

Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination: time series analysis

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SUMMARY

This paper uses the techniques of time series analysis (autocorrelation and spectral analysis) to examine oscillatory secular trends in the incidence of infectious diseases and the impact of mass vaccination programmes on these well-documented phenomena. We focus on three common childhood diseases: pertussis and mumps (using published disease-incidence data for England and Wales) and measles (using data from England and Wales, Scotland, North America and France). Our analysis indicates highly statistically significant seasonal and longer-term cycles in disease incidence in the prevaccination era. In general, the longer-term fluctuations (a 2-year period for measles, 3-year periods for pertussis and mumps) account for most of the cyclical variability in these data, particularly in the highly regular measles series for England and Wales. After vaccination, the periods of the longer-term oscillations tend to increase, an observation which corroborates theoretical predictions. Mass immunization against measles (which reduces epidemic fluctuations) magnifies the relative importance of the seasonal cycles. By contrast, we show that high levels of vaccination against whooping cough in England and Wales appear to have suppressed the annual cycle.

INTRODUCTION

Oscillatory secular trends in the incidences of infectious diseases are widely observed phenomena within human communities. In many instances the periodic or epidemic outbreaks of infection are strikingly regular in occurrence. Such patterns have aroused considerable interest amongst both epidemiologists and mathematicians (Brownlee, 1915; Soper, 1929; Bartlett, 1956; Dietz, 1976; Yorke *et al.* 1979; Anderson & May, 1982*a*). In a related field of scientific study, namely that of ecology, regular fluctuations in the abundances of various animal species have stimulated similar interest in periodic population behaviour (Poole, 1974; Bulmer, 1974; Williamson, 1975; Finerty, 1980; Potts, Tapper & Hudson, 1984). Many and varied hypotheses have been put forward to explain these patterns (Williamson, 1972; May, 1973; Finerty, 1980). Today, however, in both epi-

miology and ecology, it is widely accepted that non-seasonal fluctuations arise as a consequence of the dynamical interactions between two or more populations, whether they be host and parasite, predator and prey, plant and herbivore, or indeed, any of these combinations. Climatic factors, which sometimes vary on a regular seasonal basis, may impinge upon these longer-term fluctuations to induce complex patterns of short- and long-term cycles.

In medicine, interest in periodic epidemic phenomena played a central role in the development of modern-day epidemiological theory. The arguments over the respective roles of changes in the 'infective' power of a disease agent, and the dynamic interplay between the densities of susceptibles and immunes, make fascinating reading (see Fine, 1979). Ironically, the first detailed statistical studies of cycles in disease incidence were those stimulated by John Brownlee, who was chosen in 1914 to become the first Director of the Statistical Department of the newly formed Medical Research Council (see Brownlee, 1914, 1915, 1918, 1919, 1920; Young, 1920; Zinsser & Wilson, 1932). The irony lies in the fact that Brownlee was the major proponent of the theory of changes in disease infectivity during the course of epidemic cycles. Brownlee's hypothesis was in direct conflict with earlier work by William Hamer (Hamer, 1906) and Ronald Ross (Ross, 1908, 1911, 1915, 1916, 1917), both of whom believed that the so-called 'mass action' principle of transmission (the idea that the net rate of spread is dependent on the density of infectious people times the density of susceptible individuals) explained the regular recurrence of measles epidemics. Although instrumental in providing statistical evidence for the regularity of recurrent epidemics (employing the 'method of periodograms'; see Brownlee, 1918), the demise of Brownlee's theory of infectivity followed shortly after his death in 1927. Long-term studies of viral and bacterial diseases in colonies of mice provided convincing evidence that fluctuations in incidence were largely determined by the rate of influx of susceptible animals and the acquisition of immunity (Greenwood *et al.* 1936). Firm mathematical evidence that the mass-action principle induces oscillatory fluctuations in incidence came later from the deterministic studies of Martini (1921), Lotka (1923), Kermack & McKendrick (1927) and Soper (1929), and the stochastic work of Bartlett (1956).

Since these early beginnings, the theory of epidemic cycles, founded on the cornerstone of the mass action principle of transmission, has expanded rapidly (for reviews see Bailey, 1975; Anderson & May, 1979, 1982*b*; May & Anderson, 1979). First, there is considerable mathematical interest in models of recurrent epidemic behaviour as a consequence of their non-linear dynamical properties (see Dietz, 1976; Nussbaum, 1977; Busenberg & Cooke, 1978; Green, 1978; Smith, 1978; Yorke *et al.* 1979; Grossman, 1980; Gripenberg, 1980; Stech & Williams, 1981; Hethcote, Stech & van den Driessche, 1981, 1983; Schwartz & Smith, 1983; Aron & Schwartz, 1984). The mass-action non-linearity, combined with incubation delays in the course of infection, may induce simple cycles or two-point and higher-order cycles (moving into chaos), depending on parameter values and precise model structure. Secondly, observed seasonal changes in incidence, as opposed to longer-term fluctuations, have themselves attracted attention (London & Yorke, 1973; Dietz, 1976; Yorke *et al.* 1979; Fine & Clarkson, 1982*a*; Schwartz & Smith, 1983). This is partly a consequence of their role in helping to perpetuate

or pump longer-term oscillations, and partly due to intrinsic epidemiological interest in the climatic, environmental, social and behavioural factors which trigger seasonal changes. The third, and most recent, trend is an interest in melding epidemiological theory more closely with its empirical base (Anderson & May, 1982*a*, 1983*a*; Fine & Clarkson, 1982*a, b*, 1983). In the past, much of the theory has been rather abstract in character and of mathematical, as opposed to epidemiological, interest (or indeed relevance). Yet the principles which form the template of these models, and the model properties themselves, are of great practical relevance to the interpretation of epidemiological data and in the design of control programmes based on mass immunization (Anderson & May, 1983*a*).

This paper is concerned with the latter area. We focus on three problems arising from theoretical and observational studies on longitudinal trends in disease incidence. We examine first the statistical evidence for regularity in epidemic cycles. We base our analyses on longitudinal data of three common childhood infections, namely measles, pertussis and mumps. We pose a simple question – are such cycles more regular in occurrence than would be expected on the basis of chance fluctuations alone? We employ for the first time, to our knowledge, time-series analysis methods in the examination of this problem. Observed cycle periods are compared with those predicted by theoretical studies. The second topic concerns seasonal changes and we analyse their regularity on a year-to-year basis and make comparisons between the three diseases. The last problem concerns the impact of mass immunization on both seasonal and longer-term cycles. Theory predicts that immunization programmes will act to lengthen the inter-epidemic period (Anderson & May, 1982*a*). We examine the evidence for such behaviour by reference to measles and pertussis in England and Wales.

METHODS

We employ two complementary techniques for examining periodicities in time series: autocorrelation and spectral analysis. In this section we present a general description of the two methods, and a note on interpretation. A formal description of autocorrelation and spectral analysis techniques, and details of their application, are set out in the Appendix. Detailed reviews of both methods are given by Jenkins & Watts (1968), Chatfield (1975) and Box & Jenkins (1976).

Autocorrelation

This technique is based on the construction of a series of sample autocorrelation coefficients r_k ($k = 0, 1, \dots, N-1$, where N is the length of the time series), which reflect the correlation between observations at different distances (and, therefore, times) apart within the series. In particular, r_k ($-1 \leq r_k \leq 1$) measures the correlation between the original data and the same series with a displacement (or lag) of k observations. Autocorrelations are usually interpreted via a correlogram: a plot of r_k against the lag, k . Confidence limits for a correlogram based on randomly distributed data, and an overall test for departure from randomness, can be constructed to aid in the interpretation of results (see Appendix).

Spectral analysis

The correlogram is a natural tool for analysing periodicities in time. By contrast, spectral analysis examines the contribution of oscillations at different frequencies to the observed series. Spectral analysis is based on the concept of a theoretical (power) spectrum, which partitions the total variance (or power) of the series between sinusoidal components up to a maximum, directly measurable, frequency of one cycle every two observations (Chatfield, 1975).

The analysis of epidemiological time series has concentrated on the frequency approach. A number of authors have used a harmonic (Fourier) analysis to calculate the contribution of various frequency components to observed patterns of disease incidence (Brownlee, 1918, 1920; Bliss & Blevins, 1959; Nagasawa & Kanzaki, 1977). For a process with a continuous frequency spectrum, however, harmonic analysis does not produce a consistent estimate of the theoretical spectrum (Jenkins & Watts, 1968). Instead, we calculate a spectral estimate as the Fourier Transform of the autocovariance function, using a Tukey spectral window as a noise filter (more details are given in the Appendix). In order to strike a balance between variance and discrimination, we present the results at a range of window cut-off points: $N/3$, $(N/10 + N/3)/2$, $N/10$ (where N is the length of the series), which represent increasing degrees of spectral smoothing. The discrimination of these spectra is illustrated by the bandwidths (essentially the widths) of the associated windows. For ease in comparing the contributions of seasonal and longer-term oscillations (often widely different), we plot unlogged rather than logged spectra, and give the associated multiplicative 95% confidence limits.

Interpreting correlograms and spectra

The epidemiological series which we analyse below are characterized by strong periodicities at various frequencies. In general, regular fluctuations in a time series will generate oscillations at the same frequency in the correlogram. The equivalent spectrum will show a sharp peak at the frequency of the oscillation, with smaller peaks (harmonics) at integer multiples of this frequency. In order to reduce the asymmetry of epidemic peaks, and therefore smooth the appearance of correlograms and spectra, we log transform the data (unless otherwise stated) before analyses. Finally, 'long term' changes in the mean of the data (e.g. due to changes in vaccination coverage) would tend to dominate other effects in correlograms and spectra. We therefore remove such trends by regression, where required.

Sources of data

The measles (1948–82) and pertussis (1948–82) weekly notification data were obtained from the Annual Reviews of the Registrar General of England and Wales and the quarterly Infectious Diseases Monitors published by the Office of Population Censuses and Surveys. The data of monthly records of measles cases in Aberdeen from 1883 to 1902 were obtained from the tables published by Wilson (1904), while those for Baltimore in the United States between 1900 and 1927 were extracted from the paper by Hedrich (1933). The monthly deaths due to measles in Paris between 1880 and 1910 are listed in Brownlee (1918) and the yearly figures for London (1910–39) are from Brincker (1938) and Stocks (1942). The mumps data

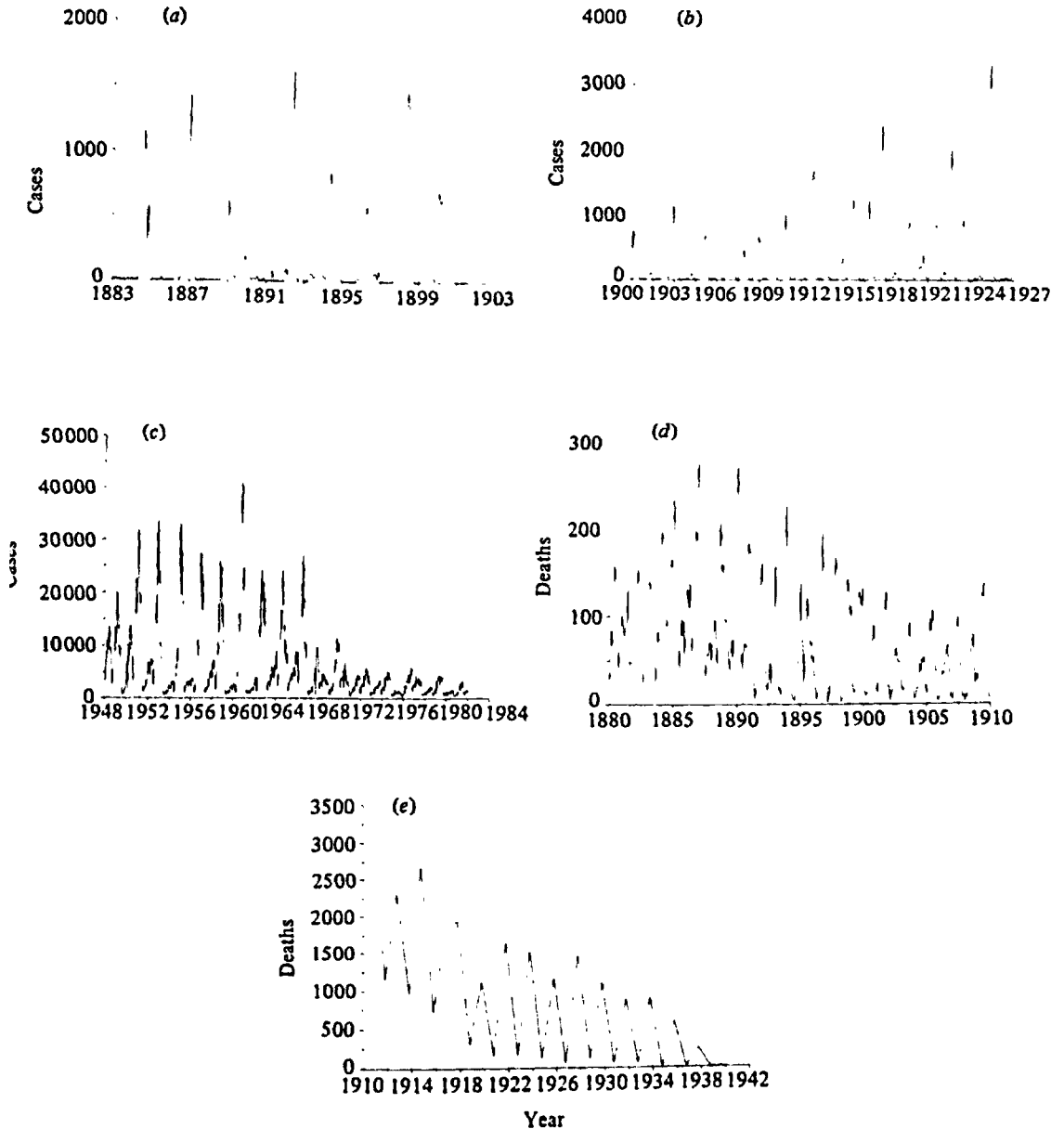


Fig. 1. Longitudinal trends in measles incidence. (a) Number of reported cases per month (per 100 000 population) in Aberdeen, 1883-1902. (b) Number of reported cases per month in Baltimore, U.S.A., 1900-27. (c) Number of reported cases per week in England and Wales, 1948-82. (d) Number of deaths due to measles reported per month in Paris, 1880-1910. (e) Number of deaths due to measles reported per year in London, 1910-39. Data sources are given in the main text.

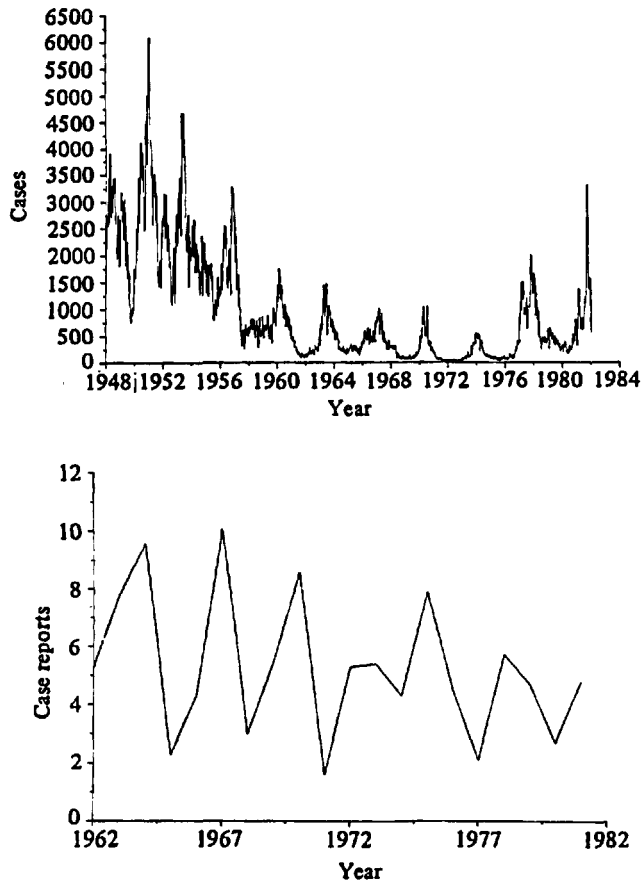


Fig. 2. Longitudinal trends in pertussis and mumps incidence. (a) Number of reported cases of pertussis per week in England and Wales, 1948-82. (b) Annual general-practitioner reports of mumps (consultation rates per 1000 population) in England and Wales, 1962-81.

in England and Wales from 1962 to 1981 come from a variety of sources which are documented in Galbraith *et al.* (1984), as are the annual trends in incidence.

RESULTS

The longitudinal records of measles incidence (England and Wales, 1948-82; Aberdeen, 1883-1902; Baltimore, 1900-27), pertussis (England and Wales, 1948-82) and mumps (England and Wales, 1962-81), plus the measles mortality data (Paris, 1880-1910; London, 1910-39), are displayed in Figs. 1 and 2.

Prevaccination periodicities

Measles. In England and Wales (1948-68) prior to widescale immunization, measles incidence cycled on a very regular 2-year period. The correlogram (a graph of the serial autocorrelation coefficients plotted against the time lag in years) is depicted in Fig. 3(a). It is a smooth two-peak oscillating curve with a major period

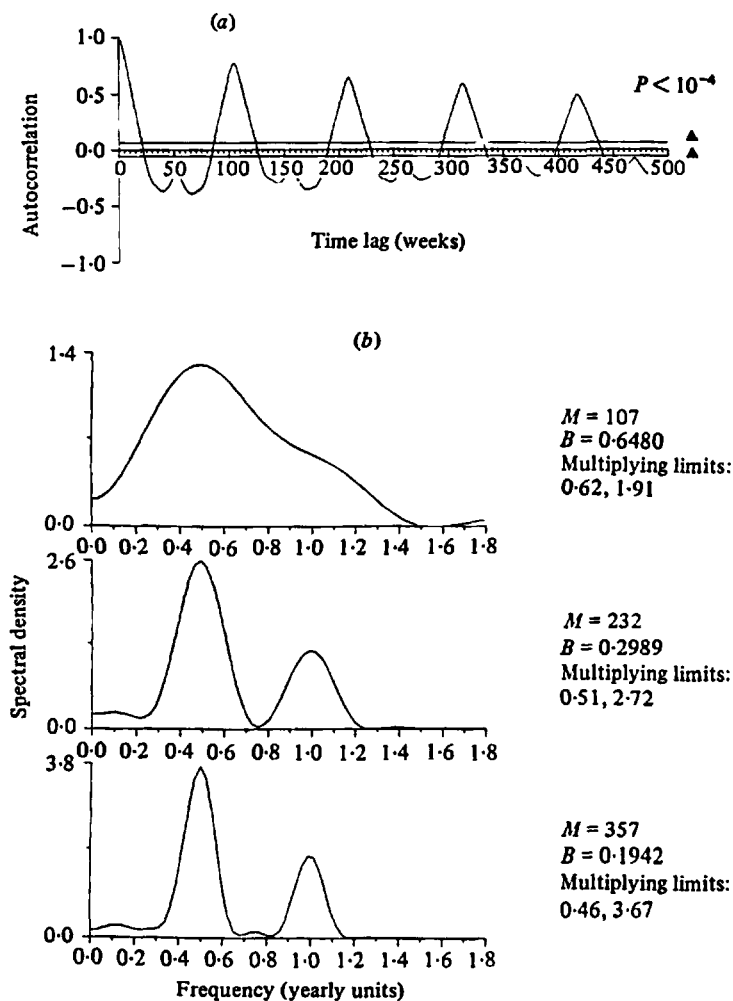


Fig. 3. (a) Correlogram of weekly measles reports for England and Wales, 1948-68. Here, and in subsequent correlograms, \blacktriangle — are 95% confidence limits for the zero correlogram from a completely random series, and p is the probability that such data could generate the observed correlogram (see the Appendix). (b) Spectra for the same series; data were mean corrected before spectral analysis. Here, and in subsequent spectra, the results are presented at a range of window cut-off points (M), and therefore bandwidths (B cycles per year); multiplicative 95% confidence limits for the spectra are also given (see Appendix).

of 2 years and a minor period of 1 year (the seasonal component). Note that the serial correlation coefficients were calculated from logarithm transformed data. The effect is to make the oscillations more symmetrical than in an arithmetic plot (compare Figs. 1 and 3). The most important features of the analysis displayed in Fig. 3(a) are the smoothness of the correlogram (indicating great regularity in the seasonal and 2-year cycles) and the dominance of the amplitude of the longer-term cycle over that of the seasonal component. Spectral analysis confirms these observations (Fig. 3b). The spectra (for various band widths - see Methods section) show sharp peaks at the 2-year frequency point (a frequency of 0.5 year^{-1}

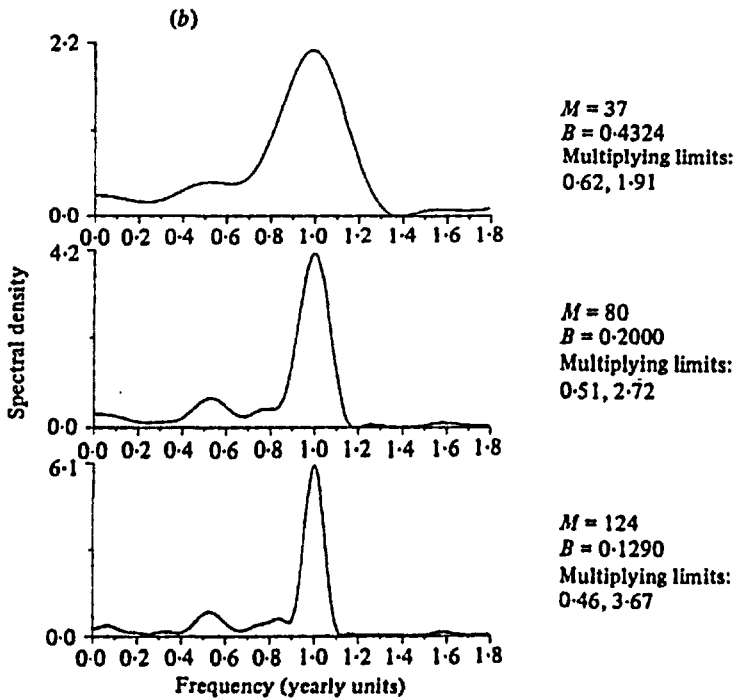
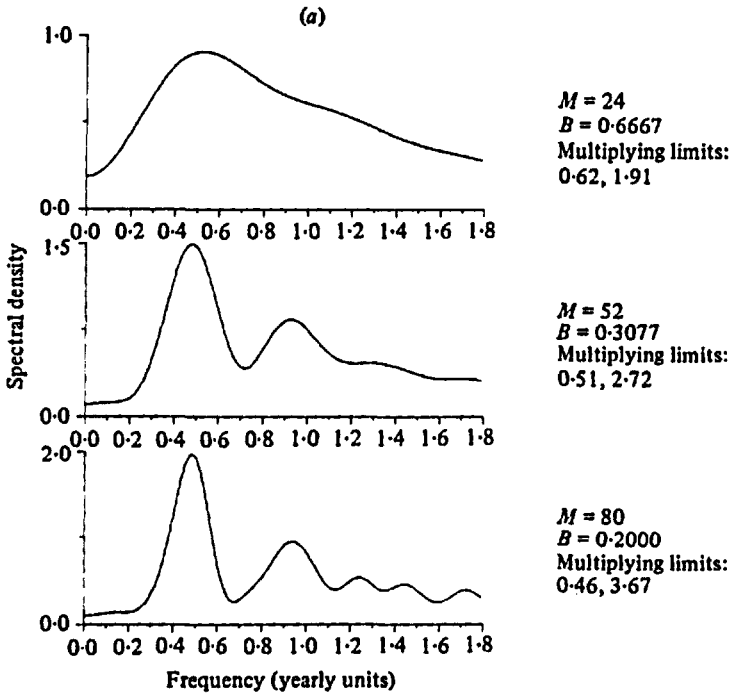


Fig. 4 (a, b). For legend see opposite.

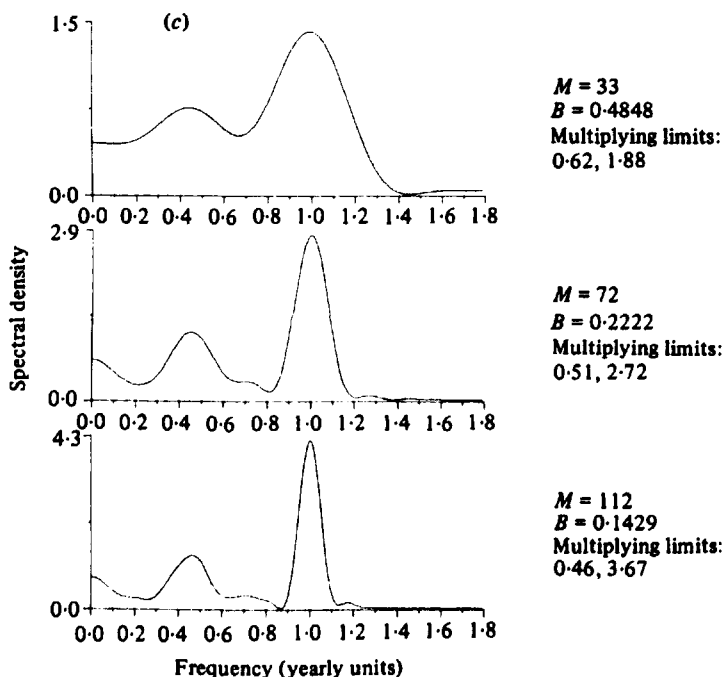


Fig. 4. (a) Spectra of monthly measles case reports for Aberdeen, 1883–1902. Data were mean corrected before spectral analysis, but not logged, due to the presence of zeros. (b) Spectra of monthly deaths due to measles reported for Paris, 1880–1910. Data were trend corrected before spectral analysis. (c) Spectra of monthly measles case reports for Baltimore, U.S.A., 1900–27. Data were trend corrected before spectral analysis.

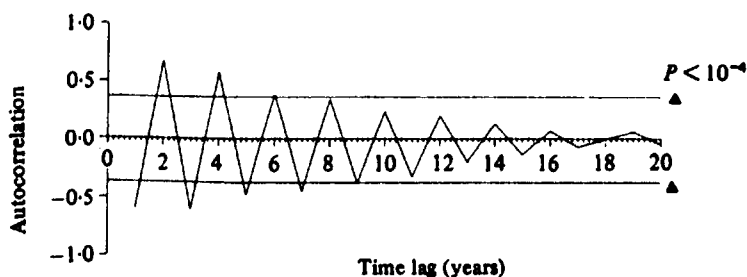


Fig. 5. Correlogram of annual deaths due to measles reported for London, 1910–39.

denotes cycles every second year) and the smaller peaks at the 1-year point (a frequency of 1.0 year^{-1}).

Similar analyses of the measles case records from Aberdeen and Baltimore, plus the measles mortality records from London and Paris show corresponding trends. A significant 2-year cycle is apparent in each case from inspection of the spectra (Figs. 4, 5). The relative importance of the seasonal and 2-year cycle components, however, varies between data sets. In England and Wales (1948–56) and Aberdeen (1883–1902) the amplitude of the 2-year cycle dominates the seasonal component. This situation is reversed in Paris (1880–1910) and Baltimore (1900–27). The

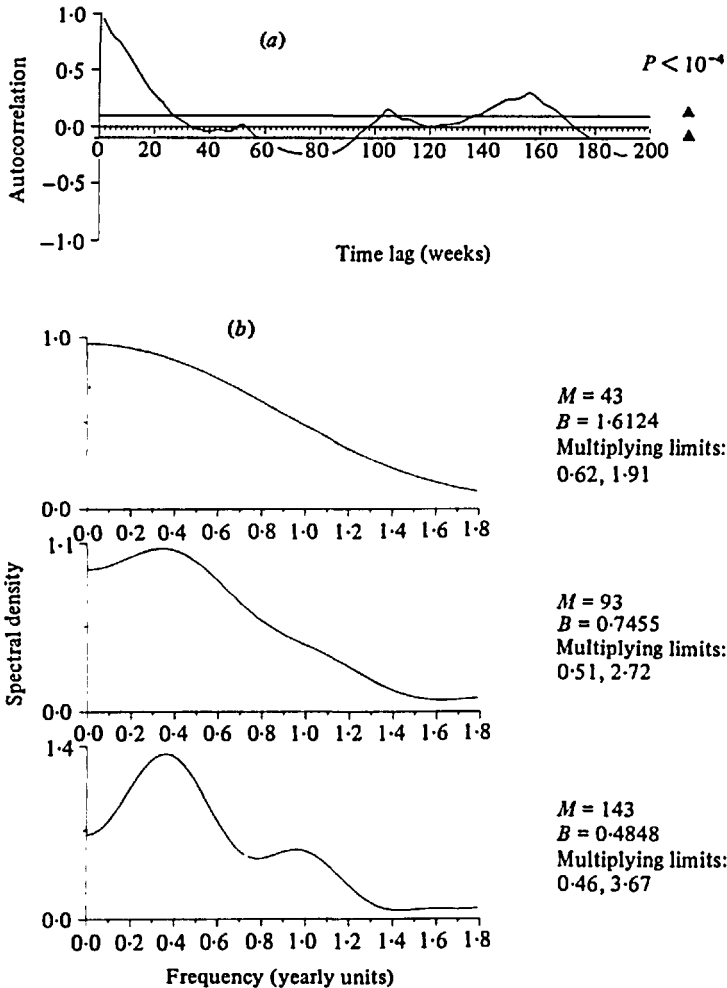


Fig. 6. (a) Correlogram of weekly pertussis case reports for England and Wales, 1948-1956. (b) Spectra for the same series. Data were mean corrected before spectral analysis.

London (1910-39) study does not reveal seasonal trends since the data are recorded as yearly case totals. It is interesting to note that the period of the long-term cycle in England remained at 2 years over the period 1910 (London only) to 1956 (England and Wales).

Pertussis. The England and Wales pertussis data, prior to mass immunization, reveals evidence of seasonal and 3-yearly cycles. The correlogram (Fig. 6a) is less smooth than the patterns recorded for measles (Fig. 3), although low-amplitude seasonal cycles and a dominant 3-year peak are apparent. The seasonal peak, just prior to the major epidemic every third year, is more marked than the earlier seasonal peaks within the long-term cycle (Fig. 6a). Spectral analysis confirms the dominance of the long-term cycle over the seasonal trend (Fig. 6b) (a peak frequency at 0.33 year^{-1}).

Mumps. The England and Wales mumps data (1962-81) are in the form of yearly

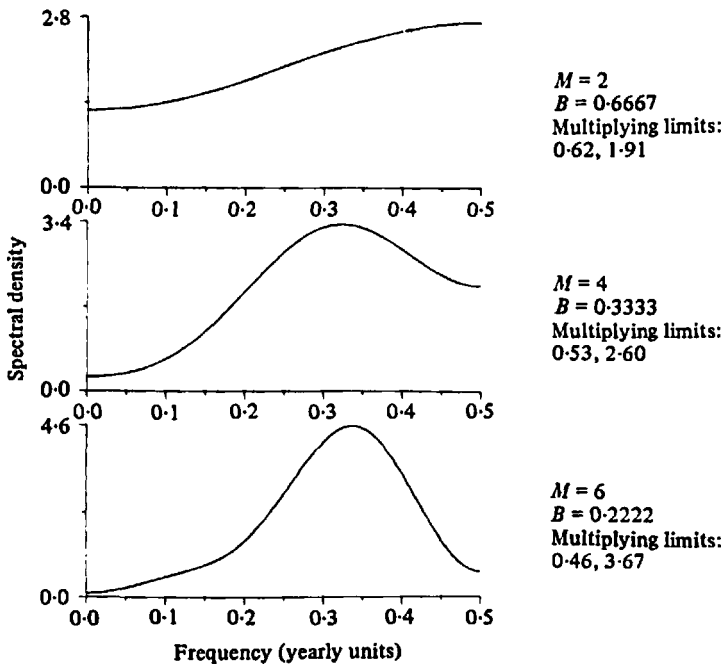


Fig. 7. Spectra of annual general-practitioner reports of mumps (consultation rates per 1000 population) in England and Wales, 1948–82. Data were trend corrected before spectral analysis.

case-records and hence do not permit an examination of seasonal trend. Spectral analysis reveals a significant average 3-year cycle (Fig. 7).

Theoretical predictions and observed trends

Simple deterministic models of recurrent epidemic behaviour predict damped oscillations in disease incidence to a stable endemic equilibrium state (Martini, 1921; Soper, 1929; Dietz, 1976; Anderson & May, 1982*a*). The predicted damping time for infections such as measles and pertussis is long, however, and a variety of processes such as seasonality in transmission and stochastic demographic effects (the inclusion of chance elements in the growth and decay of the susceptible and infectious populations) can perpetuate indefinitely the otherwise damped cycles Bartlett, 1956; (Grossman, 1980; Schwartz & Smith, 1984).

The non-seasonal oscillations arise as a consequence of the decay (by infection and recovery to an immune state) and renewal (by births) of the supply of susceptibles within the population. Simple models yield the prediction that the weakly damped oscillations have an inter-epidemic period, T , approximately given by

$$T \approx 2\pi(AK)^{\frac{1}{2}}. \quad (1)$$

Here A is the average age at infection and K is the average interval between an individual acquiring infection and passing it on to a new infective. (K is estimated as the sum of the latent plus infectious periods; Anderson & May, 1982*a*.) The precise structure of equation (1) is fairly robust to changes in model structure: it

Table 1. *Estimates of the average duration of infection, K , the average age at infection, A , and the predicted (T) plus observed inter-epidemic period*

Infection	Duration of infection (days)*	Average age at infection (years)†	Inter-epidemic period in years	
			Predicted	Observed‡
Measles	12·0	4–5	2·25–2·50	2
Pertussis	25·0	4–5	3·30–3·60	3
Mumps	19·0	6–7	3·50–3·80	3

* References: measles and pertussis, Benenson (1975); mumps, Armenian & Lilienfield (1983), Ikeda *et al.* (1971).

† These estimates are based on data from England and Wales in the period 1960–70 (Anderson & May, 1982*a*; Anderson & May, unpublished).

‡ Figures for England and Wales prior to immunization (see Figs. 1 and 2).

provides a reasonable estimate of the average period for age-structured models with incubation delays (Anderson & May, in preparation) and discrete time formulations (Anderson & May, 1982*a*). The models used in the classic studies of Soper (1929) and Bartlett (1956), for example, generate cycle periods as defined by equation (1).

To compare the predictions of equation (1) with observed trends we require estimates of A and K for measles, pertussis and mumps. These are listed in Table 1, as are the predicted and observed inter-epidemic periods. There is good agreement between the theory and the frequencies calculated by time series analyses. Seasonal factors probably act to lock the cycles into periods of integer years (Yorke *et al.* 1979).

Theory further predicts that vaccination programmes act (by the creation of herd immunity) to reduce the net force of transmission within a community and hence raise the average age at infection A (Anderson & May, 1982*a*, 1983*a*). If correct, this suggests that immunization will tend (on average) to lengthen the inter-epidemic period in relation to that pertaining prior to the introduction of control measures. We examine this prediction in the following section.

Periodicities under the impact of vaccination

We focus on two sets of data, namely the England and Wales case-records for measles and for pertussis.

Measles immunization was initiated on a large scale in 1969. The level of vaccine uptake by 2- to 3-year-old children has remained stable at around 50% of each cohort (Anderson & May, 1982*a*). The spectra (various band widths) for the period 1968–82 are presented in Fig. 8(*b*) and the correlogram in Fig. 8(*a*). These are to be compared with the spectra and correlogram in Fig. 3(*b*) and (*a*) for the prevaccination era. A substantive change is apparent. There is no longer a marked difference between the seasonal and longer-term cycles. In addition, there is evidence that the regular 2-year cycle is shifting towards a period of 2–3 years; compare the precise frequencies at which the major peaks occur in Figs. 3(*b*) and 8(*b*) (0·5 and 0·4 year⁻¹, respectively). The shift, however, is not substantive as yet, perhaps reflecting the comparatively low level of vaccination coverage.

Immunization against pertussis reached high levels of coverage in 1957. Uptake

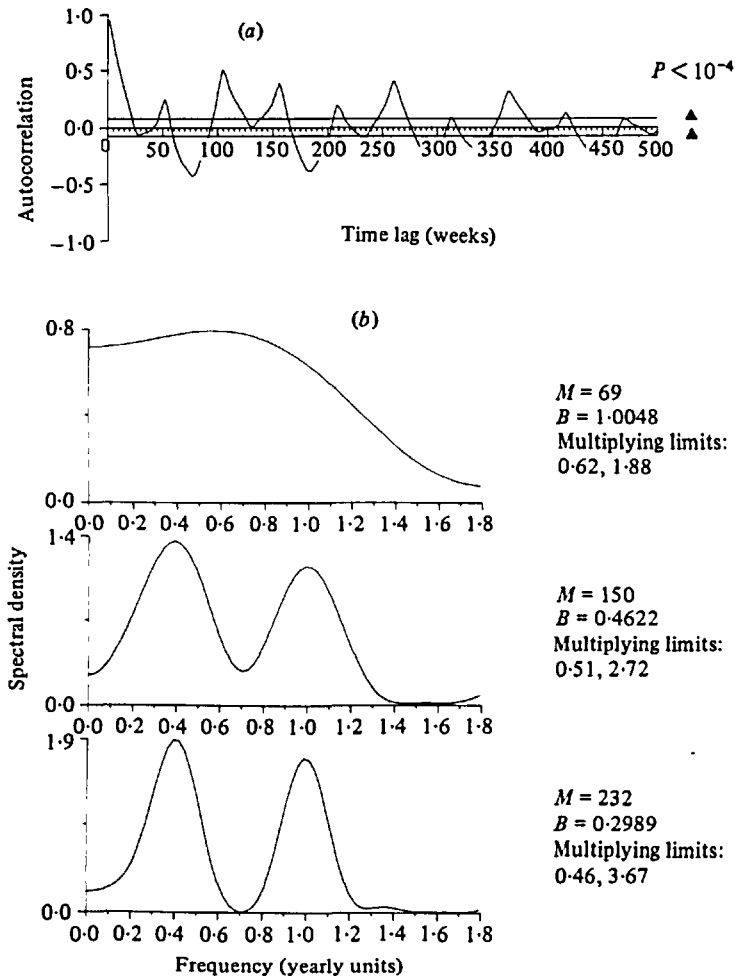


Fig. 8. (a) Correllogram of weekly measles reports for England and Wales, 1969-82. (b) Spectra for the same series. Data were trend corrected before spectral analysis.

declined, however, between 1975 and 1976 following the widely publicized concern over the safety of the vaccine (H.M.S.O., 1981). Low levels of vaccine acceptance persisted from that time to 1982. We have, therefore, divided the vaccination era in England and Wales into two periods: 1957-76 and 1977-82. The average level of immunization coverage of each yearly cohort of children attained between the ages of 1 and 3 years was between 70% and 80% (H.M.S.O., 1981) during the period 1957-76. In the latter period, 1977-82, coverage fell to 40% or less. The correllogram and spectra for the earlier period are presented in Fig. 9(a) and (b). These are to be compared with the prevaccination results presented in Fig. 6(a) and (b). Two points are striking, namely the complete elimination of the seasonal peak in the vaccination era and the lengthening of the inter-epidemic period following high levels of immunization. The period changes from a fairly regular 3-year cycle to a cycle of between 3 and 4 years. The 1977-82 section is too short a time-span for effective detection of changes in the longer-term cycles. The

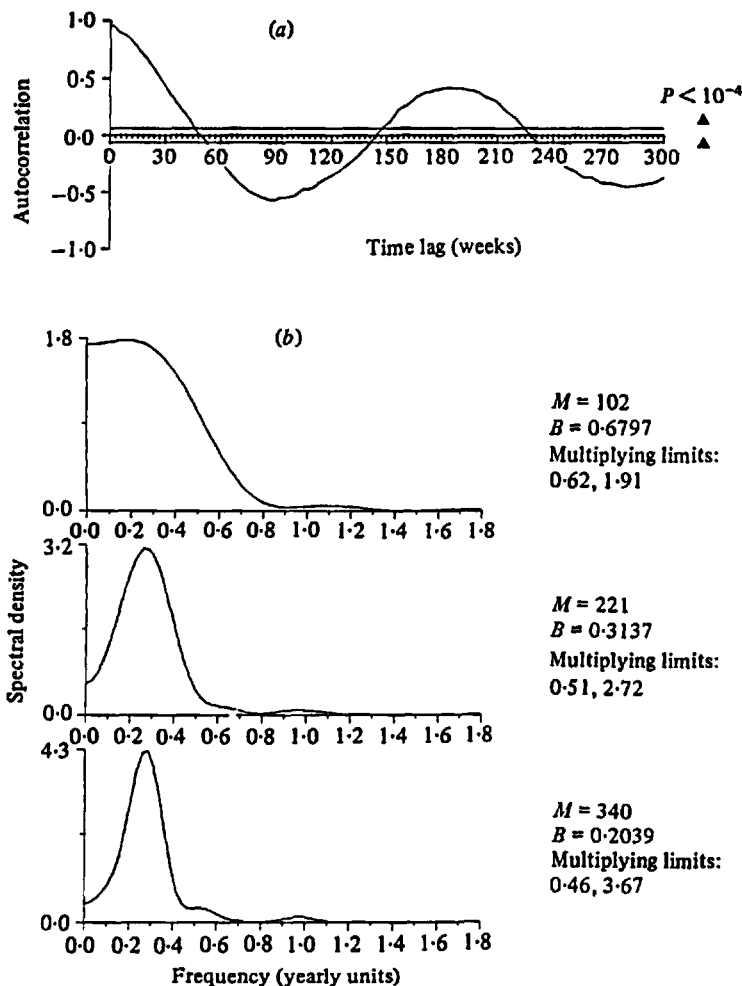


Fig. 9. (a) Correllogram of weekly pertussis case reports for England and Wales, 1957-76. (b) Spectra for the same series. Data were trend corrected before spectral analysis.

correllogram and spectra are presented in Fig. 10(a) and (b), however, to illustrate the continued suppression of the seasonal cycle.

Seasonal cycles

Aside from the long-term cycles, short-term seasonal components are detectable in all the longitudinal data collected prior to the introduction of mass immunization. The detailed weekly records for measles and pertussis in England and Wales permit close inspection. As illustrated in Fig. 11(a), the seasonal troughs in measles incidence follow a very consistent pattern from year to year, irrespective of whether or not the data were collected in the prevaccination or vaccination eras. The major trough occurs in the summer months and is followed by a rise in incidence between the end of August and the beginning of September (weeks 36-39). Peak incidence within a year invariably occurs in February or March. Small

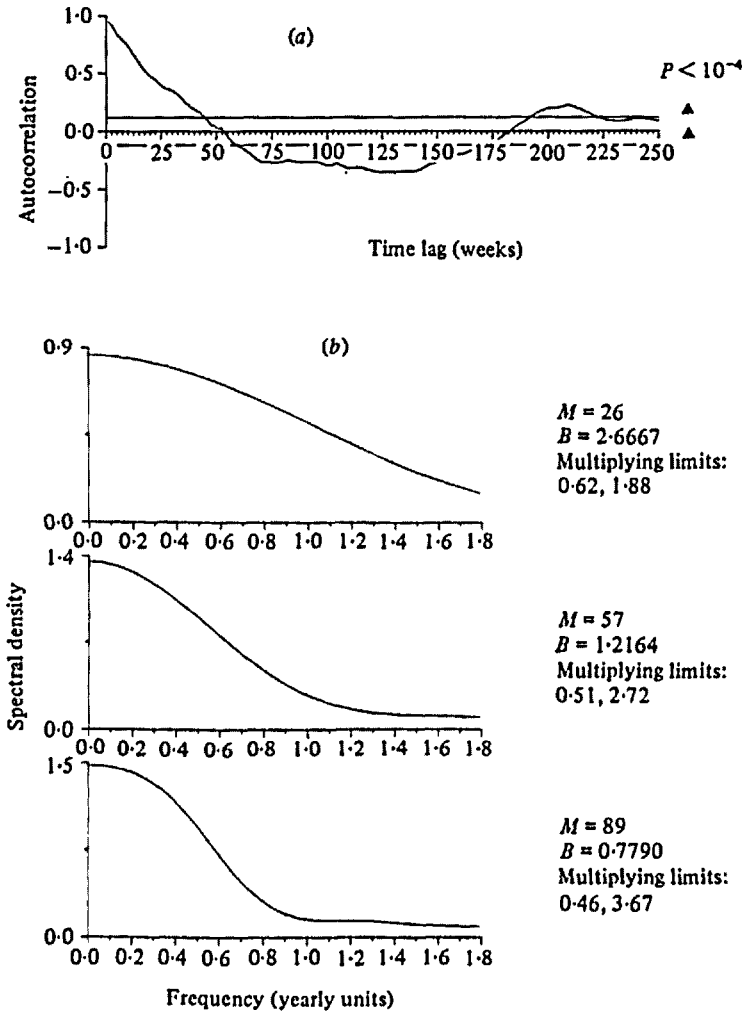


Fig. 10. (a) Correlogram of weekly pertussis case reports for England and Wales, 1977-82. (b) Spectra for the same series. Data were trend corrected before spectral analysis.

troughs are apparent in January and then again around the month of April. The association of these trends with school holiday periods is striking, as recently noted by Fine & Clarkson (1982*a*). There is no suggestion in the data that these patterns change significantly between major and minor epidemic years (the longer-term 2-year cycle). The rises in incidence, following the three troughs, all coincide with opening of school terms. Interestingly, in contrast to the conclusions reached by Fine & Clarkson (1982*a*), time series analysis reveals that the longer-term period is still apparent in the vaccination era, although the average amplitude of its cycles is only marginally greater than the average amplitude of the regular seasonal fluctuations (see Fig. 8*a*).

The longitudinal patterns for pertussis in England and Wales are somewhat different than those recorded for measles. First, the seasonal component is less marked in the prevaccination era (Fig. 11*b*). There is evidence of a trough in late

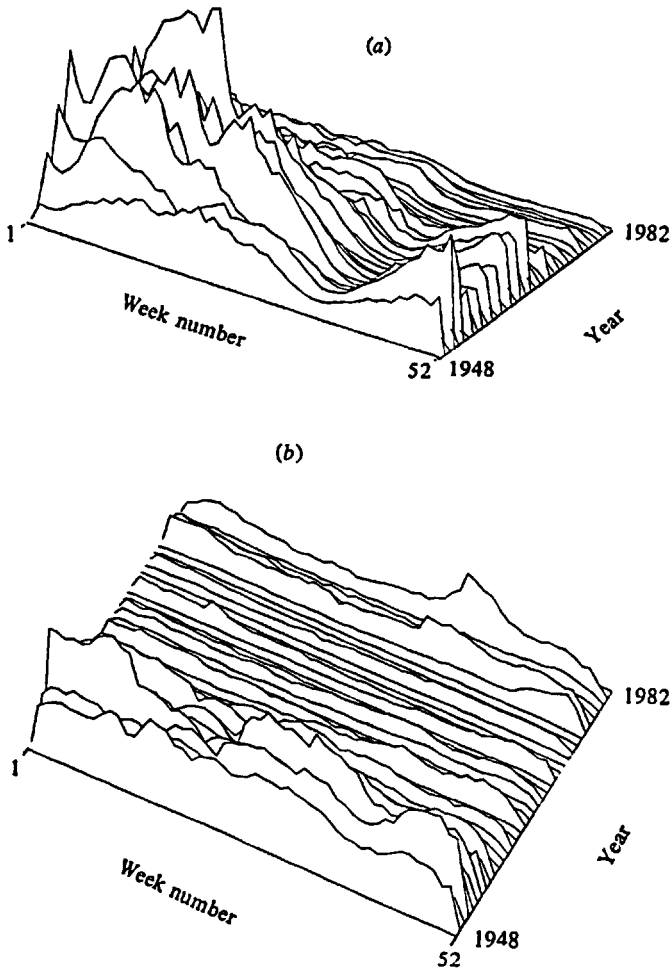


Fig. 11. Surfaces showing seasonal patterns in measles and pertussis incidence, based on weekly case reports in England and Wales, 1948–82. (a) Measles. (b) Pertussis. 1 = first week in January.

summer/early autumn, but the trends around January and April (following school holidays) are rather irregular. Secondly, the timing of peak incidence within a year varies from year to year. In some years it occurred in the winter months, in others during the summer months (Fig. 11b). The third and most dramatic difference, however, is apparent during the period of high vaccine uptake. Overall, incidence was substantially reduced and, most importantly, the seasonal component disappeared. There is a hint of its return following the decline in uptake (1977–82), but this is as yet non-significant (Fig. 10a, b). Over the period of high vaccine coverage the weekly case records varied little from week to week throughout a year (the observed seasonal variation is not significantly different from that induced by chance mechanisms alone).

DISCUSSION

The most striking feature of our statistical analyses is the significance of the seasonal and long-term cycles in the prevaccination eras. The trends for measles incidence are the most clear-cut; the regular 2-year cycle in England and Wales, Aberdeen and London is particularly notable (see Figs. 1 and 2). The records for measles in Paris show a very marked seasonal component but a less-significant 2-year cycle. Persistent annual cycles of measles are recorded in cities within developing countries with high birth rates (a high input of susceptibles per unit of time) and the observed pattern in Paris from 1880 to 1910 may reflect the high birth rate in the city during that period.

In general, the relative amplitudes of the longer-term cycles, compared with the seasonal components, are probably a reflexion of population density and birth rate. In large cities, or densely populated areas (or countries), the magnitude of the longer-term oscillations tends to be more exaggerated than is the case in less densely populated areas. Indeed, in the latter case, stochastic factors may result in disease fade out during the troughs in the epidemic cycle (Bartlett, 1960). This factor, combined with the deterministic notion of a critical density of susceptibles necessary to support an epidemic (Kermack & McKendrick, 1927; Anderson & May, 1979), leads to the observation that the long-term endemic maintenance of measles is critically dependent on community size and the net birth rate (Bartlett, 1960; Black, 1966).

Simple theory, based on compartmental deterministic models, predicts inter-epidemic periods in good agreement with observed trends in the incidences of measles, pertussis and mumps (Table 1). We suspect that similarly good agreement holds for other common infections in developed countries, such as rubella (cycles of 4–5 years) and chicken pox (cycles of 2–3 years) (Anderson & May, 1982*a*, 1983*a*) and less-well-studied infections such as human parvovirus (Anderson, 1983), coxsackievirus and echovirus. Time series analysis of the available longitudinal records of the incidences of such infections is a subject for future research.

Theory also predicts that mass immunization will act to lengthen inter-epidemic periods. Our analyses support this prediction, but suggest that the degree to which the period increases is somewhat less than that predicted by models which do not take account of age-related changes in the force of infection (Anderson & May, 1982*a*, 1983*a*). For example, standard theory (see Dietz, 1976; Anderson & May, 1983*a*) predicts that a 50% vaccination coverage will approximately double the average age at infection. In the case of measles this would yield an inter-epidemic period of between 3 and 4 years. In practice, the average age of infection has increased slightly in England and Wales (see Anderson & May, 1982*a*) as has the inter-epidemic period, but both far less than predicted. The discrepancy probably arises as a consequence of both inadequate model assumptions concerning the dependency of the force of infection on age, and the long time-periods involved for the full effects of cohort vaccination to become apparent within a community (often 20–30 years following the initiation of a programme; see Anderson & May, 1983*a*). It has recently been suggested that the force of infection for many common childhood viral and bacterial infections changes with age, moving from low levels in the 0- to 5-year age class, to high levels in the 5- to 10-year age class, to

intermediate levels among adolescents, and back to low levels in adults (Anderson & May, 1983*b*; Schenzle, 1985). For example, vaccine coverage of children of 0–5 years may move more susceptibles into a class with a high infection rate, such as the 5- to 10-year-olds, than was the case prior to immunization. The precise quantitative details of these changes will influence the net impact of any vaccination programme on both the average age at infection and the inter-epidemic period. Current research should help to clarify these issues (Schenzle, 1985; Anderson & May, in preparation).

The interesting observations of Fine & Clarkson (1982*a*) on seasonality in the transmission of measles (see also London & Yorke, 1973) are largely confirmed by our statistical studies. The association between peaks and troughs in incidence with the timing of school holiday periods is striking (see Fig. 11). The impact of vaccination, by suppressing overall incidence, reduces the difference in the relative magnitudes of the seasonal and longer-term cycles but, in our view, does not (at current levels of vaccine uptake in England and Wales) completely eliminate it. Observed patterns in whooping-cough incidence, however, are very different; high vaccine uptake totally removes the seasonal trend. We find this observation somewhat puzzling but suspect, however, that aggregation and disassembly of school-children is not the primary cause of seasonality in transmission of pertussis. Climatic factors may play an important role. It is not clear at present why such differences should exist between the observed trends of measles and pertussis incidence.

We conclude by stressing the regularity of long-term fluctuations in many childhood infections. We are in no doubt that these arise as a consequence of dynamical factors associated with the renewal and depletion of the supply of susceptible individuals within human communities. The correlogram for measles incidence in England and Wales (Fig. 3*a*), prior to widescale immunization, is (to our knowledge) the most detailed and clear-cut statistical demonstration of periodic population behaviour (seasonal and non-seasonal) published to date. These results indicate, in turn, the usefulness of time series analysis as a powerful tool in elucidating the temporal structure of epidemiological data.

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REFERENCES

- ANDERSON, M. J. (1982). The emerging story of a human parvovirus-like agent. *Journal of Hygiene* **89**, 1–8.
- ANDERSON, R. M. & MAY, R. M. (1979). Population biology of infectious diseases: I. *Nature, London* **280**, 361–367.
- ANDERSON, R. M. & MAY, R. M. (1982*a*). Directly transmitted infectious diseases: control by vaccination. *Science* **215**, 1053–1060.
- ANDERSON, R. M. & MAY, R. M. (1982*b*). The logic of vaccination. *New Scientist*, 18 Nov., pp. 410–415.
- ANDERSON, R. M. & MAY, R. M. (1983*a*). Vaccination against rubella and measles: quantitative investigations of different policies. *Journal of Hygiene* **90**, 259–325.
- ANDERSON, R. M. & MAY, R. M. (1983*b*). Two-stage vaccination programme against rubella. *Lancet* *ii*, 1416–1417.

- ARMENIAN, H. K. & LILIENFIELD, A. M. (1983). Incubation period of disease. *Epidemiological Reviews* 5, 1-15.
- ARON, J. L. & SCHWARTZ, I. B. (1984). Seasonality and period-doubling bifurcations in an epidemic model. *Journal of Theoretical Biology*. (In the Press.)
- BAILEY, N. T. J. (1975). *The Mathematical Theory of Infectious Diseases and its Applications*. London: Griffin.
- BARTLETT, M. S. (1956). Deterministic and stochastic models for recurrent epidemics. *Proceedings of the 3rd Berkeley Symposium on Mathematics, Statistics and Probability* 4, 81-109.
- BARTLETT, M. S. (1960). The critical community size for measles in the United States. *Journal of the Royal Statistical Society B*, 123, 37-44.
- BENENSON, A. S. (1975). *Control of Communicable Diseases in Man*, 12th ed. American Public Health Association, Washington, D.C.
- BLACK, F. L. (1966). Measles endemicity in insular populations: critical community size and its evolutionary implications. *Journal of Theoretical Biology* 11, 207-211.
- BLISS, C. I. & BLEVINS, D. L. (1959). The analysis of seasonal variation in measles. *American Journal of Hygiene* 70, 328-334.
- BLOOMFIELD, P. (1976). *Fourier Analysis of Time Series: An Introduction*. New York: Wiley.
- BOX, G. E. P. & JENKINS, G. M. (1976). *Time Series Analysis: Forecasting and Control*. San Francisco: Holden-Day.
- BRINCKER, J. A. H. (1938). A historical, epidemiological and aetiological study of measles (Morbilli: Rubeola). *Proceedings of the Royal Society of Medicine* 807, 33-54.
- BROWNLEE, J. (1914). Periodicity in infectious diseases. *Proceedings of the Royal Philosophical Society of Glasgow* 45, 197-213.
- BROWNLEE, J. (1915). Investigations into the periodicity of infectious diseases by the applications of a method hitherto used only in physics. *Public Health*, London 28, 125-134.
- BROWNLEE, J. (1918). An investigation into the periodicity of measles epidemics in London from 1703 to the present day by the method of the periodogram. *Philosophical Transactions of the Royal Society of London B* 208, 225-250.
- BROWNLEE, J. (1919). Periodicities of epidemics of measles in the large towns of Great Britain and Ireland. *Proceedings of the Royal Society of Medicine* 12, 77-117.
- BROWNLEE, J. (1920). An investigation into the periodicity of measles epidemics in the different districts of London for the years 1890-1912. *Philosophical Transactions of the Royal Society of London B* 209, 181-190.
- BROWNLEE, J. (1923). A further note upon the periodicity of influenza. *Lancet* i, 1116.
- BULMER, M. G. (1974). A statistical analysis of the 10 year cycle in Canada. *Journal of Animal Ecology* 43, 701-718.
- BUSENBERG, S. & COOKE, K. L. (1978). Periodic solutions of a periodic non-linear delay differential equation. *S.I.A.M. Journal of Applied Mathematics* 35, 704-721.
- CHATFIELD, C. (1975). *The Analysis of Time Series: Theory and Practice*. London: Chapman and Hall.
- DIETZ, K. (1976). The incidence of infectious diseases under the influence of seasonal fluctuations. *Lecture Notes in Biomathematics* 11, 1-15.
- FINE, P. E. M. (1979). John Brownlee and the measurement of infectiousness: an historical study in epidemic theory. *Journal of the Royal Statistical Society A* 142, 347-362.
- FINE, P. E. M. & CLARKSON, J. A. (1982a). Measles in England and Wales. I. An analysis of the factors underlying seasonal patterns. *International Journal of Epidemiology* 11, 5-14.
- FINE, P. E. M. & CLARKSON, J. A. (1982b). Measles in England and Wales. II. The impact of the measles vaccination programme on the distribution of immunity in the population. *International Journal of Epidemiology* 11, 15-29.
- FINE, P. E. M. & CLARKSON, J. A. (1983). Measles in England and Wales. III. Assessing published predictions of the impact of vaccination on incidence. *International Journal of Epidemiology* 12, 332-339.
- FINERTY, J. P. (1980). *The Population Ecology of Cycles in Small Mammals*. New Haven: Yale University Press.
- GALBRAITH, N. S., YOUNG, S. E. J., PUSEY, J. J., CROMBIE, D. L. & SPARKS, J. P. (1984). Mumps surveillance in England and Wales 1962-1981. *Lancet* i, 91-94.
- GREEN, D. (1978). Self-oscillation for epidemic models. *Mathematical Biosciences* 38, 91-111.
- GREENWOOD, M., HILL, A. B., TOPLEY, W. C. & WILSON, J. (1936). Experimental epidemiology. *M.R.C. Special Report Series* 209, 1-204. London: H.M.S.O.

- GRIPENBERG, G. (1980). Periodic solutions of an epidemic model. *Journal of Mathematical Biology* 10, 271–280.
- GROSSMAN, Z. (1980). Oscillatory phenomena in a model of infectious diseases. *Theoretical Population Biology* 18, 204–243.
- HAMER, W. H. (1906). Epidemic disease in England – the evidence of variability and of persistence of type. *Lancet* ii, 733–739.
- HEDRICH, A. W. (1933). Monthly estimates of the child population 'susceptible' to measles, 1900–1931, Baltimore, Md. *American Journal of Hygiene* 17, 613–636.
- HETHCOTE, H., STECH, H. W. & VAN DEN DRIESSCHE, P. (1981). Non-linear oscillations in epidemic models. *S.I.A.M. Journal of Applied Mathematics* 40, 1–9.
- HETHCOTE, H., STECH, H. W. & VAN DEN DRIESSCHE, P. (1983). Periodicity and stability in epidemic models: a survey. In *Differential Equations and Applications to Ecology, Epidemics and Population Problems* (ed. S. Busenberg and K. Cooke), pp. 65–82. New York: Academic Press.
- H.M.S.O. (1981). *Whooping Cough*. Reports from the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation. London: H.M.S.O.
- IKEDA, S., CHIBA, S., CHIBA, Y. & NAKAO, T. (1971). Epidemiological, clinical and serological studies on epidemics of mumps in an infant nursery. *Tohoku Journal of Experimental Medicine* 105, 327–337.
- JENKINS, G. M. & WATTS, D. G. (1968). *Spectral Analysis and Its Applications*. San Francisco: Holden-Day.
- KERMACK, W. O. & MCKENDRICK, A. G. (1927). A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society A* 115, 13–23.
- LONDON, W. P. & YORKE, J. A. (1973). Recurrent outbreaks of measles, chickenpox and mumps. I. Seasonal variation in contact rates. *American Journal of Epidemiology* 98, 453–468.
- LOTKA, A. J. (1923). Martini's equation for the epidemiology of immunising diseases. *Nature* 111, 633–634.
- MARTINI, E. (1921). *Berechnungen und Beobachtungen zur Epidemiologie und Bekämpfung der Malaria*. Hamburg: Gente.
- MAY, R. M. (1973). *Stability and Complexity in Model Ecosystems*. Princeton: Princeton University Press.
- MAY, R. M. & ANDERSON, R. M. (1979). Population biology of infectious diseases: II. *Nature*, London 280, 455–461.
- NAGASAWA, S. & KANZAKI, T. (1977). Seasonal variation in measles. *Bulletin of the Faculty of Agriculture, Shimane University*, 2, 40–47.
- NUSSBAUM, R. (1977). Periodic solutions of some integral equations from the theory of epidemics. In *Nonlinear Systems and Applications to Life Sciences* (ed. P. van den Driessche), pp. 235–255. New York: Academic Press.
- POOLE, R. W. (1974). *An Introduction to Quantitative Ecology*. Tokyo: McGraw-Hill.
- POTTS, G. R., TAPPER, S. C. & HUDSON, P. J. (1984). Population fluctuations in red grouse: analysis of bag records and a simulation model. *Journal of Animal Ecology* 53, 21–36.
- ROSS, R. (1908). *Report on the Prevention of Malaria in Mauritius*. London: Waterlow.
- ROSS, R. (1911). *The Prevention of Malaria*, 2nd ed. London: Murray.
- ROSS, R. (1915). Some *a priori* pathometric equations. *British Medical Journal* i, 546–547.
- ROSS, R. (1916). An application of the theory of probabilities to the study of *a priori* pathometry. I. *Proceedings of the Royal Society A* 93, 204–230.
- ROSS, R. (1917). An application of the theory of probabilities to the study of *a priori* pathometry: II. *Proceedings of the Royal Society A* 93, 212–225.
- SCHENZLE, D. (1985). Control of virus transmission in age structured populations. In *Mathematics in Biology and Medicine* (ed. V. Capasso). West Berlin: Springer-Verlag.
- SCHWARTZ, I. B. & SMITH, H. L. (1984). Infinite subharmonic bifurcation in an SEIR epidemic model. *Journal of Mathematical Biology* 18, 233–253.
- SMITH, H. L. (1978). Periodic solutions for a class of epidemic equations. *Mathematical Analysis and Application* 64, 467–479.
- SOPER, M. A. (1929). The interpretation of periodicity in disease prevalence. *Journal of the Royal Statistical Society A* 92, 34–61.
- STECH, H. & WILLIAMS, M. (1981). Stability for a class of cyclic epidemic models with delay. *Journal of Mathematical Biology* 11, 95–103.
- STOCKS, P. (1942). Measles and whooping cough incidence before and during the dispersal of 1930–1941. *Journal of the Royal Statistical Society* 105, 250–291.

- WILLIAMSON, M. H. (1972). *The Analysis of Biological Populations*. London: Edward Arnold.
- WILLIAMSON, M. H. (1975). The biological interpretation of time series analysis. *Bulletin of the Institute of Mathematics and its Applications* **11**, 67-69.
- WILSON, G. N. (1904). Measles: its prevalence and mortality in Aberdeen. *Report of the Medical Office of Health, Aberdeen*, pp. 41-51.
- YORKE, J. A., NATHANSON, N., PIANINGIANI, G. & MARTIN, J. (1979). Seasonality and the requirements for perpetuation and eradication of viruses. *American Journal of Epidemiology* **109**, 103-123.
- YOUNG, M. (1920). An investigation into the periodicity of epidemics of whooping cough from 1870-1910 by means of the periodogram. *Proceedings of the Royal Society of Medicine* **13**, 207-234.
- ZINSSER, H. & WILSON, E. B. (1932). Bacterial dissociation and a theory of the rise and decline of epidemic waves. *Journal of Preventive Medicine* **6**, 497-514.

APPENDIX

This appendix comprises a technical summary of autocorrelation and spectral analysis. More details are given by Jenkins & Watts (1968), Chatfield (1975) and Bloomfield (1976).

(a) Autocorrelation

(i) *Definition*. Given a time series of N observations, x_1, \dots, x_N , with mean \bar{x} , the sample autocovariance coefficient at lag k is defined as

$$C_k = \frac{1}{N} \sum_{t=1}^{N-k} (x_t - \bar{x})(x_{t+k} - \bar{x}) \quad (k = 0, 1, \dots, K). \quad (\text{A } 1)$$

The sample autocorrelation coefficient at lag k , r_k , is calculated as the ratio

$$r_k = \frac{C_k}{C_0} = \frac{\sum_{t=1}^{N-k} (x_t - \bar{x})(x_{t+k} - \bar{x})}{\sum_{t=1}^N (x_t - \bar{x})^2}. \quad (\text{A } 2)$$

(ii) *Significance tests for the correlogram*. For a white-noise process the autocorrelation function has an expected value of zero for $k > 0$. If N is large, a confidence interval around this expectation is given by $\pm \sqrt{(1/N)t_\alpha}$, where t_α is the estimated value of Student's t with $N-1$ degrees of freedom for a two-tailed confidence band of width $(1-\alpha)$ (Jenkins & Watts, 1968).

We construct an overall test for departure from randomness based on the statistic

$$S = N \sum_{k=1}^K r_k^2 \quad (\text{A } 3)$$

(Box & Jenkins, 1968). If N is large and K is much smaller than N , S has a χ^2 distribution with k degrees of freedom under the hypothesis of a zero autocorrelation function, and may be used to test this assumption.

(b) Spectral analysis

(i) *Definition*. The smoothed sample spectrum is defined as

$$\hat{f}(\omega) = \frac{1}{\pi} \left[C_0 + 2 \sum_{i=1}^{M-1} \lambda_i C_i \cos(\omega i) \right], \quad (\text{A } 4)$$

where ω is the angular frequency ($0 \leq \omega \leq \pi$), C_k is the autocovariance at $\log k$ (equation A 1), and λ_i is the lag window applied up to a cut-off point $i = M$ ($1 \leq M \leq N$).

In practice, we plot the spectral density function against frequency per unit time; rather than angular frequency. The spectral density function is calculated from

$$g(w) = \frac{\pi}{l\sigma_x^2} \hat{f}(w\pi/l), \tag{A 5}$$

where w is the frequency in cycles per year ($0 \leq w \leq l$), and σ_x^2 is the variance of the time series. The integral

$$\int_{w_1}^{w_2} g(w) dw \tag{A 6}$$

represents the proportion of the series variance accounted for by frequencies between w_1 and w_2 ; in particular,

$$\int_0^l g(w) dw = 1. \tag{A 7}$$

The time series is mean or trend corrected and tapered at each end before calculating the covariances. The tapering factors used are those of the split cosine bell:

$$\begin{aligned} &\frac{1}{2}[1 - \cos[\pi(t - \frac{1}{2})/T]] \quad (1 \leq t \leq T), \\ &\frac{1}{2}[1 - \cos[\pi(N - t + \frac{1}{2})/T]] \quad (N + 1 - T \leq t \leq N), \\ &1, \text{ otherwise} \end{aligned}$$

where $T = (Np)/2$, and p is the tapering proportion. A tapering proportion of $P = 0.1$ was used throughout these analyses.

We smooth the spectrum with a Tukey smoothing window, defined by

$$\lambda_i = \frac{1}{2}[1 + \cos(\pi i/M)]. \tag{A 8}$$

The associated bandwidth (essentially the width of the window) is given by

$$B = \frac{8l}{3M} \text{ cycles per year.} \tag{A 9}$$

(ii) *Confidence limits for the spectrum.* Asymptotic multiplicative confidence limits for the spectrum at the $100(1 - \alpha)$ th percentile are given by the factors:

$$\frac{\nu}{\chi^2\nu, \alpha/2} \text{ (lower) and } \frac{\nu}{\chi^2\nu, (1 - \alpha/2)} \text{ (upper).}$$

ν is the number of degrees of freedom of the lag window; for the Tukey window, $\nu = 2.67N/M$.