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Measles in England and Wales—I: An Analysis of Factors Underlying Seasonal Patterns

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Examination of weekly measles notifications for England and Wales, 1950–1979, reveals a regular biennial pattern of major and minor epidemics before the national immunization programme began in 1968, followed by an annual cycle of minor epidemics. Each year the reported incidence reaches its annual low between weeks 36 to 39, very close to the opening of primary schools. Analysis of these data with a simple mass action model reveals that the underlying transmission parameter has had a similar annual pattern in years of major and minor epidemics. The transmission parameter rises three times each year, coinciding with opening of school terms, and falls with school term and mid-term holidays. This pattern of the transmission parameter has been maintained in the decade since national vaccination began, indicating that the importance of schools in the annual dynamics of measles has not changed. The analysis further suggests that the national measles vaccination programme has not lowered the total number of individuals susceptible to measles in England and Wales.

Measles has long been a favourite subject for epidemiologists. Its high incidence, worldwide distribution and clinical severity have merited its inclusion among the more important public health problems. Its consistent and easily recognized clinical picture has assured the wide availability of good data. The recent development and deployment of measles vaccines have added current urgency to studies of its epidemiology. In a broader sense, the regularity of its clinical course, and the dramatic pattern of its recurrent epidemics, have made measles a prototype for studies of the dynamics of acute infection. Indeed, it is probable that the classic studies of measles by Panum,[1] Hamer,[2] Soper[3] and Bartlett[4] have contributed more to our understanding of acute contagious processes than have any other series of studies on any other disease.

The regular recurrence of epidemics in large unvaccinated populations is one of the most impressive epidemiological features of measles. These epidemics tend to occur in winter and spring months, and hence appear to oscillate between temperate regions north and south of the equator. Though a seasonal increase in incidence may occur yearly, there has been a tendency for large epidemics to occur at regular 2 or 3-year intervals in many populations of Europe and North America.[5,6,7,8] Early efforts to explain such recurrences led to a celebrated epidemiological controversy.[9] Some workers believed that the recurrences reflected regular changes in the measles agent itself[10]; whereas others argued that the periodic epidemics reflected a dynamic implication of the constant influx of susceptible children into the population.[2,3] The latter argument won the debate; and in so doing it developed an important principle of epidemic theory, generally called the epidemiological 'law of mass action'. This 'law' states that the incidence (rate) of a contagious infection in a population is a function of the number of susceptibles times the prevalence (rate) of infectious cases.

There are several ways of expressing the mass action principle, a common form being

$$C_{t+1} = C_t \cdot S_t \cdot r$$

Here S_t and C_t are the numbers of susceptibles and of cases in a present period, and C_{t+1} is the predicted number of new cases one serial interval in the future. The r is the proportionality factor, called different things by different authors—for example the 'coefficient of infectivity'[3] or the 'contact rate.'[8] Though reiteration of this simple equation (adding new susceptibles at each period to mimic births or immigrants into the population) simulates periodic waves of incidence, several workers have suggested that the simple equation is not sufficient to describe the strict seasonality and the undamped nature of observed measles waves.[11] After

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applying the equation to monthly measles data from Glasgow, Soper concluded that the r parameter must vary seasonally, perhaps related to the annual assembly and dispersal of children to and from schools.[3] Yorke and London found evidence for a very similar annual trend in r, in analyses of monthly measles data from New York and Baltimore cities, and they too suggested schools might be the determining factor.[8]

Inspection of the results of Soper and of Yorke and London (Fig. 1) reveals that their calculated r parameters rise in July or August, rather too early to be attributed to school opening. Furthermore, they describe a single wave, peaking at some time between October and February. Indeed, on this evidence alone, one might question whether such a trend would not be better explained as a weather-related effect, perhaps a concomitant of temperature, rather than as a school effect—or whether there were some fallacy in the model or in the analyses. It was in an effort to examine this apparent inconsistency that the current analyses were undertaken. They in turn lead to a deeper understanding of the seasonal dynamics of measles, and to a recognition of certain strengths and weaknesses in simple mass-action theory in epidemiology.

SOURCES OF DATA

Measles data used here are weekly notifications for England and Wales as reported to the Office of Population Censuses and Surveys, and published in the Annual Reviews of the Registrar General of England and Wales[12] and quarterly Infectious Diseases Monitors published by the Office of Population Censuses and Surveys.[13] Though weekly data are available since 1940, the pattern of reported measles was irregular during the 1940s presumably owing to the massive population disruption during that decade, and perhaps also to changes in notifying practices at the time of the introduction of the National Health Service in 1948. For this reason,

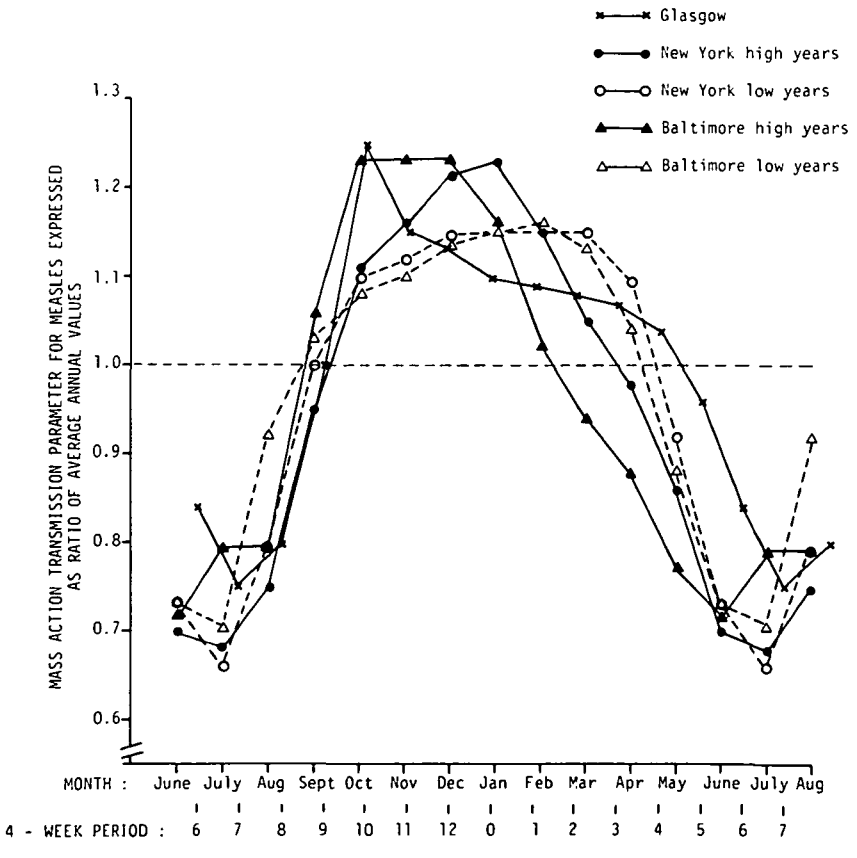

FIG. 1

Mass action transmission parameters as calculated for measles by previous authors. The monthly parameters are here plotted as ratios of the annual mean value. Soper's estimates for Glasgow were based on 4-weekly data.[3] Yorke and London's estimates for average epidemic and non-epidemic years in New York City and in Baltimore are given separately.[7,8]

only data since 1950 are examined here. These weekly notifications for the years 1950 to 1979 inclusive are presented in Fig. 2.

Measles vaccination data were drawn from annual summaries submitted by Area Health Authorities to the Department of Health and Social Security. The annual figures are set out in Table 1.

QUALITATIVE DESCRIPTION OF MEASLES TRENDS

The weekly incidence data in Fig. 2 reveal several important features of measles in England and Wales. First is the remarkably consistent biennial pattern of major and minor epidemics which prevailed from 1950 until the national measles vaccination programme began in 1968. Close inspection reveals that in each calendar year the lowest incidence was reported between weeks 36 and 39, most often in week 37 or 38, after which it rose to a peak in the next year. During major epidemic (odd numbered) years the peak was reached in the late winter or early spring, and by about the 20th week the incidence had begun to fall sharply. During minor epidemic (even numbered) years the peak was reached in the summer and the subsequent fall began about the

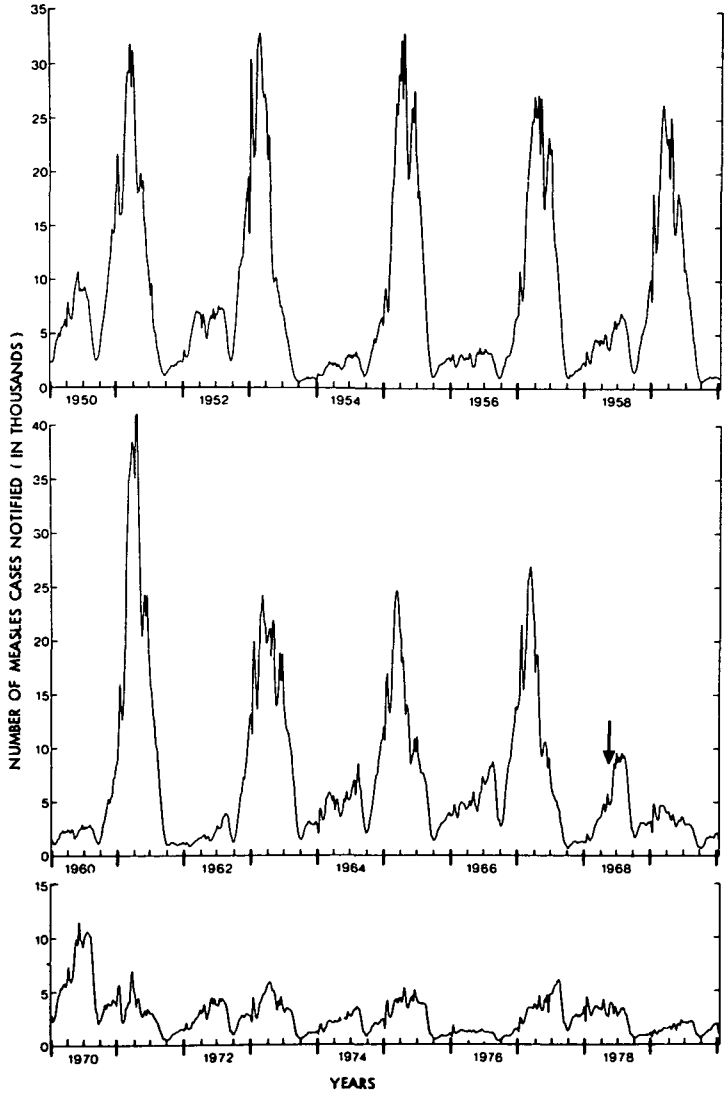

FIG. 2

Measles notifications in England and Wales, by week, 1950–79. The arrow indicates the beginning of the national measles vaccination programme in 1968.

TABLE 1

Total number of measles vaccinations reported in England and Wales, 1968–1979. (Data provided by DHSS)

Year	Measles vaccinations notified
1968	719 169
1969	398 099
1970	623 488
1971	537 765
1972	513 210
1973	478 345
1974	351 975
1975	312 084
1976	325 024
1977	315 402
1978	312 431
1979	332 267

30th week. The approximate coincidence of this pattern with the annual school year was recognized long ago.[2,3] Another prominent feature of the data is the sudden dip and peak at the end of each calendar year. This occurs for most notifiable diseases, and is due in large part to the interruption of notification by holidays, and by Christmas postal delays. An interesting artefact is the fall and subsequent sudden rise during the first quarter of 1971, which reflects accumulation of posted notifications at the termination of an extended postal strike. Though the overall incidence of measles has fallen since the immunization programme, and the clear biennial pattern was lost after 1967, the timing of the annual minimum, the rough association with school years, and the end-of-year artefacts remain. It may also be noted that the annual pattern since immunization is rather similar to that of the minor epidemic years before 1968.

We begin by examining the prevaccination trends in detail. The constancy of the 1950–1967 pattern indicated that it would not be improper to calculate an average biennial cycle, as a simple arithmetic average of the weekly notifications for 8 biennial cycles, 1950–1965. (As measles vaccines were made available in England and Wales in February 1966, two years before the start of the national programme in May 1968, we chose to omit 1966 and 1967 from the calculation of the average prevaccination cycle.) This average biennial cycle is shown in Fig. 3a. The major features prominent throughout the individual years in Fig. 2 are shown even more clearly here. Incidence reaches its annual low in week 37 before the major epidemic and in week 38 before the minor epidemic. In addition, one notes depressions during weeks 15–20 during both the major and minor epidemic year. Continuing the school-based interpretation, one might suggest that these depressions reflect the 3-week Easter holidays which occur in March or April each year. On the other hand, the interpretation of such trends is confounded by several factors. The first is the possible association of altered notification practices with school holiday periods, in particular at Christmas time. The second is the problem of delays, since notifications of incidence follow transmission events by both incubation and notification-delay periods. These factors are discussed further below.

METHODS OF ANALYSIS

The reported measles incidence data were analysed in order to reveal factors which may underlie the remarkable patterns shown in Figs. 2 and 3a. The approach was to estimate the weekly transmission parameters implicit in these data, on the assumption that they reflect a simple 'mass action' process. In brief, the mass action principle considers that the susceptibles and the infectious cases in a population mix together at random; and that a certain proportion of the contacts between two groups result in transmission of the infection. The newly infected individuals then become cases one serial interval later. Cases in one time period recover to become immunes by the next time period. For purposes of the present analysis, we describe the principle in more explicit terms.

We are considering a disease in which the infectious period is short relative to its incubation period. Successive cases appear as 'chains of transmission', and groups of cases appear as successive 'crops' or 'generations'. Each such group of cases occurs over a time period equal to the serial interval of the infection, i.e. the period between onset of infectiousness in successive cases in chains of transmission.[14] We label the successive time periods t, $t+1$, $t+2$, etc. Thus C_t and C_{t+1} reflect numbers of cases in time periods t and $t+1$, respectively, the latter cases being considered as direct consequences of the former. The simple mass action principle then states that the incidence in a subsequent time period, C_{t+1}, is a function of the product of the number of current cases (C_t) and the current number of susceptibles (S_t). Thus:

$$C_{t+1} = C_t . S_t . r_t , \qquad (1)$$

where r_t is a proportionality factor. We see by the form of equation (1) that this r_t parameter reflects the proportion of the total possible contacts between cases and susceptibles ($C_t \times S_t$) which lead to subsequent cases. Rather than prejudice ourselves as to its meaning, however, we will call r_t merely the 'transmission parameter', and discuss its implications below.

If one is to simulate a series of time periods by reiterating equation (1), it is obviously necessary to adjust the number of susceptibles successively. Thus:

$$S_{t+1} = S_t - C_{t+1} + B_t(-V_t), \quad (2)$$

meaning that the number of susceptibles remaining in the next time period (S_{t+1}) is equivalent to the number of susceptibles in this time period (S_t), lessened by the number of these which have become cases (C_{t+1}), but increased by the number of susceptibles introduced or born into the population (B_t). If vaccination is employed, the number of susceptibles effectively vaccinated in this time period (V_t) must also be subtracted. It may be noted that this simple mass action formulation does not take account of deaths among either susceptibles or cases. Such deaths are now so few in developed countries as to have little impact upon the dynamics of measles transmission.

In order to estimate the transmission parameter r_t for any time period, equation (1) is rearranged to give:

$$r_t = \frac{C_{t+1}}{C_t . S_t} \quad (3)$$

Therefore, before calculating the r_t parameters from data as represented in Figs. 2 or 3, we need to determine two things: (1) the appropriate time interval (relating C_t, C_{t+1} etc. to reported weekly incidence figures), and (2) the initial number of susceptibles (S_1).

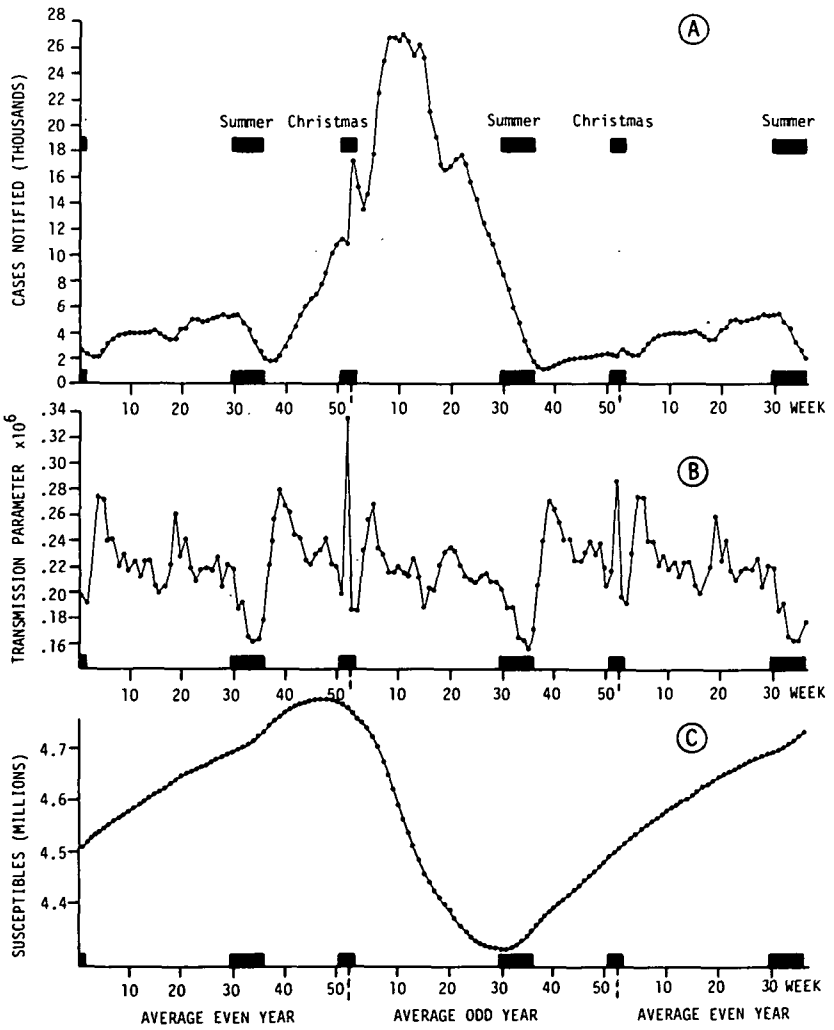

FIG. 3

Analysis of average biennial measles pattern, based on data from 1950 to 1965: (a) Average number of cases notified per week; (b) Calculated weekly transmission parameters; (c) Estimated number of susceptibles per week. Shaded blocks indicate school summer and Christmas holiday periods.

Selection of the appropriate time interval was based upon a consideration of the natural history of measles and of the form in which data are available. Infectiousness generally begins with onset of prodromal signs, about 10 days (range 8–13 days) after infection.[15] The period of transmission is short, since children are typically kept at home when the rash begins. As weekly data are directly available (Figs. 2,3), the initial analyses assumed one week to be the basic interval between successive cases. A two-week interval was also examined, by grouping cases in successive biweekly periods.

Estimation of the total number of susceptibles on 1 Jan of the years prior to immunization was made by a cohort method similar to that described by Roden and Heath.[6] Using age-specific notifications, as reported in the Annual Reviews of the Registrar General of England and Wales, the number of notifications reported for a specific birth cohort, over successive years, was subtracted from the number originally born into that cohort. It was found that the cumulative incidence of measles by the 16th birthday, amounted to about 65% of each cohort. As seroepidemiological surveys during this period showed that over 95% of 15 year olds had antibody evidence of prior measles infection (Dr C L Miller, personal communication), it is apparent that only approximately two-thirds of these infections were recognized and notified as clinical measles in England and Wales. Estimation of the true cumulative incidence in each age group was thus obtained by multiplying the reported cumulative incidence by $\frac{3}{2}$. Once this was established, a summation of numbers in each age group with no history of measles provided an estimate of the total number of susceptibles in England and Wales, on January 1 of each year. This number was found to be close to 4.5×10^6. A full discussion of these methods, and of the results of the analyses, is presented in a companion paper.[16]

RESULTS

The weekly transmission parameters for the pre-immunization years were calculated by repeatedly applying equation (3) to successive incidence data (C_t) in the average biennial cycle (Figure 3a). Thus:

$$r_1 = \frac{C_1}{(C_2)\,.\,(S_1)} = \frac{2610}{(2304)\,(4.5\times10^6)} = .196\times10^{-6},$$

$$r_2 = \frac{C_2}{(C_3)\,.\,(S_2)} =$$

$$\frac{2304}{(1976)\,(4.5\times10^6-\frac{3}{2}\,C_2+B)} = .190\times10^{-6},$$

etc.,

where $B = 12\,300$ i.e. the estimated average number of births per week. (For the purpose of this analysis of the average biennium, the number of births per week was assumed to equal the average weekly incidence of measles. Given that during the preimmunization period virtually everyone contracted measles, this was roughly true.) The r_t values so obtained are plotted in Fig. 3b.

The weekly numbers susceptible predicted in this process are presented in Fig. 3c.

The pattern of the r_t parameter shown in Fig. 3b is revealing. We may first note the similarity of the trends during both major and minor epidemics, indicating that the marked differences in incidence between these periods are attributable wholly to the different numbers of susceptibles available (Fig. 3c). Secondly we note the sharp peak occurring in week 52 of each year, reflecting the Christmas time artefact noted in Figs. 2 and 3a. More interesting features are as follows:

(1) *The transmission parameter is at a minimum in* week 34 (before the average major epidemic) or week 35 (before the average minor epidemic). State schools generally open during week 35 or week 36 in England and Wales, after the long summer holiday, which coincides with the initial annual rise in the transmission parameter. Furthermore, the reported measles incidence begins to rise in week 38 or 39, three weeks after the opening of the schools. This is consistent with a school opening effect, as measles virus transmission during the opening days of school will manifest clinically towards the end of the second week, and some of these cases will be notified during the third week of term.

(2) The pattern of the r_t parameter for each epidemic year (week 35 to week 34 of the subsequent calendar year) consists of three clear peaks, each with a steep rise and a slower decline. The divisions between these peaks coincide closely with the Christmas and Easter holidays of the school year. There appears to be a prominent dip midway through the first peak, at about week 44. This corresponds tantalizingly well with the annual week-long holiday in the autumn school term. There is also a suggestion of similar dips in the transmission parameter in the other two peaks, which may reflect the mid-term week-long holidays.

(3) In addition to the skewness of each of the 3 school-term-related peaks, it will be noted that successive peaks are of decreasing height during a major epidemic year, whereas they are of approximately the *same magnitude during a minor epidemic period.* The implications of this pattern are discussed below.

The pattern of transmission parameters based on a 2-week grouping of cases is shown by the solid line in Fig. 4. It closely resembles the trend in Fig. 3b (shown by the dotted line in Fig. 4), though with a slightly greater amplitude.

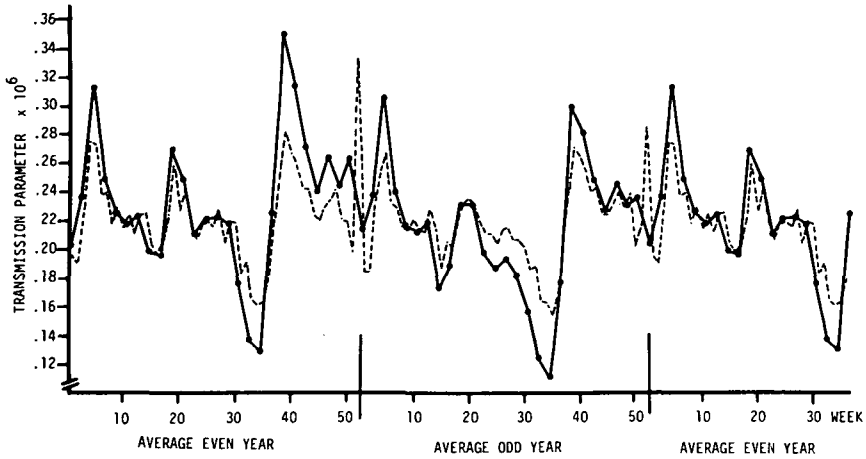

FIG. 4

Pattern of transmission parameters using cases notified 1950–65, based on:
(a) 1 week intervals (dotted line)
(b) 2 week intervals (solid line)

POST IMMUNIZATION TRENDS

Since the commencement of the national measles vaccination programme in 1968, the overall incidence pattern has lost its clear biennial regularity (Fig. 2). It is thus not appropriate to calculate an average epidemic year or biennium for this period, as was done for the preimmunization period in Fig. 3. Nonetheless, the recent r_t values can be calculated by precisely the same method as described above, using actual weekly notifications as the C_t, C_{t+1} etc values. In this period, however, vaccinations must be taken into account in estimating the number of susceptibles in successive time periods. It was thus assumed that $\frac{1}{52}$ of the total vaccinations reported for each year (Table 1) were in fact successful immunizations performed each week; and this number ($= V_t$) was removed from the susceptible pool as in equation (2). The fact that not all vaccinations are successful (because of inactive vaccine, or because the recipient had already experienced measles) is assumed to be balanced by the inevitable shortfall in the number of vaccinations reported. The calculation was begun with an assumed $S_1 = 4.5 \times 10^6$ susceptibles on 1 January 1968 which corresponds closely with the number of susceptibles estimated for that date by cumulative incidence analysis of preceding birth cohorts.[16] A number of susceptibles equivalent to $\frac{1}{52}$ of the total OPCS-registered births for that year was introduced weekly as B_t. The transmission parameters derived by this method, for the post vaccination years 1968–1977, are shown in Fig. 5a.

The pattern of r_t after vaccination shows considerably more stochastic variation than that shown in Fig. 3b. This is not surprising, considering that Fig. 3b was based on an average of 8 biennial periods of very high incidence. Nevertheless, the three annual peaks are still evident coinciding with the school terms. This pattern is clearly revealed in Fig. 5b, which presents average weekly transmission parameters for the period 1968–1979 (smoothed as $\frac{1}{4} r_{i-1} + \frac{1}{2} r_i + \frac{1}{4} r_{i+1}$). Of even greater interest, however, is the fact that the r_t parameter has remained at virtually the same order of magnitude—i.e. approximately 0.22×10^{-6}—as it was at the start of the immunization programme. The important implications of this finding are discussed below.

DISCUSSION

The remarkably consistent biennial pattern of measles in England and Wales, for the years 1950–1967, is eloquent testimony to the reputation of measles as a 'well behaved' disease. This pattern suggests that the major population centres of England and Wales behave as an epidemiological unit, as far as measles is concerned. Larger regions with greater geographic or demographic heterogeneity, are liable to lose this clear biennial pattern. Thus, although several single cities in the United States showed such 2-year cycles in the years preceding immunization (e.g. New York City)[7], different US areas were out of phase with one another, so that a single annual cycle pattern was generally evident in data from the US as a whole (e.g. 1959–1962).[17] It is interesting in this respect that national measles figures for France also show a biennial pattern during the early 1960's—but with major epidemics coinciding with minor epidemics in the British Isles, and vice versa.[18] If

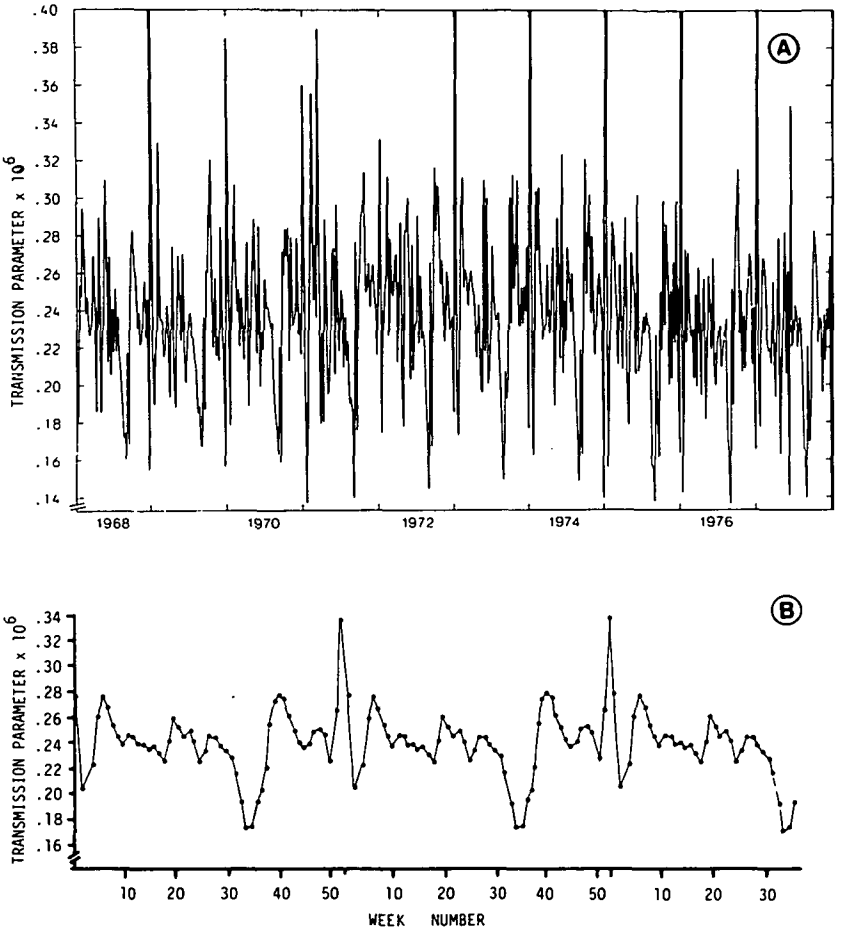

FIG. 5

Weekly transmission parameters estimated for the vaccination years. (a) Actual calculated figures, 1968–77, (b) Smoothed average weekly parameter values, 1968–79.

measles incidence for England and France were pooled for this period, the biennial pattern would be lost in favour of a single annual cycle.

These seasonal trends have attracted considerable attention in the literature. Several authors have been tempted to apply elegant harmonic function analyses to such data, finding that certain combinations of Fourier terms can achieve a reasonable fit.[19,20] However, such analyses are purely descriptive; they reveal nothing of the processes underlying such measles trends. For this explicative function, dynamic models are required, the most commonly applied being variants of the mass action model as used here.

Previous applications of mass action theory to measles have drawn upon monthly notifications data.[3,7,8,21] The form of the data forced these earlier authors into elaborate interpolations or curve-fitting assumptions in order to manipulate their data into a time scale commensurate with the natural history of measles transmission. However, much information is lost when measles incidence data are grouped over long time periods. Though monthly data overcome stochastic irregularities, they may lose detail which is crucial to interpreting underlying mechanisms.

The current analyses capitalized upon the similarity of the measles serial interval (average 10 days or less) to the weekly basis of the notifications system in England and Wales. It may be questioned whether it is worth while trying to estimate daily incidence, and to elaborate the model so as to include a frequency distribution rather than a fixed value for the serial interval, as investigated by London and Yorke.[7] This was rejected, for two reasons. First, the true daily incidence pattern is complicated by weekday-weekend effects which

influence mixing among the critical school age population. Thus it would be difficult if not misleading to derive daily figures from the weekly data. Secondly, London and Yorke[7] found that changing the assumed serial interval from a fixed value to a frequency distribution did not alter their results. We explored using a 14 day interval in these analyses, and found this had little effect on the results (Fig. 4). For these reasons, we consider that our calculated r_t values are as robust as the available data allow.

The loss of information due to using monthly rather than weekly data is evident in comparing Fig. 1 with Fig. 3b. By smoothing over week-to-week variations in incidence, r_t values were calculated which appear as relatively smooth unimodal curves, whose initial rise and subsequent pattern do not fit comfortably with the hypothesis of school-determined measles trends. Though each of the earlier authors suspected that school terms were responsible for the trend—indeed this was common epidemiological wisdom, and not dependent on such analyses—their evidence as in Fig. 1 was not in itself convincing. On the other hand, the remarkable coincidence of trends in the transmission parameter r_t calculated from weekly data provides strong support for the influence of a school term effect (Fig. 3b). This is consistent with the fact that measles incidence rates have traditionally peaked in 5 and 6 year olds in England and Wales,[16] and in the United States,[22] and with the general recognition among epidemiologists in these areas that transmission in schools is a critical feature in the community spread of measles.[23] In so confirming the school effect, this analysis provides an impressive argument for the usefulness of simple mass action theory in epidemiological analyses.

Though the result in Fig. 3b may appear impressive, it should be scrutinized critically. Just what is this transmission parameter, r_t? It has been mentioned above that different authors have called this parameter by different names, e.g. 'coefficient of infectivity'[3] or 'contact rate'.[8] Such terms may be misleading. The first implies that the parameter measures some biological characteristic of the agent—which it does not. The latter implies that it measures a sociological mixing characteristic of the population—which is only partly true.

Examination of equation (1) shows that r_t describes the proportion of the total possible contacts between susceptibles and cases that actually lead to new cases. But such a statistic has two important flaws which affect its applicability to a real-life data set such as discussed here. First, the simple mass action theory ignores the possibility that multiple case contacts may fall upon a single susceptible and hence lead to a single new case. By equation (1), 1 case mixing with 1000 susceptibles produces the same incidence as would 1000 cases mixing with 1 susceptible. In extreme situations the model becomes absurd. A logical solution to this fallacy is inherent in the so-called Reed Frost model, which introduces a binomial term to take account of the multiple contact situation, i.e. $C_{t+1} = S_t\,(1-(1-p)^{C_t})$, where p = the probability of contact between any two individuals in the population.[24] Though this is indeed a fallacy of the mass action model, it is not crucial in the current situation, as the difference between mass action and Reed Frost formulations becomes negligible when r_t is very small. Indeed, the Reed Frost p values calculated on these England and Wales data are identical to the r_t values to 3 significant figures.

A second fallacy of the simple mass action model is more crucial. This is the assumption of a single homogeneously mixing population, which is manifestly untrue for a population with the magnitude and complexity as that of England and Wales. This fallacy probably explains the right skew shape of the r_t peaks coinciding with each school term, in Fig. 3b. In reality, measles is introduced to a few schools at the beginning of each school term. Epidemics may ensue both within the schools and in the neighbourhood and families of the students of that school. Initially, a high proportion of contacts between cases and their colleagues lead to new cases. However, as the school term and the local epidemics progress, a lower and lower proportion of such contacts leads to new cases. This is because the cases are mixing little, if at all, with those schools and communities into which measles was not introduced. This may explain the progressive fall in r_t during each term. A similar argument explains why the predicted r_t of successive term peaks fall during major epidemic years. These trends in r_t are thus seen to be artefacts of its definition rather than reflections of mixing patterns in the community. This is why we have chosen to call it a 'transmission parameter' rather than a 'contact rate.'

Notwithstanding such problems in defining r_t, its analytical usefulness should not be underestimated. It is striking that the major pattern in r_t remains consistent for both pre- and post-immunization periods, revealing constant underlying dynamics, and a continued important role for schools in determining the pattern of this disease. Even more interesting, however, is the finding that the r_t parameter has remained at a similar level of magnitude in the years since the measles immunization programmes began in England and Wales (Fig. 5). A glance at equation (1) reveals that in order for incidence to increase, i.e. $C_{t+1}/C_t > 1$, the number of susceptibles in the population must exceed $1/r_t$, ie $S_t > 1/r_t$. The fact that measles still increases annually in the UK suggests that the number of susceptibles still periodically exceeds $1/r_t$ i.e. approximately $1/(2.2\times10^{-6}) \approx 4.5\times10^{6}$. This is of interest in its indication

that the measles immunization programme has not lowered the total numbers susceptible to measles in the UK—though it has slowed the input of susceptibles into the population, by vaccinating a certain proportion of each birth cohort. However, one must be wary of mistaken conclusions dependent upon the homogeneity fallacy of the model as discussed above. A more appropriate method to analyse this problem of the impact of immunization on levels of susceptibility is through the analysis of cohorts, as presented in the second paper of this series.[16]

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