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The Dynamics of Smallpox Epidemics in Britain, 1550–1800*

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Time-series analysis, a valuable tool in studying population dynamics, has been used to determine the periodicity of smallpox epidemics during the seventeenth and eighteenth centuries in two contrasting representative situations: 1) London, a large city where smallpox was endemic, and 2) Penrith, a small rural town. The interepidemic period was found to be two years in London and five years in Penrith. Equations governing the dynamics of epidemics predict 1) a two-year periodicity and 2) that oscillatory epidemics die out quickly. It is suggested that epidemics were maintained by a periodic variation in susceptibility linked either to a five-year cycle of malnutrition or to an annual cycle. Computer modeling shows how the very different patterns of epidemics are related to population size and to the magnitude of the oscillation in susceptibility.

A considerable body of information concerning smallpox epidemics in England during the seventeenth and eighteenth centuries has been accumulated (Creighton 1965; Razzell 1977), but inevitably, much of it is anecdotal or a synthesis of reports and opinions of the time. In this communication we report a new approach to the study of this highly infectious viral disease, using time-series analysis of parish register series and of the London Bills of Mortality to detect the periodicity of the epidemics. We have integrated this information into the theory of the dynamics of smallpox infections; we suggest why the epidemics probably were synchronized in rural England and why the biology of the disease was different in different communities.

Smallpox has been described as the most infectious human disease known. It was feared greatly in England from the time of the final visitation of bubonic plague in 1666 until the end of the nineteenth century, when it ceased to be endemic (Smith 1987). Hopkins (1983) gives an account of the natural history of the disease and of its lasting effects on many of the survivors. Smallpox was a relatively rare disease until the 1630s (Appleby 1981), but many accounts suggest that a particularly virulent strain began to afflict people of

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all ages in the middle and later decades of the seventeenth century (Corfield 1987), attended by a gradual but significant increase in the case fatality rate (Razzell 1977). By the first half of the eighteenth century almost everyone had suffered from the disease at some time; it was thought to be directly or indirectly responsible for one death in every five. After 1750, inoculation or variolation began to be administered more widely among the educated and the affluent (Mercer 1985), but a time lag of about 10 to 20 years occurred before the same degree of acceptance reached the northern counties of Cheshire, Cumberland, Lancashire, and Yorkshire (Smith 1987). Although smallpox remained unconquered, an increasing proportion of the population had been given immunity by inoculation. At the same time the nonimmune proportion of the population was declining, so that the potential breeding ground for smallpox was contracting steadily. At the end of the eighteenth century the incidence and mortality from smallpox were reduced very substantially, aided by the introduction of vaccination.

Smallpox was endemic in London during most of the seventeenth and eighteenth centuries, but every few years there was a marked increase in deaths. Thirty-seven epidemics have been identified between 1660 and 1799 (Appleby 1981). Razzell (1973) concludes, ". . . Demographers of the 18th century tended to be dependent on the evidence available to them and this invariably was for large towns in which only about a fifth of the population lived". Elsewhere the disease usually was absent for sustained periods, often between five and 10 years and much longer in remote communities. Sporadic outbreaks were the result of infection introduced from outside. Consequently it has been suggested that market towns and villages on main trading routes were particularly susceptible to random infection by travelers (Smith 1987). Conversely, Bradley (1971) states that ". . . inspection of parish registers reveals many parishes, including some of the smaller towns, where serious epidemics of any kind were few, or even non-existent, over the whole of the 18th century". Appleby (1981) concluded that smallpox was not controlled by the weather because the recurring epidemics do not fit any particular climatic pattern of either temperature or rainfall: epidemics came in very dry years (1731) or in wet years (1768); they broke out in warm years (1736, 1749, 1779) and in unusually cold years (1740). He firmly believed that the long-term rise and decline of smallpox was not related to changes in climate.

THE DYNAMICS OF SMALLPOX INFECTIONS

Bailey (1975) has provided a comprehensive overview of the mathematical theory of infectious diseases, which Anderson and May (1991) developed into a study of the theory of infectious epidemics when a virus is introduced into a susceptible population. Thereafter events follow very rapidly: most of the susceptibles become infected before the epidemic dies out and the survivors become immune. Their analysis may be summarized as follows.

The population, N, is assumed to remain constant where the net input of susceptibles (births) equals the net mortality μN (where μ = death rate; life expectancy = $1/\mu$). 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 infectious, βXY (where β is a transmission coefficient). Individuals move from latent to infectious at a per capita rate σ; they recover, thus becoming immune, at rate γ. The dynamics of the infection are then described by the following equations:

$$dX/dt = \mu N - \mu X - \beta XY \quad (1)$$

$$dH/dt = \beta XY - (\mu + \sigma)H \quad (2)$$

$$dY/dt = \sigma H - (\mu + \gamma)Y \quad (3)$$

$$dZ/dt = \gamma Y - \mu Z. \quad (4)$$

A model determining the fraction of susceptibles as a function of time, based on Equations (1)–(4), exhibits a damped oscillation (i.e., the cycles of the epidemics die out rapidly). The oscillation has a period (T) that is given by

$$T = 2\pi (AD)^{0.5} \quad (5)$$

where A = average age of infection once the infection is endemic and D = the sum of the latent and the infectious periods.

The fundamental requirement for the establishment and maintenance of the disease is that the population of susceptible individuals exceed a threshold density. This density (of course) depends on the birth rate, which in turn is dependent on the total size of the population (N).

A considerable body of literature now exists concerning the mathematical treatment of the population dynamics of a variety of infectious diseases, but many contain only a few references to smallpox (Anderson and May 1985, 1991; Busenberg and Martelli 1991) or none (Anderson 1982; Anderson and May 1982; Bolker and Grenfell 1992). Anderson and May (1991) estimate the interepidemic periods (T) for measles and smallpox from Equation (5); both diseases have the same value for D (12 days), but the authors quote values for the average age of infection (A) as four to five years for measles and 12 years for smallpox. The calculated interepidemic periods for measles and smallpox are given as two and five years respectively, corresponding to the observed values of T for measles (two years; England 1948–1968) and smallpox (five years; India 1868–1948). All published reports, however (Creighton 1965; Mercer 1985; Pitkanen, Mielke, and Jorde 1989; Razzell 1977), show that smallpox was predominantly a disease of younger children and that the average age of infection was much less than 12 years. Therefore we have analyzed smallpox epidemics during this period and have attempted a resolution of this apparent discrepancy.

OBJECTIVES

We have studied two widely differing communities in England during 1600–1800, thereby covering the period when smallpox was believed to be increasing in virulence. The disease is shown to be endemic, with periodic epidemics superimposed in London, whereas in Penrith periodic epidemics can be detected but smallpox did not occur in the interepidemic years. We chose Penrith as a representative small (population approximately 2,000), semi-isolated, rural community where the population dynamics are being studied in detail. It is situated in the Eden Valley in Cumbria, close to the Roman Wall and the Scottish borders.

The objectives of this study are as follows 1) to determine the periodicity of smallpox epidemics in these two communities by time-series analysis. In Penrith, the appropriate data must be derived indirectly. 2) To compare the periodicities of the epidemics with that predicted by Equation (5). 3) To demonstrate that the epidemics in both London and Penrith do not die out, as would be predicted by Equations (1)–(4) (Anderson and May 1991). 4) To determine whether the epidemics and the oscillations in smallpox deaths could be maintained and driven by external factors such as regular periods of famine. Such periods of famine, it is suggested, produced cyclic changes in susceptibility to the disease. 5) To

examine the effects of applying periodic fluctuations in susceptibility to the coupled Equations (1)–(4); we show that such computer simulations satisfactorily describe the dynamics of smallpox in both London and Penrith during the period of study. 6) To demonstrate by modeling that the two-year epidemics in London could be maintained and superimposed on the endemic state by a one-year annual cycle in susceptibility, whereas the five-year epidemics in Penrith could be maintained by a five-year cycle in susceptibility. 7) To study by time-series analysis whether the five-year smallpox epidemics at Penrith synchronize with a regular cycle in wheat prices.

THE USE OF TIME-SERIES ANALYSIS IN DEMOGRAPHIC RESEARCH

Conventional time-series analysis has proved to be a valuable technique because it allows the investigation of continuous data over time and identifies cycles in baptism and burial records. The techniques available include

1) Spectral analysis. The data series (i.e., the number of births, deaths, or other events in each year) are fed into the computer program which analyzes the relative importance (or strength) of the different cycles contained within the series and identifies their wavelength or period (i.e., the number of years for a complete cycle or oscillation). The significance of these cycles can be tested. A printout of spectral analysis is illustrated in the inset in Figure 2.

2) Filter design. When one cycle or more has been identified by spectral analysis, this program designs a filter that removes noise and other unwanted oscillations from the data series. The characteristics of the filter used (i.e., the filter window) are shown in the inset in Figure 1.

3) Filtering. The data series now can be filtered appropriately and the resulting cycles can be displayed.

4) Autocorrelation function (acf). The filtered data can be fed into this program which determines the wavelength of the oscillation(s) as well as the significance.

5) Cross-correlation function (ccf). This program compares two filtered data series over a standard time period; it provides an estimate of the significance of the correlation between them and of the delay (or lag) between the two cycles.

6) Input-output functions. This program tests whether the oscillations of one data series are driving a second series and provides an estimate of the significance of the separate cycles within complex (and frequently noisy) waveforms.

Difficulties arise for the demographer when (as would be expected in human populations) the cycles detected have a period that varies slightly (e.g., a six-year cycle may fluctuate between five and eight years); in these circumstances only a poor value for the acf at a specific wavelength is obtained.

METHODS

We extracted the data from the published records of the parish of Penrith, Cumbria (Haswell 1938); we made no attempt to test the robustness of the records, to consider the effects of immigration and emigration, or to estimate the underregistration of baptisms. Nevertheless, inspection of the registers suggests that the burial series represents a reasonably accurate record of the deaths in the community, the most important data considered in this paper. Baptisms are regarded as a record of births.

We conducted spectral analysis, filtering, autocorrelation, crosscorrelation functions, input-output functions, and coherence by Shumway's (1988) time-series computing method, using an IBM PC AT. We developed the matrix model using the 386-MATLAB package and ran it on an IBM PS/2.

The significance of the cyclic components in the data series was tested as follows. Under the null hypothesis, H_o, no cyclic component is present in the time series (which is assumed to be distributed normally about its mean). It can be shown that the peaks of the power spectrum of the time series divided by the variance are distributed proportionally to the chi-squared distribution, with two degrees of freedom (Priestley 1981). Because the variance of the time series is not known, it must be estimated from the data. The null hypothesis is checked against the largest ordinate of the power spectrum. If the null hypothesis is not accepted (i.e., if a cyclic component is present), Whittle (1952) suggests applying the test sequentially, dropping the largest peak at each stage until the null hypothesis is accepted.

SMALLPOX IN LONDON, 1647–1812

The first epidemic of smallpox in London, as shown by the Bills of Mortality (Creighton 1965), occurred in 1628, followed by a moderate epidemic in 1632 and a severe one in 1634. The London figures are lost for 1637–1646, although it is known that a major epidemic struck in 1641. The Bills of Mortality thereafter are complete for 1647–1812; smallpox was endemic during these years but retained its epidemic character (Hardy 1983). Spectral analysis of this data series shows that oscillations with wavelengths of two and three years are present and that the former is significant at the 95% level. Figure 1 shows these two- to three-year cycles after filtering; the autocorrelation function (-0.74 for a one-year lag) shows that an epidemic is extremely unlikely to occur in the year immediately following an outbreak. When the series is divided into three periods—1647–1700, 1700–1750, and 1750–1812—spectral analysis shows that the three-year cycle is more dominant during the seventeenth century, whereas the two-year cycle is of greater importance after 1750.

The two- to three-year interepidemic period for smallpox in London (where it is clearly endemic) detected by time-series analysis is at variance with the calculated and observed values of five years quoted by Anderson and May (1991). The interepidemic period (T) is dependent on the average age at infection (Equation (5)). In places where it was endemic, smallpox was almost wholly a disease of children; nearly all native inhabitants of London had been infected by age 7. In Kilmarnock in 1728–1762, the mean age at death was 2.6 years. Of a total of 613 smallpox deaths, 563 occurred to children under age 5 (Razzell 1977). By family reconstitution we have determined the ages of persons dying of smallpox at Penrith in the known epidemics of 1656 and 1661; their mean age (including two adults) was 4.5 years.

Equation (5) predicts interepidemic periods of two years when the average age of infection = 2 to 5 years. We conclude that epidemics in London broadly follow Anderson and May's dynamics but that the true calculated interepidemic period is two to three years, agreeing with the data presented in Figure 1.

Equations (1)–(4) generate a damped oscillation: that is, the predicted oscillations (epidemics) decay and die out rapidly (Anderson and May 1991). This pattern clearly does not agree with the results over 160 years presented in Figure 1, where the oscillations increase in size (amplitude) and the interepidemic period decreases. Anderson and May (1991) suggested that stochastic effects can perpetuate an oscillation, thus locking the system into sustained cycles. The biennial outbreaks of measles have fascinated

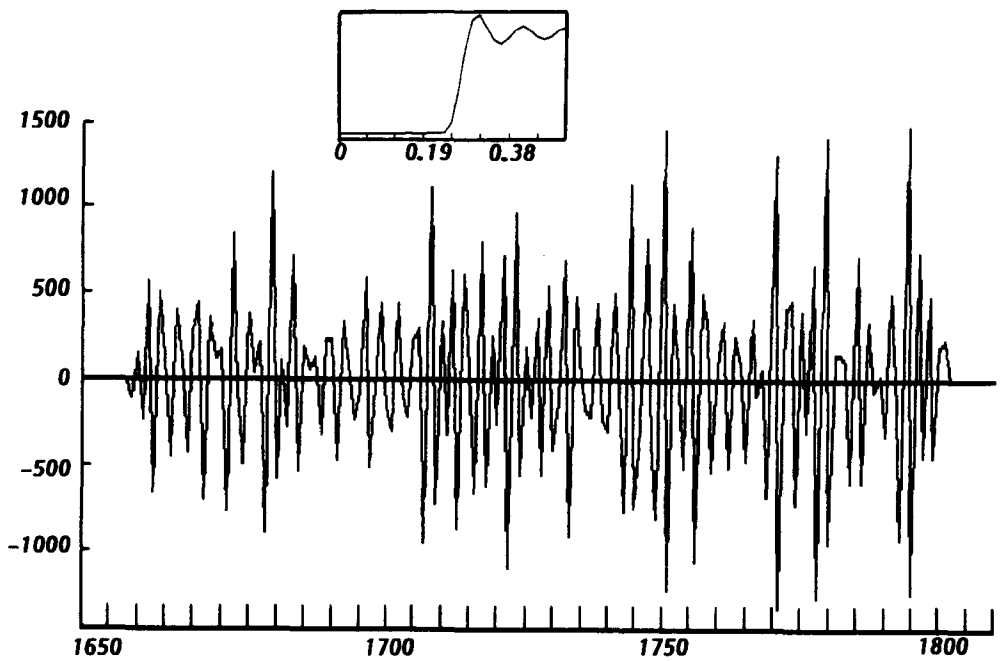

Figure 1. London smallpox deaths, 1647–1812, filtered to show short wavelength oscillations. Epidemics of two- to three-year periodicity show clearly. Inset: frequency response of filter used, i.e., filter window = wavelengths below 3.7 years; abscissa = cycles/year.

mathematical modelers of infectious diseases for many years, and different mechanisms have been suggested to explain their occurrence (Thieme 1991); one suggestion concerns the interaction of age structure and seasonal forcing associated with the school system (Schenzle 1984). Therefore it is possible that the oscillations in the smallpox epidemics in London are maintained and perpetuated by additional external factors.

WAS SMALLPOX ENDEMIC IN CITIES OUTSIDE LONDON IN THE SEVENTEENTH AND EIGHTEENTH CENTURIES?

We have many accounts of smallpox epidemics in rural England in the eighteenth century (Creighton 1965; Razzell 1977), but this does not necessarily mean that the disease was endemic; indeed, accounts of spectacular outbreaks with widespread mortality indicate a population that had not recently experienced the disease and in which most individuals were susceptible. An example is the outbreak in the Island of Foula (Shetland Islands) in 1720, where only about six persons survived out of a population estimated at 200 (Razzell 1977). The London Bills of Mortality show that smallpox was endemic in that city, but there is little corresponding direct evidence for the status of the disease in the seventeenth and eighteenth centuries in other large cities. It has been suggested, however, that smallpox was endemic in such cities as Nottingham, Chester, Northampton, Norwich, and Manchester (Mercer 1985) after 1725 and before it was brought under control by inoculation and then by vaccination. In 1774 Chester, with a population of 14,700, had 1,385 cases of smallpox with 202 deaths; 180 of these were of children under 5 (Creighton 1965).

We also have studied the records of Chester, Edinburgh, and Glasgow by time-series

analysis (data not presented here) and have shown 1) that smallpox was endemic in these cities in the eighteenth century; 2) that regular epidemics occurred, superimposed on the endemic state; 3) that these oscillatory epidemics did not die out with time; and 4) that the interepidemic period (T) was two to three years. It is evident that the dynamics of this viral disease in these cities correspond closely with those in London.

SMALLPOX EPIDEMICS IN RURAL TOWNS

Only limited information is available on smallpox epidemics in rural towns during 1600–1800, although there are many accounts of occasional major outbreaks throughout Britain (Creighton 1965; Razzell 1977). For example, "It was a major source of loss of life through the [18th] century and a disease relatively easily identified. In rural parishes and small towns it appeared every four years or so, usually in summer and sent up child mortality sharply" (Flinn 1977, p. 290). What were the interepidemic periods? Did the epidemics follow Anderson and May's dynamics? Was the disease endemic?

Penrith is a rural market town that has been chosen as an area for the intensive study of its population dynamics (Duncan, Scott, and Duncan 1992). We use it here as an example of a much smaller town in which smallpox epidemics were recorded in the parish registers in 1656 and 1661. During the period 1600–1750 the mean annual number of baptisms (60) and burials (60) remained remarkably constant in spite of oscillations. These figures suggest that the size of the population was largely unchanged over 150 years, and is estimated at about 2,000. The population increased rapidly after 1750. Penrith is situated in the Eden Valley in the far north of England and appears to have been a semi-isolated northern community living under marginal farming conditions, with frequent famines and high childhood mortality (Duncan et al. 1992). The series of child burials has been determined from the parish registers and has been analyzed to determine indirectly the evidence for the incidence of smallpox. Equations (1)–(4) and many historical reports (Creighton 1965; Mercer 1985; Razzell 1977) show 1) that the disease was confined largely to children, who formed the bulk of susceptibles in endemic or epidemic situations; 2) that an epidemic exploded suddenly but burnt out quickly; and 3) that major outbreaks tended to be confined to certain months of the year.

Spectral analysis of the child burials at Penrith shows a major peak at a frequency of 0.19 (i.e., the period of the cycles is five years). Figure 2 illustrates these five-year cycles after filtering (acf at 5 years = 0.63), which synchronize with the two recorded major outbreaks of smallpox at Penrith in 1656 and 1661.

Inspection of the child burial series at Penrith shows periodic aggregations of child deaths with high mortality for 10–12 weeks. Therefore we analyzed the series further by determining the largest total for three consecutive months in each year. Spectral analysis shows the major peak at wavelength five years; the data (1557–1812) have been filtered with the same filter as that used in Figure 2, and are shown in Figure 3. The oscillation has a wavelength of five years for 1600–1812; the acf = 0.63, but analysis of the middle period 1660–1775 reveals a higher acf of 0.71. The series of child burials (Figure 2) corresponds closely to the series of the largest three-monthly totals (Figure 3), with a high cross-correlation function of 0.95. We conclude that these five-year periodic outbreaks of child mortality, which are confined largely to three months in the year, make the dominant contribution to the five-year oscillations in child mortality. We also divided child burials at Penrith (1650–1812) into four periods and plotted them on a monthly basis. Linear filtering again revealed clear oscillations with a wavelength of five years (1650–1812).

The foregoing gives evidence of five-year epidemics at Penrith of an infectious, lethal disease with a strong seasonality, in which the epidemic burnt out rapidly (unlike the

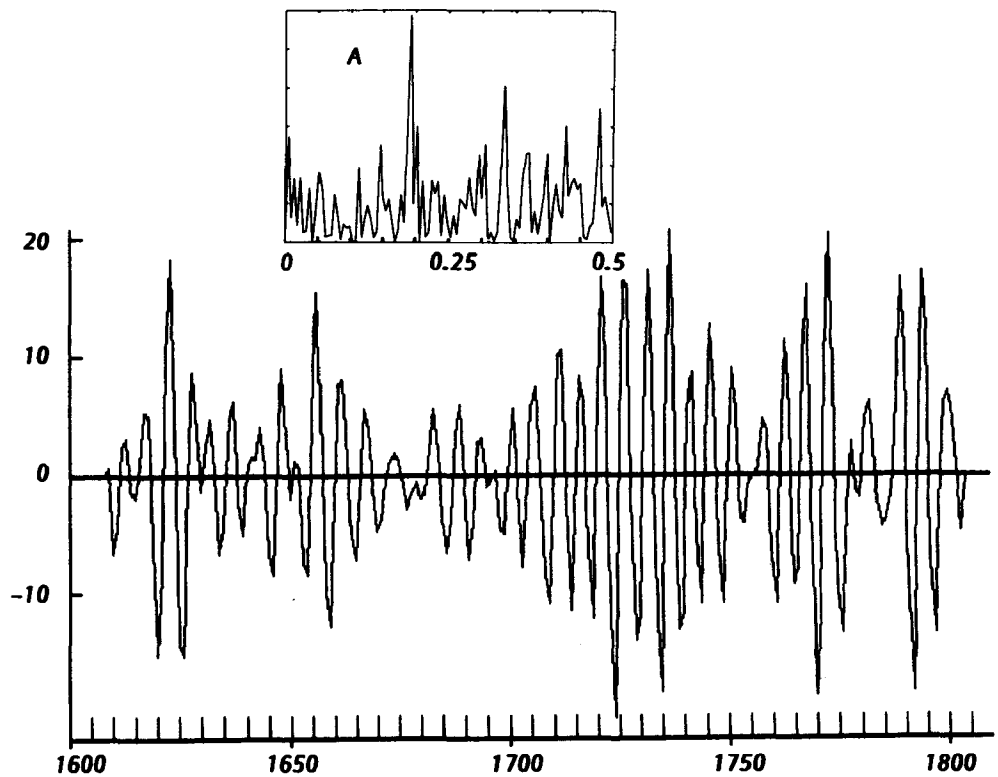

Figure 2. Child burials at Penrith, 1600–1812, showing five-year cycles after filtering. Filter window = 4–8 years. Abscissa = years. Inset (A): spectral analysis of unfiltered data; abscissa = frequency of oscillations (1/years); note major peak at five years.

plague). A comparable study of the adult burials showed no oscillations with these characteristics; the disease apparently is confined largely to the children. The peaks of these five-year cycles fit with the recorded years of smallpox outbreaks. We suggest that this study provides evidence of smallpox epidemics with an interepidemic period of five years. There is no evidence that smallpox persisted during the interepidemic years; that is, the disease was not endemic. The five-year cycles of explosive epidemics therefore do not conform to Equation (5). The situation was different from that in London, where the predicted two- to three-year outbreaks were superimposed on a persistent disease.

ORIGINS OF THE FIVE-YEAR OSCILLATION AT PENRITH

Inspection of the filtered burial series 1557–1611 shows that a five-year oscillation in adult deaths emerged clearly only after 1585, whereas this cycle in child burials is evident from 1557. Oscillations in adult and child burials are synchronous (i.e., they cross-correlate at zero lag; ccf = 0.92). Therefore we have evidence of a basic five-year cycle in total deaths developing progressively from the middle of the sixteenth century, perhaps driven by cyclical, external factors to which the children show greater sensitivity than the adults. Yet the data both for the greatest annual three-monthly totals for child burials and for monthly child burials show clearly that the seasonal, explosive outbreaks in child (but not adult)

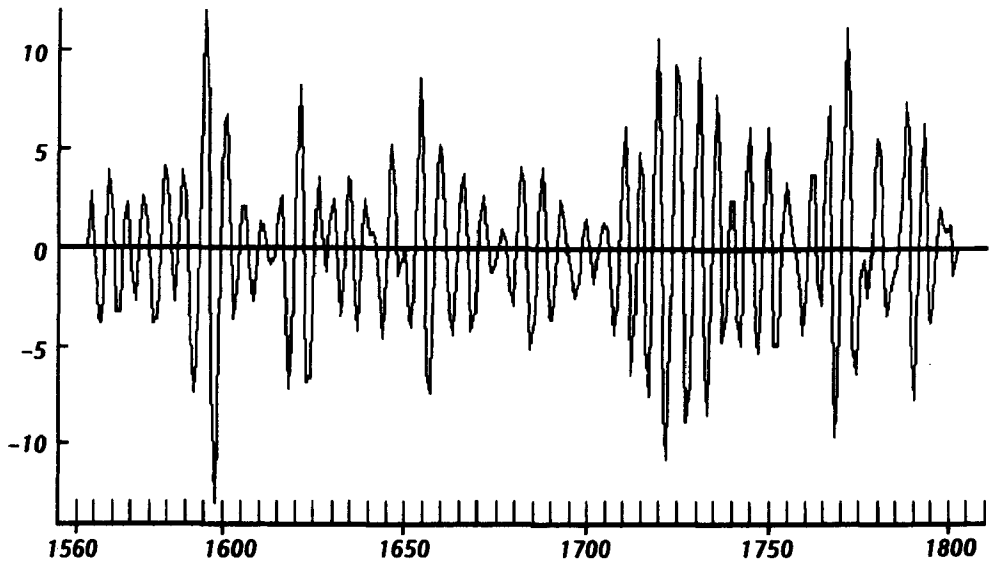

Figure 3. Child burials at Penrith, 1557–1812, plotted as the highest total for three consecutive months in each year after filtering. Filter window = 4–8 years. Abscissa = years.

mortality began sharply after 1636. This finding supports the view that a virulent form of smallpox developed during the mid-seventeenth century (Smith 1987). We conclude tentatively that the serious, lethal smallpox epidemics at Penrith began at about this time (at approximately five-yearly intervals) and were superimposed on a preexisting five-year mortality cycle.

DRIVING THE 5-YEAR EPIDEMICS AT PENRITH

How, then, were the persistent five-year cycles in child burials at Penrith, which are believed to be related at least in part to smallpox epidemics, established and determined? They do not appear to obey Equation (5); that is, the oscillations do not die out, and the interepidemic period was five years rather than two years, as would be predicted. There is good evidence that infection in many diseases is linked to poor nutrition (Scrimshaw, Taylor, and Gordon 1968), and it has been suggested that smallpox epidemics are related specifically to poverty and famine (Flinn 1977). Annual grain prices would reflect both the quality of the harvest and the level of hardship, famine and malnutrition, particularly among laborers and poorly paid individuals. The quality (as well as the quantity) of the diet of pregnant and nursing mothers is known to be particularly important in determining the children's birth weight and health. We took data for annual wheat prices for 1600–1812 from Stratton (1970) and filtered them. The resultant five-year oscillation is shown in Figure 4 (acf = 0.47). A more detailed analysis of the wheat price series (results not shown) shows that the wavelength varied between five and six years during the early years (1600–1670) but stabilized thereafter at five years. Testing the peaks displayed by spectral analysis showed that the five-year cycles were significant only at the 90% level and probably reflected an oscillation that varied between five and six years.

The five-year cycles in wheat prices synchronize with child burials at Penrith; that is, the maximum ccf value revealed by time-series analysis is at zero lag. We tested the thesis

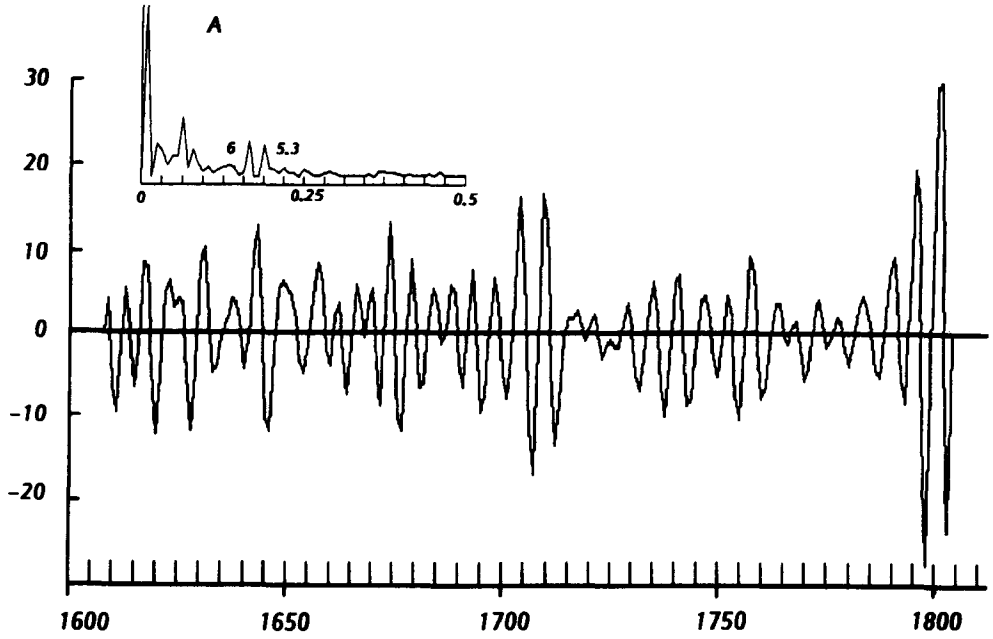

Figure 4. Wheat prices, 1600–1812, to show five-year oscillations; filter window = 4–8 years; abscissa = years. Inset (A): power spectrum of unfiltered data; 5.3- and 6-year cycles are indicated; abscissa = frequency (1/years).

that wheat prices determine child deaths by analyzing the input-output relations of the two series without filtering (Shumway 1988). Wheat prices and child burials were found to be significantly coherent in the frequency bands of five to six years ($p < 0.025$); that is, the correspondence between the two oscillations is excellent. We suggest that there is evidence that regular cycles in wheat prices drive oscillations in child deaths at Penrith, and that these deaths are associated both directly and indirectly with malnutrition.

Analysis of the index of annual wheat prices for an earlier period, 1450–1630 (data taken from Bowden 1967), shows a marked change around 1575; before this date the oscillations in prices are small and of wavelength eight to nine years. The five-year oscillation in prices became clearly established only after 1575 (Figure 5). The five-year cycle in child burials at Penrith was established during this time (see above) and cross-correlates well with the wheat index during 1557–1592 (ccf at zero lag = 0.63). We conclude that the five-year oscillation in wheat prices generated the five-year oscillation in child deaths; 100 years later the smallpox epidemics were superimposed on this preexisting and underlying fluctuation in susceptibility, thereby exacerbating the oscillations in child mortality.

Once an epidemic had burnt out, it took five to six years to build up a density of susceptibles consisting of 1- to 6-year-olds sufficient for an epidemic to be initiated. Epidemics probably originated with travelers because Penrith lay on the main road to Scotland. The spread of the disease during epidemic years would be facilitated if outbreaks of smallpox in nearby towns with similar dynamics were locked to the same cycles of hardship and famine. We suggest that regular oscillations of famine and malnutrition produced periodic fluctuations in susceptibility ($= \beta$, transmission coefficient; see Equations (1) and (2), so that the two cycles became synchronous (i.e., phase-locked). Once

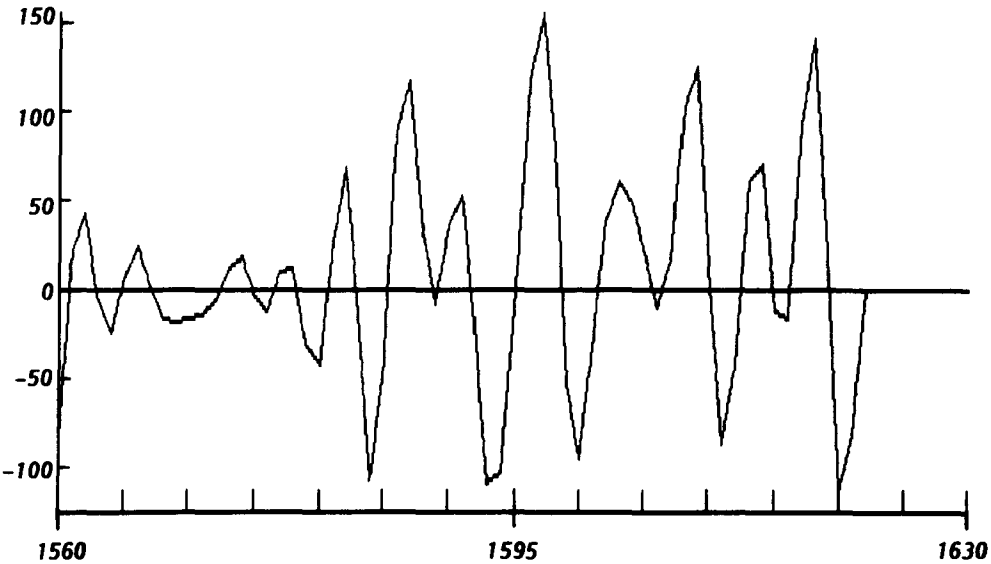

Figure 5. Wheat index numbers, 1560–1630, filtered to show five- and six-year oscillations; note that amplitude increases after 1580. Filter window = 4 to 9.1 years; abscissa = years.

established, the five-year smallpox epidemics would not die out but would be largely self-perpetuating, requiring only perpetuation by a fluctuating susceptibility.

EFFECT OF VARIATION IN SUSCEPTIBILITY

Anderson and May (1991) model the spread of a disease through a population formed completely of susceptibles; the population recovers after the initial enormous mortality, but the second epidemic is less severe because the bulk of the population is now immune. Successive epidemics are progressively less severe; the oscillations die out after some six cycles, and the population settles at its steady (endemic) level. Thereafter a system obeying Anderson and May's dynamics will not continue to oscillate (i.e., epidemics will not be seen) unless triggered by external factors. Smallpox epidemics clearly did not die out either in London (where it was endemic) or in Penrith (where it was not endemic); thus we conclude that external factors were operating to maintain the oscillations.

We consider here the theoretical effect of applying a cyclical variation in susceptibility (β) to the coupled Equations (1)–(4) on our model populations at London and Penrith. The derivation of the appropriate equations is given in the appendix but, in summary, the model considers different conditions of population size x susceptibility ($= N\beta$). The population size (N) takes into account the very different population size and density at London and at Penrith. The driving force is a cyclical variation in susceptibility (β), so that changes in its amplitude and period can be investigated by computer modeling. Two possible types of oscillations in susceptibility are considered: 1) an annual seasonality cycle and 2) a five-year cycle associated with famine and hardship, linked directly to grain prices, as described above. The following conditions are modeled:

1) *Penrith.* Oscillation in susceptibility: amplitude = 0.05; wavelength = five years (i.e., linked to grain prices). Figure 6 shows that with only this small amplitude of changes in susceptibility, very large epidemics are generated at a periodicity of five years. There are

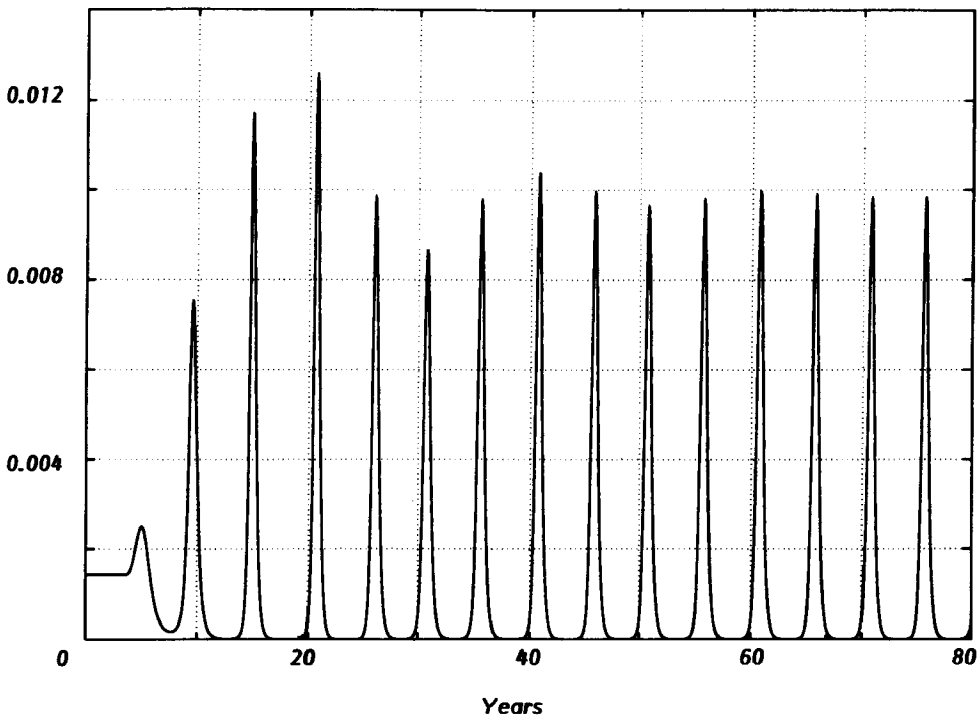

Figure 6. Computer simulation of events at Penrith, where $N\beta = 85$, $\delta\beta = 0.05$, period of input oscillation = 5 years, N = 2,200. Ordinate: number of infectives/N at any one time. Note number of infectives in the year = area under the curve for that year. Abscissa: years after the start of simulation. A small $\delta\beta$ generates large five-year epidemics.

virtually no infectives in the interepidemic period (i.e., the disease is not endemic). A corresponding simulation for the number of susceptibles shows the progressive buildup during the interepidemic period (associated with new births) and the dramatic fall at each epidemic.

2) *London*. Oscillation in susceptibility: amplitude = 0.05; wavelength = five years (grain prices); smallpox is endemic. The natural period of the system is two years (defined by Equation (5)), but with a small amplitude in the oscillation in susceptibility, the linear part of the system dominates (see appendix); the five-year sinusoidal input generates a five-year output oscillation of very small amplitude. If the amplitude of the five-year oscillation in susceptibility is increased to the much larger value of 0.25, an additional two-year epidemic is produced. The resultant period is 2,3,2,3 . . . ., although the five-year component dominates (Figure 7). The effect is alternating two- and three-year epidemics. We conclude that the five-year cycle in grain prices would be unlikely to cause such an abnormally large fluctuation in susceptibility, and thus is not the main factor governing the two- and three-year epidemics.

3) *London*. Oscillation in susceptibility: amplitude = 0.2; wavelength = one year (annual seasonality); smallpox is endemic. The system generates an epidemic every other year, so that a one-year annual input produces a two-year cycle (Figure 8); that is, an annual, seasonal variation in susceptibility is a perturbation sufficient to maintain the natural frequency of epidemics (Equation (5)) at two to three years.

The foregoing simulations simply illustrate how different patterns of epidemics

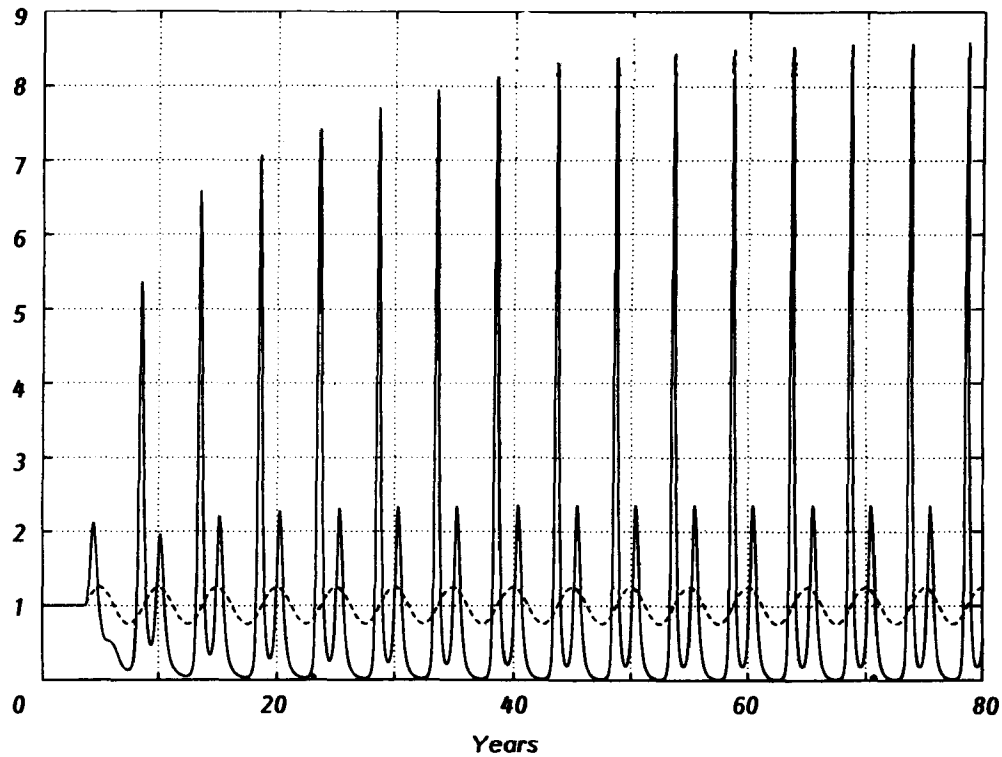

Figure 7. Computer simulation of smallpox epidemics in large conurbations where disease is endemic. $N\beta$ = 270, $\delta\beta$ = 0.25, period of input oscillation = 5 years. Ordinate: solid line, fraction of population infected, where original steady-state level = 1.0; dashed line = fractional change in β. Abscissa: years after start of the simulation. A sinusoidal five-year input generates alternating two- and three-year epidemics.

theoretically can be generated by a fluctuation in susceptibility in a system described by Equations (1)–(4). They show that the important variables are the size and density of the population, the variation in susceptibility, and the period of its oscillation. In comparing different populations, it is evident that N is not simply the total size of the population but is related more closely to the average population density. Only very small changes in susceptibility (5%) are necessary to generate large epidemics under the simulated conditions at Penrith (see Figure 6).

DISCUSSION

We have analyzed the smallpox epidemics in England in the seventeenth and eighteenth centuries, using two different representative populations to illustrate the different dynamics of the disease: 1) London, a large city, with a large population at high density, where smallpox was endemic, and 2) Penrith, a rural town with a much smaller population, part of which was at low density in scattered farms surrounding the town center; smallpox was not endemic there. Epidemics occurred at two- to three-year intervals in London. Conversely, analysis of the parish records at Penrith suggests that the epidemics there had a periodicity of five years; our current studies (data not presented here) suggest that many other rural parishes in Northwest England experienced similar five-year epidemics.

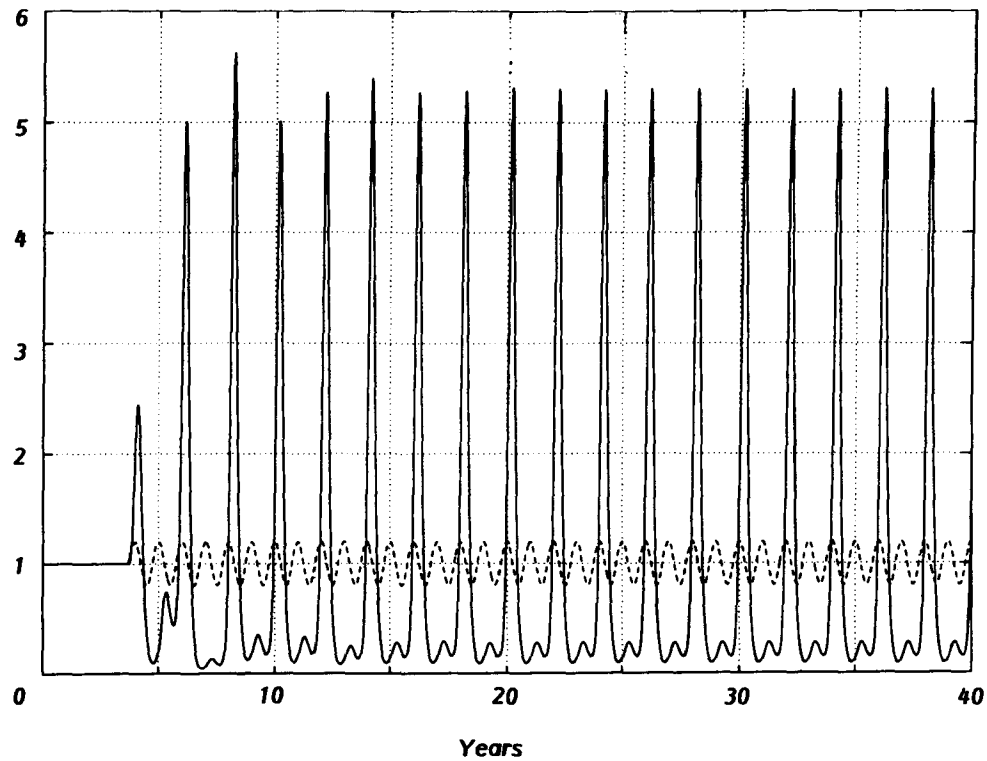

Figure 8. Computer simulation of smallpox epidemics in large conurbations with an input of a one-year sinusoidal change in β (dotted line). $N\beta = 270$, $\delta\beta = 0.2$. Ordinate: solid line = fraction of population infected, where steady-state level = 1.0; dashed line = fractional change in β. Abscissa: years after start of the simulation. One-year input generates two-year epidemics.

Equation (5) predicts that the interepidemic period for smallpox would be 2 years; Equations (1)–(4) show that oscillatory epidemics in the absence of a driving factor would die out quickly. We suggest that these apparent discrepancies between observed historical events and the theory of the dynamics of viral diseases may be resolved by driving the system with a periodic fluctuation in susceptibility to the disease. We have used computer modeling to demonstrate the effect on the population dynamics (compare Figures 6 and 2).

The five-year smallpox epidemics at Penrith synchronize and cross-correlate with the five-year cycle in wheat prices. We suggest that the consequent periodic variation in famine and hardship produced a corresponding small oscillation in susceptibility to the disease in this community living under marginal farming conditions in the Eden Valley. The five-year interepidemic period was crucial in allowing the buildup of the population of susceptibles by new births to a level sufficient for an epidemic explosion, which could be triggered by a periodic fluctuation in susceptibility. We suggest that the smallpox epidemics in children were superimposed on preexisting cycles of general mortality associated with famine. These results may be compared with those for the more diffuse population in the Åland (Finland) archipelago in 1750–1805 (prevaccination). There, spectral analysis demonstrated a strong seven-year periodicity, reflecting the longer time necessary to build a cohort of susceptibles (Mielke et al. 1984). Smallpox was a winter disease in Finland (Jutikkala and Kauppinen 1971); there is evidence that smallpox epidemics were triggered by a lowered resistance associated with winter/spring food shortages (Mielke et al. 1984).

A considerable literature examines the relationship between grain prices (on one hand) and mortality and susceptibility to disease (on the other). A positive association between fluctuations in wheat prices and deaths from epidemic disease (typhus, smallpox, and fevers) has been described by Galloway (1985, 1988), who found that 46% of deaths among persons over age 5 in France in 1677–1734 were associated with fluctuations in grain prices. In England (1675–1755) the figure was lower: 24% of noninfant deaths were associated with grain price fluctuations. Dyson (1991) has provided an analysis of the interaction between famine conditions and epidemics in southeast Asia.

Smallpox deaths in London for the period 1670–1830 varied significantly in response to grain prices. Landers (1987) has shown that smallpox and "fevers" stand out from other causes of death in London in this period in that their age distribution points to a heavy contribution from recent migrants. He argues that this situation arose because immigrants from the countryside would not have had the same exposure as Londoners to infections such as smallpox that were endemic in London, and would not have acquired immunity. Thus the association between price fluctuations and smallpox mortality in London reflected rural stress in periods of high prices. Insofar as urban mortality responded to price movements, it did so because of the immigration of adolescents and young adults who lacked immunological protection against specific infections. Therefore Landers suggests that the major impact of variations of food availability on mortality was indirect; it caused migration and exposure to disease rather than working directly through changes in susceptibility to infection. Our studies however suggest that most of the adult population outside London had not escaped infection during childhood and thus were immune, so that migration probably was of secondary importance.

Lee (1981) found only a weak relationship between fluctuations in wheat prices and mortality for the period 1541 to 1871: only 16% of the short-run variation in mortality was associated with price changes. The pattern of the lag between price fluctuations and mortality was suggestive: mortality rose in the same year only when prices were high. Otherwise it fluctuated sympathetically after a delay of one or two years. Outright starvation probably was uncommon, but high prices might lead to a gradual physical weakening of segments of the population because they were forced to draw first on financial or food reserves and then on bodily reserves. Lee also suggested that harvest failure promoted short-run migration in search of food and work, which may have helped the spread of disease.

Lee's econometric analysis agreed broadly with Appleby's (1975) conclusion that although variations in food prices might be significant in a regional context, they were not important in determining national fluctuations in mortality. High food prices were not a significant cause of catastrophic mortality after the mid-seventeenth century. Yet a more subtle analysis of the association between mortality and food price fluctuations reveals that the connection was always weak, but was not broken entirely until the mid eighteenth century. Slack (1979) concluded that "while some increases in mortality undoubtedly did coincide with periods of near-famine, many more did not and the relative importance of diseases associated with malnutrition is not yet established" (p. 10). Computer modeling studies (see above), however, show that only very small fluctuations in susceptibility are sufficient to trigger epidemics in a system that is fundamentally oscillatory. The thesis that each insult from illness or injury leaves the individual more susceptible to disease has been modeled by Alter and Riley (1989).

Lunn (1991) provides a detailed review of current beliefs on the interaction between nutrition, immunity, and infection. He concludes, "It has become generally accepted that malnutrition predisposes an individual to infectious diseases. Moreover, when illness does strike, it is likely to be more severe, prolonged and carries an increased risk of death" (p. 136). Not all infections are affected equally; among viral diseases, smallpox is regarded as

less strongly dependent on nutritional states (Chandra 1983). An association between malnutrition and host's depressed resistance to infection has been recognized for centuries (Lunn 1991); more recently it has become clear that tissues associated with the immune system (thymus, spleen, lymph nodes, tonsils) are more sensitive to nutritional deficits than many other organs of the body (Chandra 1980). Lunn (1991) concludes that malnutrition is associated with a lowering of immunocompetence, which is expressed as a greater susceptibility to infectious disease.

Recent studies in historical epidemiology, particularly those in Hertfordshire in 1911–1930, have shown that nutrition during pregnancy and infancy is critically important for growth and development and for the subsequent health of the adult (Barker 1992a, 1992b). A high neonatal mortality and a high incidence of low birth weight are associated directly with poor maternal nutrition (Barker and Osmond 1986). Death rates of men from ischemic heart disease who weighed less than 8.2kg at one year of age were three times greater than among those who weighed more than 12.3kg (Barker et al. 1989). Ischemic heart disease, stroke, hypertension, and obstructive lung disease now are believed (Barker et al. 1991) to originate through impaired growth and development during fetal life and infancy; they may be consequences of "programming" whereby a stimulus or an insult at a critical period of early life results in long-term changes in physiology or metabolism. "Programming" occurs because organs mature during periods of rapid growth in fetal life and infancy, and there are critical windows of time during which maturation must be achieved. Nutritional deprivation in early life can affect the size of many organs; which organ is affected depends on the precise time at which undernutrition occurs (Barker 1992a).

The population at Penrith was living under marginal conditions. Any fluctuations in the availability or quality of food would have had profound effects, both immediately in neonatal mortality and susceptibility to disease, and in the longer-term health of the adults. The positive cross-correlation and synchronization of grain prices with child and adult mortality in 1560–1800, and with smallpox epidemics in 1630–1800 at Penrith, support these findings that famine and malnutrition during pregnancy and lactation not only caused death directly by starvation but also had more profound and longer-lasting effects on the children's health.

Time-series analysis is a valuable tool for the historical demographer. The existing literature on smallpox epidemics in England is inevitably anecdotal; statistics of smallpox deaths are provided in Bills of Mortality, and we have a number of quite detailed accounts of major, sporadic outbreaks of the disease in different parts of England during this 200-year period. We have attempted to provide the first detailed, quantitative description of these epidemics in two very different, representative situations: a large city where smallpox was endemic and a small rural town where the disease did not persist between epidemics.

Mathematical theory of infectious diseases predicts 1) that the interepidemic period for smallpox is two to three years, and 2) that oscillatory epidemics die out quickly unless the system is perturbed in some way. We have shown clearly for the first time that these oscillations are not damped out, and that regular epidemic episodes persisted for more than 150 years in both situations. The interepidemic period is two to three years in large conurbations (in agreement with 1)), whereas it is five-years in Penrith (and other rural towns).

We explain these apparent discrepancies as follows. Each system will tend to resonate at its natural frequency, determined by its population size and density (which govern the birth rate of new susceptibles and the ease of spread of the disease) and by its sensitivity to external factors. If the external factors fluctuate regularly (one-year or five-year cycles), they are sufficient to perpetuate the oscillatory epidemics. These dynamics of smallpox can be demonstrated readily by mathematical modeling and computer simulation: in London the system naturally oscillates with a two- to three-year periodicity (see Equation (5)) and

requires only a minor perturbation. In Penrith, however, approximately five years are required for an adequate buildup of susceptibles, whereupon an epidemic can be triggered by a periodic small change in susceptibility.

APPENDIX
DERIVATION OF EQUATIONS FOR MODEL

The theoretical effects of a sinusoidal variation in β (susceptibility or transmission coefficient) on Equations (1) to (4) are modeled (Olsen, Truty, and Schaffer 1988; Olsen and Schaffer 1990). Three changes have been applied to Equations (1)–(4): 1) The latent stage of the infection is ignored, and the latents are incorporated into infectives. 2) The death rate from smallpox, α, is included in the equations. In order that the average population remain constant under these circumstances, the birth rate must be $\mu N + \alpha Y$. 3) In Equations (1)–(4) the variables X, Y, and Z give the absolute numbers in each class, but when the approach described in Anderson and May (1991) is used, the equations are written in terms of the fraction of the population in each class by defining three new variables

$$x = \frac{X}{N}; \quad y = \frac{Y}{N}; \quad z = \frac{Z}{N}.$$

When these changes are incorporated, Equations (1)–(4) reduce to

$$\frac{dx}{dt} = \mu + \alpha y - \mu x - N\beta xy \tag{A1}$$

$$\frac{dy}{dt} = N\beta xy - (\mu + \alpha + \gamma)y. \tag{A2}$$

Note that it is necessary to solve only two equations because the fraction of the population that is immune, Z, can be deduced from the fact that $x + y + z = 1$. Because the effect differs with different population sizes (N), Equations (A1) and (A2) are considered as a nonlinear system that is driven by variations in $N\beta$. For given values of death rate (μ), smallpox death rate (α) and recovery rate (γ), the natural frequency of the system is determined by the value of $N\beta$. For small amplitudes of the variation ($\delta\beta$) the response is approximately linear; thus the output is sinusoidal for a sinusoidal variation in $\delta\beta$ at the same frequency but with different amplitude and phase. As $\delta\beta$ is increased, the nonlinear effects come to dominate and the response becomes nonsinusoidal.

The system is assumed to start in steady state: the original oscillations are damped out. The driving force for the system is a variation in susceptibility, β, which consists of one of two sinusoidal oscillations: 1) an annual seasonality cycle or 2) a five-year cycle associated with famine and hardship. These variations in β generate two- to three-year epidemics superimposed on a steady endemic level in London and create five-year epidemics in Penrith following a steady buildup of susceptibles. The dynamics of these populations are simulated by assuming $\mu = 0.04$, $\alpha = 4.0$, $\gamma = 20.0$ (i.e., the average age at death = 25 years, the latent and infectious periods = 14 days, and one-sixth of those infected die of the disease). $N\beta = 85$ at Penrith; $N\beta = 270$ at London.

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