Measles immunization strategies for an epidemiologically heterogeneous population: the Israeli case study

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SUMMARY

Although the vaccine against measles has been routinely applied over a quarter of a century, measles is still an active disease in Israel. The January 1991 outbreak caused high morbidity in infant and adolescent populations and high mortality, especially among nomad Bedouins in the southern region of the country. The Bedouins form a small fraction of the total Israeli population (*ca.* 2%), but it is thought that they may experience significantly higher rates of transmission than the majority group. In this work we use deterministic compartmental mathematical models to define the optimal immunization strategy for a population consisting of a majority group characterized by low transmission rates and a minority group characterized by high transmission rates; this study allows both for transmission differences between the two groups, and for possible differences in the average cost (or difficulty) in reaching individuals for vaccination. Our analysis shows that the optimal vaccination policy for such a population involves different strategies for the two groups: a smaller fraction is to be vaccinated in the minority group if transmission in this group is not much larger than in the majority group, whereas, if the difference in transmission is very large, a higher proportion is to be vaccinated in the minority group. The advantage of this non-uniform vaccination policy is that it involves vaccination of a smaller fraction of the total population (and costs less, if there are differential costs between the groups), as compared with the proportion vaccinated under the conventional uniform vaccination policy. The implications of our results for vaccination policies for other minority groups, or for other infectious diseases which are characterized by epidemiological heterogeneity, are as yet to be examined.

1. INTRODUCTION

In Israel, the vaccine against measles has been routinely applied 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 (Shwartz 1984). This immunization program resulted in a dramatic decline in morbidity, disappearance of massive epidemics, and has increased the average age at infection (Giladi *et al.* 1987; Danon *et al.* 1992)

Outbreaks of measles were recorded in Israel in 1975, 1982 and 1985. In January 1991 a new measles epidemic broke out, whose characteristics illustrate the special epidemiological status of this country. During the first months of the epidemic, 320 cases of measles were reported, 300 of them in or near the southern Israeli town of Beer Sheba. 28 out of 100000 cases were reported among Jews, and 260 out of 100000 cases among nomad Bedouins. The latter group also suffered a relatively high mortality among the infected individuals. The reported immunity level is relatively low among Bedouins, 77% in 1989, as compared with 85.66% in the Jewish group. Another characteristic of the Bedouin group is a relatively high young–old mixing rate, due to the special nature of their communal nomad life. Note that the current estimates of the Israeli population size are 3717100 Jews and 70400 Bedouins (Central Bureau of Statistics 1991).

The aim of the present work is to examine the effects of demographic and epidemiological heterogeneities, such as those described above, on the prospects of disease eradication. To this end we analysed a simple model for an epidemiologically non-uniform population, consisting of a majority group with relatively low transmission rates and a minority group whose transmission rates are relatively large. Inter-group contacts are taken to be very small compared with intra-group contacts. Implications of our simple model for real-life vaccination strategies will be discussed.

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2. A SIMPLE MODEL FOR A POPULATION DIVIDED INTO TWO EPIDEMIOLOGICALLY DIFFERENT GROUPS

Our model is an adaptation of a general model for a transmission of an infectious disease in a spatially heterogeneous population (Hethcote 1978; May & Anderson 1984; Anderson & May 1991). The general model considers a population divided into n groups, with N_i being the population size or density in the ith group ($i = 1, 2, \ldots, n$). The population in group i is divided into three compartments: susceptibles X_i, infectious, Y_i, and immune individuals, Z_i. New infections appear in the ith group at a rate equal to the number of susceptibles times the force of infection, λ_i:

$$\lambda_i = \sum_j \beta_{ij} Y_j, \tag{1}$$

where the transmission parameter β_{ij} represents the probability that an infectious individual in group j will infect a susceptible individual in group i, per unit time. The dynamics of this system obeys the following three differential equations:

$$\left.\begin{aligned} \dot{X}_i &= \mu N_i(1-p_i) - (\lambda_i + \mu) X_i, \\ \dot{Y}_i &= \lambda_i X_i - (\mu + v) Y_i, \\ \dot{Z}_i &= vY_i - \mu Z_i + \mu N_i p_i. \end{aligned}\right\} \tag{2}$$

In (2), μ is the average birth rate, assumed equal to the death rate, so that N_i is constant; v is the rate of recovery of infectious individuals to the immune group; p_i is the fraction of newly born individuals that are vaccinated near birth. The equilibrium values of (2) for the numbers of susceptibles and infectious individuals in the ith group, X_i^* and Y_i^*, are substituted in (1) to yield:

$$\lambda_i^* = \frac{\mu}{\mu + v} \sum_{j-1}^{n} \beta_{ij} N_j (1-p_j) \frac{\lambda_j^*}{\lambda_j^* + \mu}. \tag{3}$$

As discussed in May & Anderson (1984) and references therein, the eradication criterion corresponds to all $\lambda_i^* \to 0$.

Denoting the fraction of the newborns in the ith subpopulation that are immunized under the optimal schedule as p_i, the critical set of p_i values corresponding to the eradication threshold obeys the set of relations:

$$\sum_{j-1}^{n} \left[\frac{\beta_{ij} N_j (1-p_j)}{\mu + v} - \delta_{ij} \right] \lambda_j^* = 0, \tag{4}$$

where $\delta_{ij} = 1$ for $i = j$, and $\delta_{ij} = 0$ otherwise. The constraining relation among the immunized fractions p_i in the various groups that are consistent with eradicating the infection is given by

$$\det \left\| \frac{\beta_{ij} N_j}{\mu + v} (1-p_j) - \delta_{ij} \right\| = 0. \tag{5}$$

The above model is now adapted for considering a population divided into two groups: group A characterized by a relatively low transmission rate β; group B characterized by a relatively high transmission rate $\alpha\beta (\alpha > 1)$. The size of group B is assumed to be much smaller than that of group A: $N_A = (1-f)N$; $N_B = fN$, with N being the total population size or density and $f \ll 1$. Contacts between individuals in the two groups are assumed to be weaker than within groups, with the inter-group transmission parameter having a value $\epsilon\beta$ for the effect of group A on group B, $\epsilon(\alpha\beta)$, for the effect of group B on group A, $(\epsilon \ll 1)$. Under the latter assumption the force of infection (1) may be written explicitly, as follows:

$$\lambda_A = \beta(Y_A + \alpha\epsilon Y_B), \tag{6}$$

$$\lambda_B = \beta(\epsilon Y_A + \alpha Y_B). \tag{7}$$

Substituting (6) and (7) in (5) and defining $\rho \equiv \beta N/(\mu + v)$ we obtain

$$\det \begin{vmatrix} \rho(1-f)(1-p_A) - 1 & \alpha\epsilon\rho f(1-p_B) \\ \epsilon\rho(1-f)(1-p_A) & \alpha\rho f(1-p_B) - 1 \end{vmatrix} = 0. \tag{8}$$

The constraining relation between the threshold values of the unvaccinated fractions in the two groups, $q_A = 1 - p_A$ and $q_B = 1 - p_B$ is thus

$$F \equiv \alpha(1-\epsilon^2) f(1-f)\rho^2 q_A q_B - (\alpha f q_B + (1-f) q_A)\rho + 1 = 0. \tag{9}$$

We now seek the optimal vaccination policy, which usually is defined as that which minimizes the total fraction of the population that must be vaccinated to achieve eradication; that is, which minimizes the overall population vaccinated,

$$P = (1-f) p_A + f p_B. \tag{10}$$

More generally, however, there are likely to be differences in how easy it is to administer vaccination to individuals in different groups, deriving from social or logistic factors. For the two-group case studied here, we take the 'effective cost' of vaccination, on average, in the majority group A to be unity, and the relative such 'effective cost' in group B to be C (with, in the present case, $C \geqslant 1$). For this sensible generalization of previous work, we thus define the cost-weighted overall population to be vaccinated, P', as

$$P' = (1-f) p_A + C f p_B. \tag{11}$$

Equivalently, we can write

$$P' = [1 - f + Cf] - Q', \tag{12}$$

with Q', the cost-weighted overall population unvaccinated,

$$Q' = (1-f) q_A + C f q_B. \tag{13}$$

The aim is now to maximize Q' (or minimize P'), subject to the critical threshold constraint of equation (9); of course q_A or q_B must also obey $1 \geqslant q_A, q_B \geqslant 0$. A dimensionless measure of the relative efficiency of different strategies is

$$\hat{Q} = Q'/(1 - f + Cf). \tag{14}$$

Here $\hat{Q}$ is the cost-weighted proportion unvaccinated, relative to the effective cost of vaccinating everyone (that is $1 - f + Cf$). The earlier kinds of analyses of vaccination in heterogeneous populations, which

ignored differential difficulties or costs between groups, are of course recovered by putting $C = 1$ (whereupon $Q = Q' = \hat{Q}$).

The problem of choosing the values of q_A and q_B that maximize the Q' or $\hat{Q}$ of equation (13) or (14), subject to the constraining equation (9), may be solved by standard Lagrange multiplier techniques. The critical fractions of groups A and B that remain unvaccinated, under the optimal program, are:

$$(1-f)\,q_A = \frac{\alpha-\epsilon(\alpha C)^{\frac{1}{2}}}{\alpha\rho(1-\epsilon^2)}, \tag{15}$$

$$fq_B = \frac{1-\epsilon(\alpha/C)^{\frac{1}{2}}}{\alpha\rho(1-\epsilon^2)}. \tag{16}$$

The relative efficiency of this optimal program, as defined in equation (14), is then

$$\hat{Q} = \frac{C+\alpha-2\epsilon(\alpha C)^{\frac{1}{2}}}{\alpha\rho(1-\epsilon^2)(1-f+Cf)}. \tag{17}$$

Equations (15–17) will indeed be the solution, provided that

$$\epsilon \leqslant \left(\frac{C}{\alpha}\right)^{\frac{1}{2}} \quad \text{and} \quad \left(\frac{\alpha}{C}\right)^{\frac{1}{2}}, \tag{18a}$$

$$\frac{1-\epsilon(\alpha/C)^{\frac{1}{2}}}{(1-\epsilon^2)\,\alpha} \leqslant f\rho, \tag{18b}$$

$$\frac{\alpha-\epsilon(\alpha C)^{\frac{1}{2}}}{(1-\epsilon^2)\,\alpha} \leqslant (1-f)\,\rho. \tag{18c}$$

The first of these requirements will usually mean that ϵ must be small (unless α and C happen to be roughly equal). This, in turn, means that the second and third requirements are likely to be satisfied so long as

$$\alpha f\rho \geqslant 1 \quad \text{and} \quad (1-f)\,\rho \geqslant 1. \tag{18d}$$

The function $\hat{Q}$ is monotonically decreasing with α; the function q_A is monotonically increasing (for $\alpha \to \infty$, $q_A \to 1/(1-f)\,\rho$), and the function q_B is monotonically decreasing with α (for $\alpha \to \infty$, $q_B \to 0$). In the special case $C = 1$ and $\alpha = 1$ we recover the results of May & Anderson (1984), namely $(1-f)\,q_A = fq_B = 1/(1+\epsilon)\rho$. In this case, the fraction that can remain unimmunized is inversely proportional to the group's size.

Consider now the alternative strategy in which the same vaccination program is applied to the two groups, so that $p_A = p_B = p$. Denoting by $q_i = 1-p_i$ the proportion of unvaccinated individuals in group i, and by q the overall proportion of unvaccinated individuals, we obtain from (9):

$$\alpha(1-\epsilon^2)f(1-f)\,\rho^2q^2-(\alpha f+1-f)\,\rho q+1 = 0, \tag{19}$$

$$\rho q = \frac{(\alpha f+1-f)-[(\alpha f+1-f)^2-4(1-\epsilon^2)\,\alpha f(1-f)]^{\frac{1}{2}}}{2\alpha(1-\epsilon^2)f(1-f)}. \tag{20}$$

If $\epsilon \ll 1$ so that $\epsilon^2 \to 0$, then, choosing the solution with the negative square root, we obtain

$$q = \begin{cases} 1/\alpha f\rho & \text{for } \alpha \geqslant (1-f)/f \\ 1/(1-f)\rho & \text{for } \alpha < (1-f)/f. \end{cases} \tag{21}$$

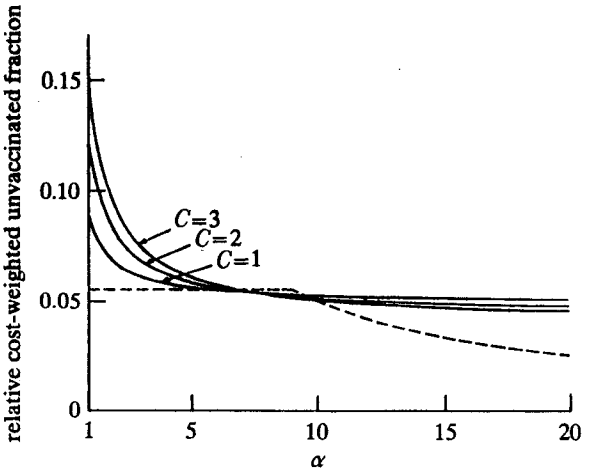

Figure 1. Computations, for different values of α and C, of the relative cost-weighted unvaccinated fraction under the non-uniform optimal vaccination strategy, $\hat{Q}$ (solid lines) compared with the unvaccinated fraction under the optimal uniform policy, q (broken line); $f = 0.1$, $\epsilon = 0.1$, $\rho = 20$.

Equation (21) defines the proportion of the total population that has to be vaccinated under the uniform vaccination policy. We also require that $1 \geqslant q \geqslant 0$, which is likely to be the case under condition (18).

The results of our analysis are shown in figure 1, where we use equation (17) to compute the relative cost-weighted unvaccinated fraction in the total population, under the optimal non-uniform policy ($\hat{Q}$). This policy is compared with the optimal uniform policy ($q_A = q_B = q$; equation (21)). Note that realistic variation in the value of C, the relative average cost of vaccination, does not have a qualitative effect on the results.

3. DISCUSSION

We used a simple mathematical model to explore the effect of epidemiological heterogeneities on the optimal vaccination policy, where the optimization problem is defined as disease eradication with minimum number (or, more generally, minimum cost) of vaccinated individuals. Our analysis shows that the optimal policy involves different strategies for the two groups. This conclusion is in general accordance with Anderson & May (1984), which suggests that in simple models of spatially heterogeneous populations the fraction that is to be vaccinated under the optimal vaccination policy is inversely proportional to the group size. The new elements in the present model are the assumptions that the population can be subdivided also according to the transmission parameters and that the average cost of vaccination may vary in the two groups. Our analysis shows that in this case the fraction to be vaccinated in the minority group is smaller than in the majority group, if the transmission coefficient in this group is not much larger than in the majority group. In contrast, if the difference in transmission coefficients between the two groups is very large, a higher proportion is to be vaccinated in the minority group. If this non-uniform policy is adapted, a smaller fraction of the total population should be vaccinated for achieving disease

eradication, as compared with the proportion that needs to be vaccinated under the conventional uniform vaccination policy. These conclusions are valid for any realistic difference in the average vaccination cost between the two groups. The general conclusion from our results is that when the goal is disease eradication with minimum cost then vaccination programs should involve different proportions of individuals in the different epidemiological groups. This result may be generalized to account for other minority groups, characterized by relatively small size, relatively low contact with the majority group, and relatively high intra-group transmission rates. The conclusions of the present study should hold generally, as long as the transmission rates between groups are relatively low.

The present work focused on defining the optimal vaccination strategies for countries with significant epidemiological heterogeneity. However, it is plausible that the conditions for implementing the optimal strategy cannot be met at present. In another work (Agur *et al.* 1993) we put forward a practical method for preventing measles epidemics. This method is based on periodic vaccination across several age cohorts. Our theoretical results suggest that, by using this strategy, measles epidemics can be altogether prevented.

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REFERENCES

Agur, Z., Cojocaru, L., Mazor, G., Anderson, R. M. & Danon, Y. L. 1993 Pulse mass measles vaccination across age cohorts. (Submitted.)

Anderson, R. M. & May, R. M. 1984 Spatial, temporal, and genetic heterogeneity in host populations and the design of immunization programmes. *IMA J. Math. Appl. Med. Biol.* **1**, 233–266.

Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control.* Oxford University Press.

Central Bureau of Statistics 1991 *Statistical abstracts of Israel*, vol. 42. Jerusalem.

Danon, Y. L., Adir, Y., Avned, A., Zaaida, Y. & Green, M. S. 1992 Prevalence of antibiotics against measles, mumps and rubella in Israeli young adults. *Isr. J. med. Sci.* **28**, 293–296.

Giladi, M., Schulman, A., Kedem, R. & Danon, Y. L. 1987 Measles in adults: a prospective study of 291 consecutive cases. *Br. med. J.* **295**, 1314–1315.

Hethcote, H. W. 1978 An immunization model for heterogeneous population. *Theor. Popul. Biol.* **14**, 338–349.

May, R. M. & Anderson, R. M. 1984 Spatial heterogeneity and the design of immunization programs. *Math. Biosci.* **72**, 83–111.

Slater, P. E. 1991 Measles containment in Israel. *Isr. J. med. Sci.* **27**, 19–21.

Shwartz, T. A. 1984 Prevention of measles in Israel: implications of long term partial immunization program. *Publ. Health Rep.* **99**, 272–277.

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