time series model, also called the *transfer function*, considers the series for the five age groups simultaneously, and the relationships among the age groups appear in cross-correlation matrices produced for the final model. We discuss two types of correlation. First, a simple sample correlation matrix disregards any time association and shows merely the correlation among five series of data. Second, a more complete picture of the correlations among the series takes into account correlations between different series at different time points. We use a *cross-correlation function* (CCF) to identify between-series correlation in the same way that the ACF identifies within-series correlation. The CCF describes the relationships among the series at various lags of time. For example, for a lag of one month, the cross correlation function is a 5×5 matrix, the i,jth entry of which is the correlation between series i at time t and series j at time $t-1$. As for univariate modelling, we first made each series stationary with use of appropriate differencing. Statistically significant spikes in the CCF identify appropriate lags for the multiple model. For example, if the CCF is significant for data values k months apart, we include a term for k months back in the model. Finally, we fit an ARIMA model to the noise component, the residuals from the transfer function on the differenced series. To optimize fit, the model residuals must be consistent with white noise and independent of the component time series. We assessed forecast accuracy in the same manner as with the univariate approach.

Excess mortality

We defined a statistical period of excess when the observed number of deaths for one month exceeded the 95 per cent confidence limit based on the forecast from the model. We called a period that shows a statistical excess a 'false positive' or pseudoepidemic if there was no epidemiologic confirmation. We called a period a 'false negative' if the statistical model failed to show an excess when there was epidemiologic confirmation of epidemic influenza.

RESULTS

Pneumonia and influenza models

The models that resulted for each age group appear below. If we altered the model form in the process of fitting the entire series, we give the date for each series that the model was changed. If not so specified, the model form remained the same throughout.

Univariate models

Less than 1-year-olds

$$(1-\phi_1 B)(1-\phi_{12} B^{12})\, Y_t = \text{noise}.$$

1 to 14-year-olds

$$(1-\phi_{12}B^{12})Y_t=(1-\theta_1 B)(1-\theta_{12}B^{12})\,\text{noise}.$$

15 to 44-year-olds

$$(1-\phi_{12}B^{12})Y_t=(1-\theta_1 B-\theta_{12}B^{12})\,\text{noise}.$$

45 to 64-year-olds

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t=\text{noise}.$$

65-year-olds and over

$$(1-\phi_{12}B^{12})Y_t=\text{noise}.$$

Total of all ages

(1/62 – 12/67):

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t=c+\text{noise}$$

(1/68 – 12/83):

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t=\text{noise}.$$

The model for infants and adults implies that pneumonia and influenza deaths in these age groups are related for periods of 1, 12, and 13 months apart (since $(1-\phi_1 B)(1-\phi_{12}B^{12})=1-\phi_1 B-\phi_{12}B^{12}+\phi_1\phi_{12}B^{13}$, a linear comibination of these previous time periods). The series for the elderly shows a relationship for 12 months apart, only. For ages 1–14, residuals from 1, 12, and 13 months back appear in the forecast for the current month; for ages 15–44, residuals from 1 and 12 months prior appear.

Multivariate model

(1/62 – 12/71)

$$(1-\phi_1 B-\phi_{12}B^{12})Y_t=\text{noise}$$

(1/72 – 12/83)

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t=\text{noise}.$$

For the pneumonia and influenza data, the highest simple correlation is between the age groups 15–44 and 45–64 (correlation of 0·7). The group over 65 shows correlations between 0·3 and 0·7 with all age groups except the infants. The cross-correlations for the multiple series for the pneumonia and influenza data suggest that the series for the infants leads the elderly by 6 months; the young adults series leads the adults by 2 months. The data for children follow the three older age groups by 9 and 15 months.

Models for all causes

Unlike the pneumonia and influenza models, all univariate series for all-causes deaths produced the same final model. Also, unlike the pneumonia and influenza case, the multivariate model for all-causes deaths did not change in the process of fitting. (Details of the all-causes models appear in the Appendix.)

For the all-causes data, the highest simple correlation is between the age groups 45–64 and over 65 (correlation of 0·8). The group over 65 shows little correlation with other age groups. The

Table I. Residuals from the final age-specific models used to forecast expected deaths from pneumonia and influenza and from all causes, United States, 1968–1983

Age group (years)	Residuals: Univariate Mean (st. dev.)	Residuals: Multivariate Mean (st. dev.)
A. Deaths attributed to pneumonia and influenza		
less than 1	−2·5 (60·2)	2·0 (59·6)
1–14	1·8 (20·7)	0·7 (23·0)
15–44	−6·6 (62·2)	−0·1 (28·7)
45–64	−1·6 (73·2)	−0·8 (66·1)
65+	−0·5 (522·1)	7·2 (317·0)
Total	−7·6 (532·5)	na
B. Deaths attributed to all causes		
less than 1	* (143·6)	−10·1 (147·3)
1–14	* (101·0)	1·5 (97·2)
15–44	* (403·5)	24·1 (349·2)
45–64	* (873·1)	7·9 (759·3)
65+	* (3386·3)	222·4 (2939·0)
Total	* (5765·3)	na

* |Mean| < 0·001
na: not applicable

groups 15–44 and 1–14 are slightly correlated (correlation of 0·4). The cross-correlations indicate that the children lead the young adults with positive correlation at lag 9 months, and are led by the elderly series with a negative correlation at lag 12 months. Mortality in the 45–64 group leads the elderly with negative correlation at a lag of two months.

Model fit

None of the series shows residuals (from either the univariate or the multivariate models) with mean significantly different from zero, the mean of a white noise process (Table I). The residuals from the multivariate model for pneumonia and influenza mortality generally show more variability than do those for the univariate model (with the exception of the 1–14 age group) and have larger mean values. For all-causes models, on the other hand, the multivariate models have less variability than the univariate for all series except the less than one-year-olds, but the mean values for the multivariate models remain substantially higher than those for the univariate approach. The univariate modelling of all-causes data produces generally smaller and less variable errors than does the univariate modelling for pneumonia and influenza (Table II). The accuracy of the forecast as measured by per cent error increases with age, a reflection of increasing numbers in the groups (data not shown).

Excess mortality

The highest rates of excess mortality attributed to pneumonia and influenza occur in each age group during the 1968–69 pandemic year, except among the elderly (Table III). The highest rate of excess mortality in the elderly occurred during the 1975–76 epidemic year associated with the

Table II. Percentage error of forecasting of pneumonia and influenza and for all-causes mortality using alternative time series models, United States, 163 months, 1968–1983

	Percentile of Distribution for:			
	Univariate		Multivariate	
Percentage error*	Pneumonia and influenza	All-causes	Pneumonia and influenza	All-causes
−30	5	0	5	0
−20	12	0	13	0
−10	32	2	35	0
0	60	49	67	43
10	76	95	70	99
20	85	100	81	100
30	90	100	95	100

* Percentage error = [(actual-forecast)/actual] × 100.

A/Victoria (H3N2) strain (51·9/100,000); the rate in the elderly during the 1968–69 pandemic was slightly lower (44·2/100,000). We observed a steady increase in excess mortality with increasing age.

There were fewer periods of excess mortality observed for all-causes deaths during the study period (Table IV). No excess mortality occurred with infants for either the univariate or the multivariate model. The 1968–69 pandemic year included the highest rates of excess mortality in middle-aged adults, but was only the second highest rate in the elderly. For those over 65 years of age, the largest excess mortality occurred in 1980–81 when the A/Texas (H3N2) and A/Bangkok (H3N2) strains predominated.

The multivariate model generally forecasts a lower epidemic threshold than does the univariate approach and gives a larger estimate of excess mortality (Tables III and IV). This is reflected by more epidemic periods identified statistically by the multivariate model than confirmed epidemiologically.

Both A/H3N2 and B virus circulated in 1970–71. No months exceeded the Serfling epidemic threshold, but three months exceeded the Serfling forecast for at least three consecutive weeks.[20] The 1973–74 and 1981–82 seasons showed significant influenza B activity. Weekly CDC surveillance information collected from 121 U.S. cities for both of these years showed pneumonia and influenza mortality consistently above the forecast but below the epidemic threshold.[21,22] A more sensitive epidemiologic definition by Serfling (that is, a lower epidemic threshold) could have found these periods epidemic. An epidemic of pneumonia and influenza mortality was not detected epidemiologically for January 1977. Influenza B viral activity at that time was associated with mortality elevated above the Serfling forecast for this month as well but below the epidemic threshold.[23] The excess mortality in 1980 which occurred for the all-causes models for two summer months coincided with a severe heat wave that year.[24]

Based on a forecast from the multivariate model, an excess occurred in 1978–79 for pneumonia and influenza. The A/Brazil (H1N1) virus caused elevated morbidity for two weeks in January but no elevation in mortality.[25] This seems to be the only indisputable false positive that results from these models.

The multivariate model tends to detect excess pneumonia and influenza mortality one month earlier than does the epidemiologic criterion. For deaths attributed to all causes, the multivariate

Table III. Excess mortality attributed to pneumonia and influenza during influenza epidemics, United States, 1968 1983 rate per 100,000 (number of excess deaths)

		Period of excess mortality (lab isolates for morbidity and mortality)									
		12/68–3/69	12/69–2/70	1/72–2/72	12/72–2/73	1/75–3/75	2/76–4/76	1/78–2/78	2/80–3/80	12/80–2/81	2/83–4/83
Age (years)	Subtype:	A/HK/(H3N2)	A/HK/(H3N2)	A/Eng/(H3N2)	A/Eng/(H3N2) A/PorC/(H3N2)	A/Vic/(H3N2)	A/Vict/(H3N2)	A/USSR/(H1N1) A/Braz/(H1N1)	B/HK	A/Bank/(H3N2)	A/Chile/(H1N1)
<1	univ	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
	mult	0·2	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
1–14	univ	0·5 (256)	0·0	0·0	0·1 (62)	0·0	0·0	0·0	0·0	0·0	0·0
	mult	0·5 (285)	0·0	0·0	0·1 (73)	0·0	0·0	0·0	0·0	0·0	0·0
15–44	univ	0·0	0·0	0·0	0·4 (389)	0·0	0·0	0·0	0·0	0·0	0·0
	mult	1·4 (1142)	0·6 (505)	0·0	0·6 (500)	0·4 (329)	0·4 (373)	0·2 (156)	0·0	0·2 (204)	0·0
45–64	univ	10·9 (4512)	4·2 (1742)	4·9 (2109)	4·8 (2054)	2·7 (1190)	2·8 (1236)	2·1 (914)	1·2 (515)	1·6 (707)	0·0
	mult	11·2 (4653)	4·6 (1931)	0·5 (205)	4·6 (1981)	2·6 (1135)	2·7 (1185)	1·4 (613)	0·0	1·5 (674)	0·0
65+	univ	34·0 (6686)	12·4 (2495)	0·0	0·0	24·5 (5557)	45·8 (10655)	30·3 (7420)	0·0	18·2 (4783)	0·0
	mult	44·2 (8704)	12·0 (2418)	4·8 (998)	30·2 (6504)	24·7 (5613)	51·9 (12082)	30·4 (7439)	16·2 (4166)	20·4 (5350)	11·2 (3060)
All ages	univ	6·9 (13871)	2·8 (5788)	4·2 (8694)	3·8 (8044)	2·6 (5530)	5·6 (12225)	3·2 (7013)	1·9 (4422)	2·5 (5672)	0·7 (1685)
	mult*	7·3 (14784)	2·4 (4854)	0·6 (1203)	4·3 (9058)	3·3 (7077)	6·3 (13640)	3·7 (8208)	1·8 (4166)	2·7 (6228)	11·2 (3060)

* Sum of multivariate excesses over all age groups

Table IV. Excess mortality attributed to all causes during influenza epidemics, United States, 1968 1983 rate per 100,000 (numer of excess deaths)

		Period of excess mortality (lab isolates for morbidity and mortality)									
		12/68–3/69	12/69–2/70	1/72–2/72	12/72–2/73	1/75–3/75	2/76–4/76	1/78–2/78	2/80–3/80	12/80–2/81	2/83–4/83
Age (years)	Subtype:	A/HK/(H3N2)	A/HK/(H3N2)	A/Eng/(H3N2)	A/Eng/(H3N2) A/PrtC/(H3N2)	A/Vic/(H3N2)	A/Vict/(H3N2)	A/USSR/(H1N1) A/Braz/(H1N1)	B/HK	A/Bank/(H3N2)	A/Chile/(H1N1)
<1	univ	0·00	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
	mult	13·54 (462)	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
1–14	univ	0·00	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
	mult	0·52 (283)	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·5 (254)	2·8 (1344)
15–44	univ	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
	mult	3·24 (2660)	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·9 (959)	0·0
45–64	univ	29·9 (12398)	18·9 (7939)	10·4 (4461)	7·4 (3208)	5·2 (2280)	12·0 (5281)	9·0 (3990)	4·8 (2157)	0·0	0·0
	mult	33·6 (13898)	22·4 (9420)	20·6 (8854)	10·5 (4535)	4·5 (1975)	11·9 (5245)	9·9 (4374)	4·3 (1921)	12·3 (5451)	0·0
65+	univ	0·0	0·0	52·4 (11003)	45·4 (9774)	39·0 (8860)	146·1 (34004)	72·7 (17811)	90·2 (23184)	139·7 (36680)	0·0
	mult	132·5 (26077)	62·8 (12637)	129·0 (27111)	87·4 (18802)	41·8 (9492)	112·4 (26167)	88·1 (21596)	79·0 (20319)	146·2 (38399)	59·8 (16406)
All ages	univ	23·3 (46904)	0·0	10·6 (22227)	0·0	1·3 (2913)	18·9 (41163)	13·0 (28790)	0·0	19·7 (45143)	0·0
	mult*	21·5 (43380)	10·8 (22057)	17·2 (35965)	11·0 (23337)	5·3 (11467)	14·4 (31412)	11·7 (25970)	9·8 (22240)	19·1 (43850)	7·0 (16406)

* Sum of multivariate excesses over all age groups

excess is early for the 1–14 age group, and the univariate excess is early for the 15–44 age group; all other models yield results consistent with the epidemiologic definition.

DISCUSSION

Excess mortality conveys a message that people are dying at a rate greater than expected. In practice, however, this excess is an estimated quantity based on a series of assumptions. First, we assume that we can estimate an expected rate of death, yet no single method for forecasting influenza mortality has gained universal acceptance. Second, we assume the validity of the epidemic threshold, yet this is an arbitrary choice which the investigator can raise or lower. Third, we assume that the data used to make that forecast as well as those included in the observed mortality are valid, despite the acknowledged limitations, of death certificate data.[26,27,28] Nevertheless, since the time of William Farr, epidemiologists have found excess mortality statistics valuable in the assessment of the timing and impact of fatal epidemic diseases, especially influenza.[29]

Examination of excess mortality attributed to influenza by age group enables one to assess the relative impact of various subtypes and strains on different age groups. For example, the absence of excess mortality among children and young adults during the influenza B epidemic in 1979–80 is inconsistent with the higher attack rate in these groups for the B subtype.[30] One possible explanation, however, is a lower case-fatality rate in younger persons compared to the elderly, reflecting the increased susceptibility of elderly persons to fatal complications of influenza infection. The relatively low mortality rate in 1979–80 among the elderly, on the other hand, is consistent with a lower attack rate (or less severe disease) in those over 65 years of age.[30] Comparison of age-specific morbidity and mortality data from population-based studies could address these hypotheses.

An important advantage of a multivariate model is the ability to measure correlations among the mortality experiences of different age groups. While these may be statistical artifacts without epidemiologic interpretation, such findings could lead to the recognition of previously unsuspected biologic phenomena. In this study, for example, we noted several statistically significant, although small, correlations among age groups. The relatively high simple correlation between young adults and middle-aged adults for pneumonia and influenza and that between middle-aged adults and the elderly for all causes mortality suggest the possibility of increased transmission between persons in the correlated age groups or a relationship between susceptibility to fatal disease among the age groups. We can explore either hypothesis more directly with use of morbidity and laboratory data. Also, these correlations may be sensitive to the age groups for which the data were collected. Consequently, one should use these correlations only to stimulate new hypotheses about the epidemiology of influenza.

The comparison of modelling methods in this report suggests guidelines for the use of time series in epidemiologic forecasting. The choice between the use of univariate and the multivariate models depends on the intended use of the analysis. The multivariate approach offers the advantages of insight into the relationships among component series and a more sensitive and timely detection of epidemics. The primary disadvantage of the multivariate approach is its difficulty of use. Computer packages to implement multiple time series analysis are not available widely and require a significant investment of time to use. In addition, one must interpret the results from the multivariate model carefully at each stage of the iterative model fitting process.

In its application to influenza mortality data, multiple time series models appear to have potential use in generating hypotheses regarding the relationships among individuals in different age groups. Similar research for other time series (for example, geographic) also could prove

fruitful. Multivariate time series models also give more accurate forecasts of observed data that could provide precise estimation of the impact of influenza. The complexity of the modelling process, however, makes the use of these models for continuous surveillance less attractive.

Before one can recommend the general implementation of multiple time series modelling, further research is needed. Particularly, the observation that the multivariate forecast is generally lower than that of the univariate approach needs mathematical treatment. In general, application of multiple time series models to other epidemiologic problems should prove useful, particularly when more easily used software programs develop as a result.

APPENDIX: MODELS FOR ALL-CAUSES MORTALITY

With analysis of the ACF's of the five age series for the deaths from all causes, we detected non-stationarity. We differenced each series once, which eliminated trend and reduced the series to white noise. Each series contained an AR(12) coefficient to incorporate information from the 12 previous months in the forecasts. The month for which the model changed and the models that resulted for each age group appear below.

Univariate models

Less than 1-year-olds

(1/62 – 12/73)

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t = c + \text{noise}$$

(1/74 – 12/83)

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t = c + \text{noise.}$$

1 to 14-year-olds

(1/62 – 12/78)

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t = c + \text{noise}$$

(1/79 – 12/83)

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t = c + \text{noise.}$$

15 to 44-year-olds

(1/62 – 12/69)

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t = c + \text{noise}$$

(1/70 – 12/83)

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t = c + \text{noise.}$$

45 to 64-year-olds

(1/62 – 12/80)

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t = c + \text{noise}$$

(1/81 – 12/83)

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t = c + \text{noise.}$$

65-year-olds and over

$(1/62-12/70)$

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t=c+\text{noise}$$

$(1/71-12/83)$

$$(1-\phi_1 B-\phi_2 B^2)(1-\phi_{12}B^{12})Y_t=c+\text{noise}.$$

Total of all ages

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t=c+\text{noise}.$$

Multivariate model

$$(1-\phi_1 B)(1-\phi_{12}B^{12})Y_t=\text{noise}.$$

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