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"Pulse Mass Measles Vaccination Across Age Cohorts"

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These are preliminary lecture notes, intended only for distribution to participants.

Pulse Mass Measles Vaccination Across Age Cohorts

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Abstract

Although the vaccine against measles has been routinely applied over a quarter of a century, measles is still an active disease in Israel, erupting every 5 – 7 years. Recent serological analyses have shown that only 84.66% of Israelis, aged 18 years, have anti-measles IgG antibodies. Considering the high infectivity of the virus and the high immunity levels required for disease eradication, the Israeli vaccination policy against measles is now being re-evaluated. In the present work non-age structured and age-structured deterministic models are employed for examining the effect of current and putative vaccination programs on epidemic profiles. Motivated by a theory of population dynamics in perturbed environments we examine the possibility of replacing the conventional vaccination strategy by a *pulse* strategy, i.e., periodic vaccination of several age cohorts at the same time. Base on the analysis of the mathematical models we suggest that vaccination of only .85 of children aged 1-7 years, once every five years suffices for preventing the epidemics in Israel and in other developed countries, where infection rate is highest amongst school children. Our theoretical results provide encouraging indication that pulse strategy should be seriously considered.

1. Introduction

The vaccine against measles has been routinely applied in Israel since February 1967 at 9 months of age. Since 1971, due to a high percentage of vaccine failures, infants have been vaccinated at the age of 12 months, and since 1975 at the age of 15 months [1]. This immunization program resulted in a dramatic decline in morbidity, an increase in the inter-epidemics intervals from two years to five years, and has increased the average age of infection [2]. However, despite the high compliance of the Israeli population the results are far from satisfactory. The measles immunity level, reported in 1989, is 84.66% [3], but a somewhat lower level was reported in some minority groups, such as Bedouins (77%) [4]. These levels are too low to confer herd immunity, i.e., immunity levels adequate for interrupting transmission [5], hence the quasi-periodic eruption of the disease every 4-7 years. The situation is not better in other developed countries. In the USA and the UK persistent outbreaks are reported, particulary in adolescents and college students, and experts warn a resurgence of the current epidemic is likely without sustained immunization effort.

The present discouragement concerning the prospects of measles eradication resulted in new guidelines for measles immunization, both in the USA and in Israel. Thus for both the USA and Israel a first dose is now applied at 15 months of age and a second dose at around six years. These guidelines are based on the conventional concept of a time-constant immunization effort. In such strategies, vaccination affects the amplitude and the period of the epidemics, but it does not antagonize the natural dynamics of the disease. In contrast, a theory of population dynamics in harshly varying environments suggests that when the environmental pattern imposed on the population takes the form of discrete episodes of devastation, it is the spacing of these episodes that determines population persistence [6-8]. Based on this theory we examined the hypothesis that measles epidemics can be more efficiently

controlled when the natural temporal process of the epidemics is antagonized by another temporal process i.e., by a vaccination effort that varies significantly and abruptly in time. We refer to this policy as *pulse vaccination* and show theoretically that pulse vaccination of children aged 1-7 years, once every five years, may suffice for preventing the epidemics.

2. Simulations of an Age-Structure Model with Different Vaccination Strategies

To check the effect of pulse strategy on the epidemics profile we employ an age-structured compartmental model, which was introduced by Anderson & May [9] for analyzing the transmission dynamics of vaccine-preventable childhood infectious diseases. The model represents changes, with respect to age and time, in the population of (i) infants protected by maternal antibodies, (ii) susceptible individuals, (iii) infected, but as yet noninfectious individuals, (iv) infectious individuals, and (v) immune individuals. This model has been extensively studied under a large range of constraints and is widely employed in the investigation of epidemiological problems. Implementing in this model the Israeli demographic parameters we investigated the efficacy of current and novel vaccination strategies.

Israel's epidemiological scene is heterogenous in nature, involving a majority group whose parameters are those characteristic of the industrialized world, and a few minority groups, such as Bedouins and immigrants from less developed countries, characterized by higher young-old mixing and higher infection rates. In this report we focus on measles epidemiology in the majority group whose total size is 3,717,100 and life-expectancy is 75 years [9]. In the absence of detailed age-structured seroprevalence data for measles in Israel prior to immunization, we assumed similar characteristics between Israel and UK; both countries have a similar demographic structure and both experi-

enced biannual measles epidemic in the pre-vaccine era. Thus, in our simulations, the mean virus latent period and the mean duration of infectiousness are taken to be 7 days each, the duration of maternal antibody protection is 91.25 days and the age-dependent force of infection is given below (Table 1). The average age at infection, calculated from Table 1, is 4.5 years [10].

Age group	0.5–5	5–10	10–15	15–20	20–75
Force of Infection	0.184	0.579	0.202	0.1	0.1

The model incorporates age-dependent mixing, essentially meaning that infants in the 5–10 age classes mix most amongst themselves, i.e., in schools, and also that there is a relatively high rate of mixing between the 5-10 and the 0.5-5 age classes, as well as between the previous group and the 10-15 age-classes [10].

Model's simulations with no vaccination yield a two-year-cycle epidemics (Fig. 1), as indeed was reported in Israel before the onset of vaccination in 1967 [3]; most of the infected individuals appear to be children under 10 years of age (Fig. 2B,C). Under no further perturbation the oscillations will decay and the system will slowly return to a steady-state level of infection. However, this will never be the case, and certainly not in Israel, where the total population size and epidemiological structure are frequently perturbed, due to immigration and other factors.

To see the effect of vaccination on the epidemics profile we now implement vaccination at 12 months of age. Results, presented in Figs. 3,4, clearly demonstrate that the level of vaccination determines the amplitude, as well as the period of the epidemics. One may note in these curves that vaccinating 80% to 90% of one-year old infants generates an interval of five to six years between successive epidemics. Indeed, such inter-epidemic intervals are currently reported for Israel [11]. Clearly, then, the reported coverage

levels are too low for disease eradication, while a coverage level larger than 95%, required for herd immunity (results not shown; [10]) are difficult to obtain in practice. Thus, our simulations support previous conclusion from the theoretical and empirical work that continuing application of a single dose vaccination may be helpful in decreasing the frequency and magnitude of epidemics, but not for preventing them.

Now, let us replace the conventional policy, in which the level of vaccination is uniform over time, by a nonuniform *pulse* policy, i.e., periodic vaccination of several age groups at the same time. We have done so by simulating various levels of vaccination of different age cohorts. In Fig. 5 a single pulse vaccination is applied to 85% of the children aged 1-7 years. The vaccination is timed to occur at about one year prior to the predicted arrival of the next epidemic (see Fig. 1). These results show that a single pulse vaccination generated a 7 years epidemic-free interval. Note, however, that the amplitude of the epidemic in the 8th year is extremely large, most infected individuals being in the 0-4, and 5-9 groups (Fig. 5B,C). Continuing the simulations with a similar pulse vaccination one year prior to each prospective epidemic, we note that the inter vaccination intervals become shorter until they stabilize at about 5 years. Under this strategy the epidemics are suppressed, and they continue to be suppressed as long as we continue to employ this strategy (Fig. 6). Note that, the timing of the pulse between prospective epidemics is not critical; efficacy of the pulse vaccination is guaranteed as long as it precedes the onset of the prospective epidemic. It should be noted that efficacy of the pulse vaccination depends on the vaccination level, p, and on the vaccinated cohorts. In the present simulations, with $p = .85$, efficacy is guarranteed only if all 1-7 cohorts are immunized.

To understand the special properties of the pulse vaccination policy we will first examine the simplest model for measles epidemiology, where the age-structure effects are ignored. Once the basic properties of this model are understood we will examine the effects of the pulse policy on an age-

structured population.

3. The Rationale for Pulse Vaccination

A simple model — no age-structure

The simplest model describes the dynamics of two compartments in the population, the susceptible individuals and the infected individuals [12-14]. Assuming that all variations within each compartment are negligibly small, the overall dynamics can be described by the following simple system of equations:

$$\begin{aligned} \frac{dX}{dt} &= \mu N - (\beta Y + \mu)X \\ \frac{dY}{dt} &= \beta XY - (\mu + v)Y. \end{aligned} \tag{1}$$

In (1) X and Y are the number of susceptible and infectious individuals, respectively, μ is the birth rate, taken as equal to the death rate, N is the total population size and β and v are the transmission rate and the recovery rate, respectively.

It is well known that if the (infection) reproduction rate, $R_0 = \frac{\beta N}{\mu + v}$, is larger than unity, then the above system has one stable equilibrium

$$X^* = \frac{\mu + v}{\beta}, \quad Y^* = \frac{\mu(R_0 - 1)}{\beta}. \tag{2}$$

The stability of the endemic state (2) allows for damped oscillations, the period of which is approximately

$$T = 2\pi\sqrt{AK}, \tag{3}$$

where A is the average age at infection, and $K = \frac{1}{v}$ is the infectious period; the infection will die out when $R_0 < 1$.

As already noted, the coverage level that is required for herd immunity ($\approx 95\%$) is difficult to obtain in practice. Our new idea is to replace the current concept, by which vaccination effort is spread homogenously in time, by

pulse vaccination, i.e., vaccination of several age groups at discrete moments. In mathematical terms, discrete time vaccination can be represented by Dirac functions as inputs to the above system, causing discontinuous jumps in the state of the systems [15].

By considering a string of Dirac inputs at the moments t_k, $k = 1, 2, 3 \ldots$, the previous system becomes the following *set* of systems

$$\frac{dX}{dt} = \mu N - (\beta Y + \mu)X \quad \text{for } t \in (t_{k-1}, t_k) \tag{4}$$

$$X(t_k+) = (1 - p_k)X(t_k) \quad \text{for } t = t_k \tag{5}$$

$$\frac{dY}{dt} = \beta XY - (\mu + v)Y. \tag{6}$$

In (5) p_k is the proportion of vaccinated individuals at time t_k ($k = 1, 2, 3 \ldots$).

If we succeed in keeping the number of susceptibles below a critical value,

$$X \leq X_c = \left(\frac{\mu + v}{\beta}\right), \tag{7}$$

so that $Y' < 0$, we can prevent the eruption of the epidemics. To this end we now apply the *pulse* vaccination policy. The timings of vaccination, t_k, $k = 1, 2, 3 \ldots$, are chosen such that X never exceeds X_C (Fig.7).

Remark :. This discrete time vaccination strategy has the effect of replacing the characteristic periodic behaviour of Y by an *aperiodic* behavior, i.e., a monotonic decay. From the medical point of view this means that the number of infected individuals monotonically decreases and the epidemics are altogether prevented.

If this pulse policy is adopted it becomes essential to evaluate the moments t_k. Suppose that $p_k = p$ and $t_k - t_{k-1} = \tau$ for all k, so that

$$X(n\tau+) = (1 - p)X(n\tau) \qquad n = 1, 2, \ldots \tag{8}$$

where τ is chosen such that condition (7) holds for all t.

Now we wish to evaluate τ, that is to determine the frequency of pulse vaccination. To facilitate the analysis we recall that in our domain of investigation, defined in (7), endemic infection tends to zero. For this reason we can now neglect the "Y" term in (4). We also replace the number of susceptibles, X, by their fraction, so that (4) becomes

$$\frac{dx}{dt} \simeq \mu(1-x), \tag{9}$$

where $x = \frac{X}{N}$. Let $x(0)$ be the fraction of susceptibles just after the first pulse vaccination at time $t = 0$ and $x(0-) = x_c$, so $x(0) = (1-p)x_c$. Let $x(t)$ be the fraction of susceptibles at the time of the second pulse vaccination, so that $t \rightarrow \tau$ and $x(\tau-) = x_c$. From (9) we obtain

$$\tau = \frac{1}{\mu} ln[1 + \frac{px_c}{1-x_c}]. \tag{10}$$

We note that $x_c = \frac{1}{R_0}$, so that the larger the reproduction rate of the infection the smaller is x_c. For small x_c we can make the approximation:

$$\tau \simeq \frac{px_c}{\mu}. \tag{11}$$

But since $\frac{x_c}{\mu} \simeq \frac{L}{R_0} \simeq A$, then (11) can be replaced by

$$\tau \simeq pA. \tag{12}$$

The meaning of (12) is that when pulse vaccination involves a large p, the inter-vaccination intervals are roughly equal to the average age at infection.

Effect of age-structure

Using the age-structure model [9] we showed that a pulse vaccination strategy may effectively control the epidemics. We then used the analysis of a simple model, to provide an insight about the conditions for the efficacy of the pulses and their spacing. Now the readers may wish to check whether this mathematical reasoning applies also when we take into account the important

effect of age-structure, i.e. the significant differences between age cohorts in contact rates [14, 16].

To facilitate the illustration we simplified the complete age-structure simulation model, employed above, to a two age-groups model (0-5 years, 5-10 years), where the two groups differ in transmission coefficient, β_i. Note, that in real-life measles infections are predominant among school children and it is commonly accepted that the transmission coefficient, β, is much larger in school children than it is in younger or older individuals.

$$\frac{dX_1}{dt} = \mu N - (\beta_{11}Y_1 + \beta_{12}Y_2 + \delta)X_1 \tag{13}$$

$$\frac{dY_1}{dt} = (\beta_{11}Y_1 + \beta_{12}Y_2)X_1 - (\delta + v)Y_1. \tag{14}$$

$$\frac{dX_2}{dt} = \delta X_1 - (\beta_{21}Y_1 + \beta_{22}Y_2 + \delta)X_2 \tag{15}$$

$$\frac{dY_2}{dt} = \delta Y_1 + (\beta_{21}Y_1 + \beta_{22}Y_2)X_2 - (\delta + v)Y_2. \tag{16}$$

In (13-16) X_i and Y_i are the number of susceptible and infected individuals, respectively, in age class i, and β_{ij} is the transmission coefficient arising from the contact of susceptibles in age class i with infectious individuals in the age class j, and δ is the age transition coeficient. Looking at the imaginary parts of the eigenvalues (i.e. ω) one can calculate the period of the oscillations, $T = \frac{2\pi}{\omega}$, for specific parameter values. Under a given set of parameters ($N = 3,717,000, \mu = 0.01$ years^{-1}, $\beta_{11} = \beta_{12} = \beta_{21} = 0.00001$ years^{-1}, $\beta_{22} = 0.0001$ years^{-1}, $\delta = 0.2$ years^{-1}), the inter-epidemic interval is about 1.7 years. Implementing now a constant vaccination, with coverage rate $p = .85$, for the newborns, by replacing the first term in (13) by $\mu N(1-p)$, we obtain an inter epidemic period of 3.7 years. A larger inter-epidemic period (4.025 years) is obtained when vaccinating at birth is replaced by a continuous vaccination upon transition from the younger to the older age class, i.e. at the age five; in the model this correspond to replacing the first term in (15) by $\delta(1-p)X_1$. Note that this two age classes

model, while providing an insight on the role of age-structure, is only a rough approximation of the more elaborate model used in our simulations.

The present results showed that when the transmission coefficient of the older age classes is much larger than that of the younger age classes, the effect of a constant vaccination of children upon entering the high risk age is similar to that of vaccination at birth; both increase the inter-epidemic interval by roughly the same period, i.e. five years. This is the crucial observation which justifies the use of the *pulse* vaccination.

Now, a pulse vaccination at five years intervals of the population aged 1-7 years, has two effects: i) a continuous vaccination of the older age-class is obtained (those who pass into the higher age classes are already vaccinated); ii) prior to the onset of each epidemic the density of susceptibles in the total population is reduced below the critical value (thus preventing the epidemics).

4. Discussion

The results of our analysis suggest that with the observed trend of age-specific infection rates (low in the very young, high in the child population and low in the adult age groups) a pulse vaccination once every five years may completely eliminate the epidemics. The cost of this strategy (measured by the total number of vaccinations) is lower than the current strategy of two doses applied to all children at the age of one and six. An auxillary advantage of the pulse strategy may be in the easier organization and higher compliance, due to the effect of "campaigning".

A serious question may arise, concerning the expected, albeit very low, numbers of infected infants, under our suggested policy. When this is of much concern, or when the pulse strategy is still under examination, vaccination of one year old infants can still take place, so that pulse vaccination will only replace the second dose.

Our analysis implies that the interval between successive vaccination pulses is roughly similar to the average age at infection and our computer simulations suggest that this interval is roughly 5 years. Evaluation of the average age at infection of unvaccinated populations in developed countries as 5 years [15] supports our analysis.

It should be noted that the approach suggested here is quite radical, and it is likely that most countries that have routine immunization programs will not easily yield to such harsh changes in policy. However, as current programs are experiencing extreme difficulties in achieving eradication, extreme measures may be required. Clearly, more work needs to be done before the suggested policy can be implemented. Further work is warranted for exploring parameter sensitivity and programmatic vaccine uptake. However, the results we have already obtained provide encouraging indication that this option needs further consideration.

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Figure Legends

Fig.1 Temporal changes in the number of reported cases of measles infection ($\times 10^3$) in an unvaccinated population over 3.5 days intevals following perturbation of the five age class model from its equilibrium state (perturbation induce by reducing the fractions susceptible in each age class by a factor

0.8). Total population size is 3,717,000, for equations and other parameters see ([10].

Fig.2 Temporal changes in the number of reported cases of measles infection per age class; detail of Fig. 1. **A.** Total population; **B.** age class 0-4; **C.** age class 5-9; **D.** age class 10+.

Fig.3 Temporal changes in the number of reported cases of measles infection with continuous vaccination, $p = 0.85$, of infants at age 12 months. See Fig. 1 for details of the simulations.

See Fig. 1 for other parameters.

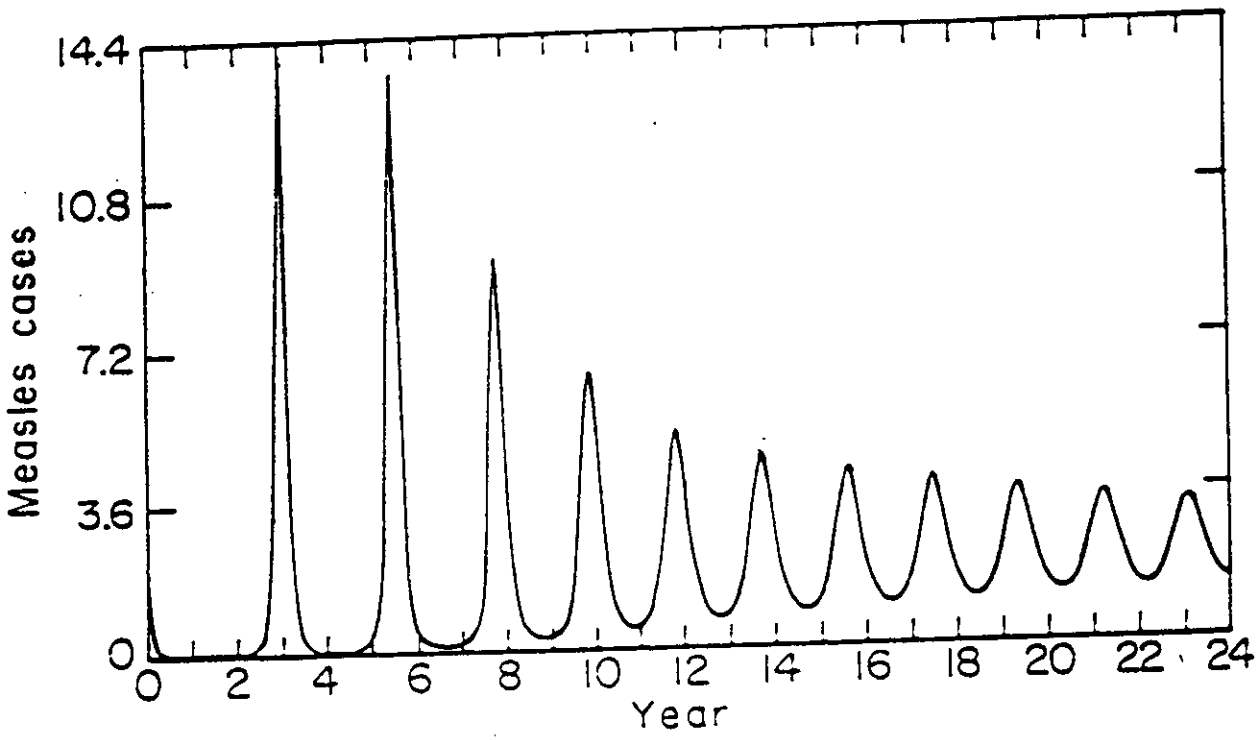
Fig.4 As in Fig. 3, but $p = .91$.

Fig.5 Temporal changes in the number of reported cases of measles infection with a single *pulse* vaccination (timing id denoted by arrow), $p = 0.85$, of children aged 1-7 years. **A.** Total population; **B.** age class 0-4; **C.** age class 5-9; **D.** age class 10+.

See Fig. 1 for other parameters.

Fig.6 The effect of the *pulse* vaccination strategy on the number of reported cases of measles infection, time of pulses is denoted by arrows. See Fig. 5 for details of the simulations.

Fig.7 The effect of the *pulse* vaccination strategy on the fraction of susceptibles.The interval between the pulses, τ, is chosen so that the fraction of susceptibles never exceeds a critical value, x_c (see text for further details).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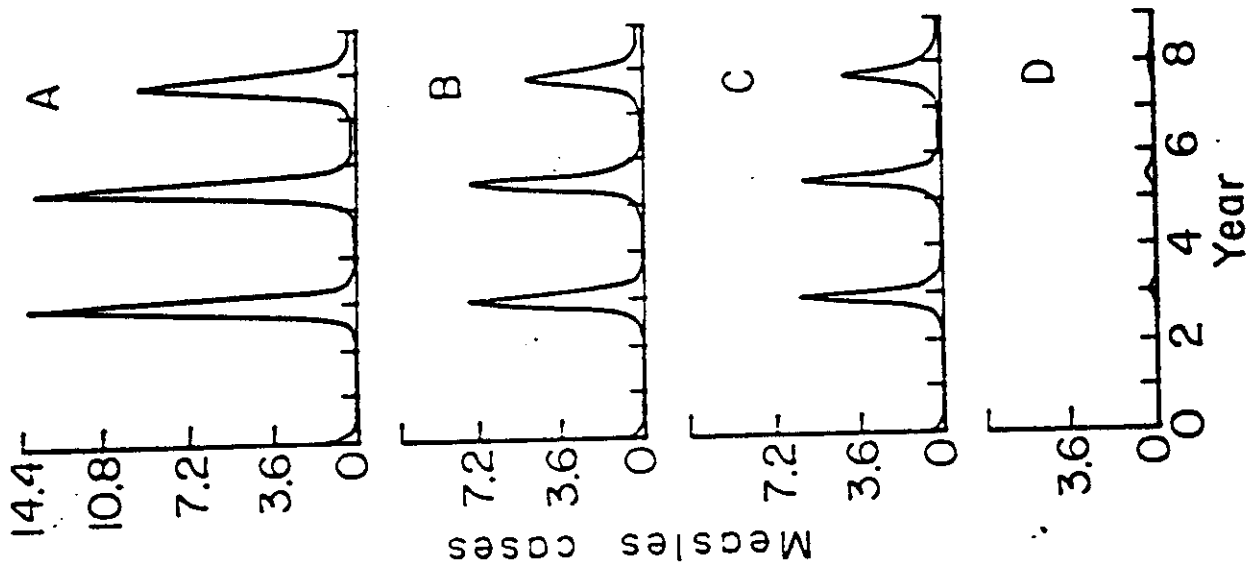
10.8
7.2
3.6
0
Measles cases
0 2 4 6 8 10 12 14 16 18 20 22 24
Year

Fig. 1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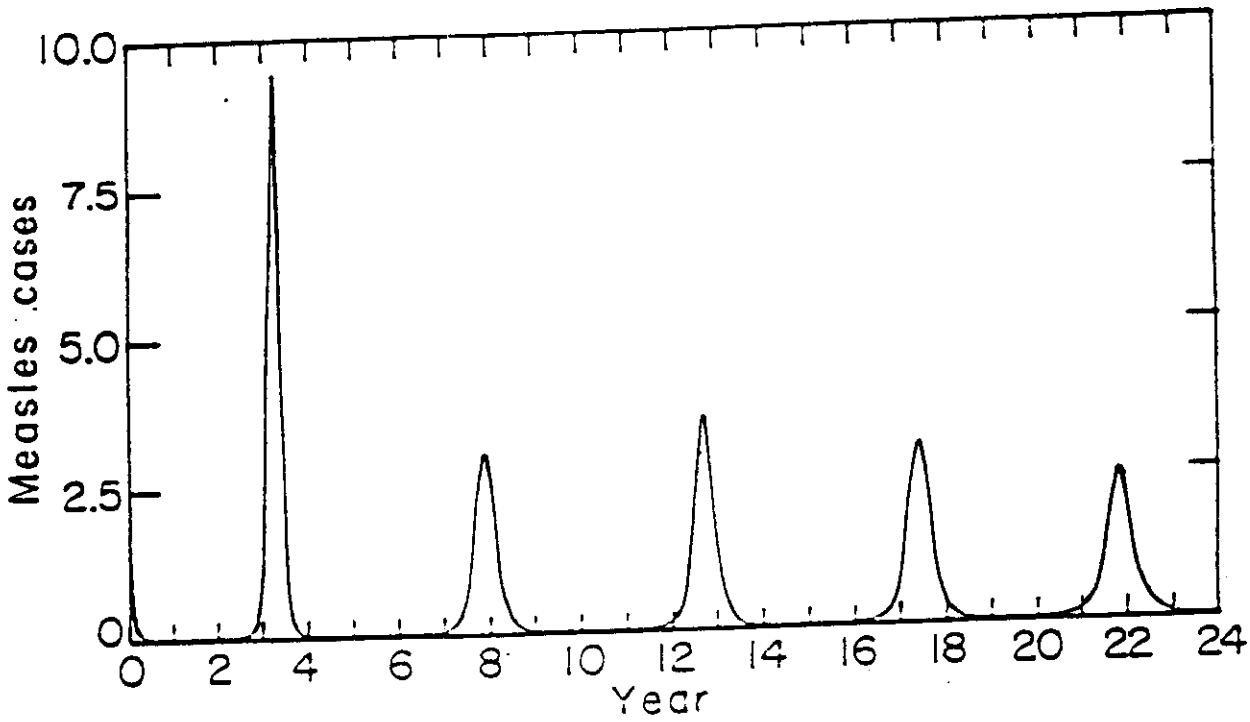
B
C
D
14.4
10.8
7.2
3.6
0
Measles cases
0 2 4 6 8
Year

Fig 2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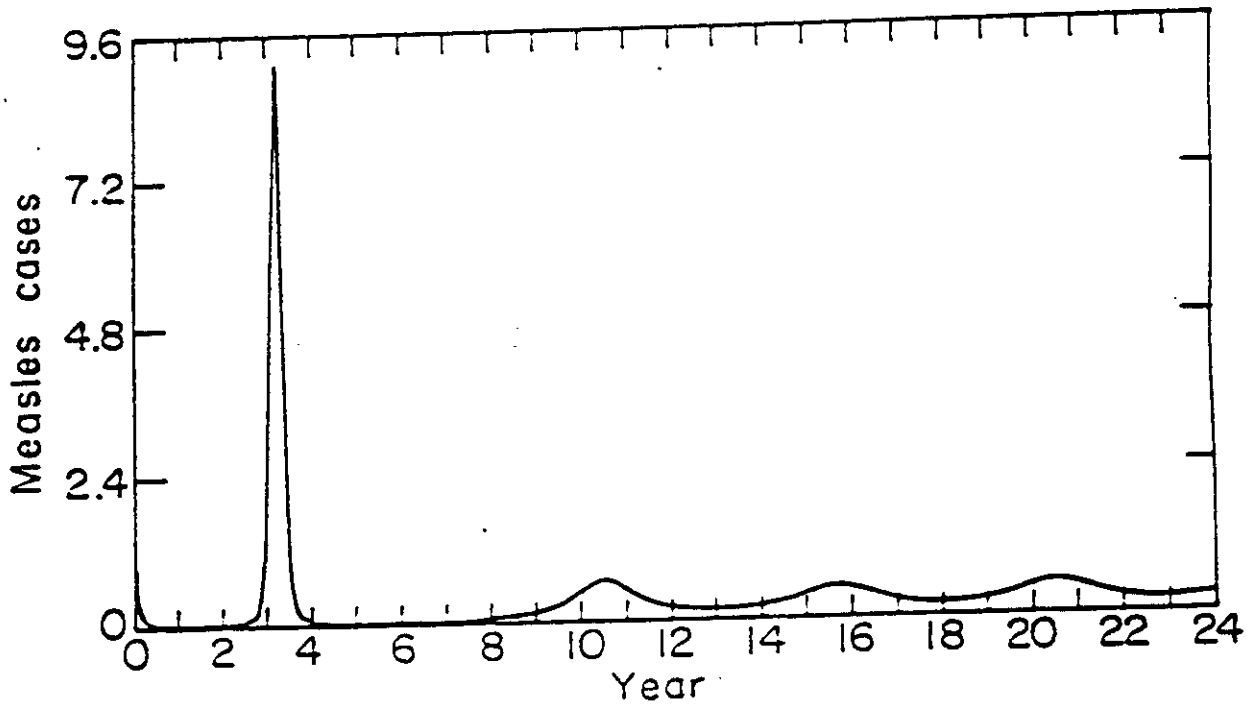
7.5
5.0
2.5
0
Measles cases
0 2 4 6 8 10 12 14 16 18 20 22 24
Year

Fig.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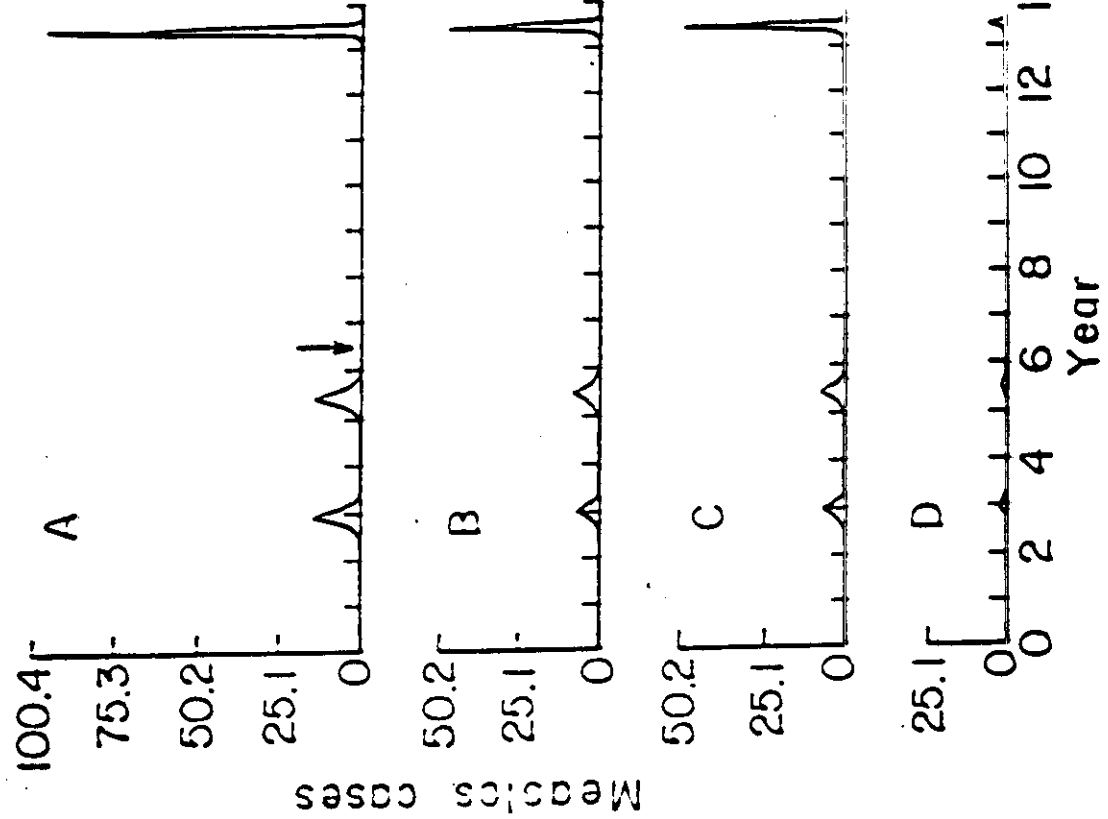
7.2
4.8
2.4
0
Measles cases
0 2 4 6 8 10 12 14 16 18 20 22 24
Year

Fig.


A
B
C
D
100.4
75.3
50.2
25.1
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50.2
25.1
0
50.2
25.1
0
25.1
0
0 2 4 6 8 10 12
Year
Measles cases

Fig 5

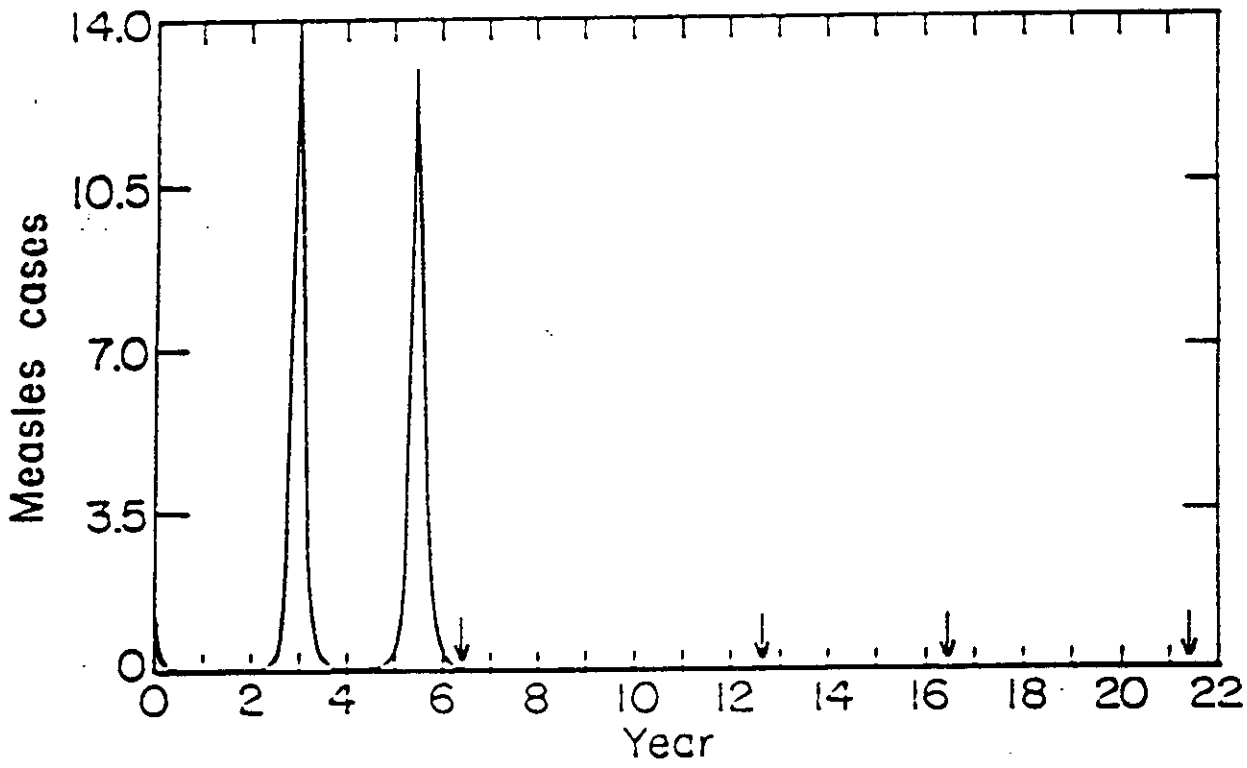
Measles cases
14.0
10.5
7.0
3.5
0
0 2 4 6 8 10 12 14 16 18 20 22
Year

Fig. 6

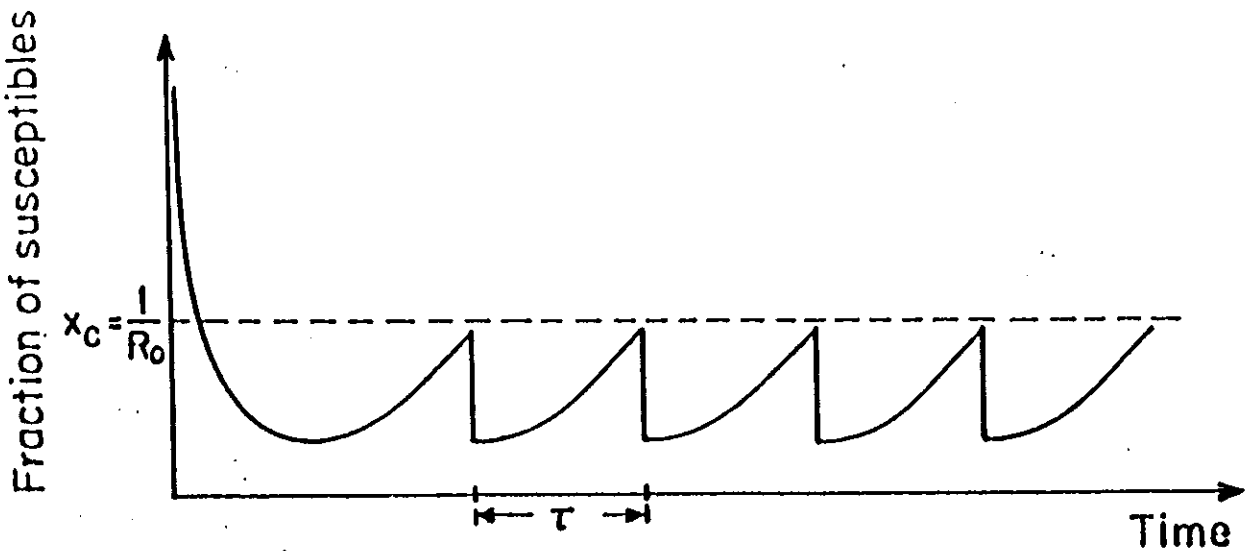

Fig.1