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The effects of population density and malnutrition on the dynamics of whooping cough

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SUMMARY

Liverpool, a seaport in NW England, suffered severely from lethal infectious diseases in the second half of the 19th century: the population was densely crowded and malnourished and life expectancy was low. Time-series analysis shows that the epidemics of whooping cough (i) had an interepidemic interval of 2·9 years, 1863–85, which lengthened to 3·4 years, 1885–1900 (ii) were strongly coherent with wheat prices ($P < 0{\cdot}001$) and (iii) also correlated with cycles of seasonal weather conditions. It is suggested from mathematical modelling that the epidemics in this compromised population were maintained (i.e. the system was driven) by an oscillation of malnutrition and by seasonal weather conditions. A model that incorporates both the dynamics of whooping cough and the demographic characteristics of the population is presented. It has been shown to replicate the dynamics of the epidemics and has been used to predict the changes with time of (i) the force of the infection and (ii) the proportion of those infected with whooping cough who died.

INTRODUCTION

During the second half of the 19th century the public health problems in Liverpool (an important seaport in north-west England) were severe and eventually led to the appointment of W. H. Duncan, the country's first Medical Officer of Health. Duncan gave evidence on the conditions under which by far the greater part of the population of the borough lived – typically 25% of his patients were living in cellar dwellings with between 15 and 30 people in an airless room [1, 2]. The problems had been exacerbated by the stream of Irish refugees in the 1840s fleeing from the potato famine and in 1847 some 300000 had landed in Liverpool. Of these 8000 died and many moved inland or migrated to the USA, but the numbers staying in Liverpool are estimated variously as between 80000 and 160000 who located themselves in every available niche, including cellars that had been closed under the provisions of the Health Act of 1842 [1, 2]. Mortality was high and the life expectancy at birth in Liverpool was below 25 years, much less than the value of 57 years for rural England at that time [3].

Lethal infectious diseases were rife in Liverpool and, in addition to the major outbreaks of typhus and cholera, scarlet fever, measles and whooping cough took a heavy toll of children's lives for the remainder of the century.

We have previously shown that the epidemiology of whooping cough in London during the 18th century can be described by the mathematics of linearized systems: the interepidemic interval is determined by the population size/density and by susceptibility to the disease. Susceptibility was governed by fluctuating

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levels of malnutrition which were directly associated with oscillations in the wheat prices [4].

In this communication, we use time-series analysis to elucidate the dynamics of whooping cough in Liverpool and to determine whether annual or seasonal external factors acted to drive the epidemics, incorporating the results into a nonlinear model. Finally, we develop a new demographic model of the expanding population of Liverpool during 1863–1900 which incorporates the whooping cough mortality and which allows further insight into the epidemiology of the disease.

THEORY OF WHOOPING COUGH EPIDEMICS

The theory of the epidemics of infectious diseases has been widely studied [see 5–10 for detailed accounts] and basic models have been presented, which cover the spread of the infective agent in a population, a proportion of which is made up of non-immune, and hence susceptible, individuals who may be exposed to the disease and become infected. Of these, a proportion will die but the majority will recovery and will then be immune. These are termed SEIR (susceptibles-exposed-infectives-recovered) models and can be summarized as follows. The population, N, is assumed to remain constant where the net input of susceptibles (new births) equals the net mortality, μN (where $\mu =$ the overall death rate of the population, and hence the life expectancy of the population $= 1/\mu$). The population is divided into susceptibles (X) latents (infected, not yet infectious, H), infectious (Y) and recovered (and hence immune, Z). Thus, $N = X+H+Y+Z$. It is assumed that the net rate at which infections occur is proportional to the number of encounters between susceptibles and infectives, βXY (where β is a transmission coefficient). Individuals move from the latent to infectious categories at a *per capita* rate, σ, and recover, so becoming immune, at rate γ. The dynamics of the infection as it spreads through these classes are then described [5] by the following equations:

$$dX/dt = \mu N - \mu X - \beta XY, \quad (1)$$
$$dH/dt = \beta XY - (\mu+\sigma)H, \quad (2)$$
$$dY/dt = \sigma H - (\mu+\gamma)Y, \quad (3)$$
$$dZ/dt = \gamma Y - \mu Z. \quad (4)$$

However, the conclusions from this modelling are that the epidemics would decay unless the system were 'pumped up' in some way [5] whereas, in reality, outbreaks of many infectious diseases persist for long periods and we have developed a linearized model in which the epidemics are driven by periodic variations in the transmission coefficient (or susceptibility), $\delta\beta$. This modelling and its application to various lethal infectious diseases have been described in detail elsewhere [4, 11, 12]; in brief, the system can be characterized by its natural (resonant) undamped frequency, ω_r, and by its damping factor, ξ, which is a dimensionless ratio in the range 0 to 1 and is a measure of the degree of damping within the system, i.e. the attenuation of the amplitude of the oscillation at its resonant frequency. The damping factor is given by

$$\xi = \frac{N\beta}{2(\mu+\nu)} \quad \left(\frac{\mu}{N\beta-(\mu+\nu)}\right), \quad (5)$$

where
$N =$ number in the population,
$\mu =$ death rate $= 1/$life expectancy,
$\beta =$ transmission coefficient (susceptibility to disease),
$\nu =$ rate of recovery from disease $= 1/$infectious period.

For the values of μ, ν and $N\beta$ that are used to describe the whooping cough epidemics in Liverpool, ξ is small (much less than 1), indicating that the system is lightly damped. Since ξ is small, the frequency response of the system is very sharp and a driver that has a frequency that is the same as the resonant frequency, ω_r will be amplified. The period of the resonant frequency of the system, T, is given by

$$T = \frac{2\pi}{\sqrt{\mu[N\beta-(\mu+\nu)]}}. \quad (6)$$

Thus, the important conclusion from this non-linear modelling of a driven system is that the interepidemic interval, T, for a particular population is determined by $N\beta$, the product of population size and susceptibility to the disease (equation (6)). Although N is most conveniently measured by the absolute numbers in the city of Liverpool, in reality the density of the individuals will be an equally important component of N and would have had a major effect on the dynamics of infectious diseases in Liverpool in the second half of the 19th century.

Two assumptions are made in the foregoing modelling: (i) the population remains constant and (ii) those dying of whooping cough are not considered in the dynamics. These were both important factors in

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Liverpool during the period of this study, where numbers were expanding rapidly and there was a considerable fatality rate from the disease. In the Appendix we present a model for the overall population dynamics of Liverpool which takes into account the rapidly expanding numbers of people within the city boundaries. The model is based on our original nonlinear model of infectious diseases [4, 11, 12] and includes the birth rate, the rate of recovery, the death rate because of the disease and the death rate of the population *excluding* deaths from whooping cough.

The model was run, incorporating the known demographic variables for Liverpool and the results are presented below.

METHODS

Annual whooping cough deaths and life expectancy in Liverpool, 1863–1900, were taken from the Reports of the Liverpool Medical Officer of Health. Population size, life expectancy and the ratio of births:deaths were calculated from the data given in these sources and from the Liverpool Council Proceedings. Time-series analysis and modelling were carried out using the MATLAB packages. The annual wheat price series for England was taken from the data given by Stratton [13]. Mean seasonal temperatures were taken from Manley [14] and mean seasonal rainfall was taken from Wales-Smith [15]. The seasons were defined as follows, winter: December (of the preceding year), January and February; spring: March, April and May; summer: June, July and August; autumn: September, October and November.

There are no comments by the Medical Officer of Health in the Annual Reports at that time concerning difficulties in the diagnosis of whooping cough. Deaths from croup and bronchitis were listed under separate categories. Although the disease might have been confused with acute bronchiolitis, a severe infection in young infants, perhaps exacerbated by respiratory syncytial virus, Christie [16] states that, when the paroxysmal stage is developed, the whoop, the vomit and the typical spasms are so characteristic that the diagnosis can hardly be missed by default. Furthermore, McKeown and Record [17] state that whooping cough was fairly clearly identified on clinical groups in the second half of the 19th century and medical experience of this and other infectious diseases was then much greater than it is today. We conclude that the sharp fluctuations in the annual number of deaths from whooping cough revealed by time-series analysis reflect accurately the periodicity of the epidemics of this disease.

RESULTS

Pattern of the epidemics

Annual whooping cough deaths in Liverpool, 1863–1900, are shown plotted in Figure 1 and major epidemics superimposed on a basal, endemic level are evident. There is a progressively falling trend through this period, during which the amplitude of the epidemics decays so that in the later years the system approaches on endemic situation. Spectral analysis suggests that the series may be subdivided as follows: (i) 1863–85, oscillations of wavelength 2·9 years ($P = 0{\cdot}05$) and 5 years ($P < 0{\cdot}05$) (ii) 1885–1900, a single oscillation of wavelength 3·4 years (not significant). We conclude that the interepidemic interval over the period 1863–1900 was approximately 3 years and the epidemics are shown after filtering in Figure 2 (filter window = 2 to 6 years).

Driving the epidemics

There is a 5·3 years oscillation detectable in the series of national wheat prices which is shown in Figure 3; there is also a clear, falling trend after 1883. This 5·3-year oscillation correlated with the corresponding 5-year oscillation in whooping cough deaths as shown by the cross-correlation function at zero lag (Fig. 4; years 1863–93). Whooping cough deaths were also strongly and significantly coherent with wheat prices, $P < 0{\cdot}001$, as follows: 1863–85, 4·8 to 5·3, 3·5 and 2·9 year wavebands; 1885–1900, 9, 5·3, 4, 3·2 to 3·5 year wavebands. All coherences were at zero lag.

The 3-year epidemics also correlated with seasonal conditions: during 1863–85 with mild winters and with low autumn temperatures, whereas, after 1885, the mortality peaks correlated strongly with cold dry weather in spring.

It is suggested, therefore, that the results are consistent with a system that is driven, i.e. the epidemics do not decay because they are primarily maintained by an oscillation in malnutrition in this compromised population (reflected in raised wheat prices) which has a wavelength that is approximately twice that of the epidemics, and secondarily by an oscillation in seasonal climatic conditions, the fre-

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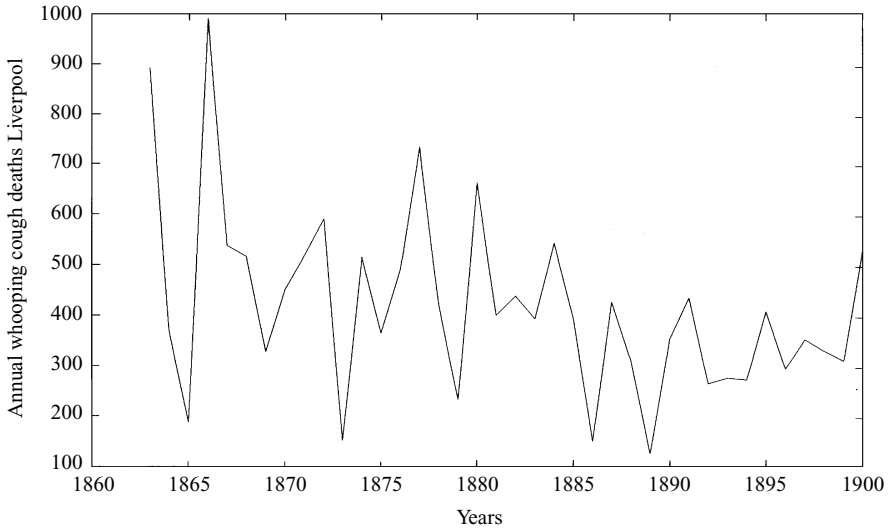

Fig. 1. Annual whooping cough deaths in Liverpool, 1863–1900.

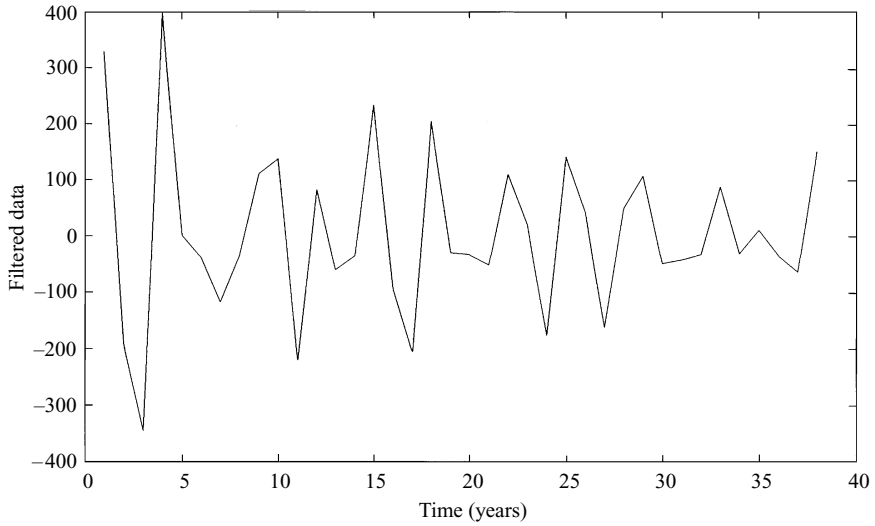

Fig. 2. Filtered whooping cough deaths in Liverpool, 1863–1900. Filter window = 2–6 years.

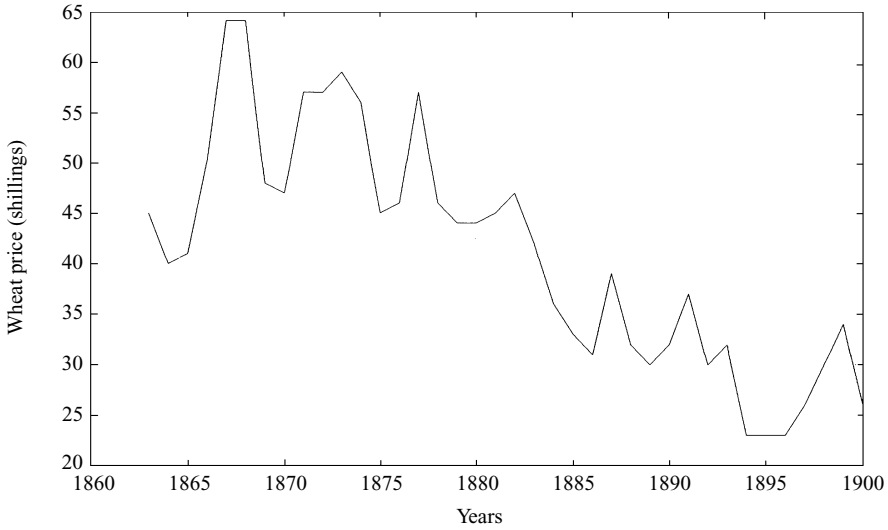

Fig. 3. Annual, national wheat prices, 1863–1900.

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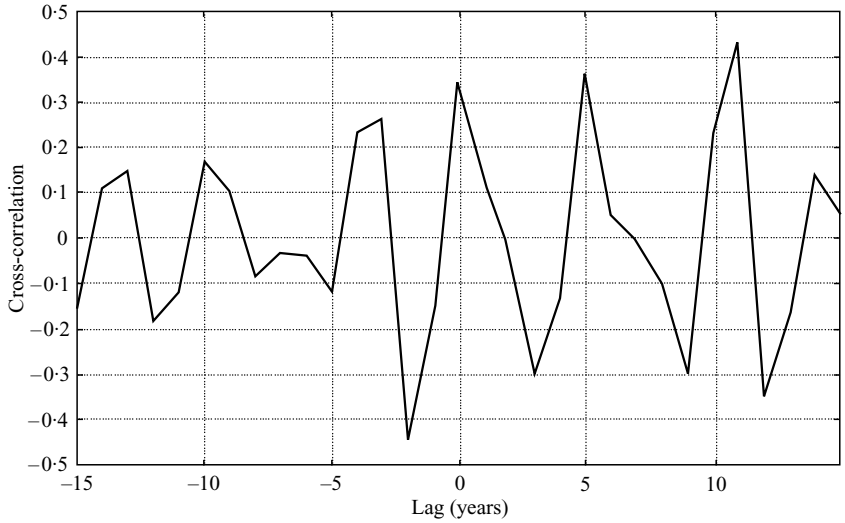

Fig. 4. Cross-correlation function, wheat prices *vs.* whooping cough deaths, 1863–93. Filter window = 2–6 years, Ccf = +0·35 at zero lag.

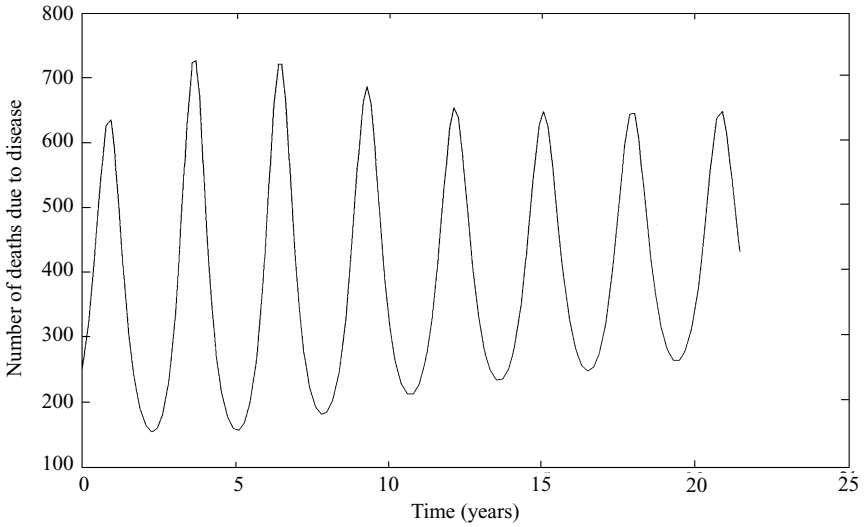

Fig. 5. Modelling the whooping cough epidemics at Liverpool 1863–85 driven by an oscillation in $\delta\beta$ at ω_r ($\lambda = 2{\cdot}9$ years).

quency of which is ω_r, the resonant frequency of the system.

Modelling the population dynamics during the first period, 1863–85

The whooping cough deaths and the population dynamics in Liverpool during the first period, 1863–85, shown in Figure 1, are modelled using the equations developed in the Appendix. The criteria that have to be satisfied by the final modelling are (i) The size of the population of Liverpool in 1863 and its growth by 1885. (ii) The known average infectious period for whooping cough. (iii) The calculated life expectancy at birth for the population in Liverpool at this time, determined from the statistics of the Medical Officer for Health. (iv) The inter-epidemic interval, T, determined by time-series analysis from the data series (see above). (v) The epidemic/endemic ratio which is defined as:

$$\frac{\left(\begin{matrix}\text{total number dying in}\\ \text{an epidemic year}\end{matrix}\right) - (\text{endemic level})}{(\text{endemic level})}.$$

Obviously this will vary in a natural population but an approximate mean value can be determined by inspection of Figure 1. (vi) The value for $N\beta$, which can be calculated from equation (6) for a given value of T.

These basic criteria are:

(i) Initial N for Liverpool (1863) = $4{\cdot}5 \times 10^5$.

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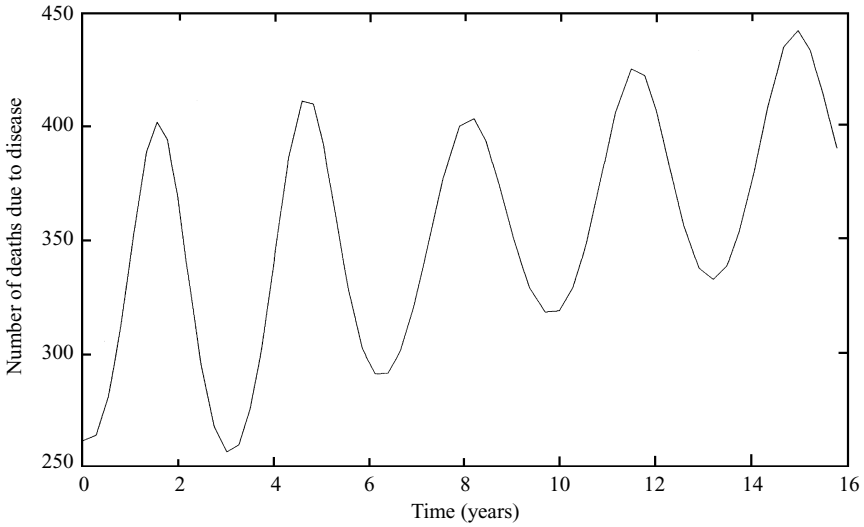

Fig. 6. Modelling the whooping cough epidemics at Liverpool during the later period 1885–1900. Driver = an oscillation in $\delta\beta$ at ω_r ($\lambda = 3{\cdot}4$ years).

(ii) Final N for Liverpool (1885) $= 5{\cdot}4 \times 10^5$.
(iii) Mean life expectancy at birth for the population = 23 years.
(iv) $T = 2{\cdot}9$ years.
(v) Period of variation in $\delta\beta$ ('the driver') = 2·9 years (i.e. the system is driven by seasonal temperatures oscillating at ω_r).
(vi) $N\beta = 112$.
(vii) Infectious period, $D = 27$ days (taken from the value given by Anderson and May [7]).
(viii) Epidemic/endemic ratio at the start of modelling $\approx 1{\cdot}8$.

It was found that these basic criteria imposed severe constraints on the modelling of the epidemics during 1863–85 and the best approximation to reality (as shown in Fig. 1) is given in Figure 5 which was produced by setting the other variables as follows:

(i) Ratio of births/deaths in the population *excluding* those dying of whooping cough = 1·43 which is in good agreement with the demographic statistics
(ii) Fraction of infectives dying of whooping cough = 0·32
(iii) Amplitude of the oscillation in $\delta\beta = 0{\cdot}05$.

This modelling predicts accurately the final population size in Liverpool in 1885 ($5{\cdot}4 \times 10^5$); it describes a system driven only by an oscillation in the transmission coefficient or susceptibility, $\delta\beta$ at ω_r; the epidemic/endemic ratio falls steadily and agrees broadly with Figure 1; the interepidemic interval, T, is correct. However, it is not completely satisfactory because the epidemics are too regular when compared with Figure 1 and we conclude that the nutritive levels (as reflected in the annual wheat prices), both in the long-term trend and in the short wavelength oscillations had a major impact on the dynamics of the disease and that two independent factors interacted synergistically to drive the system.

Modelling the population dynamics during the second period, 1885–1900

After 1885, the basal, 'endemic' level of whooping cough in Liverpool stabilized at a lower level and the amplitude of the epidemics was reduced. Spectral analysis suggests that the mean interepidemic interval had lengthened to 3·4 years.

The basic criteria for modelling the dynamics of whooping cough in Liverpool after 1885 were:

(i) Initial N for Liverpool (1885) $= 5{\cdot}4 \times 10^5$.
(ii) Final N for Liverpool (1900) $= 6{\cdot}7 \times 10^5$.
(iii) Mean life expectancy for the population = 26 years.
(iv) $T = 3{\cdot}4$ years.
(v) Period of variation in $\delta\beta$ (driver) = 3·4 years
(vi) $N\beta = 100$.
(vii) Infectious period, $D = 27$ days [7].
(viii) Epidemic/endemic ratio at the start of modelling $\approx 0{\cdot}5$.

Again, it was found that these basic criteria imposed severe constraints on the modelling of the epidemics during 1885–1900 and the best approximation to reality (see Fig. 1) is shown in Figure 6 which was produced by setting the other variables as follows:

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(i) Ratio of births/deaths *excluding* those dying of whooping cough = 1·55.
(ii) Fraction of infectives dying = 0·14
(iii) Amplitude of the oscillation in $\delta\beta = 0{\cdot}018$.

DISCUSSION

The numbers in this crowded population in Liverpool increased steadily during the second half of the 19th century, rising from $4{\cdot}5 \times 10^5$ in 1863 to $6{\cdot}7 \times 10^5$ in 1900. However, in contrast, the mean annual number of whooping cough deaths over this period fell progressively (see Fig. 1); this change is particularly apparent after 1880.

We have previously reported that annual wheat prices provide an excellent measure of the fluctuating levels of nutrition in England in earlier centuries. Mortality cycles were directly correlated with a short wavelength oscillation in wheat prices [18]; wheat prices and nutritive levels during pregnancy had a major effect on neonatal mortality, and postneonatal mortality was directly affected by wheat prices in the first year of life [19]. Inadequate nutrition in pregnancy is known to cause low birth weight in infants with a greater susceptibility to infectious diseases [20]. This short wavelength oscillation in wheat prices also generated a corresponding oscillation in susceptibility to smallpox which was sufficient to trigger epidemics of the disease in the rural towns of England in the 17th and 18th centuries [18, 21, 22]. About 60% of the weekly expenditure of the poor families in England in the mid-19th century went on bread and it is not surprising that their basic nutrition was so sensitive to the sharply fluctuating wheat prices.

The national wheat price series (Fig. 3) shows a steady fall in its trend after 1880 to about one quarter by 1900 and this was accompanied by a marked improvement in nutritive levels, general health and living standards. Thus, the progressive change in the nutrition of the population at Liverpool was paralleled by the decline in the lethality of whooping cough and we suggest that this was because of an accompanying reduction in susceptibility (β) and, more particularly, in the proportion of infectives that died from the disease.

The results of time-series analysis and modelling are consistent with the hypothesis that the epidemiology of whooping cough can be described by the mathematics of nonlinear systems and that the epidemics were maintained and driven by an oscillation in the transmission coefficient (or susceptibility), $\delta\beta$. The interepidemic interval, T, was 2·9 years during the period 1863–85 which lengthened to 3·4 years after 1885.

The oscillations in whooping cough deaths (i.e. the epidemics) were strongly coherent ($P < 0{\cdot}001$) with the oscillations in wheat prices at zero lag and we suggest that a cycle of malnutrition acted as a driver for the system, 'pumping-up' alternate epidemics and preventing their decay because its wavelength (5·3 years) was approximately twice the interepidemic interval (2·9 years).

Thus we conclude that the major factor that determined the dynamics of whooping cough in Liverpool was the nutritive level of the bulk of the population who were sensitive to the prevailing wheat price which had two main effects. Firstly, improved nutrition, which accompanied the *falling trend* in prices, particularly after 1880, reduced both susceptibility (thereby modifying the dynamics of the system) and lethality (thereby reducing the number of deaths from the disease). Secondly, the *oscillation* in wheat prices drive the system and maintained the epidemics.

However, the densely-crowded conditions and inadequate nutrition (causing raised susceptibility) in Liverpool, particularly among the poorer classes, meant that the dynamics of the disease were dominated by a relatively high value for $N\beta$ which resulted in a characteristic resonant frequency and a mean interepidemic interval, T, of 2·9 years (equation (6)). Consequently, it is probable that the epidemics were also directly driven at their resonant frequency by cycles in seasonal conditions that oscillated at this frequency.

These conclusions are in accord with an analysis of dynamics of whooping cough epidemics in London in the 18th century (i.e. 100 years previously) which can be described by the mathematics of linearized dynamic systems and the interepidemic interval is determined by $N\beta$: it changed in London from 5 years (1720–50) to 3 years (1750–85) before returning to 5 years (1785–1812). Susceptibility (β) was governed by the wheat prices and it is suggested that the epidemics in London were driven by fluctuating seasonal temperatures which interacted with wheat prices. During 1750–85, the population in London rose and the trend in prices increased markedly, resulting in a rise in $N\beta$ and, consequently, a reduction in the interepidemic interval from 5 to 3 years. After 1785, the wheat prices fell and conditions in London ameliorated so that β fell and T returned to 5 years [4]. One hundred years

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later, the conditions in London during 1750–85 were replicated in the densely-crowded and malnourished population in Liverpool, 1863–85, where the high value for $N\beta$ produced a mean T of 2·9 years. As conditions in Liverpool improved after 1885, particularly associated with much cheaper wheat (Fig. 3), the interepidemic interval lengthened (mean $T = 3{\cdot}4$) and the amplitude of the epidemics was reduced.

The extended model presented in this communication, which incorporates the demographic and epidemiological characteristics of the system under study, represents an advance on the linearized [4] and nonlinear models [11] of the epidemics of infectious diseases that we have presented previously. The present model incorporates changes in population size and the fraction of the infectives that die from the disease. Some of the parameters, such as the size of the population, infectious period and mean life expectancy, are known (or can be estimated) for a given disease in any particular population. The interepidemic interval, T, can be determined by time-series analysis of the data series. The value of $N\beta$ for the particular set of circumstances can be calculated from equation (6). The output of the modelling, when these values for the different variables are incorporated, can then be compared with reality (Fig. 1) and the other variables (amplitude of $\delta\beta$, proportion dying from the disease) can then be adjusted accordingly. These different parameters impose tight constraints on the modelling but we find that, with most systems studied, one set of values will replicate the dynamics of the epidemics and the demographic growth of the population.

It is possible thereby to make certain predictions about the behaviour of the disease; for example the proportion of those infected by whooping cough in Liverpool that are predicted by the modelling to die during 1863–85 is 0·32, but this value fell to 0·14 during the ameliorated conditions after 1885, as would be expected. The modelling also predicts that the force of the infection (the amplitude of $\delta\beta$) falls from 0·05 in the first period to 0·018 after 1885.

The modelling that we have described is, inevitably, a simplification of the actual events that occurred during the whooping cough epidemics in the crowded and unsanitary conditions that existed in Liverpool a century ago. For example, studies of measles epidemics today, particularly in Africa, show that family size is an important factor in the epidemiology of this disease. Secondary cases exposed to 2 or more index cases of measles had a higher case fatality rate than did children exposed to a single index case [23]. Girls have a higher case fatality rate from measles than boys in West Africa and cross-sex transmission of this disease may be an important determinant of the severity of infection [24]. However, secondary cases infected by a child of the opposite sex had a higher risk of death than did secondary cases infected by a child of the same sex. The risk of cross-sex transmission of infection was significantly greater for female than for male secondary cases but when this difference in risk of exposure to infection from the opposite sex was taken into account, the difference in risk of death between girls and boys disappeared [25].

The annual reports of the Medical Officer of Health of Liverpool for 1899 records that before any diminution in the formidable disease of whooping cough could be looked for, some means of isolation would have to be found for the infected children. He includes a table which traces the infection of 15 children from a single source which confirms the importance of the density component of N in the maintenance of the epidemics in Liverpool. We do not have other information concerning the outbreaks and spread of whooping cough in individual houses, comparable with the detailed statistics available in developing countries today. Nevertheless, we believe that the modelling provides a good description of the basic epidemiology of whooping cough and its interrelationships with the demography and living conditions in Liverpool a century ago.

In conclusion, the extended model developed in this communication not only confirms the findings of the earlier models of driven systems [4, 11] but greatly increases our understanding both of the underlying dynamics of the disease and of the population demography at the time. The modelling reveals the severe conditions that existed in Liverpool, even up to 1885. Average life expectancy at birth was only 23 years, very much lower than for rural England at that same time and this markedly affected the dynamics of whooping cough. This poor life expectancy in Liverpool was primarily the result of high child mortality from the infectious diseases, measles, whooping cough, scarlet fever and, to a lesser extent following widespread vaccination, smallpox. The poor living conditions at high density and inadequate nutrition caused a high β and greatly increased the spread of the disease, the frequency of the epidemics and the proportion of the infectives dying. The improvement in nutritional standards after 1885, consequent upon steadily falling wheat prices, markedly reduced the

lethality of these diseases, so that childhood mortality and life expectancy had greatly improved by 1900.

APPENDIX

The population was assumed to remain constant in the previous linearized [4] and nonlinear [11] models and those dying of whooping cough were not considered. These are both important factors in Liverpool in the second half of the 19th century, where numbers were expanding rapidly and there was a considerable fatality rate from the disease. In developing the modelling of the epidemics within the overall population dynamics when the population is *not* assumed to remain constant and incorporating the death rate from the disease, equations (1)–(4) can be replaced by:

$$\mathrm{d}X/\mathrm{d}t = \gamma N(t) - \mu X(t) - \eta X(t) - \beta(t)\, X(t)\, Y(t), \tag{7}$$
$$\mathrm{d}Y/\mathrm{d}t = \beta(t)\, X(t)\, Y(t) - \mu Y(t) - \nu Y(t) - \alpha Y(t), \tag{8}$$
$$\mathrm{d}Z/\mathrm{d}t = \eta X(t) + \nu Y(t) - \mu Z(t), \tag{9}$$

where
$X(t)$ = the number of susceptibles;
$Y(t)$ = the number of infectives;
$Z(t)$ = the number of immunes;
N = the total size of the population;
γ = the birth rate;
μ = the death rate *excluding* deaths because of whooping cough;
η = the rate of vaccination (not relevant to whooping cough in the 19th century);
ν = the rate of recovery;
α = the death rate because of the disease;
$\beta(t)$ = the 'force' of the infection.

Since the total size of the population, $N(t)$, satisfies $N(t) = X(t) + Y(t) + Z(t)$, the third differential equation can be replaced by

$$\mathrm{d}N/\mathrm{d}t = (\mu + \nu)\, X(t) + (\mu + \nu)\, Y(t) - \mu N(t). \tag{10}$$

If the force of infection remains constant, so that $\beta(t) = \beta_0$, the behaviour of the population depends upon the difference between the birth rate, γ, and the rate at which people are dying, both because of the disease and from other causes. We are concerned in this modelling with the effects of periodic changes in the force of the infection about a mean level, β_0, so that $\beta(t)$ is assumed to have the form

$$\beta(t) = \beta_0 + \beta_1 \sin \omega t, \tag{11}$$

where ω is the frequency of the periodic variation and β_1 its magnitude. If $X_0(t)$, $Y_0(t)$ and $N_0(t)$ denote the solution of the differential equations when $\beta(t) = \beta_0$, then it is convenient to define

$$X(t) = X_0(t) + X_1(t), \tag{12}$$
$$Y(t) = Y_0(t) + Y_1(t), \tag{13}$$
$$N(t) = N_0(t) + N_1(t), \tag{14}$$

where $X_1(t)$, $Y_1(t)$ and $N_1(t)$ denote the *variations* from the solution obtained when β_0 is constant. Substituting these expressions into the differential equations in (7), (8) and (10) leads to

$$\begin{bmatrix} \dot{X}_1(t) \\ \dot{Y}_1(t) \\ \dot{N}_1(t) \end{bmatrix} = A(t) \begin{bmatrix} X_1(t) \\ Y_1(t) \\ N_1(t) \end{bmatrix} + b(t) \sin \omega t + \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix} f(X_1(t), Y_1(t), \beta_1), \tag{15}$$

where

$$A(t) = \begin{bmatrix} -\mu - \eta - \beta_0 Y_0(t) & -\beta_0 X_0(t) & \gamma \\ \beta_0 Y_0(t) & \beta_0 X_0(t) - \mu - \nu - \alpha & 0 \\ \mu + \eta & \mu + \nu & -\mu \end{bmatrix} \tag{16}$$

$$b(t) = \begin{bmatrix} -\beta_1 X_0(t)\, Y_0(t) \\ \beta_1 X_0(t)\, Y_0(t) \\ 0 \end{bmatrix} \tag{17}$$

and

$$f(X_1(t), Y_1(t), \beta_1) = \beta_0 X_1(t)\, Y_1(t) + X_0(t)\, Y_1(t)\, \beta_1 \sin \omega t + X_1(t)\, Y_0(t)\, \beta_1 \sin \omega t + X_1(t)\, Y_1(t)\, \beta_1 \sin \omega t. \tag{18}$$

The term $f(X_1(t), Y_1(t), \beta_1)$ describes the nonlinearities inherent within the system, but in cases where the variations in the force of the infections are small, the system can be approximated by the (time-varying) *linear* system

$$\begin{bmatrix} \dot{X}_1(t) \\ \dot{Y}_1(t) \\ \dot{N}_1(t) \end{bmatrix} = A(t) \begin{bmatrix} X_1(t) \\ Y_1(t) \\ N_1(t) \end{bmatrix} + b(t) \sin \omega t. \tag{19}$$

This approximation is reasonable when modelling variations in the number of infectives around an endemic level. The time-varying nature of the linear system is a result of the changes in $X_0(t)$ and $Y_0(t)$

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because of the increasing population size. For the birth rates and death rates appropriate for Liverpool during the period under study, these values are changing slowly relative to the oscillations in the force of the infection. As a result, the behaviour of the system can be determined by the roots of the characteristic equation which, for the values of the parameters used in the model, takes the form,

$$(s-q)(s^2+2\xi\omega_n+\omega_n^2), \tag{20}$$

where there are a complex conjugate pair of roots in the left half plane and a real root at $s = q$ which lies in the right half plane. This unstable real root is a consequence of the increase in the population because the birth rate exceeds the death rate. Because the rate of population growth is relatively slow, q is small and this root is close to the origin of the s-plane.

The presence of the complex conjugate pair of roots indicates that the system has a resonance at frequency

$$\omega_r = \omega_n \sqrt{(1-2\xi^2)}. \tag{21}$$

If q is taken to be small, then the natural frequency of the system, ω_n, can be approximated by

$$\begin{aligned}\omega_n^2 \approx & -\mu\beta_0 X_0(t)+\mu(\mu+\nu+\alpha)+\mu(\mu+\eta+\beta_0 Y_0(t)) \\ & -\beta_0 X_0(t)(\mu+\eta+\beta_0 Y_0(t))+(\mu+\nu+\alpha) \\ & (\mu+\eta+\beta_0 Y_0(t))+\beta_0^2 X_0(t) Y_0(t)-\gamma(\mu+\eta)\end{aligned} \tag{22}$$

Similarly, ξ, the damping factor for the resonance is approximately given by

$$\xi \approx \frac{3\mu+\eta+\nu+\alpha+\beta_0(Y_0(t)-X_0(t))}{2\omega_n}. \tag{23}$$

For typical values of the parameters used in this model, ξ is small, indicating that the system is lightly damped and, as a result, will amplify any periodic variations in the force of infection, $\beta(t)$ which have a frequency close to ω_r.

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