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INTERNATIONAL CENTRE FOR SCIENCE AND HIGH TECHNOLOGY
c/o INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS 34100 TRIESTE (ITALY) VIA GRIGNANO, 9 (ADRIATICO PALACE) P.O. BOX 586 TELEPHONE 040-224572 TELEFAX 040-224575 TELEX 460449 APH I

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"Chance and Chaos in Measles Dynamics"

B.T. Grenfell
Department of Zoology
Cambridge University
Cambridge CB2 3EJ
U.K.

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Chance and Chaos in Measles Dynamics

By B. T. GRENFELL†

University of Cambridge, UK

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SUMMARY

This paper examines the impact of seasonality and chaotic dynamics in simple models for the population dynamics of measles on the probability of fade-out of infection. It uses Monte Carlo simulations of the seasonally forced SEIR model, with parameters appropriate to a city of 1 million people. The incidence of fade-out in a spatially homogeneous model is compared with simple spatial models involving various degrees of coupling between subareas. The results indicate a significant degree of fade-out of infection, which is not consistent with previously derived criteria for the persistence of measles. Lowering the degree of spatial coupling does not substantially reduce the extent of fade-out. A simple non-linear analysis of the simulated series is presented, and the epidemiological implications of these results are discussed.

Keywords: CHAOS; FADE-OUT MODELS; MEASLES; SEASONALITY; STOCHASTIC PROCESSES

1. INTRODUCTION

In his recent paper, Bartlett (1990) raised some important questions about the current interest in ascribing irregularities in the incidence of measles epidemics to chaotic dynamics. The chaotic approach is the latest in a large body of work (reviewed by Hethcote and Levin (1989)) which seeks to explain the pattern and persistence of epidemics of childhood diseases. Another, complementary, aim of epidemiological theory has been to quantify conditions for the maintenance of infection in human communities. In particular, the seminal work of Bartlett (1956, 1957, 1960) identifies an urban population of around 250000 as a lower stochastic threshold for the persistence of measles. The present paper will use Monte Carlo simulations of simple measles models (Olsen *et al.*, 1988; Olsen and Schaffer, 1990) to explore the relationship between chaos and persistence. We begin with a brief review of the background to the problem.

1.1. *Detecting Chaos in Measles Time Series*

Recently, several groups, notably Schaffer and his co-workers, have identified measles (and other childhood infections) as probably the best candidates in ecological systems for the detection of chaotic population fluctuations (Schaffer, 1985; Schaffer and Kot, 1985a, b; Drepper, 1988; Olsen and Schaffer, 1990; Sugihara and May, 1990; Sugihara *et al.*, 1990). In analyses based on the comparatively long notification time series available for measles, Olsen *et al.* (1988) and Olsen and Schaffer (1990) propose evidence for chaos from some European and American cities, based on the

†*Address for correspondence*: Zoology Department, University of Cambridge, Downing Street, Cambridge, CB2 3EJ, UK.

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reconstruction of attractors, and the calculation of Lyapunov exponents (measuring instability) and correlation dimensions. For measles in New York, Sugihara and May (1990) have also suggested evidence for chaos, based on the internal predictability of the series. By contrast, the much studied measles series for England and Wales (Bartlett, 1957; Fine and Clarkson, 1982a, b; Anderson *et al.*, 1984; Dietz and Schenzle, 1985) does not show evidence for chaos according to these methods (Schaffer, personal communication, and Sugihara and May (1990)—although it is detected according to the analysis of Drepper (1988)). Recently, Sugihara *et al.* (1990) have suggested that the effect may be due to averaging over the larger spatial scale of England and Wales; evidence for this source of heterogeneity is discussed later. Casdagli (1992) reviews the performance of time series methods for detecting chaos in systems subject to significant noise.

1.2. *Models*

The main focus in modelling measles dynamics (as reviewed by May (1988)) is to account for the dramatic recurrent epidemic behaviour of the infection before the vaccine era and its response to mass immunization (Fine and Clarkson, 1982a, b). These analyses have been based on various refinements to the basic Hamer–Soper model (En'ko, 1889; Hamer, 1906; Martini, 1921; Soper, 1929; Bailey, 1957), which is currently commonly expressed in terms of the so-called SEIR epidemiological model (e.g. Schaffer (1985) and Bartlett (1990)):

$$\left.\begin{aligned} \frac{dS(t)}{dt} &= m\{1 - S(t)\} - b\,I(t)\,S(t), \\ \frac{dE(t)}{dt} &= b\,I(t)\,S(t) - (m+a)\,E(t), \\ \frac{dI(t)}{dt} &= a\,E(t) - (m+g)\,I(t). \end{aligned}\right\} \qquad (1)$$

Here, the dynamics of susceptible (S), infected but not yet infective (E), infective (I) and recovered (and immune) individuals (R) are represented by a simple deterministic model in continuous time, which assumes a constant total population size $S+E+I+R$, with rate parameters determining average life expectancy ($1/m$), incubation ($1/a$) and infectious ($1/g$) periods, and a constant infectivity coefficient b (E and the explicit inclusion of mortality rates are minor additions to the basic Soper model; Bartlett (1990)). Equations (1), which generate weakly damped oscillations, have been refined in a variety of ways to produce sustained epidemics. Hethcote and Levin (1989) review progress in this area, which has involved developing the basic model to allow for stochastic effects and various sources of heterogeneity in infection (seasonality, age structure, spatial distribution, etc.). Currently the most refined deterministic description of pre- and post-vaccination measles incidence in large communities is provided by a combination of age structure (Anderson and May, 1983; Dietz and Schenzle, 1985) and seasonal variations in contact rate associated with school cohorts (Schenzle, 1985).

The proponents of chaos in measles analyse a simpler refinement of equations (1), based on a periodically varying contact rate

$$b(t) = b_0\{1 + b_1 \cos(2\pi t)\} \quad (2)$$

(Schaffer, 1985). The propensity for this modification to cause sustained oscillations is well known (e.g. Dietz (1976) and Aron and Schwartz (1984)). However, Schaffer (1985) uses a comparatively high amplitude in the contact rate ($b_1 = 0.28$) to demonstrate relatively irregular chaotic epidemic behaviour in the model. He counters criticism of this large variation in contact rate on biological grounds (e.g. Dietz and Schenzle (1990)), by defining it as an 'effective' amplitude which allows the simple SEIR model to mimic the non-linear behaviour of observed measles data.

One problem with the deterministic SEIR model at this level of seasonal forcing is that it generates very low incidences of infectives in the troughs between large epidemics (Olsen and Schaffer, 1990). Olsen *et al.* (1988) and Olsen and Schaffer (1990) address this problem by recasting equations (1) and (2) as a stochastic model (Bartlett, 1957), which they explore by Monte Carlo simulation. Not surprisingly, for very large populations (5 million) the results of deterministic and stochastic models coincide. However, in a simulation of measles in Greater Copenhagen (population 1 million) Olsen *et al.* (1988) introduce an infective immigration parameter to prevent fade-out of infection. This population level is considerably higher than Bartlett's fade-out threshold, or that observed from other empirical studies (Black, 1966; Cliff and Haggett, 1988). It prompts the following questions: how does the high level of seasonal forcing in the chaotic SEIR model affect the degree of fade-out of the infection, and what effect does the introduction of simple spatial heterogeneities affect the behaviour of the model? In the present paper, these questions are considered via Monte Carlo simulations of equations (1) and (2). The following three sections respectively describe the details of the simulations, document and analyse their results and discuss the epidemiological implications of these findings.

2. MODEL STRUCTURE

2.1. *Basic Simulations*

The Monte Carlo simulations of the stochastic analogue of equations (1) and (2) were carried out on standard lines (Bartlett, 1957). For comparison, the epidemiological parameters assumed by Olsen *et al.* (1988) for Copenhagen were adopted—these, along with the transitions used in the model, are summarized in Table 1. Rather than adopting an exponential time to the next event, Olsen *et al.* (1988) used a constant time step. Simulations using both methods indicate broadly similar results, although the exponentially distributed time is adopted here since, in this non-autonomous system, a constant time step would appear to disregard at least some variation in b as it changes through time (in other words, a random time to the next step generates a variation in the next value of b). Simulations were started near the deterministic equilibrium and run for 100 years before recording results to eliminate initial transients (longer initial periods do not affect the following results). The following analyses are based on 200 years of simulated monthly data.

2.2. *Spatial Heterogeneities*

Two basic strategies have been adopted for the inclusion of spatial heterogeneity in Monte Carlo simulations of measles. The first (Bartlett, 1957) assumes the random

TABLE 1

Parameter values and transitions used in the measles Monte Carlo simulations described in the main text

SEIR model parameters† (Olsen et al., 1988)	
a	48.67
g	56.19
b_0	0.0010107
b_1	0.28
m	0.02
υ‡	21.024
Transitions and rates§	
$\rightarrow S$	$m\{S(t)+E(t)+I(t)+R(t)\}$
$S\rightarrow E$	$b(t)\,S(t)\,I(t)$
$E\rightarrow I$	$a\,E(t)$
$I\rightarrow R$	$g\,I(t)$
$S\rightarrow$	$m\,S(t)$
$E\rightarrow$	$m\,E(t)$
$I\rightarrow$	$m\,I(t)$
$R\rightarrow$	$m\,R(t)$
$\rightarrow I$§§	υ

†All parameters are in units year^{-1}, except b_0 (year^{-1} infective^{-1}) and b_1 (dimensionless).
‡Constant immigration rate of individuals into the populations (for spatial simulations, this is split equally between subareas).
§For the spatial model, these transitions are computed for each area, and the cross-infection rate calculated from equation (3).
§§The small increase in population which this implies does affect the simulations over the time periods examined.

diffusion of infectives between adjacent squares of a spatial grid. The second (Murray and Cliff, 1975) assumes cross-infection between infectives and susceptibles in different subdivisions of the grid. This preliminary analysis assumes the simplest spatial arrangement, in which the model city of 1 million inhabitants is divided equally into two halves. For the analyses reported here, the infective diffusion and cross-infection models give qualitatively similar results. We adopt the latter model in subsequent simulations, since it gives a simpler transition to the two extremes of uncoupled and completely coupled systems. In particular, the net infection rate per susceptible in area j ($j=1, 2$) can be expressed as

$$\lambda_j = b\{I_j(t) + c\,I_k(t)\} \tag{3}$$

($k\neq j$, $k=1, 2$), so that $0\leqslant c\leqslant 1$ defines a range from completely uncoupled to completely coupled systems in terms of infection. The average infection coefficient b_0 was adjusted (to $b_{0c}=b_0/(1+c)$) to give the same net equilibrium infection rate for each area as for the homogeneously mixed city as a whole.

2.3. *Analyses*

The following section characterizes the simulated time series in terms of simple autocorrelations and univariate spectra, as well as squared coherency spectra between different areas in the simulated city. A simple non-linear graphical analysis is also performed exactly along the lines set out by Olsen *et al.* (1988): the simulated time series of monthly cases is embedded in three dimensions with an embedding lag of

3 months, and a return map is calculated from a vertical Poincaré section through the origin. A relatively conservative fade-out criterion of 1 month without cases (cf. the figure of 3 weeks adopted by Bartlett (1957)) was applied to the simulations.

3. RESULTS

3.1. *Homogeneous Mixing*

Fig. 1 displays a time series analysis for the simplest case in which the two city subdivisions mix homogeneously with each other (i.e. $c=1$ in equation (3)). The correlogram and spectrum of total cases (Figs 1(b) and 1(c) respectively) indicate strong periodicities at frequencies of around 0.32 and (to a lesser extent) 1 cycle per year, with a harmonic of the former at 0.6 per year. For comparison, Fig. 1(c) also plots the spectrum from a spatially undivided simulation—as expected, the two simulations produce very similar spectra. Measles incidence for the two subareas of the homogeneously mixing city are very similar; the squared coherency spectrum between the two areas (Fig. 1(d)) illustrates a very close correlation except at high frequencies.

Olsen *et al.* (1988) also find significant spectral peaks at 0.31 and 1 cycle per year in their analysis of 50 years of simulated data, along with a further peak at 0.54 per year which is absent from Fig. 1(c). As illustrated by the time plot (Fig. 1(a)), the simulated series alternates periods of large epidemics with a period of around 3 years, interspersed with more irregular eras of biennial cycles. The biennial periodicity may be due to the duration of these latter epochs in the analysed series, or to differences in the simulation method.

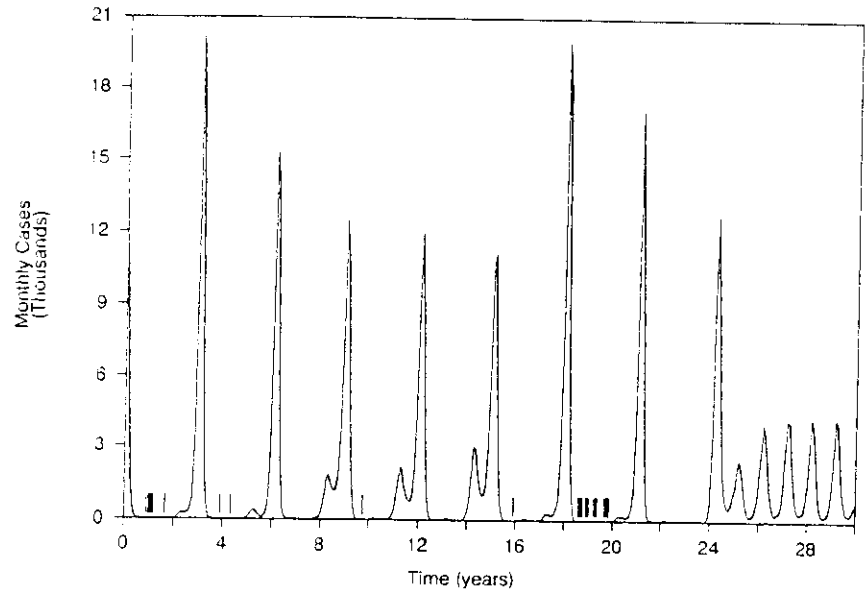
3.1.1. *Fade-out of infection*

Fig. 1(a) marks points in the simulated time series where fade-out (as defined earlier) occurs—essentially, there is a high probability of fade-out (as defined by Bartlett (1957)) after each major epidemic. Table 2 summarizes the incidence of fade-out as the proportion of months in which cases are absent. Around 5% of the time, notifications are absent from the simulated city. Compared with the available empirical evidence from the UK, the USA and Pacific islands (Cliff and Haggett, 1988), this is a very high figure for such a large city and is not consistent with the previously derived threshold of 250000–500000 (Bartlett, 1957; Black, 1966; Cliff and Haggett, 1988). The discrepancy is confirmed by the observed data for Copenhagen, where *no* months with zero cases were observed in the period 1928–68 (Table 3; L. F. Olsen, personal communication).

TABLE 2

Incidence of fade-out in measles time series for Copenhagen: proportion of months without measles cases in the simulations described in the main text

Simulation	*Proportional fade-out*
No spatial subdivision	0.0588
2 areas, $c=1$	0.0508
2 areas, $c=0.1$	0.035
2 areas, $c=0.01$	0.0354
2 areas, $c=0$	0.027



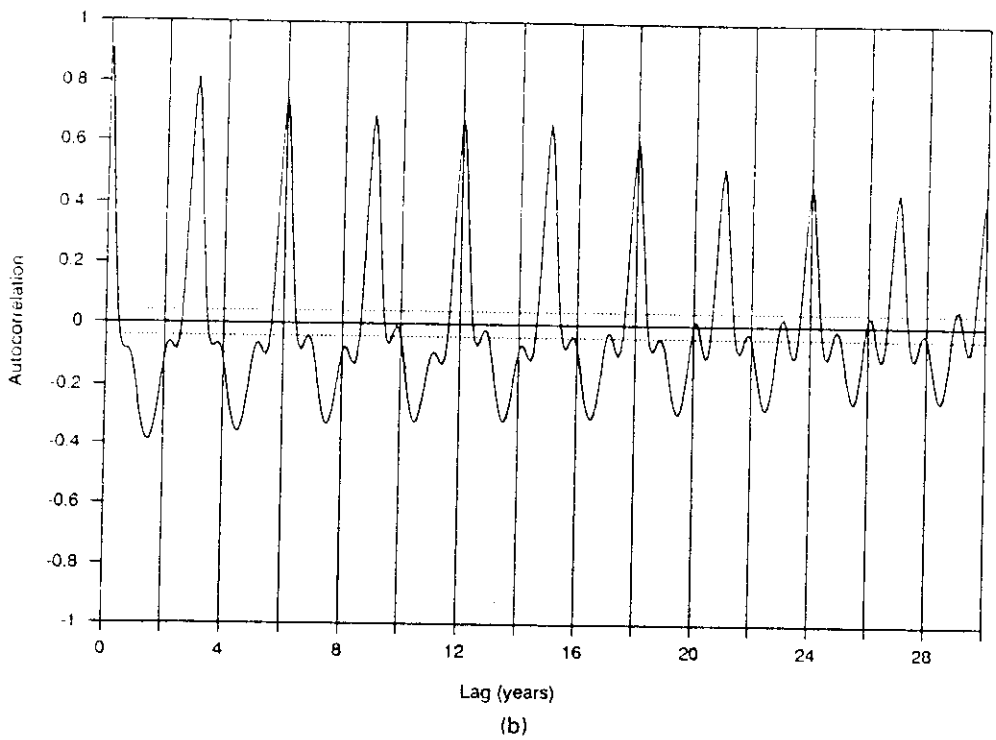
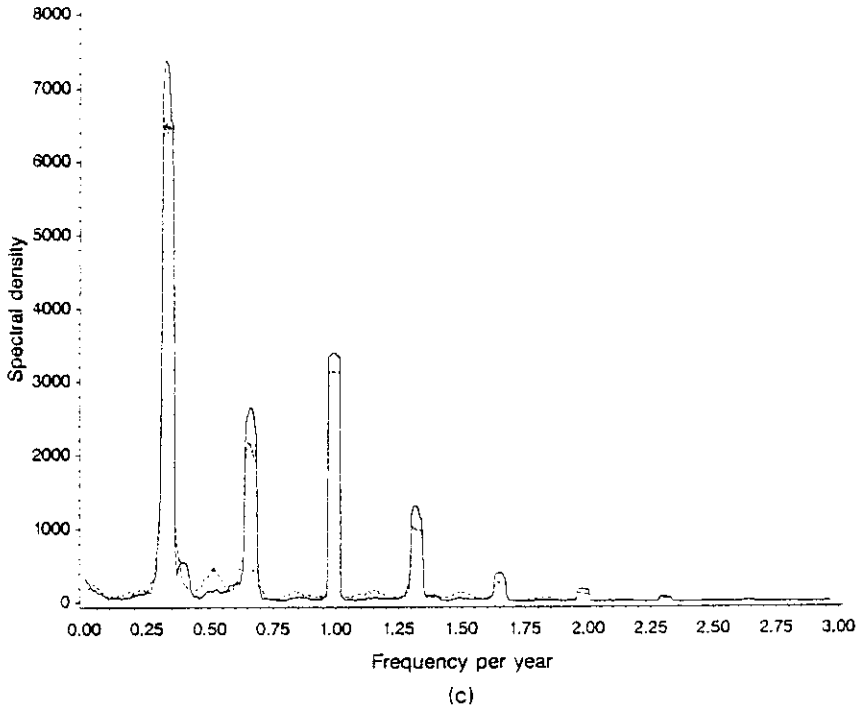


Fig. 1. (a) Time plot of part of the simulated monthly measles time series described in the text: the simulation assumes two spatial areas with a homogeneous infection rate ($c = 1$ in equation (3); the figure shows total monthly notifications and notifications for one subarea (the other is very similar); vertical bars denote months with no cases); (b) autocorrelogram for the equivalent full series of 2400 monthly points; (c) spectrum of total cases (·····, equivalent spectrum from a simulation with no spatial subdivision); (d) squared coherency spectrum between individual area time series (the spectra were calculated by smoothing the periodogram with a 10-point average; other degrees of smoothing produce similar qualitative results); the data were square root transformed and mean corrected before analysis (Olsen *et al.*, 1988)



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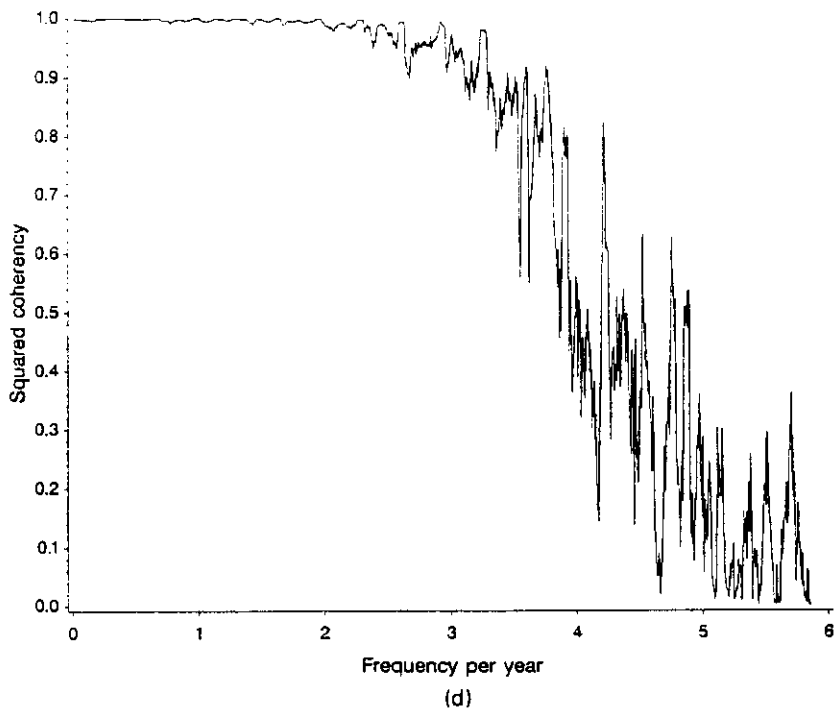

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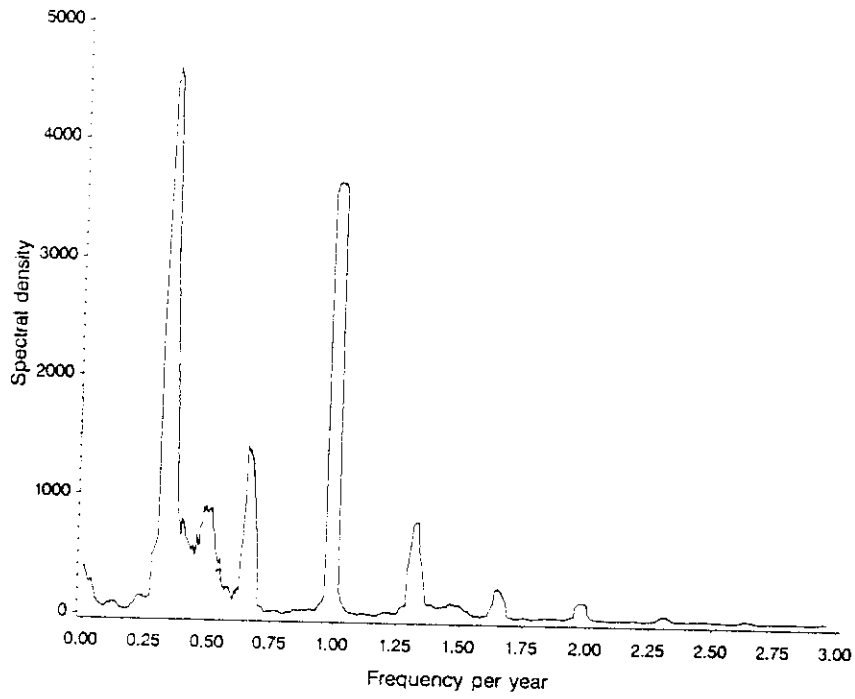
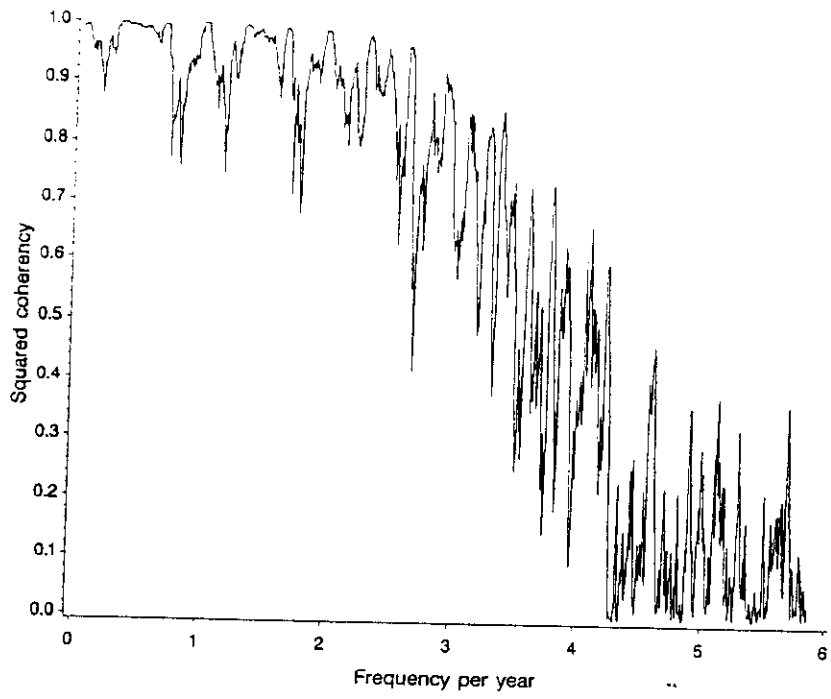
Fig. 1. (*continued*)

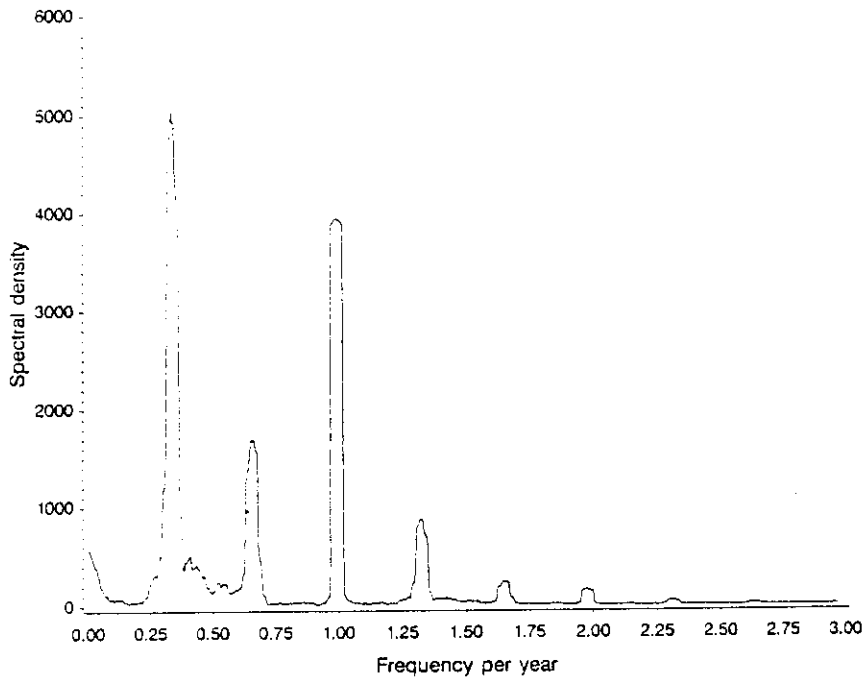


(a)



(b)

Fig. 2. Spectral analysis for the simulations with partial spatial coupling—details are given in Fig. 1: (a), (b) spectrum of total cases and squared coherency spectrum between subareas for $c=0.1$; (c), (d) as for (a) and (b) respectively with $c=0.01$; (e), (f) as for (a) and (b) respectively with $c=0$



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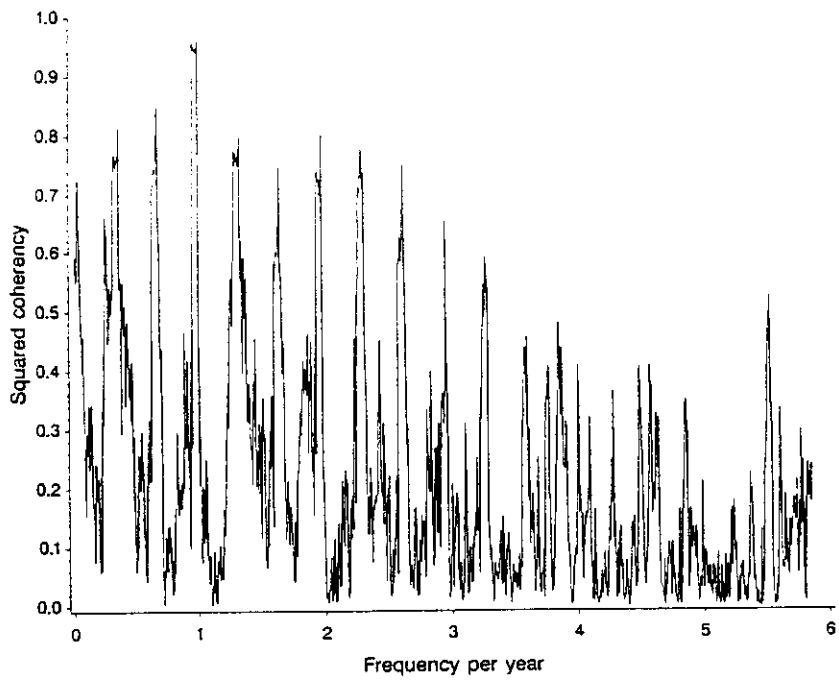
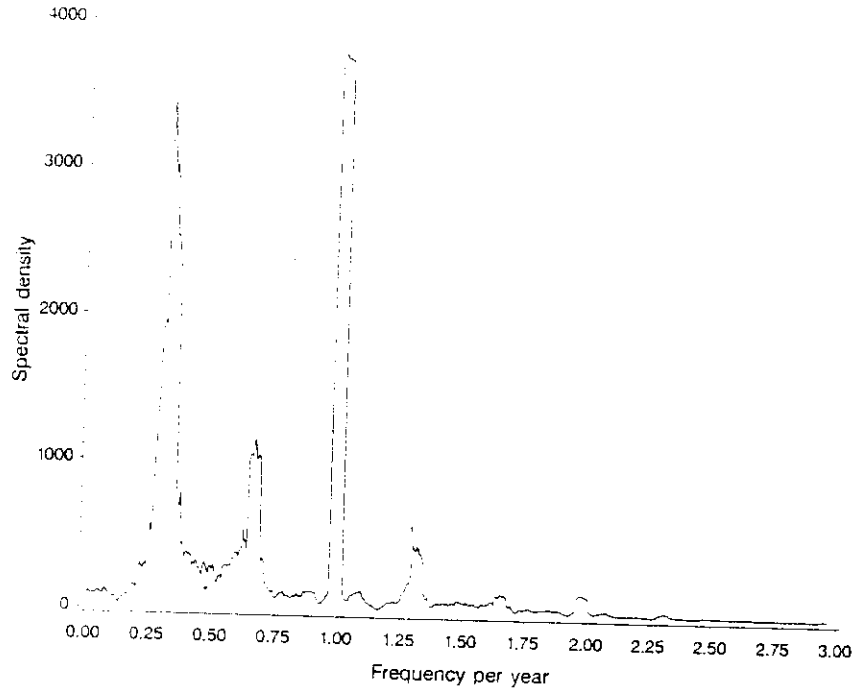


(d)

Fig. 2. (*continued*)



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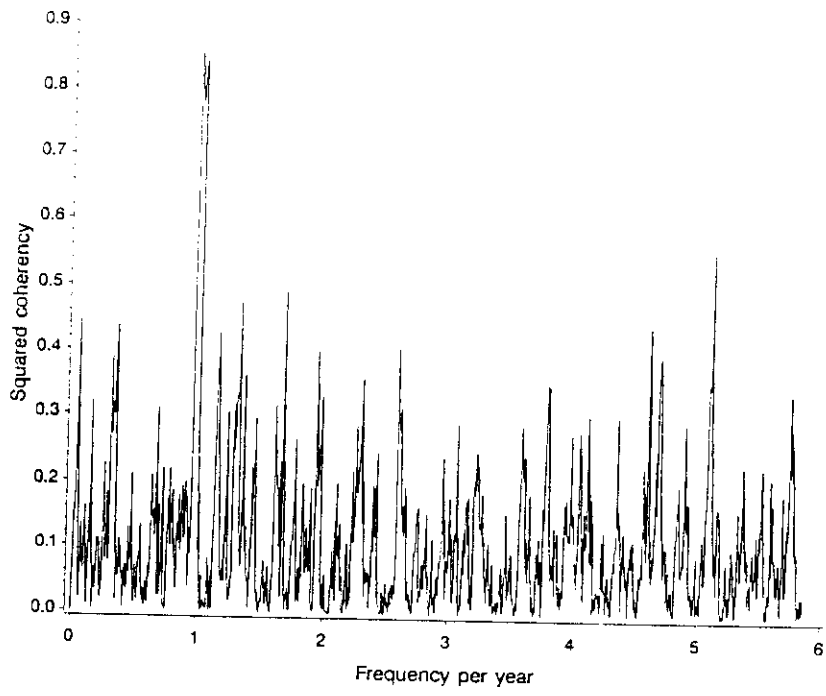


(f)

Fig. 2. (*continued*)

TABLE 3

Incidence of fade-out in measles time series for Copenhagen: observed lower tail frequencies of monthly measles incidence for the period 1928–68

Cases per month	*Proportional frequency*
0	0
1	0
2	0.002
3	0.002
4	0
5	0.008
6	0.004
7	0.008
8	0.004
9	0.006
10	0.006

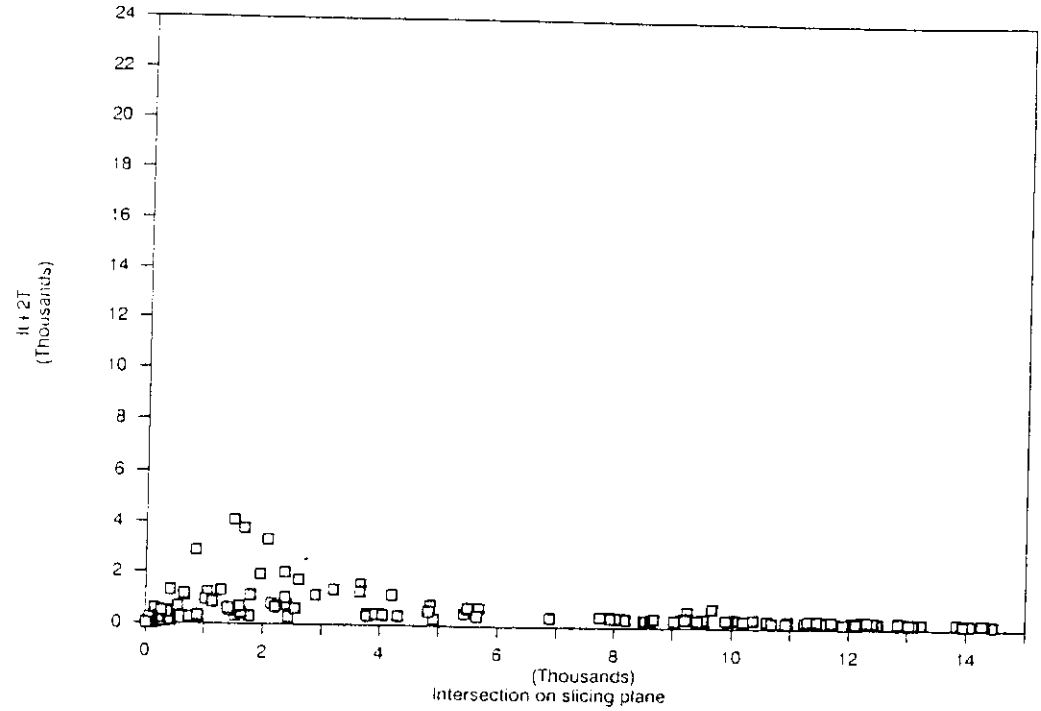
3.1.2. *Effects of spatial heterogeneity*

Table 2 also shows the effect of reducing the degree of coupling (lowering c in equation (3)) on the proportional fade-out of infection. Overall, the transition from the extreme cases of a single population group to a sum of two completely uncoupled areas ($c = 0$) produces a reduction of about 100% in the degree of fade-out. However, even in the uncoupled case, there is still a considerable degree of fade-out. Fig. 2, which presents a spectral analysis for the various spatially heterogeneous cases, sheds light on these results. As the degree of coupling declines, the correlation between subareas (shown by the coherency spectra in Figs 2(b), 2(d) and 2(f)) is gradually reduced, except at the common driving frequency of 1 per year in b. The spectra for total cases (Figs 2(a), 2(c) and 2(e)) also indicate this strong annual periodicity, as well as the lower frequency major epidemics described above. The lower frequency peak is also apparent, to a reduced extent, in the uncoupled ($c = 0$) simulation. This occurs because the strong common driving frequency in b often produces periods of synchronous major epidemics. The associated synchronous minima in the infective time series generate the significant degree of fade-out in the uncoupled system shown in Table 2.

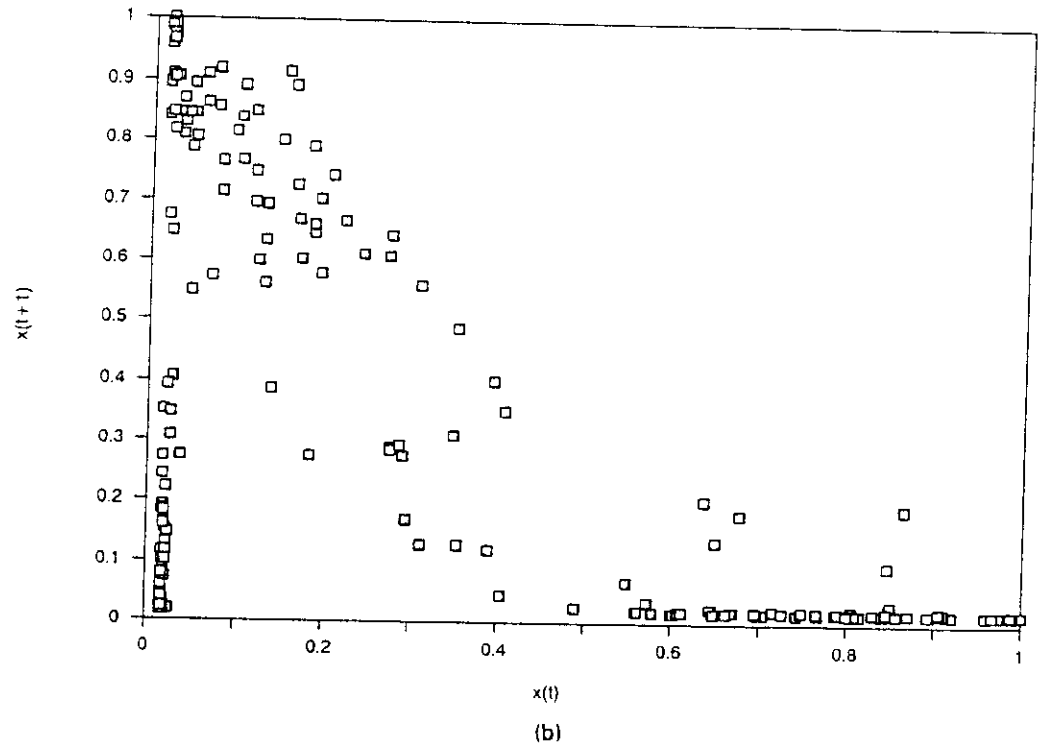
In summary, introducing a very simple degree of spatial heterogeneity does not greatly reduce the propensity for large amplitude variations in the infection coefficient to induce fade-out at this population level (Table 2). Preliminary experiments with larger spatial grids also qualitatively bear out this result, which echoes the findings of Bartlett (1957). These results are also very sensitive to the assumed immigration rate of infectives. For example, doubling the immigration rate eliminates fade-out but produces time series dominated by annual fluctuations, which do not correspond with the empirical data (Olsen *et al.*, 1988).

3.1.3. *Non-linear behaviour*

Fig. 3 presents a simple graphical analysis of the non-linear properties of the homogeneously coupled ($c = 1$) and uncoupled ($c = 0$) simulations. It shows Poincaré sections and return maps estimated from the time series of total cases exactly as prescribed by Schaffer and Kot (1985a, b). As expected, the homogeneous case produces a humped map which is qualitatively very similar to that derived by Olsen *et al.* (1988),

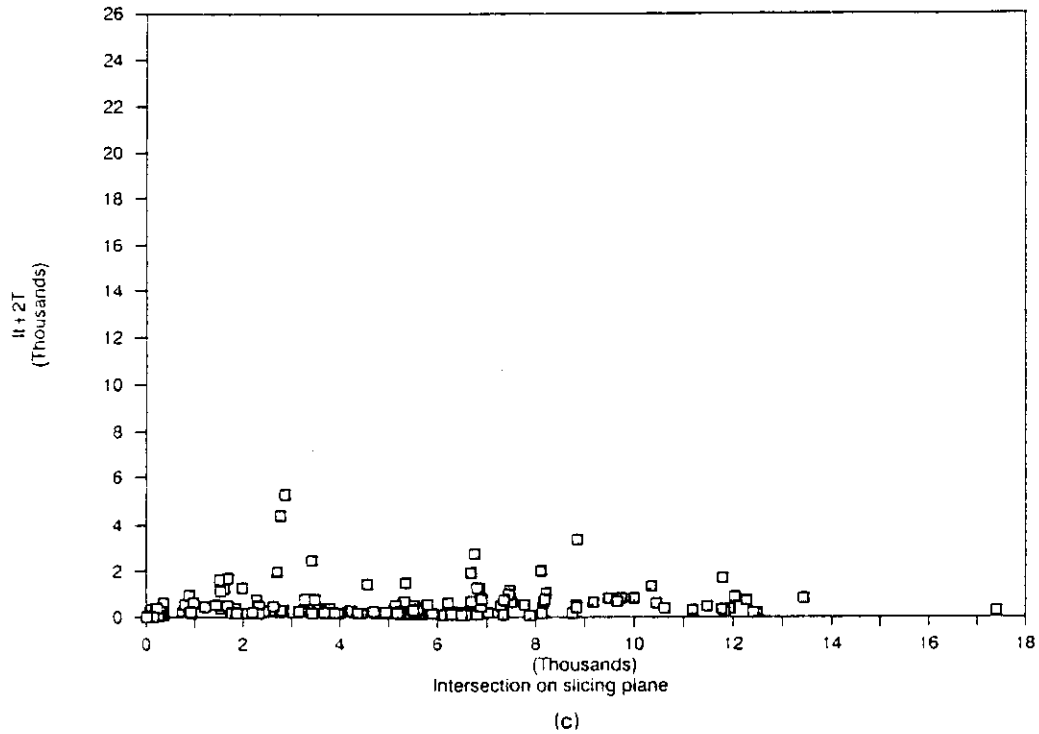


(a)



(b)

Fig. 3. Poincaré sections and return maps (calculated as described by Schaffer and Kot (1985a, b)) for total case time series from measles simulations with $c=1$ ((a) Poincaré section; (b) return map) and $c=0$ ((c) Poincaré section; (d) return map): the map co-ordinates (x_{t+1}, x_t) are successive points from projections of the Poincaré section on to a quadratic polynomial fit (Olsen *et al.*, 1988)



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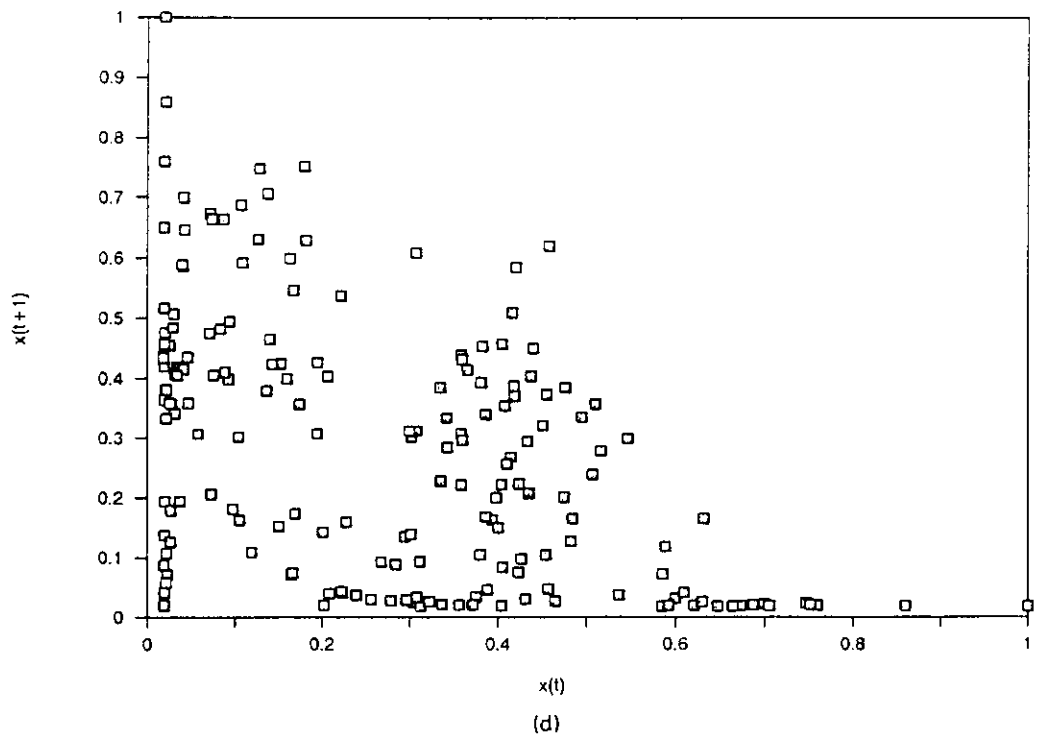

(d)

Fig. 3. (*continued*)

and which they adduce as evidence for low dimensional chaos. Although the section and map of the uncoupled series are more variable, it again produces an approximately one-humped map. It would be interesting to extend this simple analysis to examine how the degree of coupling affects other quantitative measures of stability, dimension and predictability.

4. DISCUSSION

The introduction of ideas from non-linear dynamics into epidemiology has proved very stimulating. In particular, the idea of chaotic dynamics raises the possibility of new interpretations for the irregularities which are apparent in many notification time series. On a more applied epidemiological front, questions about the predictability of epidemics (Sugihara and May, 1990) may also present fruitful areas for future research. However, as pointed out by Bartlett (1990) and Dietz and Schenzle (1990), theoretical analyses along these lines must be based on models of appropriate biological complexity. The results reported here underline the difficulties of using a strongly sinusoidally forced SEIR model in this context. In fact it is likely that the minimum appropriate degree of complexity should involve a combination of age structure and more epidemiologically realistic seasonality, as set out for example by Schenzle (1985). For instance, Olsen and co-workers (personal communication) have recently carried out further Monte Carlo simulations of measles dynamics in Copenhagen based on a (non-age-structured) SEIR model with a more realistic seasonal forcing function (Kot *et al.*, 1988). Although their results indicate a lower degree of fade-out (around 1% of months compared with over 5% for the sine wave forcing function), this still does not account for the observed persistence of infection (Table 3). Work currently in progress indicates that the interaction of seasonality and age structure may account for this discrepancy (Bolker and Grenfell, 1991).

In an interesting discussion on their paper, Olsen *et al.* (1988) underline the importance of spatial heterogeneity, and in particular partial coupling between cities, in the perpetuation of childhood diseases. Although the simulation with no coupling described here suggests that such factors may not entirely explain persistence in highly seasonally forced systems, the question of coupling is important. In particular, more work is needed to examine the impact of seasonality on the balance between fade-out and coupling in larger spatial grids with smaller individual population sizes (Bartlett, 1957, 1960). These questions can also be examined in terms of the available empirical data. For example, although the measles incidence pattern for England and Wales in the pre-vaccination period (1950–66) is very regular (Fine and Clarkson, 1982a; Anderson *et al.*, 1984), there are significant heterogeneities between cities

TABLE 4

Correlation matrix of weekly returns for measles in five English cities: 1950–66†

	London	Liverpool	Manchester	Birmingham
Liverpool	0.142			
Manchester	0.588	0.304		
Birmingham	0.750	0.212	0.405	
Sheffield	0.703	0.214	0.467	0.809

†Data from Registrar General's weekly reports.

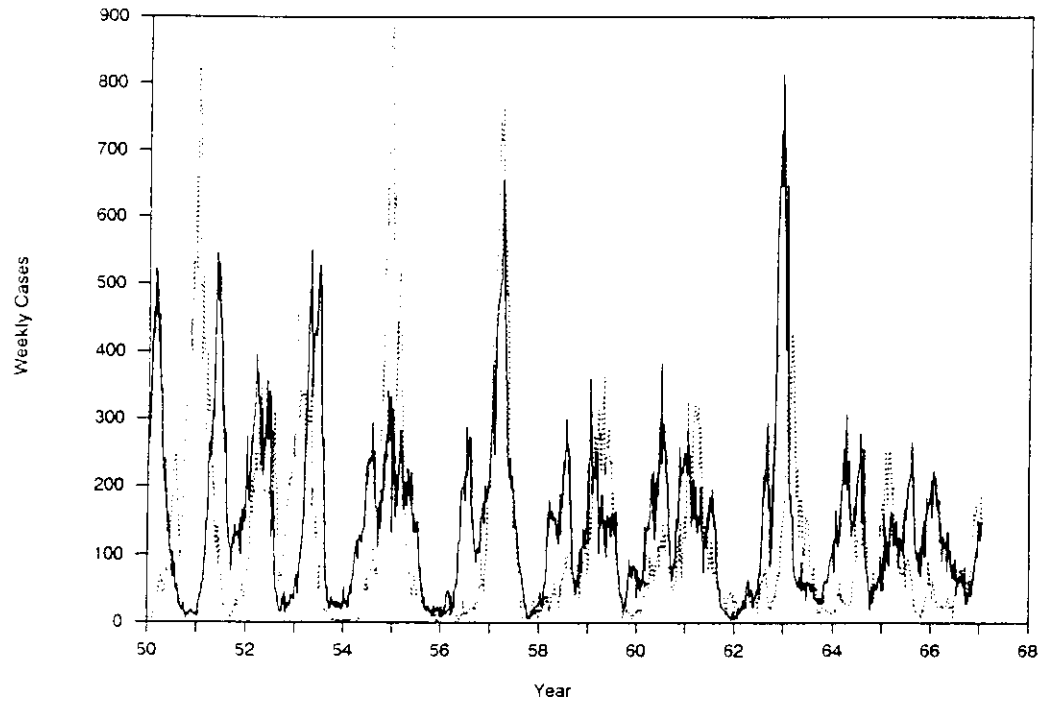

Fig. 4. Weekly measles notifications for Liverpool (——) and Manchester (·····) for 1950–66

(Bartlett, 1957; Cliff and Haggett, 1988). Table 4 shows a correlation matrix for the weekly reports from London, Birmingham, Liverpool, Manchester and Sheffield over this period. Although the coupling is fairly high overall, Liverpool has a relatively low correlation, even with its near neighbour Manchester. Fig. 4 shows a time plot for Manchester and Liverpool, which appear to be significantly out of phase for the first half of the series. Whether this effect (which is much more apparent in the post-vaccination series; Bolker and Grenfell (1991)) is due to epidemiological or other factors is not immediately clear. It illustrates that the population dynamics of childhood diseases still present unanswered questions which the new non-linear methods may provide very useful tools for examining.

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