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Population Biology

Pulse mass measles vaccination across age cohorts

(age structure/mathematical model/Israel/Dirac function/campaign strategy)

Z. AGUR[†‡§], L. COJOCARU[†], G. MAZOR[¶], R. M. ANDERSON[‖], AND Y. L. DANON[††]

[†]Department of Applied Mathematics and Computer Science, The Weizmann Institute of Science, Rehovot 76100, Israel; [‡]Department of Zoology, Oxford University, South Parks Road, Oxford OX1 3PS, United Kingdom; [¶]Department of Statistics, School of Mathematical Sciences, Tel-Aviv University 69978, Israel; [‖]Department of Biology, Imperial College of Science, Technology and Medicine, Prince Consort Road, London SW7 2BB, United Kingdom; and [††]The Children's Medical Center, Kipper Institute of Immunology, The Beilinson Medical Center, Petach-Tikva, 49104, and Sackler School of Medicine, Tel Aviv University, Israel

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ABSTRACT **Although vaccines against measles have been routinely applied over a quarter of a century, measles is still persistent in Israel, with major epidemics roughly every 5 years. Recent serological analyses have shown that only 85% of Israelis aged 18 years have anti-measles IgG antibodies. Considering the high transmissibility of the virus and the high level of herd immunity required for disease eradication, the Israeli vaccination policy against measles is now being reevaluated. Motivated by theoretical studies of populations in perturbed environments, we examined the possibility of replacing the conventional cohort vaccination strategy by a *pulse* strategy—i.e., periodic vaccination of several age cohorts at the same time. Numerical studies of a deterministic age-structured model suggest that vaccination, which renders immunity to no more than 85% of the susceptible children aged 1–7 years, once every 5 years will suffice to prevent epidemics in Israel, where infection rate is highest amongst schoolchildren. The model suggests that by using such a strategy the density of susceptible individuals is always kept below the threshold above which recurrent epidemics will be maintained. Analysis of simpler, non-age-structured, models serves to clarify the basic properties of the proposed strategy. Our theoretical results indicate that the advantages and disadvantages of a pulse strategy should be seriously examined in Israel and in countries with similar patterns of measles virus transmission.**

Introduction

The vaccine which protects against measles virus infection 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 and an increase in the interepidemic intervals from 2 years to about 5 years (Fig. 1) and has increased the average age at infection over that pertaining prior to control (2). However, despite the high compliance of the Israeli population, the results are far from satisfactory. The level of herd immunity to the viral infection, reported in 1989 for the 18-year-old cohort, is 84.66% (3), but a somewhat lower level was reported in minority groups, such as Bedouins (77%) (4). These levels are too low to interrupt transmission (5), hence the quasiperiodic eruption of the disease approximately every 5 years. This situation pertains in a number of developed countries at present. In the United States and the United Kingdom outbreaks are reported, particularly in adolescents and college students, and public health authorities warn that a resurgence of measles in the United States is likely without sustained and improved immunization effort (6).

The current situation concerning the prospects of measles eradication in Israel stimulated the production of new guidelines for measles immunization. A first dose is recommended at 15 months of age and a second dose at 6 years. These guidelines are based on the conventional concept of a constant immunization effort each year (i.e., cohort immunization). In such strategies, vaccination affects the amplitude and the period of the epidemics, but it does not induce a very severe perturbation of the natural dynamics of transmission. 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 (7–9). 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 present mathematical models suggesting that pulse vaccination of children aged 1–7 years, once every 5 years, may suffice for preventing recurrent epidemics in Israel.

Simulations of an Age-Structured Model with Different Vaccination Strategies

To assess the effect of pulse strategy on the transmission and persistence of the virus, we employ an age-structured compartmental model (10–13) for 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 wide range of constraints and is widely employed in the investigation of epidemiological problems. We studied the properties of this model using the Israeli demographic parameters to assess the efficacy of cohort (current) and pulse (a new approach) vaccination strategies.

Israel's epidemiological setting is heterogeneous in nature, involving a large majority group whose parameters are those characteristic of the industrialized world, as well as a few minority groups, such as Bedouins. In the majority group, as in many countries of the industrialized world, the main route of transmission is within school playgrounds and classrooms. This pattern does not hold for the Bedouins, where transmission appears to be characterized by higher young–old mixing and higher infection rates (4). In this report we

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[§]To whom reprint requests should be sent at the [‡] address.

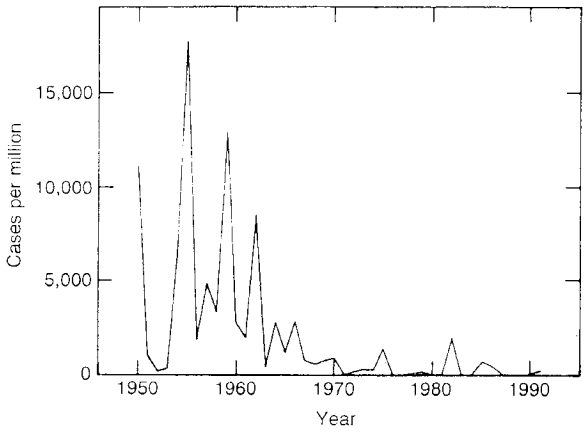

FIG. 1. Reported cases of measles in Israel during the period 1950–1991.

focused on measles epidemiology in the majority group, whose total size is 3,717,100 and where life expectancy is approximately 75 years from birth (14).

In the absence of detailed age-structured seroprevalence data for measles in Israel prior to immunization, we assumed similar characteristics between Israel and the United Kingdom; both countries have the highest levels of transmission among schoolchildren and both countries experienced biannual measles epidemics in the pre-vaccine era. Thus, in our simulations we employed the age-dependent forces of infection as estimated for the United Kingdom prior to the introduction of mass vaccination (10). The average age at infection, calculated from Table 1, is approximately 5 years. The mean latent period and the mean duration of infectiousness are taken to be 7 days each, and the duration of maternal antibody protection was set at 91.25 days on the basis of published studies (10). The model incorporates age-dependent mixing, calculated according to a 5 × 5 "Who acquired infection from whom" (WAIFW) matrix as defined in ref. 10, with the assumption 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 (WAIFW I; see refs. 10 and 15 for a detailed account).

Model simulations with no vaccination yielded a 2-year period for the epidemics (Fig. 2), 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. 3 *B* and *C*). Under no further perturbation the oscillations will decay and the system will slowly return to a steady-state level of infection. However, due to seasonal changes in the transmission coefficient the damped oscillations may be transformed into persistent recurrent epidemics (11). Moreover, in Israel the total population size and certain epidemiological parameters are frequently perturbed, due to immigration and other factors.

Table 1 Force of infection values used in the simulations

Age group	Force of infection, year^{-1}
0.5–5	0.184
5–10	0.579
10–15	0.202
15–20	0.1
20–75	0.1

Values from ref. 10.

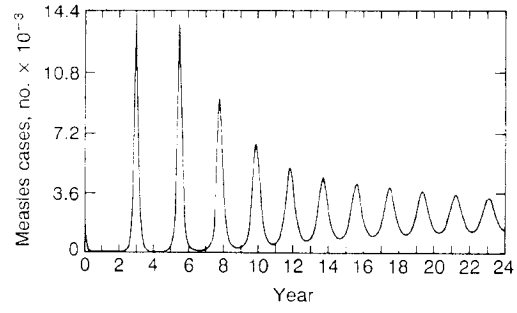

FIG. 2. Temporal changes in the number of measles infections in an unvaccinated population. Shown are simulation results of the age-structured, five-age-class model (10). Simulations were carried out by perturbing the system from its equilibrium state (perturbation was induced by reducing the fractions susceptible in each age class by a factor of 0.8). Calculations were performed for 3.5-day intervals (note that the higher resolution in our simulation as compared with previously published simulations of this model results in higher precision). Total population size is 3,717,000 (for equations and other parameters see refs. 10 and 15).

To see the effect of vaccination on the simulated epidemiological pattern, we introduced vaccination at 12 months of age. Results, presented in Fig. 4, clearly demonstrate that the level of vaccination determines the amplitude as well as the period of the epidemics. One may note in these simulated patterns that vaccinating 80–90% of 1-year-old infants generates an interval of 5–6 years between successive epidemics. Indeed, such interepidemic intervals are currently reported for Israel (ref. 16; see also Fig. 1). The model therefore suggests that the reported coverage levels are too low to block transmission. Experience in Israel has shown that a coverage level larger than 95%, required for herd immunity (10), is difficult to obtain in practice. Thus, our simulations support previous conclusions from theoretical and empirical work that continuing application of repeated cohort vaccination to 1-year-old infants may be helpful in decreasing the frequency and magnitude of epidemics, but it will not block transmission unless vaccination coverage attains very high levels.

We now replace the conventional policy, in which the level of vaccination is uniform over time, by a nonuniform pulse

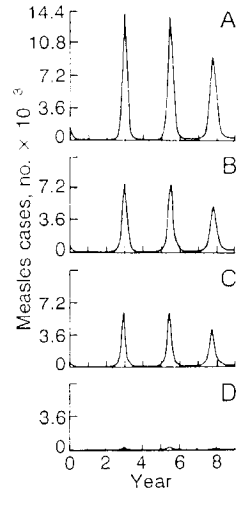

FIG. 3. Temporal changes in the number of measles infections per age class (detail of Fig. 2). (*A*) Total population. (*B*) Age class 0–4. (*C*) Age class 5–9. (*D*) Age class 10+.

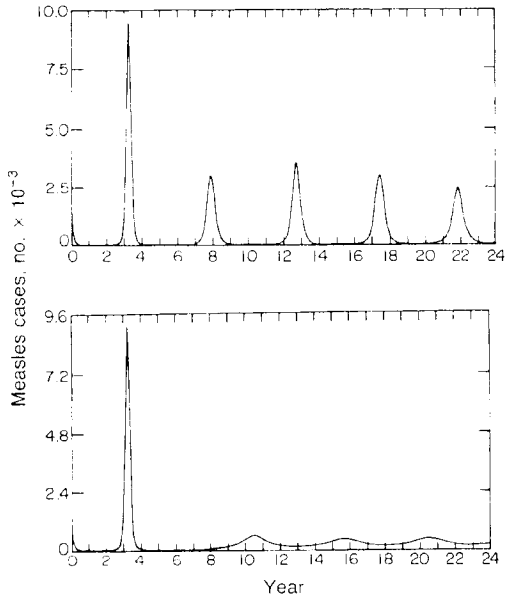

FIG. 4. Temporal changes in the number of reported cases of measles infections with continuous vaccination, $p = 0.85$ (*Upper*) or $p = 0.91$ (*Lower*), of infants at age 12 months. See Fig. 2 for details of the simulations.

policy—i.e., periodic vaccination of several age groups at the same time. We simulate this policy by setting various levels of vaccination of different age cohorts. In Fig. 5 a single pulse vaccination is applied, 1 year prior to the predicted onset of the epidemic, to 85% of the children aged 1–7 years. Results show that a single pulse vaccination generates a 7-year epidemic-free interval. However, the predicted amplitude of the epidemic in the 8th year is extremely large, most infected individuals being in the 0–4 and 5–9 groups (Fig. 5 *B* and *C*). Continuing the simulations with a similar pulse vaccination 1 year prior to each prospective epidemic, we note that the intervaccination intervals become shorter until they stabilize at about 5 years. Under this strategy the epidemics are suppressed, and they continue to be so as long as we consistently employ this strategy (Fig. 6). It should be

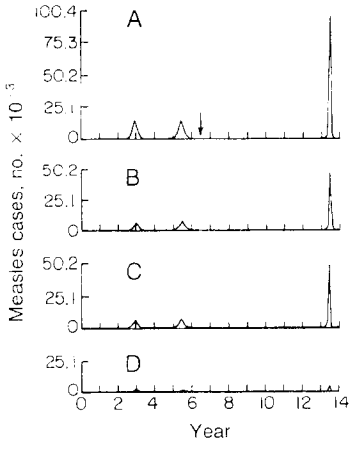

FIG. 5. Temporal changes in the number of reported cases of measles infection with a single pulse vaccination (time of pulse is denoted by arrow), $p = 0.85$, of children aged 1–7 years. (*A*) Total population. (*B*) Age class 0–4. (*C*) Age class 5–9. (*D*) Age class 10+. See Fig. 2 for other parameters.

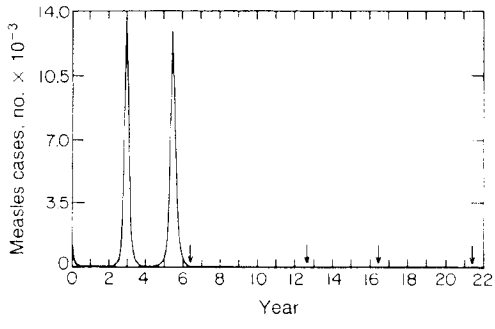

FIG. 6. The effect of the pulse vaccination on the number of reported cases of measles infection. Timings of pulses are denoted by arrows. See legend to Fig. 5 for details of the simulations.

stressed that in our simulations efficacy of the pulse vaccination does not depend on the exact timing of the pulses prior to each epidemic. Efficacy depends on the vaccination or the coverage level, p, and on which age cohorts are vaccinated. In the present simulations, with $p = 0.85$, efficacy is guaranteed only if the 1–7 age classes are immunized every 5 years; lower levels of vaccination require smaller intervals between pulses to guarantee the high levels of herd immunity necessary for preventing a further epidemic (see below).

The Rationale for Pulse Vaccination

To illustrate the special properties of the pulse vaccination policy, we examine in more detail some very simple non-age-structured models (it should be stressed, however, that in the assessment of the coverage levels and the timing between pulses we employed the full age-structured model). The simplest model one can use describes the dynamics of two compartments in the population, the susceptible individuals and the infected individuals (13, 17, 18). If all variations within each compartment are small, the overall dynamics can be described by the following system of equations:

$$\frac{dX}{dt} = \mu N - (\beta Y + \mu)X$$

$$\frac{dY}{dt} = \beta XY - (\mu + \nu)Y. \qquad [1]$$

X and Y are the numbers of susceptible and infectious individuals, respectively, μ is the birth rate, taken as equal to the death rate, N is the total population size (a constant), and β and ν are the transmission rate and the recovery rate, respectively. It is well known for this model that if the basic reproductive number, $R_0 = \beta N/(\mu + \nu)$, is larger than unity, then the system has one stable equilibrium:

$$X^* = \frac{\mu + \nu}{\beta}, \qquad Y^* = \frac{\mu(R_0 - 1)}{\beta}. \qquad [2]$$

This stable state is approached by damped oscillations, the period of which is approximately

$$T = 2\pi\sqrt{AK}. \qquad [3]$$

A is the average age at infection ($A = 1/\lambda$, where λ is the force of infection; in the case of strong homogeneous mixing, $\lambda = \beta Y$) and $K = 1/\nu$ is the average infectious period. The infection will die out when $R_0 < 1$.

As already noted, the coverage level that is required for herd immunity to block the transmission (≈95%) is difficult

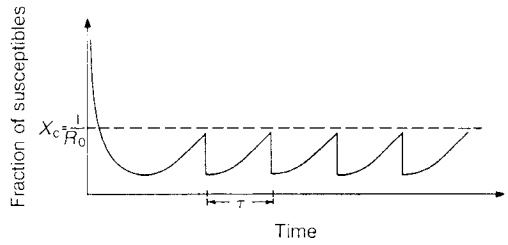

FIG. 7. Schematic illustration of the effect of the pulse vaccination strategy on the fraction of susceptibles. The interval between the pulses, τ, is chosen so that the fraction of susceptibles never exceeds a critical value, X_c (see text for further details).

to obtain in practice. The new approach is to replace the current concept, by which vaccination effort is spread homogeneously 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 δ functions as inputs to the above system, causing discontinuous jumps in the state of the systems (20).

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

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

$$X(t_k-) = (1 - p_k)X(t_k) \quad \text{for } t = t_k \qquad [5]$$

$$\frac{dY}{dt} = \beta XY - (\mu + \nu)Y. \qquad [6]$$

In Eq. 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,

$$X \leq X_c = \left(\frac{\mu + \nu}{\beta}\right), \qquad [7]$$

so that $Y' < 0$, we can prevent the persistence of recurrent 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).

This discrete time vaccination strategy has the effect of replacing the damped oscillatory behavior of Y by an aperiodic behavior—i.e., a monotonic decay. From an epidemiological standpoint 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

$$X(n\tau+) = (1 - p)X(n\tau) \qquad n = 1, 2, 3, \ldots, \qquad [8]$$

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 Eq. 7, endemic infection tends to zero. For this reason we can now neglect the Y term in Eq. 4. We also replace the number of susceptibles, X, by their fraction, so that Eq. 4 becomes

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

where $x = X/N$. 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 $t \to \tau$ and $x(\tau-) = x_c$. From Eq. 9 we obtain

$$\tau = \frac{1}{\mu} \ln\left(1 + \frac{px_c}{1 - x_c}\right). \qquad [10]$$

For small x_c we can make the approximation:

$$\tau \simeq \frac{px_c}{\mu}. \qquad [11]$$

But since $x_c/\mu \simeq L/R_0 \simeq A$ (L being the average life expectancy, $L = 1/\mu$; ref. 13), approximation μ can be replaced by

$$\tau \simeq pA. \qquad [12]$$

The meaning of approximation **12** is that when pulse vaccination involves a high coverage level (i.e., a large p), the intervaccination intervals are roughly equal to the average age at infection. It should be stressed, however, that the above analysis provides only a crude conceptual understanding of the impact of pulse vaccination; the precise calculations must be based on the age-structured simulation model.

Discussion

The simulations of the full age-structured model, where the WAIFW I matrix is employed, 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 5 years, rendering immunity to 85% of children aged 1–7, may prevent the epidemics. If we take into account a 5% vaccine failure this rate actually means a compliance level of 90%. Note, however, that in our simulations, even if the coverage level is as low as 75% the pulse strategy is still efficient, given that it is applied every 4–5 years. A pulse interval of 3–4 years is required if the coverage level is 70% and, in general, our numerical and analytical results suggest that the pulse interval should decrease with decreasing coverage level. The cost of this strategy (measured in the total number of vaccinations) is lower than that of the current strategy of two doses, applied to all children at the ages of 1 and 6. Under the pulse strategy only some fraction of the population has to receive a second vaccination. An auxiliary advantage of the pulse strategy may be the higher compliance, due to the effect of "campaigning" prior to the launch of a vaccination day or week.

It is important to stress that the improved efficiency of the pulse strategy lies in the discrete vaccination, rather than in the elevated level of vaccinated individuals. To illustrate this point, we simulated a strategy in which vaccination was applied continuously to 1-year-old (85%) and 6-year-old children (25% of the susceptibles). Although such a strategy involved a slightly higher coverage level than the pulse strategy of 85% of the susceptibles aged 1–7, it was inferior to the latter in allowing small epidemics whose intervals were about 6 years (results not shown).

To intuitively understand the effect of the pulse strategy, one should recall that we are dealing with a population where the transmission coefficient among schoolchildren is much larger than that in the younger age classes. In such a population the unvaccinated younger age-groups alone would have a relatively long interepidemic interval (>5 years) in the absence of contact with other age-groups, whereas the unvaccinated population as a whole would have a 2-year-

interepidemic interval. As the total population in which mixing occurs between age classes is dominated by the high transmission coefficient in schoolchildren, vaccination upon entering school increases the interepidemic interval of the whole population to 5 years. In this respect continuous cohort vaccination at 5 years of age is somewhat similar to vaccination at birth. This is the crucial observation which justifies the use of the pulse vaccination every 5 years. A pulse vaccination program at 5-year intervals of the population aged 1–7 years has two effects: (*i*) a continuous vaccination of children upon entering school is obtained and (*ii*) prior to the potential onset of each epidemic, the density of susceptibles in the total population is reduced below the threshold required to generate a new epidemic. It should be stressed that in the simulations the density of unvaccinated infants is always kept below the epidemic threshold.

Our analysis of a simplified, mass action law, model implies that the interval between successive vaccination pulses is roughly similar to the average age at infection and our computer simulations, involving a more complex age-structured population, suggest that this interval is roughly 5 years, when the vaccination level is 85%. The results from the more complex model are therefore in accord with the analytical result derived from the simple model, since in line with observations in unvaccinated populations in developed countries the average age at infection in the age-structured model was set at approximately 5 years. Analyses based on both the simple and complex models reveal a further property which is more of relevance in developing countries, where the average age at infection in unvaccinated communities is typically lower in urban centers than in developed countries and where levels of vaccine coverage are often low (i.e., <65% by age 5 years). In these circumstances, analyses suggest that the optimum interval between pulses to suppress epidemic outbreaks may be too short to make a pulse program a sensible strategy by comparison with repeated cohort immunization.

A further problem of practical relevance concerns the persistence of infection (albeit in a small number of individuals) between pulses. If coverage via the pulse program is heterogeneous in a spatial context, then the persistence of infection may facilitate local epidemics in children in areas where the pulse program achieved only low levels of vaccine uptake. One possible way around this problem would be to continue cohort vaccination of 1-year-old infants, but to replace the second vaccination dose phase of the current cohort immunization program with a pulse application across the 1- to 7-year-olds. Further dangers arise if the optimum interval between pulses for a specified population is not maintained. Pulsing more frequently than the optimum is not a problem, but if the interval is longer than suggested by our calculations, then small epidemics will be initiated. Their magnitude can be suppressed by the immediate implementation of the pulse once a rise in case reports is noted via epidemiological surveillance. Of particular importance in this context is the role of various heterogeneities (spatial, behavioral, operational) in determining the optimum interval between pulses.

More broadly, the central question raised by these simple analyses conveys the message for the design of public health policy where mass immunization is considered. Most developed countries have well-established cohort immunization programs in place with varying degrees of success. However, virtually all countries are encountering difficulties in eliminating transmission of the measles virus even when vaccination coverage is very high (e.g., the United Kingdom and the United States). This is largely due to the persistence of pockets of susceptibility, often in poor communities in large urban centers. In these cases a "pulse campaign" may be a sensible approach as an addition to the current cohort program. It should be noted that in Brazil, the pulse vaccination strategy is currently applied and appears more successful in compliance and organization than the continuous vaccination strategy (19). Similar principles apply in the Israeli setting, with respect to minority ethnic groups, such as the Bedouins or some religious sects, which might be difficult to reach via conventional public health programs. Ultimately, the desirability of adding a pulse campaign, or even replacing cohort immunization with a pulse program, will depend on two factors. These are the risks attached to each approach (or a combination of both) and the costs of implementation and long-term maintenance. The latter factor is of particular importance since no country is an island fortress with respect to the introduction of infection, due to global mixing patterns facilitated by air travel. To protect a defined population against measles, very high levels of herd immunity must be maintained even when the infection is very rare, or even absent, in the population. Our simple analyses of the possible merits of pulse vaccination program serve to highlight the need for further research based on more complex models that mirror both cohort and pulse vaccination, as well as more detailed discussions of practicalities, costs, and risks.

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