Epidemic influenza in Greater London

By C. C. SPICER and C. J. LAWRENCE

Department of Mathematical Statistics and Operational Research,
University of Exeter, Streatham Court, Rennes Drive,
Exeter, EX4 4PU

SUMMARY

The Kermack & McKendrick theory of epidemics has been applied to data on deaths from influenza and influenzal pneumonia in Greater London in the years 1950–78. As a whole the theory gives a good description of the data, and the estimated values of the parameters can be plausibly related to the natural history of the disease. However, the possibility exists that the agreement is merely empirical, and field studies would be required to confirm its validity.

INTRODUCTION

The use of mathematical methods in the U.S.S.R by Baroyan, Rvachev and others (1971, 1977) as an aid to the control of influenza epidemics has led to a reconsideration of the classical formulation proposed by Kermack & McKendrick (1927). This model of the epidemic process is in essence so simple that its applicability to real epidemics seems unlikely. However, in the U.S.S.R. it has been claimed to give a useful approximation not only to individual epidemics in single cities but also to the spread of influenza through the Soviet Union. The present study is an extension of a previous one (Spicer, 1979) which suggested that the model was applicable to influenza epidemics in England and Wales. The specification of the model used here differs from that used previously in assuming that the values of the parameters are independent of time, and is based on continuous not finite difference methods.

A recent symposium organized by the Sandoz Institute was devoted to the applicability of mathematical models to influenza epidemics. The proceedings volume from this symposium (Selby, 1982) contains an excellent critical review of the history and theory of the subject by P. M. Fine.

MATERIALS AND METHODS

The basic equations for the progress of an epidemic in a fixed population put forward by Kermack & McKendrick (1927) take the following form: Let N = total population, S = susceptibles, I = infected and infectious cases, R = those removed from the infected state, $N = R + S + I$. Then the equations are

$$dS/dt = -\lambda IS, \tag{1}$$

$$dI/dt = \lambda IS - \beta I, \tag{2}$$

$$dR/dt = \beta I, \tag{3}$$

where λ is a parameter representing the rate per unit time at which susceptibles are producing infectious cases. β is the rate at which infectious cases are being removed by recovery or death.

A considerable simplification is introduced by the fact that the infectious period of influenza is about 1 week, which makes it plausible to assume in equations (1)–(3) that both β and λ are independent of time and it is therefore possible to express the solution of the equations in parametric form (see Bailey, 1975) as follows:

$$\beta t = \int_0^\phi \frac{dw}{1 - w - \dfrac{S_0}{N} \exp\left(-\dfrac{\lambda N}{\beta} w\right)}, \tag{4}$$

where S_0 is the initial number of susceptibles and the ratio β/λ has the nature of a threshold population, N_T, below which a progressive epidemic will not occur since $dI/dt \leqslant 0$. The variable ϕ is the proportion of the total population which has been infected by time t.

In principle, if the total initially susceptible population is known (and hence $I_0 = N - S_0$, the initial inoculum of infected cases) and also the times t at which a given fraction of infected cases have occurred, the parameters λ and β can be determined by numerical integration.

In England and Wales the only directly observed quantity is the number of deaths from influenza and influenzal pneumonia that have occurred by time t, as given in the Registrar General's weekly returns and the OPCS monitor reports.

Where, as in the U.S.S.R., the new clinical cases are reported daily, there are fluctuations in the daily rate due to the reluctance of patients to report just before the weekend and a corresponding willingness to report just after, and other sociological factors. Use of the cumulative proportion of deaths avoids some of the problems that these difficulties raise.

If it is assumed that the cases are removed by death or recovery at constant, but differing, rates per unit time then we can add two further equations to the set (1)–(3):

$$\text{(alive)} \quad dA/dt = \alpha I, \tag{5}$$

$$\text{(dead)} \quad dD/dt = \mu I, \tag{6}$$

where $(\alpha + \mu) = \beta$ and $(A + D) = R$.

Since

$$\frac{dD}{dt} = \frac{\mu}{\beta} \cdot \frac{dR}{dt} \cdot D = \frac{\mu}{\beta} \cdot R \tag{7}$$

and equation (4) becomes

$$\beta t = \int_0^{\beta D/\mu} \frac{d(\beta D/\mu)}{1 - w - (S_0/N) e^{-(N/N_T) w}}, \tag{8}$$

where N_T, the threshold population, has been written for β/λ.

The original ϕ, which was the proportion of all cases of the disease to the total population at risk, has now been replaced by the ratio of dead to a related

parameter $N' = \mu N/\beta$. There are then four parameters to be estimated from the observed deaths: β, S_0/N, N/N_T and N'. This was done by using a standard optimizing program to minimize the squared differences between observed and expected values.

Fitting the cumulative deaths is somewhat suspect statistically owing to the correlations between the errors in successive values. As an alternative the cumulative curve of weekly deaths was smoothed using a cubic spline and the parameters estimated by fitting the derivatives of the spline to the expression

$$\frac{dR}{dt} = \beta\left(N - R - \frac{S_0}{N}\exp\left(-\frac{N}{N_T}R\right)\right)$$

and then using equation (4). Both these methods gave closely concordant results.

It was found that the fitting process needed to be started from the peak of the epidemic curve, as the denominator in the integral tends very rapidly to zero in the tails. There is an arbitrary element in choosing a point for the start and end of the epidemic, but variations of two weeks or so in the choice do not disturb the estimates by more than 5–10 % if the curve is fitted from an origin at the peak. The beginning and end of the epidemic were fixed after examining the weekly deaths from the beginning of November to the end of April.

The parameter (S_0/N) cannot be estimated with any precision if S_0 is nearly equal to N, since the denominator in equation (9) tends to zero and the numerical integration becomes impracticable. This occurs when there is a small initial number of cases, as is quite plausible in the present case. The parameter can be set at any value from 0·99 to 0·9999 without materially altering the estimates of the others.

A check on the methods of fitting was made using the generalized logistic curve (Nelder, 1961) with known parameters. This function gives a range of skewed sigmoid curves resembling the epidemic data, but has an explicit solution, so that results obtained by numerical integration can be checked against known values. Fitting this function via the integral introduced no serious bias into the estimates of the parameters.

RESULTS

The agreement between the observed and calculated results for the three main antigenic variants (see Table 1) can be judged from Figs. 1, 2 and 3. These show the relationship between the times at which the cumulative proportions of deaths were predicted and those at which they occurred, the origin being at the calculated peak and time scaled in units of $1/\beta$, i.e. the mean infectious period of the disease. This method of plotting is useful in displaying the discrepancies in the tails more clearly than the untransformed cumulative proportions.

The values of the fitted parameters for the main epidemic years are given in Table 1, together with an indication of the major antigenic types of virus prevailing. The initial epidemic of Asian influenza in 1957/8 cannot be reliably fitted as it was bimodal with one peak in early autumn followed by another at the usual point in winter. In the other years omitted, the numbers of cases were too small for reliable estimates of the parameters to be made.

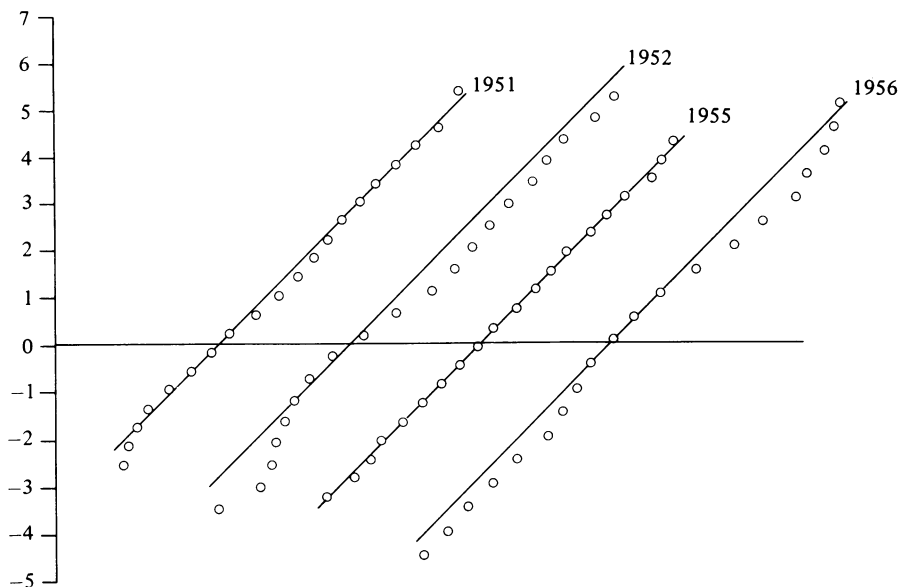There are no systematic differences between the years or strains of virus in their
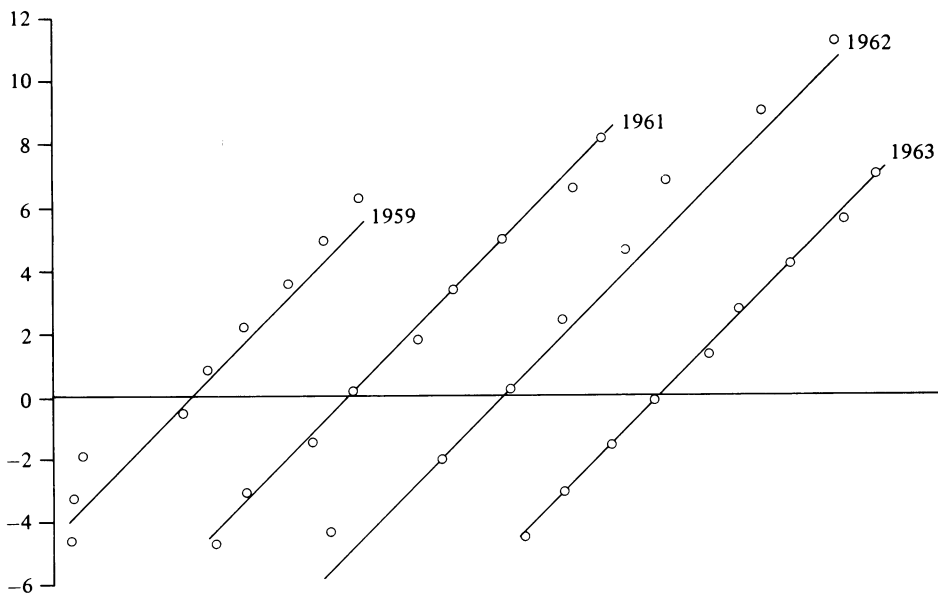
Fig. 1

Fig. 2

type of disagreement with theory, but there are clearly systematic deviations from the fitted curve in some of the epidemics. The very poor fit to the 1952 curve was due to a major outbreak of respiratory disease caused by smog in the early part of the year. The fitting program allowed for this by shifting the origin.
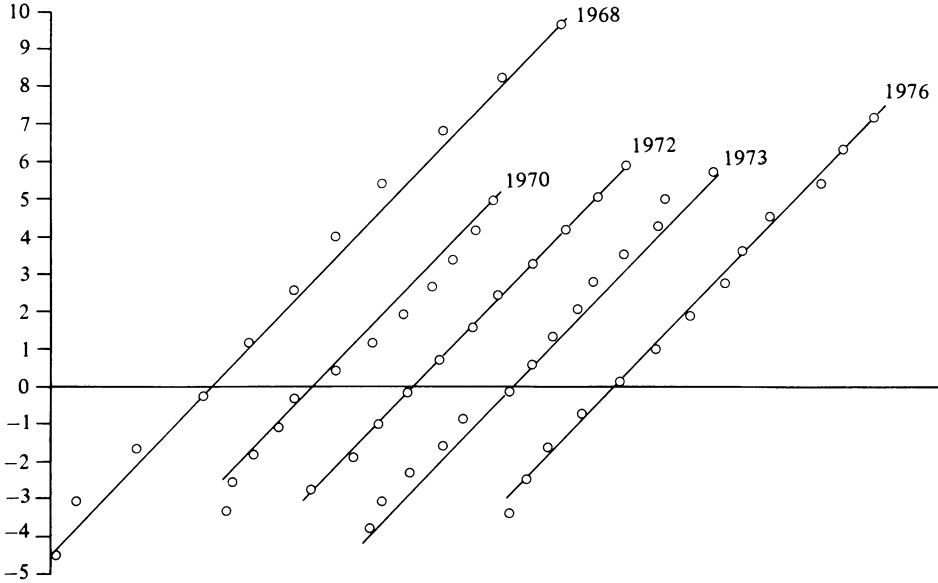
Fig. 3

Figs 1–3. These figures show the relationship between the observed and calculated times at which successive cumulative proportions of cases occurred. The origin is at the peak of the epidemic and time is scaled in units of the calculated average infectious period $(1/\beta)$. The lines represent perfect agreement and all pass through zero and have a slope of 45°.

Table 1. *Parameters of Kermack/McKendrick-type models fitted to weekly deaths from influenza and influenzal pneumonia in Greater London*

Year(s)	Number of peak week	N'	N/N_T	β	Major influenza strain prevalent
1950–1	5	1840	3·52	2·52	A′
1952–3	5	1471	2·74	2·17	
1954–5	6	493	2·11	2·52	
1955–6	6	370	1·95	1·98	
1959	9	805	2·45	0·73	A2 Asian
1960–1	7	267	2·02	0·62	
1961–2	2	209	1·46	0·45	
1963	8	210	1·63	0·69	
1967–8	2	683	2·35	0·70	A2 (+A-Hong Kong?)
1969–70	1	1117	3·51	1·33	A-Hong Kong
1971–2	2	201	2·20	1·15	
1972–3	6	357	2·16	1·36	
1976	7	918	2·89	1·13	
1978	7	205	2·13	1·32	

(The value of S_0/N is about 0·999 in all epidemics.)

DISCUSSION

The above results seem to show that, empirically, the epidemic curve of influenza deaths in Greater London is often quite well described by the Kermack & McKendrick equations in their simplest form. It is difficult to say how far the parameters of the curve can be interpreted in terms of the underlying model. There seems to be a decline in the number of susceptibles as measured by N' following the establishment of the A′ and A-Hong Kong strains, possibly due to the arrival of A-Victoria in 1976 as a major variant. A similar picture is shown by the threshold ratio N/N_T. But in both cases other parameters are concerned which there is no way of estimating since $N' = N\mu/\beta$ and $N/N_T = N\lambda/\beta$ and λ and μ are unknown. The ratio $N'/(N/N_T) = \mu/\lambda$ does decline as a strain becomes established but this could be due to variations in either μ or λ or both, though it seems more likely that the death rate from influenza declines rather than that its transmissivity or infectiousness increases, as the virus and host adapt to one another.

The relation between the value of β and the prevailing epidemic type of the virus could arise from variations in the infectious period of the strain, if the present model is valid. On the other hand it could be interpreted as an adjustable scale parameter in fitting the epidemic curve empirically, which determines the spread of the curve.

There is very little information in the literature on the excretion period of the influenza virus. The U.S.S.R. studies were based on data ascribed to Zhdanov, Soldviev & Epshtein (1958), but we have not been able to verify this reference. These data give an average infectious period of 1·25–1·5 days but do not approximate well to an exponential curve. Elvebaek et al. (1976) in their simulation studies on influenza epidemics remark on the absence of information and assume a latent period of three days followed by three days of exponential decline.

Laboratory studies of the excretion of the virus in human volunteers reported by Reeve et al. (1980) indicate a mean value of $3·4 \pm 0·8$ days for the shedding of a recombinant H1N1 strain, and the authors also state that a high proportion of volunteers shed virus for up to seven days. In experiments with H3N2 strains the average duration of shedding was reported by Moritz et al. (1980) as $2·3 \pm 1·4$ days. There are no obvious differences between antigenic types in these studies but they do indicate that the infectious period could be determined more accurately if necessary.

If the model does have some relationship to reality it must be very insensitive to heterogeneity in the age structure of the population and in the transmissivity parameter λ, which must vary widely between different sections of the community. The model also gives no direct explanation of the seasonal incidence of the disease.

A possible explanation of the winter incidence is that the value of λ depends on seasonal climatic factors and during the autumn is increased, thus decreasing N_T and raising the threshold ratio to an epidemic level. During the warmer months the value of λ is so low that no epidemic can be maintained, though the virus continues to be prevalent on a small scale.

It is a necessary consequence of this hypothesis that the effect of season is a trigger action in autumn, after which the epidemic pursues a course determined mainly by the size of the susceptible population and the infectious period of the disease.

Table 2. *Parameters of Kermack/McKendrick models fitted to total influenza deaths in great cities of England and Wales. Data from Logan & MacKay (1951)*

Year	N'	N/N_T	β
1918	49830	3·08	2·00
1921/2	12110	2·71	3·10
1923/4	8910	2·40	2·65
1926/7	8730	2·96	3·25
1928/9	15930	3·31	2·58
1932/3	11440	2·91	1·64
1936/7	7852	4·48	2·73
1943/4	5854	3·15	1·84

If there is a steady flow of susceptibles into the population, as is the case with measles, the disease will have a natural period T given by

$$T = \frac{2_\pi}{\sqrt{\left[(k\lambda) - \frac{k\lambda}{4\beta}\right]^2}}$$

(for details see Bailey, 1975), where k is the rate of inflow of susceptibles. Taking a representative value of β of about 1·5, a value of 0·01 for $(k\lambda)$ gives a period T of about 60 weeks. An approximately yearly period like this could reinforce the seasonal factor to perpetuate the winter incidence of the epidemic. It is interesting that at least two major epidemics, 1918 and 1957, have occurred quite out of season, possibly because the number of susceptibles was large enough to compensate the high value of the threshold population.

In an attempt to throw more light on the effect of population heterogeneity the model was fitted to the total influenza deaths in the great cities of England and Wales in the major epidemic years from 1918 to 1943 using data published by Logan & MacKay (1951). It was felt that heterogeneity in these data was so great that the model would be very implausible. The data, in fact, fitted about as well as that for Greater London. The fitted parameters are given in Table 2, where it will be seen that β and N/N_T were quite similar to those of A' virus in 1950–6. It is interesting that the parameters for the second 1918 epidemic differed strikingly from the other epidemics only in the very large value of N'. As the data related only to deaths this would have been due to the known high mortality for the virus in question, as well as to the presence of a large population of susceptibles, but the overall fit of the model is not good for this epidemic.

The similarity of these results to those for Greater London shows that a very considerable increase in heterogeneity does not seriously alter the descriptive capacity of the model. It would be natural therefore to assume that the model merely provides an empirical family of curves with appropriate properties for fitting epidemic data. On the other hand the fitted parameters have quite reasonable values in terms of the theory, while those of a purely empirical function such as the generalized logistic cannot be interpreted at all. Unless some objective evidence becomes available, for example direct estimates of the susceptible population or the infectious period, the choice between these two views is a matter of taste. But, in the meantime, the model does seem to present a plausible account of the epidemic behaviour of influenza.

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