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

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"Measles Immunization Strategies for an Epidemiologically Heterogeneous Population: The Israeli Case Study"

Z. Agur
Dept. of Applied Mathematics & Computer Science
The Weizmann Institute of Science
Rehovot 76100
Israel

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

Z. AGUR[1,2], Y.L. DANON[3], R.M. ANDERSON[4], L. COJOCARU[1], AND R.M. MAY[2]

[1] *Department of Applied Mathematics and Computer Science, The Weizmann Institute of Science, Rehovot 76100, Israel.*

[2] *Department of Zoology, Oxford University, South Parks Road, Oxford, U.K.*

[3] *Kipper Institute of Immunology, Children Medical Center, The Beilinson Medical Center, Petach-Tikva, 49104, and Sackler School of Medicine Tel Aviv University, Israel.*

[4] *Department of Biology, Imperial College of Science, Technology & Medicine, Prince Consort Road, London SW7 2BB, U.K.*

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 are suspected of experiencing 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 a low transmission rates and a minority group characterized by high transmission rates. 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 transmis-

sion 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 nonuniform vaccination policy is that it involves vaccination of a smaller fraction of the total population, as compared to 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, such as AIDS, 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 (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. 28/100,000 cases were reported among Jews and 260/100,000 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 to 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 3,717,100 Jews and 70,400 Bedouins (Statistical abstracts of Israel, 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 analyzed a simple model for an epidemiologically nonuniform 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 to intra-group contacts. Implications of our simple model for real-life vaccination strategies will be discussed.

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 (May & Anderson 1984). The general model considers a population divided into n groups, with N_i being the population size in the i-th group ($i = 1, 2, \ldots n$). The population in group i is divided into three compartments: susceptibles X_i, infections, Y_i, and immune individuals, Z_i. New infections appear in the i-th 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 3 differential equations:

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

In (2) μ is the per capita 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 i-th 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 in 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 set of p_i values corresponding to eradication obeys the set of relations:

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

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

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

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 high transmission rate $\alpha\beta(\alpha > 1)$. The size of group B is assumed to be much smaller than that of group A. $N_A = (1-f)N$; $N_B = fN$ for N being the total population size 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 replacing $\rho \equiv \frac{\beta N}{\mu+\upsilon}$ we obtain

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

$$\alpha(1-\epsilon^2)f(1-f)\rho^2(1-p_A)(1-p_B) - (\alpha f p_B + (1-f)p_A)\rho + 1 = 0. \tag{9}$$

We are searching now the optimal general vaccination policy. In other words we wish to maximize the fraction of unvaccinated individuals

$$Q = (1-f)q_A + fq_B,$$

subject to the constraint that the set of q_A, q_B obeys (9) and also

$$1 \geq q_A, q_B \geq 0.$$

This problem is solved by standard Lagrange multiplier techniques. Choosing the solution with negative square root, one obtains the critical fraction remaining unimmunized, under the optimal immunization program, as follows:

$$(1-f)q_A = \frac{\alpha - \epsilon\alpha^{\frac{1}{2}}}{\alpha(1-\epsilon^2)\rho}. \tag{10}$$

$$fq_B = \frac{1 - \epsilon\alpha^{\frac{1}{2}}}{\alpha(1-\epsilon^2)\rho}. \tag{11}$$

The total fraction remaining unimmunized becomes

$$Q = \frac{1 + \alpha - 2\epsilon\alpha^{\frac{1}{2}}}{\alpha(1-\epsilon^2)\rho}. \tag{12}$$

Equations (10 –12) will indeed be the solution, provided that

$$\epsilon \leq \frac{1}{\alpha^{1/2}},$$

$$\frac{1 - \epsilon\alpha^{1/2}}{(1-\epsilon^2)\alpha} \leq f\rho,$$

$$\frac{\epsilon - \epsilon\alpha^{1/2}}{(1-\epsilon^2)\alpha} \leq (1-f)\rho.$$

This is likely to be the case if

$$\alpha f\rho \geq 1 \quad \text{and} \quad (1-f)\rho \geq 1. \tag{13}$$

Remark: The function Q is monotonically decreasing with α.

For $\alpha \to \infty$

$$Q \to \frac{1}{\rho}.$$

The functions q_A and q_B are monotonically increasing and monotonically decreasing with α, respectively. For $\alpha = 1$ we obtain

$$(1-f)q_A = \frac{1}{(1+\epsilon)\rho},$$

$$fq_B = \frac{1}{(1+\epsilon)\rho}.$$

One may note that when $\alpha = 1$ the fraction that can remain unimmunized in group A is smaller than in group B; in group A the unimmunized fraction increases with increasing α (for $\alpha \to \infty$, $q_A \to \frac{1}{(1-f)\rho}$), whereas in group B the unimmunized fraction decreases with increasing α (for $\alpha \to \infty$, $q_B \to 0$).

Considering a particular case in which the same vaccination program is applied to the two groups, we can write $p_A = p_B = p$. 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):

$$\alpha(1-\epsilon^2)f(1-f)\rho^2 q^2 - (\alpha f + 1 - f)\rho q + 1 = 0, \tag{14}$$

$$\rho q = \frac{(\alpha f + 1 - f) - [(\alpha f + 1 - f)^2 - 4(1-\epsilon^2)\alpha f(1-f)]^{1/2}}{2\alpha(1-\epsilon^2)f(1-f)}. \tag{15}$$

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

$$q = \begin{cases} \frac{1}{\alpha f \rho} & \text{for } \alpha \geq \frac{1-f}{f} \\ \frac{1}{(1-f)\rho} & \text{for } \alpha < \frac{1-f}{f}. \end{cases} \tag{16}$$

Equation (16) defines the proportion of the total population that has to be vaccinated under the uniform vaccination policy. We also require that $1 \geq q \geq 0$, which is likely to be the case under condition (13). The results of our analysis are displayed in Figure 1, where we use Eqns. (10–12) to compute, for different values of α, the proportions of individuals that can remain unvaccinated under the optimal nonuniform policy in the majority group (q_A), minority group (q_B) and the total population (Q). In addition we use Eq.(16) to compute the proportion of individuals that can remain unvaccinated under the optimal unifom policy ($q_A = q_B = q$).

3. DISCUSSION

We employed 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 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 spatially heterogenous populations the fraction that is to be vaccinated under the optimal vaccination policy is inversely proportional to the group size. The new element in the present model is the assumption that the population can be subdivided also according to the transmission parameters. 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 nonuniform policy is adapted a smaller fraction of the total population should be vaccinated for achieving disease eradication, as compared to the proportion that needs to be vaccinated under the conventional uniform vaccination policy.

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 generalised to account for other minority groups, or for a putative anti-HIV vaccine, where groups, usually denoted as *high risk populations*, are characterized by relatively small size, relatively low contact with the majority group and relatively high intra-group transmission rates. Our analysis should be applicable as long as the inter-groups transmission rates are very 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 carrying the optimal strategy cannot be met at present. In another work (Agur *et al.* 1992) 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 using this strategy measles epidemics can be altogether prevented.

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Figure Legends

Fig.1 Computations, for different values of α, of the proportions of individuals that can remain unvaccinated under the nonuniform optimal vaccination strategy in the majority group (q_A; Eq. 10), minority group (q_B; Eq. 11) and in the total population (Q; Eq. 12), as compared to the proportion of individuals that can remain unvaccinated under the optimal unifom policy ($q_A = q_B = q$; Eq. 16); $f = 0.1, \epsilon = 0.1$.

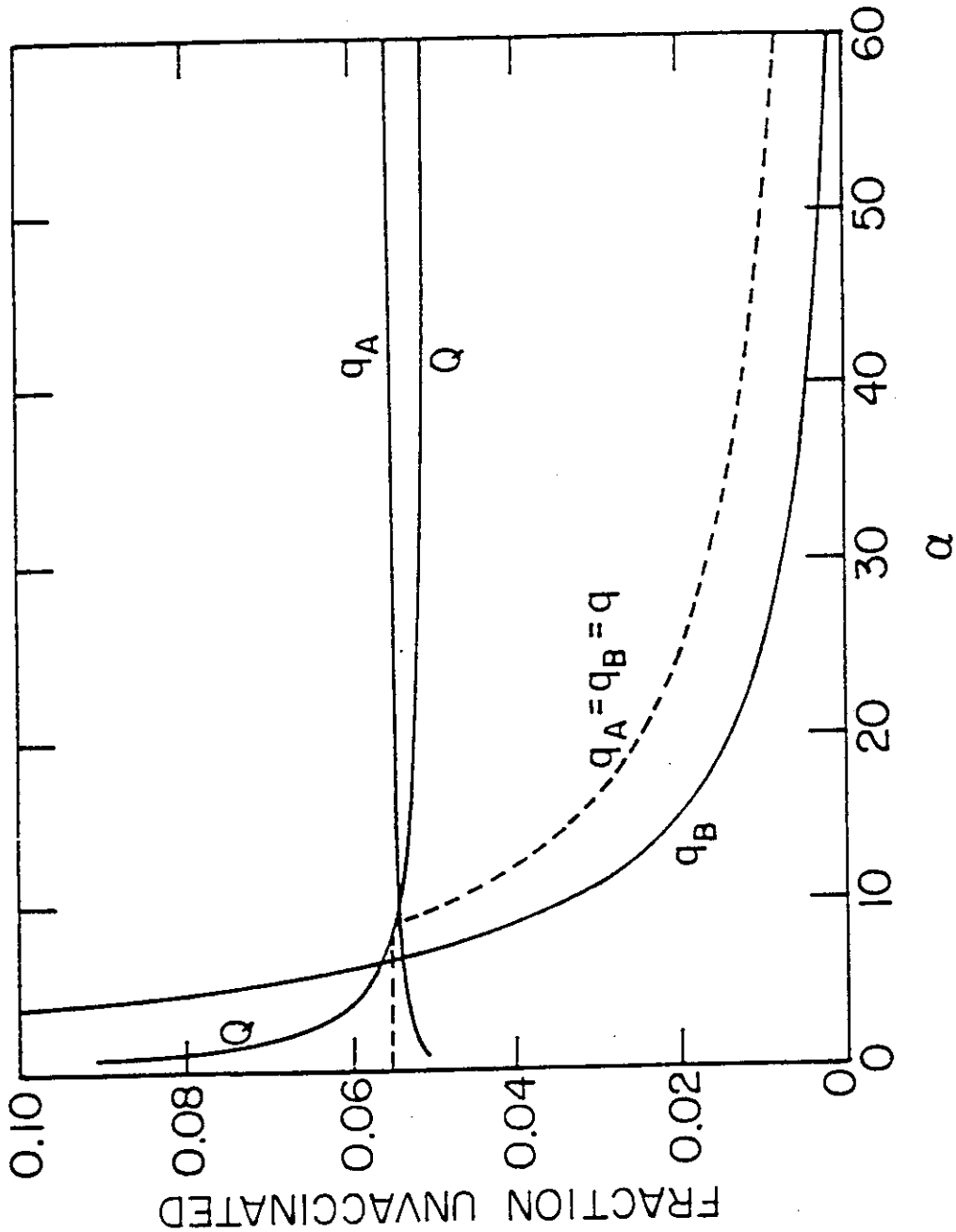
FRACTION UNVACCINATED
0.10
0.08
0.06
0.04
0.02
0
0
10
20
30
40
50
60
α
q_A
Q
$q_A = q_B = q$
q_B
Q

Fig. 1