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Childhood Infectious Diseases in LDCs: Immunization Program Design and Evaluation Using Demographic-Epidemiologic Models

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Abstract

Mass immunization programs have recently been implemented in a number of LDCs. A common method for evaluating their morbidity and mortality impact is to compare observed changes in the under-five mortality rate, the case-fatality rate, the age distribution of case deaths, the mean age at infection, the inter-epidemic interval, and disease incidence with the values predicted by standard epidemiologic models. However, since the demographic structure of the population can have a strong influence on childhood disease transmission patterns and immunization program impact in LDCs, comparisons with standard epidemiologic models can be misleading. Therefore it is crucial that the mortality and morbidity impact of immunization programs in LDCs be based on dynamic demographic-epidemiologic models formulated explicitly for such populations.

In this paper, we present a demographic-epidemiologic model of infectious disease transmission for airborne diseases such as measles, rubella, and chicken pox. The model is quite flexible and, with appropriate parameters, applies to both developed and developing countries; thus it is a generalization of standard epidemiologic models. It is shown that the predictions of the demographic-epidemiologic model are substantially different from those of the standard model and are in greater agreement with morbidity and mortality patterns observed in LDCs. A simulation version of the model is used to explore two issues in immunization program policy: the potential morbidity and mortality effects of lowering the minimum age for measles immunization from 9 to 6 months, and the relative merits of an intensive campaign aimed at children 9-23 months old versus a less intensive immunization program integrated into existing MCH services and aimed at children 9-59 months old.

Large scale-immunization programs have been in effect in a number of countries for several years, sparking interest in the question of how best to evaluate their impact on morbidity and mortality among children. The mortality impact of an immunization program is often assessed by considering changes in the mortality rate of children less than five years old, in the age distribution of case deaths, in the case-fatality rate, and in the proportion of all deaths in young children due to the disease in question, and then asking whether the observed changes are consonant with the anticipated mortality impact of an immunization program--despite the considerable disagreement about what the anticipated mortality impact of an immunization program might be (Koenig, Fauveau, and Wojtyniak 1989; UNICEF 1987). The epidemiologic impact of immunization programs is commonly assessed by comparing indices such as the mean age at infection, changes in the inter-epidemic interval, and reductions in the incidence of disease with the corresponding values predicted by standard epidemiologic models (Taylor et al. 1988; Guyer and McBean 1981). Rarely do such comparisons with anticipated mortality and morbidity effects leave demographers or epidemiologists sanguine about the observed impact of immunization programs.

In less developed countries (LDCs), the practice of evaluating immunization programs against the morbidity and mortality predictions of standard epidemiologic theory may be inappropriate for several reasons. The standard epidemiologic models, developed for populations that are not growing, can be misleading when applied to populations with moderate to high growth rates: the demographic structure of the standard models is inappropriate for LDCs. Furthermore, immunization in the standard epidemiologic models is assumed to occur at a precise target age, such as 9 months for measles, but this degree of precision is seldom achieved in LDCs. For these and other reasons, the predictions of standard epidemiologic models may be incorrect when applied to LDCs. Hence, standard epidemiologic models are poor tools with which to predict the morbidity and mortality impact of immunization programs and poor standards by which to judge immunization program efficacy.

In order to more accurately capture the process of disease transmission in LDCs, we have developed a model that incorporates both the demographic

and the epidemiologic structure of the population. The model contains two submodels: a demographic submodel that describes the distribution of individuals among different ages, and an epidemiologic submodel that describes the distribution of individuals at each age among epidemiologic classes. Because the model has complete demographic and epidemiologic structure, it yields more detailed, and hopefully more accurate, predictions of the mortality impact of an immunization program within a particular demographic setting than does the standard model. The model is flexible and, with appropriate parameters, may be applied to both developed and developing countries. When demographic and epidemiologic parameters describing conditions in LDCs are employed in the model, the predictions are in close agreement with observed demographic and epidemiologic patterns in developing countries.

In the following section, we discuss in greater detail the shortcomings of the standard epidemiologic models in describing disease transmission patterns in LDCs. We then describe the mechanics both of the standard model and of our demographic-epidemiologic model, and compare their predictions--the "rules of thumb" of epidemiologic theory--with observed disease transmission dynamics and immunization program impact in LDCs. Finally, we use a simulation version of our demographic-epidemiologic model to explore issues in immunization program policy relevant to LDCs.

BACKGROUND

There are many mathematical models of the aerogenic transmission of childhood infectious diseases and of their control by immunization (e.g., Kermack and McKendrick 1927; Dietz 1976; Schenzle 1984; Anderson and May 1985; Hethcote 1976; Fine and Clarkson 1982a,b). Most models incorporate demographic and epidemiologic features of more developed countries (MDCs), and so describe fairly well the behavior of such infectious diseases as measles and pertussis in MDCs. However, these models do not accurately describe the epidemiologic phenomena typical of developing countries.

Substantial differences exist between the predictions of these infectious disease transmission models (hereafter called the "MDC

models" because they reflect the demographic and epidemiologic structure characteristic of MDCs) and the observed patterns of disease transmission and immunization program effectiveness in LDCs. For example, between 1980 and 1985 an intensive measles immunization program in Kinshasa, Zaire resulted in the immunization of almost 60 percent of children 12-23 months old, yet "two results expected from [disease transmission models]--a reduction in measles incidence greater than the level of vaccination coverage and a shift in the age distribution of measles to older children--have not occurred in this African urban population" (Taylor et al. 1988: 792). In addition, the predicted increase in the interval between epidemic outbreaks of measles was not observed: epidemics continued to occur biennially. In Yaoundé, Cameroon, the results of an extensive measles immunization program were also inconsistent with the predictions of the MDC models of disease transmission: although a slight shift upward in the mean age of infection was observed, there was no corresponding lengthening of the inter-epidemic interval (Guyer and McBean 1981).

In addition to their failure to describe accurately the response to immunization programs in LDCs, MDC models cannot explain the seemingly random fluctuations in disease prevalence and the variations in inter-epidemic intervals among developing countries (see Figure 1): in some countries major disease outbreaks occur at regular intervals, but the prevalence of disease is fairly low between outbreaks; in other populations the ongoing level of disease is high, and epidemic disease outbreaks are less pronounced and irregularly timed.

There are at least three major reasons that MDC models of childhood disease transmission do not work well for developing countries. First, these models reflect demographic conditions that prevail in MDCs rather than in LDCs: low fertility, little or no mortality until old age, and very slow, if any, population growth. Since the demographic structure of the population can profoundly affect disease transmission patterns and immunization program effectiveness (John 1990a,b; Tuljapurkar and John 1990), a model that incorporates the demography of LDCs should correspond more closely to observed epidemiologic patterns in these countries. Second, MDC models assume that children are immunized

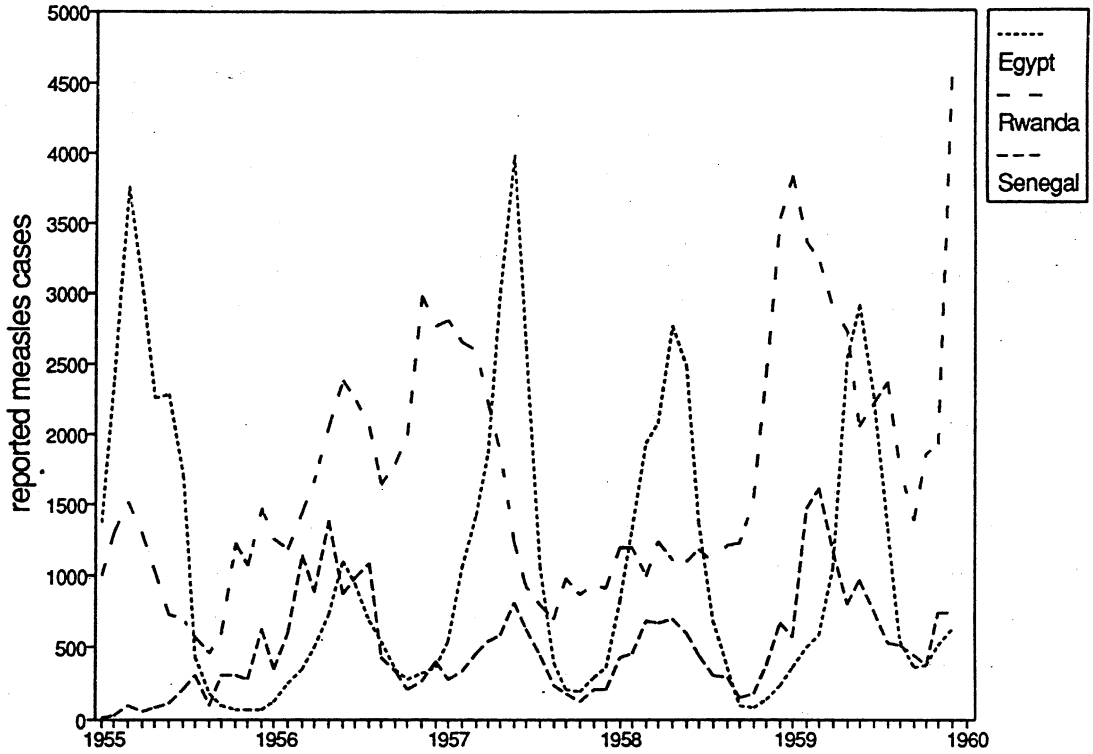

Figure 1. Reported measles cases by month in three LDCs, 1955-1959. source: World Health Organization, Annual Epidemiological and Vital Statistics, 1955-1959.

at a precise target age (such as 9 months for measles) or over a very narrow age range (9 to 11 months); yet few LDCs achieve this precision in immunization, instead immunizing children over a much wider age range (see Figure 2). And third, MDC models tend to ignore the role of spatial density in the transmission of disease. Yet there is evidence that both the rate and the infection efficiency of contacts between people are functions of the spatial density of the host population:

> The well-known difference between urban and rural areas in the age when infection...occurs can be clearly demonstrated....[I]t may be in these densely populated cities, individual households become less important and tend, in an epidemiological sense, to fuse into one superunit. Thus, the one factor that has been found to correlate with the difference in...[transmission] rates is the density of susceptibles. This density may be important both at the level of the household and also at the level of the community. It doubtless has its effect through control of the number and range of contacts between susceptibles and of the frequency of opportunity for spread of the disease. (Black 1962, 248-249)

Thus, particularly in the context of the extremely rapid growth of urban populations seen in many LDCs, the spatial density of population can be important to the behavior of childhood infectious diseases.

To address the problems inherent in MDC models, we have developed a model of airborne childhood infectious disease transmission and control appropriate for both LDCs and MDCs; complete mathematical details are given elsewhere (John 1990a,b; Tuljapurkar and John 1990; John and Tuljapurkar 1990). The distinctive features of our model are that (i) it incorporates fertility and mortality schedules of LDCs, and hence describes growing populations; (ii) disease transmission patterns depend upon the population's demographic structure and vice versa; (iii) transmission dynamics are allowed to change as the spatial density of the population changes as a result of population growth or urbanization; and (iv) immunization schedules can vary from a single, precisely targeted age to a wide age range (say, 9-59 months). When fertility, mortality, and immunization schedules for MDCs are used in our demographic-epidemiologic model, it accurately reflects MDC disease transmission patterns. The demographic-epidemiologic model

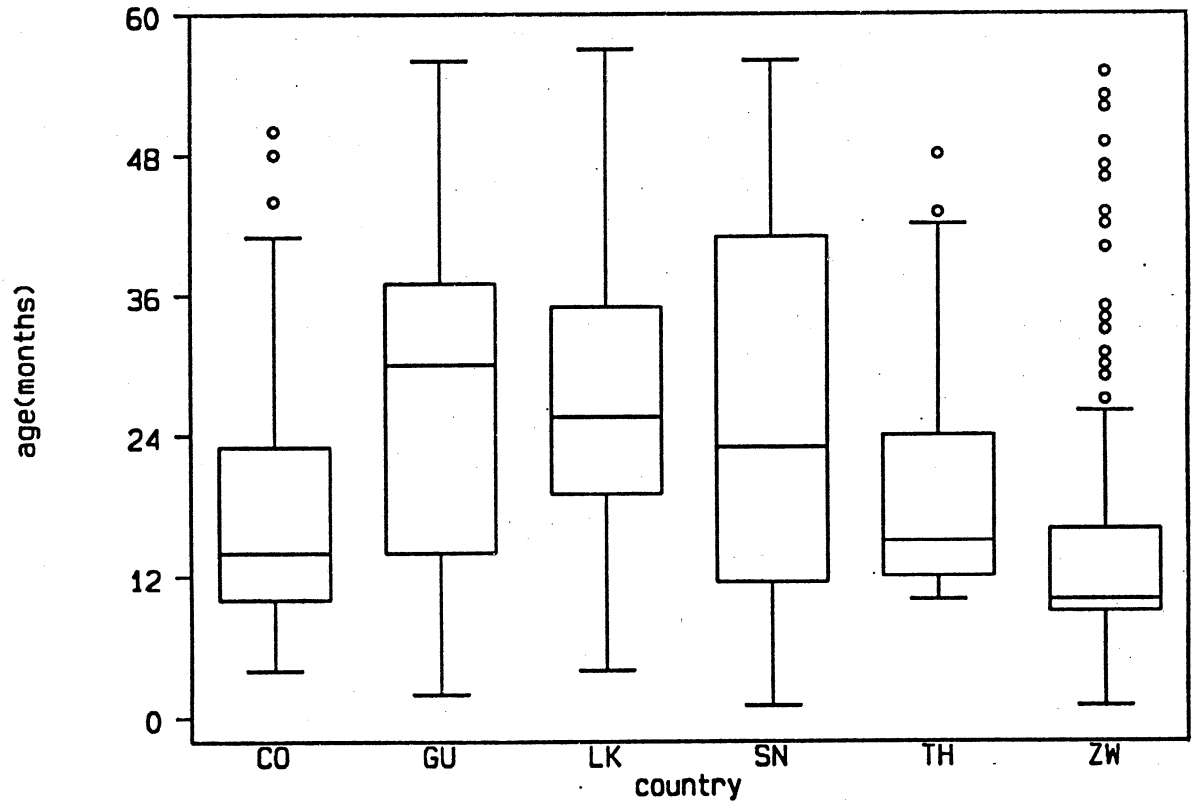

Figure 2. Distribution of reported age at measles vaccination for living children aged 48-59 months at survey in Colombia (1986), Guatemala (1987), Sri Lanka (1987), Senegal (1986), Thailand (1987), and Zimbabwe (1988/9). source: Demographic and Health Surveys. (See note 1 for a description of boxplots.)

(hereafter the "DE model") thus generalizes the standard MDC disease transmission models.

The DE model can be used to determine how the response of disease transmission patterns to immunization programs in LDCs differs from that in MDCs. The DE model can also be used to explore questions in immunization program design. For example, for any given specification of the demographic and epidemiologic parameters, the potential impact of an immunization program can be determined and alternative immunization delivery strategies compared; the effects of changes in the host population due to child survival programs, family planning programs, and urbanization can be studied; and the short-run fluctuations in disease transmission dynamics can be predicted.

We use the DE model in this paper to examine issues raised following an immunization campaign in the Congo (Dabis et al. 1988), in which children aged 9 months or older were vaccinated against measles. As a result of this immunization policy, subsequent measles cases were concentrated in children aged 6 to 8 months old--children who were no longer protected by maternally derived antibodies, but had not yet been vaccinated. Thus Dabis et al. noted:

> With the current pattern of measles...in Pointe-Noire, the optimum age for measles vaccination remains at nine months....Reducing the age at vaccination...would result in an increase in the proportion of vaccine failures....Whether this undesirable effect of vaccinating before nine months of age would be counterbalanced by a significant reduction in measles morbidity and mortality needs to be studied....
>
> Major obstacles to increasing vaccination coverage need to be identified and remedied. Increasing access to the health system implies that more vaccination centers will be accessible and, more importantly, that vaccinations will be performed daily in existing facilities....Integrating curative and preventive services is essential to ensure that all children aged nine months and older are screened any time there is contact with the health system and that they are vaccinated....(1988: 177)

The DE model allows us to address two important questions. First, what are the potential epidemiologic and demographic effects--both short-run (transient) and long-run (equilibrium)--of lowering the minimum age for immunization for a disease such as measles from nine

months to six months? And second, can a given epidemiologic goal (such as a target reduction in disease incidence) be achieved by implementing a less intensive immunization program integrated into existing health care services and aimed at children 9-59 months old, instead of by implementing an intensive immunization program for children 9-23 months old?

DISEASE TRANSMISSION MODELS

The simplified disease transmission mechanism for airborne diseases such as measles is the same in both MDCs and LDCs: infants born to mothers who are immune to the disease are protected from infection for several months by trans-placental maternal antibodies; the infectivity of the disease is high; an individual is both infected and infectious at the roughly same time; case-fatality rates in infancy and childhood are moderate; and recovery from disease results in subsequent immunity. Thus in the population there are four epidemiologic classes of people: protected by maternally derived antibodies, susceptible to infection, infected/infectious, and recovered/immune; the model traces the progression of individuals among epidemiologic classes (see Figure 3).

Initially, the population consists of infants protected by maternal antibodies and of susceptible individuals who interact (i.e., mix) in some way. A disease outbreak is initiated in the population by an infected/infectious individual who interacts with other individuals. Each time he or she encounters a susceptible individual, the latter may be infected with a probability proportional to the virulence of the infective organism. The rate at which people interact is a property of the population, while the infectivity of the disease is a property of the infective organism. At the earliest stage of the outbreak, most encounters by infectious individuals will be with susceptible individuals, so the disease spreads quickly. When the illness runs its course in the infected individual, he or she is then immune to reinfection. As the disease works through the population, the proportion of susceptibles decreases while the proportion immune increases, so it becomes less likely that an infected individual will encounter susceptible individuals and create new infections. If the proportion

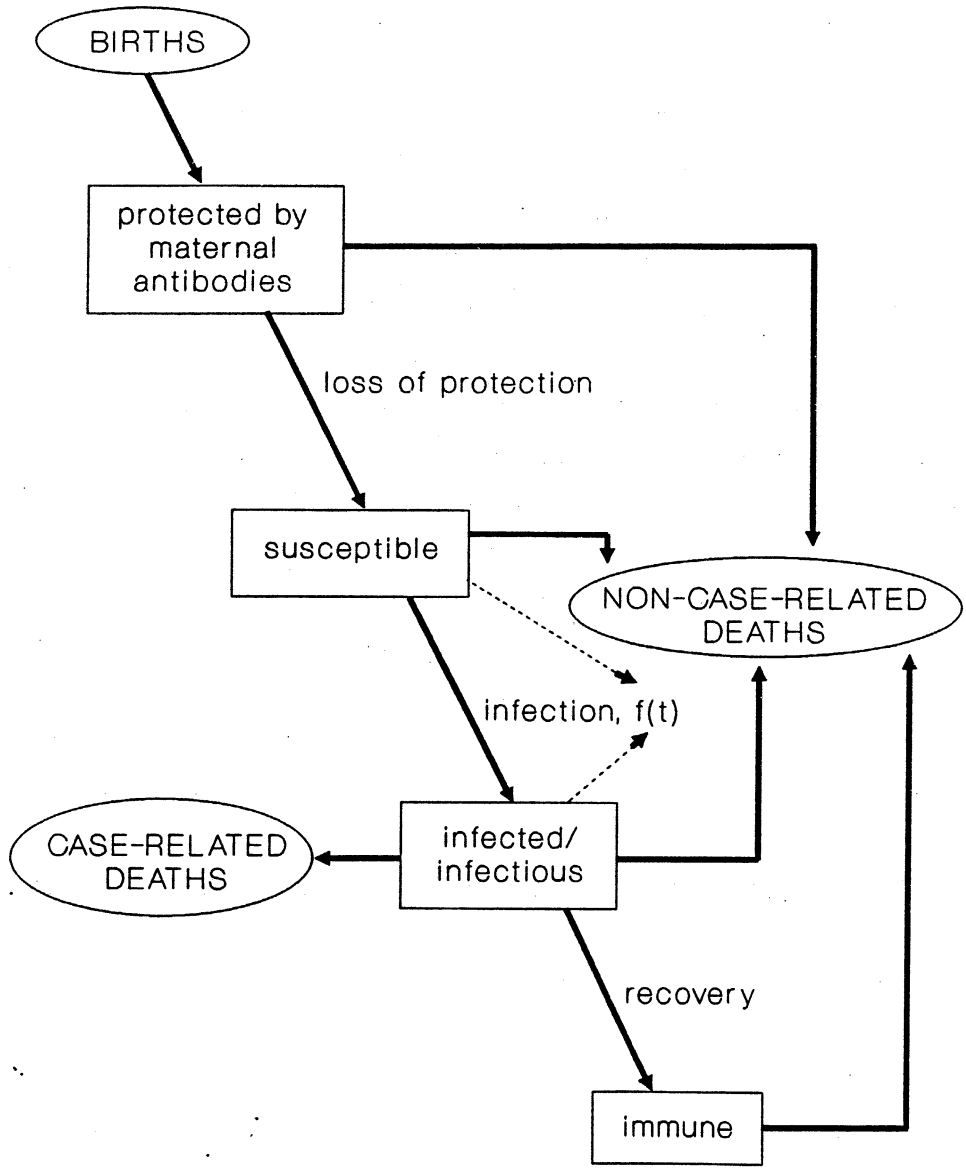

Figure 3. State transition diagram for movement among epidemiological classes. The rate of loss of maternal antibodies and the rate of recovery are independent of the epidemiologic composition of the population, while the infection rate, f(t), depends upon the proportion of the population susceptible and the proportion infectious.

of immune individuals is high enough, the disease will die out, even though there are still some susceptible individuals in the population; this is the phenomenon of "herd immunity." If, on the other hand, susceptibles are born into the population at a sufficiently high rate, the disease may not die out but may instead become endemic.

The concept of herd immunity--that some individuals will escape infection because they are lost in the herd of immune individuals and thus very unlikely to encounter an infected individual--gives rise to the analogous concept of the critical level of immunization in the population: the proportion of the population that must be immunized by a set age in order to eradicate the disease from the population. The critical level of immunization is less than 100 percent since immunization creates, in essence, artificial herd immunity. The more infectious the disease, the higher the critical level of immunization.

This simple model of mixing, infection, and recovery is common to the standard, MDC model of airborne disease transmission and to our DE model of airborne disease transmission. We next consider briefly the particular elements of the MDC model and list its predictions (the "rules of thumb" of standard epidemiologic theory). We then turn to the DE model, list its predictions, and ask whether they agree more closely with observation from LDCs than do the predictions of the MDC model.

Transmission and immunization models for MDCs

The MDC models incorporate demographic and epidemiologic parameters characteristic of MDCs. The crucial epidemiologic assumptions are that the rate of spread of disease is independent of the spatial density of the host population, and is proportional to both the number of susceptibles and the number of infected in the population. The pivotal demographic assumption in the MDC model is that the host population is not growing; this assumption governs the rate at which new susceptibles flow into the population, and hence influences the rate at which disease spreads.

In the MDC model, the force of infection at time t, $f(t)$--the rate at which new infections occur in the population--is proportional

to a product of the number of susceptible people, $X(t)$, and the number of infectious people, $Y(t)$:

$$f(t)=cX(t)Y(t). \qquad (1)$$

Here the constant of proportionality, c, depends upon the frequency and closeness (effectiveness) of contacts between susceptible and infectious individuals.

This formulation is the catalytic model of infection: infectives act as a catalyst in disease spread. Since the force of infection depends equally on the number of infectious and the number of susceptible people in the population, this model implies that the disease should spread as rapidly in a population with a large number of susceptible and few infectious people as in a population with few susceptibles and many infectious people. In addition, if the population were growing in a fixed area, so that the spatial density of the population was increasing at the rate of population growth, the infection rate would grow at the same rate as the population. Neither of these implications of the catalytic model is plausible for LDCs.

Finally, in the MDC model it is often assumed that immunization takes place at a precisely targeted age, such as at birth or 9 months, and that all immunizations are effective: there is no interference by maternally derived antibodies.

The MDC model yields several predictions that are relevant to disease transmission patterns in a non-growing population with little or no infant and child mortality:

i. the number of susceptibles in the population remains the same in the presence and the absence of immunization;
ii. the mean age at infection in the population increases following immunization;
iii. in the presence of even modest levels of immunization, the inter-epidemic period will lengthen;
iv. since the proportion of each cohort that must be immunized to eradicate the disease is less than 1.0 (herd immunity), at any

given level of immunization coverage the percentage drop in the incidence of disease should be greater than the level of immunization coverage.

The predictions of the MDC model correspond well, on the whole, to broad features of disease transmission patterns in many European countries. For example, in the UK, where only a portion of children are immunized against measles, the mean age at infection for measles has risen from about 6 years (pre-immunization) to about 10 years.

On the other hand, in its simplest form the MDC model cannot explain the seasonal patterns of measles outbreak observed in many MDCs since the disease transmission dynamics in the model settle to a constant level of disease prevalence. However, a variant of the MDC model does exhibit seasonal patterns of disease outbreak if seasonally fluctuating transmission is included in the model. Thus Schenzle (1984) successfully modeled the seasonal pattern of measles epidemics in Germany by incorporating a transmission pattern reflecting seasonal changes in school attendance.

Transmission and immunization models for LDCs

The demographic structure ignored by the MDC models can be important when there is strong feedback between the demography of the host population and the disease transmission patterns. Many diseases such as measles exhibit high case-fatality among young children in developing countries; the control or elimination of such a disease would affect demography because changing mortality would change the population age structure. Conversely, change in the demographic structure of the host population may alter the incidence both of the disease in question and of other diseases. Such feedback is *a priori* likely to be very important in rapidly growing populations with high infant and child mortality rates.

The DE model addresses these issues by incorporating the demographic and epidemiologic structure of the population in two dependent submodels. In the DE model, the demographic structure of the host population is determined by the population's age patterns of maternity and mortality,

which jointly dictate the population's growth rate and age distribution (Lotka 1931; Coale 1972). The distribution of individuals among the four epidemiologic classes at each age is governed by epidemiologic parameters: the age pattern of loss of maternal antibodies, the duration of illness, the age-specific case-fatality rate, the age-specific risk of immunization, and the age-specific force of infection.

The demographic structure of the population and the epidemiologic behavior of the infectious disease are linked by the force of infection at time t, $f(t)$, which depends upon the population's demographic and epidemiologic structure at time t. The function $f(t)$ may also depend upon the population's spatial density, d, through two parameters: $m(d)$, the mixing rate, and $e(d)$, the infectivity rate:

$$f(t) = 1-[1-e(d)y(t)]^{m(d)} \qquad (2)$$

where $y(t)$ is the proportion of the population infected at time t, which in turn depends upon the age structure of the population. Thus changes in the demographic structure of the host population arising from changes in maternity or mortality patterns may precipitate changes in disease transmission patterns. The force of infection also depends upon the spatial density of the host population. As the population's spatial density, d, increases, the number of contacts between people will increase, but not necessarily at the same rate as the increase in population density. Similarly, as spatial density increases, the infection efficiency of each contact ought to decrease: for example, an individual in Guatemala City experiences many more encounters with other people in a given time interval than does an individual in the village of Espirito Santo, but a smaller proportion of the encounters in Guatemala City are likely to be sufficiently close to transfer infection. The age pattern of immunization--the rate of immunization of susceptibles at each age--is described in the DE model by an age-specific force of immunization schedule for children less than 60 months old, which corresponds to actual immunization practices in many LDCs.

The DE model is relatively complex since it requires complete age schedules of fertility, mortality, case-fatality, immunization, and social interaction. There are two techniques for dealing with such a model. First, the model can be simplified by assuming age-independence for most of the model parameters, thereby focusing simply on the effects of a growing population with variable spatial density on disease transmission; this technique is employed in this section. Alternatively, one can retain the age-dependence of the model parameters and simulate the behavior of the model for a particular set of parameters; this technique is used in the next section.

With the simplified DE model, one can look at the effect of population growth and changing spatial density on such aggregate epidemiologic indicators as the mean age at infection, the inter-epidemic period, and the critical level of immunization. The predictions of the DE model--the new "rules-of-thumb"--are strikingly different from those of the MDC model:

i. the equilibrium proportion of infected individuals in the population (the equilibrium disease prevalence) increases as the population growth rate increases, both when there is no immunization in the population and when there is an ongoing immunization program;

ii. the mean age at infection in the population need not increase following immunization, since the remaining post-immunization cases may be concentrated in the youngest and the oldest children; however, the age distribution of cases may change substantially;

iii. the inter-epidemic period will not necessarily increase following implementation of an immunization program in a growing population: when the level of immunization is a small fraction of the critical level of immunization, changes in the inter-epidemic period are quite small, but when the level of immunization approaches the critical level for eradication, the inter-epidemic period will show a substantial increase (see Figure 4);

iv. the percentage drop in the incidence of disease, for any given level of immunization, will be smaller in a growing population than in a stationary population: for example, immunization of

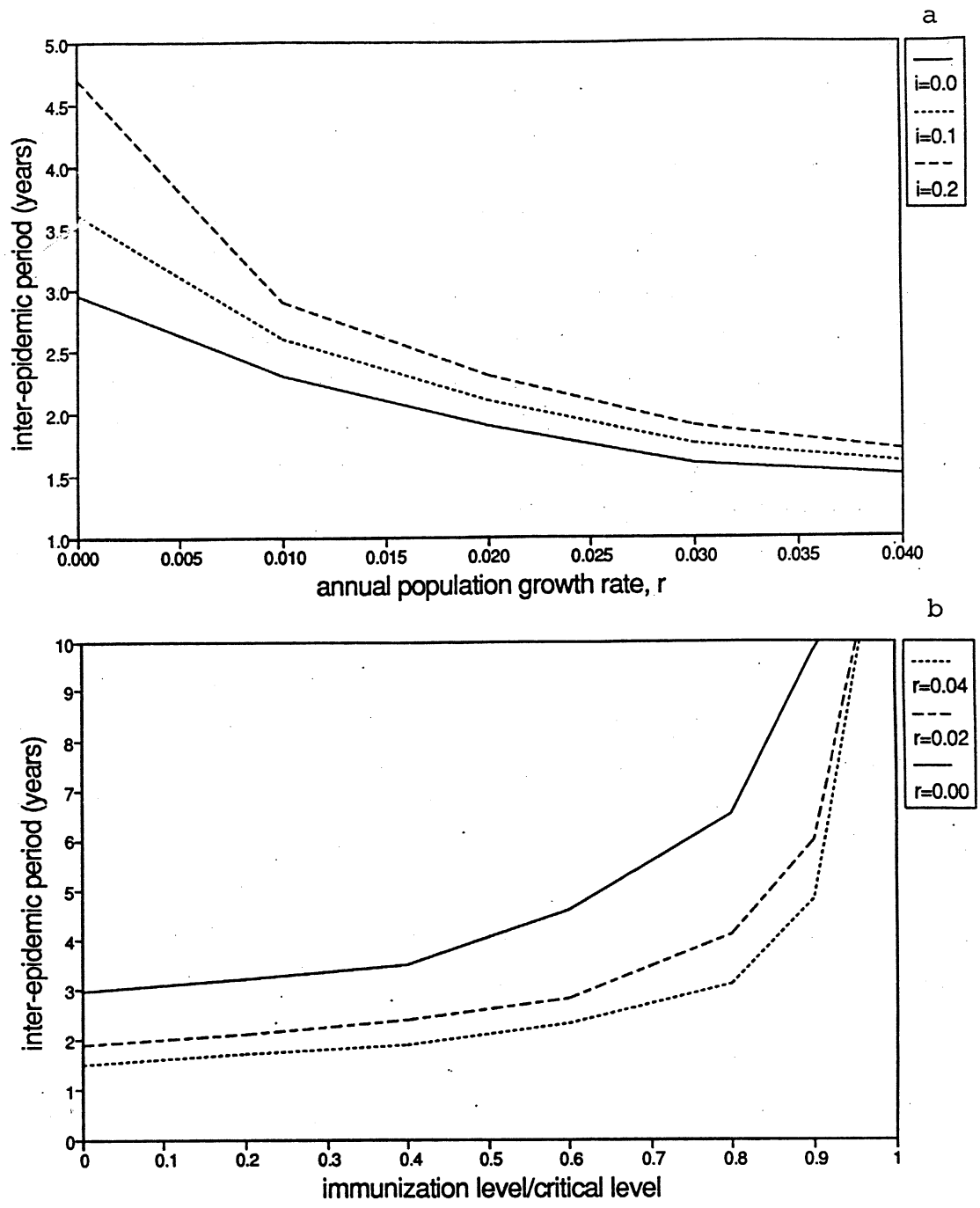

Figure 4. (a) Inter-epidemic period as a function of population growth rate, r, at different levels of immunization, i. (b) Inter-epidemic period as a function of the level of immunization, which is expressed as a proportion of the critical level of immunization, for populations with different growth rates, r.

50 percent of children might induce a drop in disease incidence of 60 percent in a stationary population, but of only 52 percent in a rapidly growing population.

Thus, the DE model is consistent with the failure to observe a significant change in the inter-epidemic interval in both Yaoundé and Kinshasa since, in rapidly growing populations, the model predicts that the inter-epidemic period increases substantially only for immunization at nearly the critical level. The predictions of the DE model are also consistent with the failure of Taylor et al. (1988) to see either a reduction in disease incidence greater than the level of immunization coverage or an increase in the mean age of measles infection.

The DE model can also explain fluctuations, both regular and irregular, in disease incidence observed in LDCs: the key lies in the relationship between the demographic and epidemiologic submodels. Demographic equilibrium--the stable population--is conventionally defined as a steady state of exponential population growth in which the proportion of the population at each age remains constant, implying that the number of individuals at each age and the annual number of births grow at the same exponential rate as does the population as a whole. Epidemiologic equilibrium is reached when the proportions of susceptible, infectious, and immune individuals in the population remain constant, again implying that the number of individuals in each epidemiologic class grows at the same exponential rate as does the population as a whole. In addition, epidemiologic equilibrium implies that the force of infection has attained a constant value. However, the force of infection can only be constant under conditions of demographic equilibrium. Thus if the population is subject to random fluctuations in its birth and death rates, or to seasonal variations in births and deaths, it cannot reach an epidemiologic steady state. Instead, *the population will display random fluctuations in disease incidence and seasonal patterns of disease incidence, both of which may be driven by underlying demographic fluctuations* (John 1990b; Tuljapurkar and John 1990).

ILLUSTRATION: TARGET AGES FOR MEASLES IMMUNIZATION

A simulation (numerical) implementation of the DE model was used to explore two questions in immunization program design. First, what would be the effect of lowering the minimum age of immunization from 9 to 6 months? And second, how does the range of ages at which immunizations are delivered affect immunization program outcome? Thus the key question in these studies is whether there is an *additional* benefit either from immunizing children at lower ages or from administering vaccinations to children over a wide age range.

In the simulation model, an immunization program was introduced into a population of 500,000 that was initially at demographic and epidemiologic equilibrium. The population was then followed for 20 years so that the fluctuations caused by immunization and the post-immunization equilibrium could be assessed.

In the numerical study, the demographic and epidemiologic parameters--age patterns of maternity and mortality, maternal antibody loss, exposure, and case-fatality--reflected features of the urban areas of many developing countries: high fertility, moderately high mortality, early exposure, and moderate case-fatality. The age pattern of mortality from causes other than the disease under study was based on a standard life table, with an expectation of life at birth of 55 years (Coale and Demeny 1983). The fertility schedule (total fertility rate of 6.7 births per woman) was derived from fertility schedules of African populations. The maternity and mortality schedules jointly determined the age structure of the host population. The age pattern of loss of maternal antibodies was based on data from Kenya (Kenyan Ministry of Health and WHO 1977) and the Congo (Dabis et al. 1989) (Figure 5a). The case-fatality schedule was based on measles case-fatality data from West Africa (Foster 1984) (Figure 5b). Immunization programs reflected immunization delivery schemes in areas where precise targeting of children by age for immunization is difficult. The annual risk of immunization was set at zero below a designated minimum age (6 months or 9 months) and above a designated maximum age (23 months or 59 months). All eligible children between the minimum and maximum ages were at the same annual risk of immunization. For sufficiently wide target age

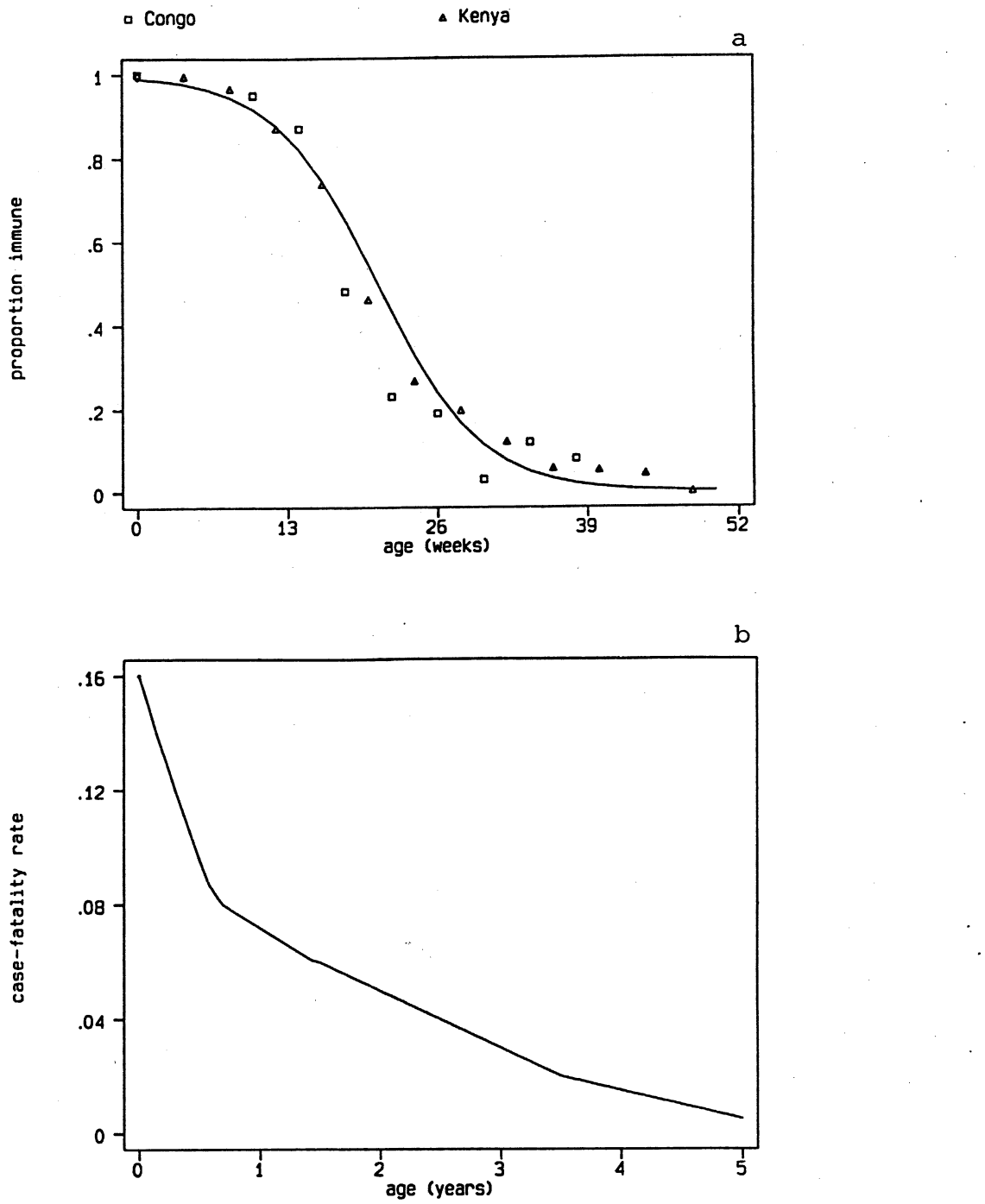

Figure 5. Age-specific epidemiological parameters used in the numerical studies. (a). Age pattern of loss of maternal antibodies in Kenya and the Congo, and the age pattern used in the model. (b) Age-specific case-fatality rates.

ranges, annual immunization program efforts on the order of 0.6 correspond to cohort immunization coverage by age 5 of 0.95 or more and are sufficient to eradicate the disease from this population.[1]

Children eligible for vaccination were those in the target age range who had not had the disease or been immunized. This meant that some infants who were still protected by maternal antibodies would be vaccinated. In such instances, vaccination was assumed to have no effect, but the inoculated infant was believed to be immunized and no longer eligible for vaccination. Following the loss of passive immunity, the infant would eventually be at risk of infection. In the absence of disease, the model reduces to a standard Leslie matrix population projection model. To validate the model, it was iterated to check for convergence to pre-immunization demographic and epidemiologic equilibria. Several epidemiologic indices (including the period age distribution of cases, the share of case deaths among all deaths to children 1 to 4 years old, and the annual disease incidence for all ages) generated by the model were tested to ensure that they fell within the range of pre-immunization values reported for African populations (Dabis et al. 1988; Taylor et al. 1988; Guyer and McBean 1981).

Minimum age for immunization

The effect of lowering the minimum age for immunization from 9 months to 6 months was compared for several pairs of immunization programs, four of which are presented in Table 1. In three cases, variation among pairs arises from the maximum age for immunization or annual risk of immunization, while the variation within a pair comes from the minimum age at immunization (9 months versus 6 months). In the fourth case, the maximum age of immunization is 59 months; for a minimum age of immunization of 9 months, the annual risk of immunization is 0.5, and for a minimum age of immunization of 6 months, the annual risk of immunization is 0.46, so that in the two regimes, approximately the same *number* of immunizations are delivered each year.

Table 1: Immunization program parameters for the pre-immunization baseline population and the four case studies: minimum age for immunization, maximum age for immunization, and annual risk of immunization, i, for eligible children

Case		minimum age	maximum age	i
Baseline		--	--	0.00
Case I	a	6 mo.	59 mo.	0.50
	b	9 mo.	59 mo.	0.50
Case II	a	6 mo.	23 mo.	0.50
	b	9 mo.	23 mo.	0.50
Case III	a	6 mo.	23 mo.	0.70
	b	9 mo.	23 mo.	0.70
Case IV	a	6 mo.	59 mo.	0.46
	b	9 mo.	59 mo.	0.50

The effect of lowering the minimum age of immunization is assessed through its impact on: annual disease incidence, age pattern of disease incidence (annual incidence among children under age 5, and proportion of cases occurring in children less than 9 months old), and mortality effects (case-fatality rate for cases at all ages, case-fatality rate among children less than 5 years old, and the share of all infant deaths and of all toddler (12-23 months old) deaths represented by case deaths).

Disease incidence dynamics. The introduction of any immunization program reduces the equilibrium incidence of disease in the population, although the transient (short-run) incidence may increase. In this model the additional equilibrium impact of lowering the minimum age for immunization from 9 months to 6 months on equilibrium annual incidence is modest (see Table 2 and Figure 6). For example, an annual force of immunization of 0.5 for children 9 to 59 months old (Case I) results in a drop in equilibrium annual disease incidence from 38 cases per 1,000 population to 10 cases per 1,000 population. Including infants 6 to 8 months old in the immunization program induces only a small additional reduction, to 8 cases per 1,000 population (Figure 6a).

Among children less than 5 years old, lowering the minimum age of immunization from 9 months to 6 months can apparently have a marked effect on the post-immunization equilibrium incidence of disease (Table 2), particularly when the targeted age range is narrow (Figure 6b). When the annual *number* of immunizations delivered is held constant (Case IV), however, the effect of lowering the minimum age of immunization on equilibrium disease incidence among children less than 5 years old is negligible, implying that the impact of changing the minimum immunization age stems from the larger number of immunizations delivered rather than from lowering the minimum age of immunization.

The potential pitfalls inherent in evaluating a dynamical system when it is not at equilibrium--that is, shortly after an immunization program is initiated--are illustrated clearly by the temporal pattern of annual incidence. For example, in Case I (Figure 6a) immunization between ages 6 and 59 months produces an inter-epidemic period which

Table 2: Period epidemiologic indices at pre-immunization equilibrium and at post-immunization equilibrium for four sets of immunization programs

	Baseline	Case I		Case II		Case III		Case IV	
		a	b	a	b	a	b	a	b
Annual incidence per 1,000 population	38	8	10	20	23	15	17	10	10
Annual incidence per 1,000 children 0-4 yrs.	178	31	42	79	93	52	68	39	42
Share of cases 0-4 yrs. in 0-8 month-olds	.088	.088	.091	.091	.092	.099	.101	.091	.091
Case-fatality rate	.045	.040	.043	.038	.040	.035	.038	.040	.043
Case-fatality rate 0-4 yrs.	.051	.054	.054	.053	.053	.052	.052	.053	.054
Case deaths per infant death	.078	.018	.021	.040	.046	.029	.039	.021	.021
Case deaths per toddler death	.49	.15	.18	.28	.32	.20	.26	.17	.18

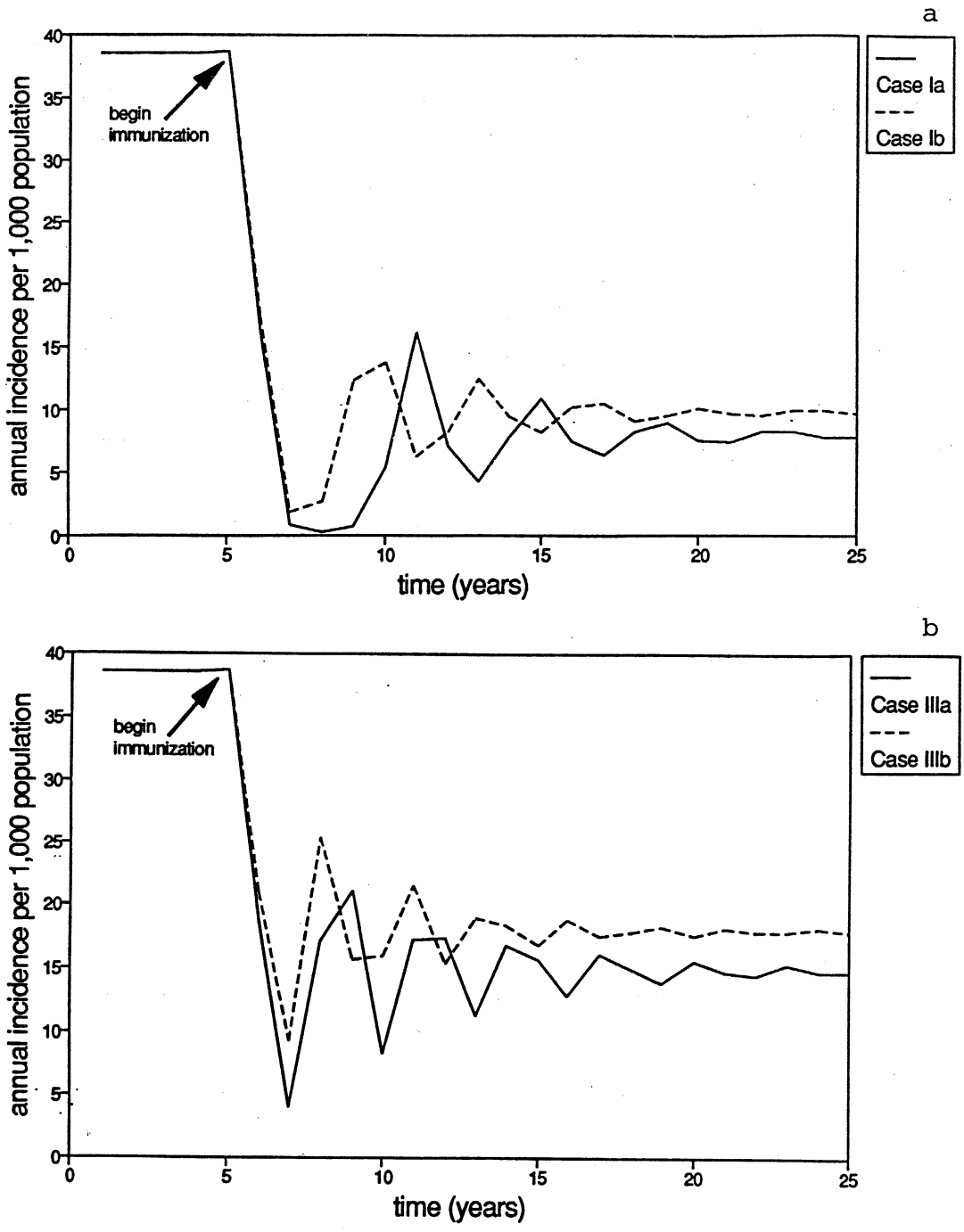

Figure 6. Annual disease incidence, with introduction of an immunization program in year 5. (a) Case Ia: minimum age for immunization is 6 months and maximum is 59 months; Case Ib: minimum age for immunization is 9 months and maximum is 59 months. (b) Case IIIa: minimum age for immunization is 6 months and maximum is 23 months; Case IIIb: minimum age for immunization is 9 months and maximum is 23 months.

is slightly longer than that produced by the same annual risk of immunization for children between 9 and 59 months old: in the former case, because the number of immunizations delivered is slightly higher than in the latter case, the time lag for the population of susceptibles to be replenished by births is greater. Two or three years following the implementation of an immunization program (year 7 or 8 in Figure 6a), the marginal effect on annual disease incidence of lowering the minimum age at vaccination appears only slight. Four years following implementation (year 9), however, it appears that lowering the minimum age of immunization to 6 months substantially reduces the annual incidence of disease compared to the 9-59-month regime, yet six years following initiation of immunization (year 11), the opposite appears true. These important transient effects of an immunization program would be obscured in a static program impact model.

Age patterns of disease and mortality effects. Each immunization program, regardless of the minimum age of immunization, decreases the proportion of cases occurring in children less than 5 years old. Immunization reduces the force of infection and hence increases the mean age at infection. The magnitude of this effect depends not only on the scale of immunization, but also on the age structure and demographic dynamics of the host population. If the minimum age for immunization is 9 months in this model, the proportion of all cases that occur in infants shows little change; if the minimum age is 6 months, the proportion of cases in infants decreases. When only children less than 5 years old are considered, the proportion of cases occurring in infants less than 9 months old (often called the "unpreventable cases") is slightly higher than before immunization (Table 2), although of course the absolute number of cases in infants 0 to 8 months old decreases.

The age distribution measures discussed thus far are period indices rather than cohort indices. Because the population is growing, period measures do not reflect the actual experience of any birth cohort: period measures over-represent the youngest age groups relative to cohort measures, thus understating the impact of an immunization program

on a cohort of children. Furthermore, any index of morbidity or mortality that depends upon the age distribution of cases will, when based on period data, misstate the actual experience of a birth cohort.

In contrast to the period age distribution of cases, the cohort age distribution of cases is sensitive to the minimum age at immunization, even when the number of immunizations is held constant. Lowering the minimum age for immunization, either for a given number of immunizations or for a given annual risk of immunization, always shifts the cohort age distribution of cases to higher ages.

Changes in the age distribution of cases are reflected in changes in the aggregate case-fatality rate. When changes in the age distribution of cases stemming from a reduction in the minimum age at immunization are small, the effect on period case-fatality rates, both overall and among children less than 5 years old, will also be small (Table 2). Because the upward shift in the age distribution induced by an immunization program is more pronounced in the cohort age distribution of cases than in the period age distribution, the period measure of case-fatality overstates the aggregate case-fatality rate and hence understates the actual effect of an immunization program on the mortality of a birth cohort.

Wide vs. narrow target age ranges

To explore the role of age range in immunization effectiveness, we considered two programs that had the same annual number of vaccinations but different ages of eligibility for vaccination. In the first program, vaccinations were given to susceptible children between ages 9 and 59 months; the annual risk of immunization was 0.3, (i.e., each year 30 percent of remaining susceptible children between 9 months and 5 years old were immunized). In the second program, vaccinations were administered to children between ages 9 and 23 months, and the risk of immunization was correspondingly higher: 0.6. Thus the first program is perhaps appropriate for integration into a ongoing primary health care program, while the second is perhaps more consistent with an independent, specialized immunization program.

Judged by many epidemiologic indices, the two programs--intense immunization over a narrow range of ages, and less intense immunization over a wider range of ages--were virtually indistinguishable. When the same number of immunizations were delivered in the two programs each year, the annual incidence, the number of cases among children 0-8 months old, and the total number of cases each year were essentially the same in the two programs, suggesting that comparable long-run results can be obtained by high effort, narrow age-range programs or by low effort, broad age range programs.

There were, however, some differences in period epidemiologic indices between the two immunization programs. When immunizations were concentrated in the 9-23-month age group, the proportion of immunizations that are "wasted" by administration to children protected by maternal antibodies was twice that when the immunizations were spread among children 9-59 months old, but nonetheless was still quite low (reflecting in part that in the parameter set used in this numerical model, 95 percent of children were susceptible to infection by age 9 months). When the immunizations were concentrated among children 9-23 months old, the age distribution of remaining cases was slightly older, both for the period and the cohort, than when immunizations were administered to children 9-59 months old (see Figure 7). Hence, the number of case deaths will be slightly lower if immunization effort is concentrated at younger ages. Therefore, if the principal goal of an immunization program is to decrease the incidence of the disease in the population, the goal can be reached either by concentrating a large number of immunizations among young children in a narrow range of ages, or by spreading the same number of immunizations over a wider range of ages. If, in addition to decreasing the incidence of the disease, the goal is to decrease the number of deaths due to disease, then concentrating immunizations among children at the youngest ages is a slightly more advantageous strategy, since this scheme results in an age distribution of remaining cases that is slightly older than when immunizations are delivered to a wider age range.

The numerical results presented above reflect the numerical values chosen for the epidemiologic and demographic parameters in the model,

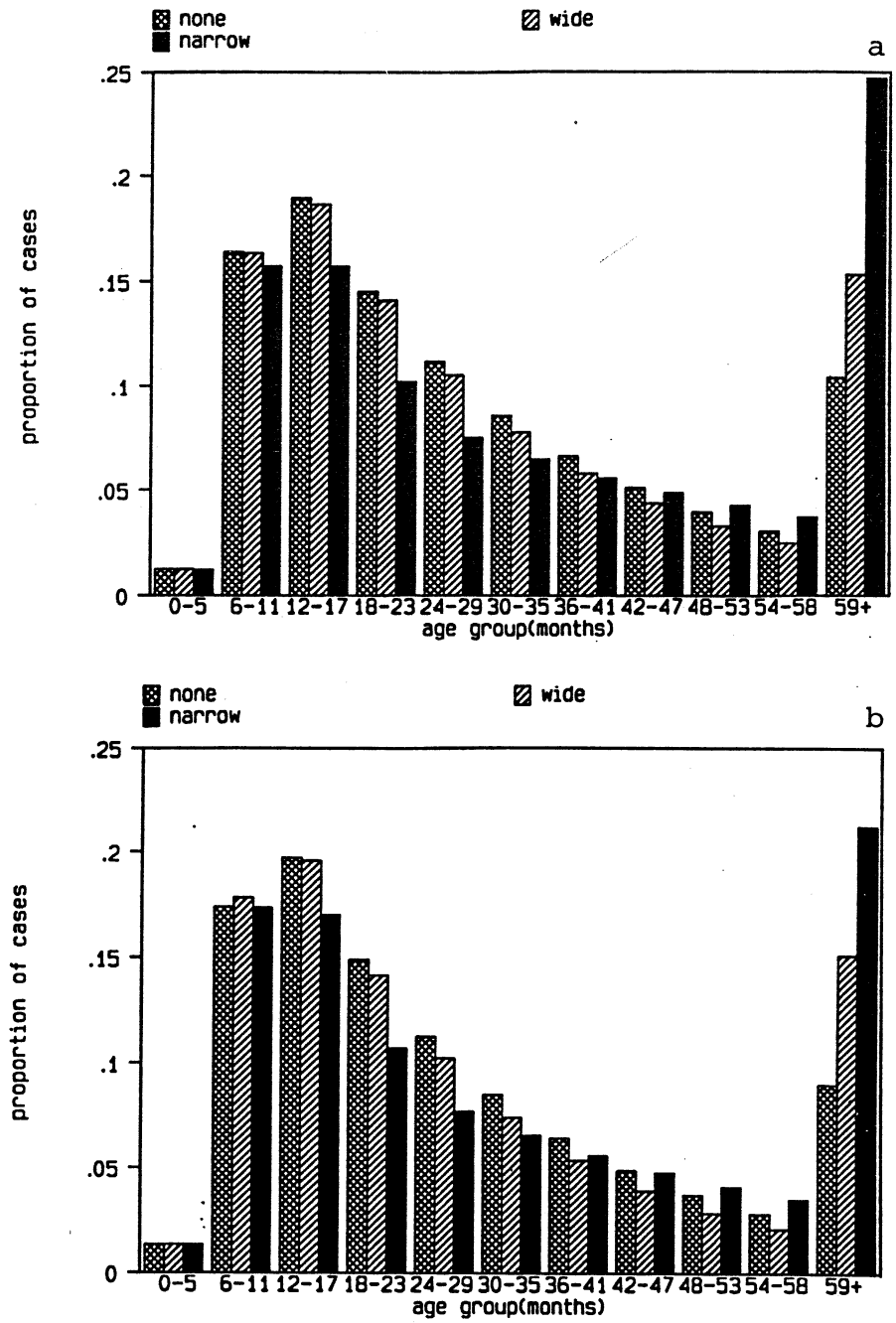

Figure 7. Comparison of wide and narrow immunization age ranges, in which "none" is the equilibrium age distribution with no immunization, "narrow" is the equilibrium age distribution for immunization administered at ages 9-23 months, i=0.6, and "wide" is the equilibrium age distribution for immunization administered at ages 9-59 months, i=0.3. (a) cohort distribution. (b) period distribution.

and are meant to be illustrative. If, for example, higher case-fatality rates in infancy and early childhood had been used, the mortality impact of lowering the minimum age of immunization or of targeting a narrow range of ages may have been more pronounced. Similarly, the chosen age patterns of exposure, susceptibility, and maternal antibody loss will influence the findings slightly. Implementing the model for a particular area requires demographic and epidemiologic data appropriate to that setting.

DISCUSSION

When designing immunization programs for developing countries, one is rarely faced with fine-tuning details of immunization delivery, such as whether the optimum age for immunization is 8 or 9 months. Rather, one weighs the merits of substantial program modifications: immunization starting at 6 rather than 9 months and available to children under age 2, or age 3 or age 5; annual mass vaccination days versus continuous delivery of immunization; a one-stage program or a two-stage program; integration of immunization into the existing health care system or creation of an independent immunization program.

Mathematical models of disease transmission and control are essential tools for immunization program design and evaluation. In this paper, we presented a fully age-structured model of disease transmission that accounts explicitly for the influence of host population demographic structure on disease transmission patterns. Several mortality and morbidity predictions of the model differ from the predictions of MDC models of disease transmission and are in much better agreement with observed patterns in LDCs. The model represents a powerful tool for evaluating the potential mortality and morbidity effects of different immunization programs, for anticipating the dynamic behavior of disease in the population, and for examining the influence of demographic variation on disease transmission patterns.

The epidemiologic response of the model depends strongly on the demographic structure of the host population: for example, as the growth rate of the population increases, disease incidence will increase, the critical level of immunization will increase, and the mean age

at infection will decrease. In rapidly growing populations, immunization has little observable effect upon the period between epidemic outbreaks of disease unless the level of immunization nears the critical level, at which point an abrupt increase in inter-epidemic interval occurs. This prediction of the demographic-epidemiologic model differs from predictions of the MDC model and more closely reflects observations in LDCs of no discernible change in the inter-epidemic period.

Using demographic-epidemiologic models as simulation tools, partial answers to the queries of Dabis and coworkers posed earlier can be stated. First, for plausible demographic and epidemiologic conditions, lowering the minimum age at immunization may not have a substantial impact on period measures of disease transmission, unless a concerted effort is made to immunize children 6-9 months old.

The second, and perhaps more intriguing, observation is that for this set of epidemiologic and demographic parameters the same epidemiologic goals can be reached either by immunizing children in a wider range of ages at a lower annual rate, or by immunizing children in a narrow range of ages at a higher annual rate. This implies that less intensive immunization programs, incorporated into the existing health infrastructure, may in the long run be as effective as intensive immunization programs--and in fact may be more effective in terms of improving child health if immunization at an MCH clinic is combined with other preventive medicine services.

Notes

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1. The distributions are presented as structural boxplots. For each population, the median age at immunization, the median age of immunizations administered at ages greater than the median age (the "upper hinge," which is approximately the 75th percentile) and the median age of immunizations administered at ages less than the median age (the "lower hinge," which is approximately the 25th percentile) are graphed as the center, upper and lower bars of a box. A line is then extended from the upper hinge to the "upper adjacent value": the observation whose value is closest to, but less than, that of the upper hinge plus 1.5 times the difference between the upper and lower hinges. Any observations which are greater than the adjacent value are deemed outliers and plotted individually. The lower half of the boxplot is constructed in an analogous manner.

2. Two important distinctions must be made in the discussion of immunization programs. First, the age-specific risk of immunization is *not* the same as the level of immunization coverage either of a cohort by a specified age a' or of children less than age a' in a given period. Second, the proportion of a cohort alive at age a' and immunized is *not* the same as the proportion of the birth cohort immunized before age a', since some members of the birth cohort will die before immunization, while others will die after immunization but before age a'.

   The annual risk of immunization is the proportion of susceptibles who are immunized each year. The relationship between the age-specific risk of infection and the level of cohort immunization coverage by a given age is analogous to the relationship between the age-specific force of mortality and the proportion of a cohort still alive at a specified age. In the absence of disease, for example, an annual force of immunization of 0.2 for susceptible children implies that 63 percent of each birth cohort would be immunized

by age 5; an annual force of 0.3 implies, in the absence of disease, coverage of 78 percent by age 5. In the presence of disease, the correspondence between the force of immunization and cohort coverage differs because the pool of susceptible individuals is depleted by both immunization and illness: immunization and illness are competing risks.

Since, in this model, only susceptible children are at risk of immunization, the quantitative relationship between the risk of immunization and either the period or the cohort proportion of children immunized by a specified age depends upon the recent history of immunization and illness in the population: this history determines the composition of the current pool of susceptible children. The risk of immunization may therefore be interpreted as a measure of immunization program effort at any point in time (i.e., the proportion of susceptible children within the target age range who will be immunized at time t), while cohort immunization coverage by age a' may be regarded as a measure of *cumulative* immunization program effort over a given period of time within a particular epidemiologic context (i.e., the proportion of children in a birth cohort who, at a given risk of immunization while in the target ages, are both alive and immunized by age a'). The narrower the target age range, the more nearly synonymous the two measures become, so that, were immunizations given over an extremely narrow age range, program effort (current risk of immunization) and immunization coverage by the maximum of the target age range would be virtually identical.

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Table 1: Immunization program parameters for the pre-immunization baseline population and the four case studies: minimum age for immunization, maximum age for immunization, and annual risk of immunization, i, for eligible children

Case		minimum age	maximum age	i
Baseline		--	--	0.00
Case I	a	6 mo.	59 mo.	0.50
	b	9 mo.	59 mo.	0.50
Case II	a	6 mo.	23 mo.	0.50
	b	9 mo.	23 mo.	0.50
Case III	a	6 mo.	23 mo.	0.70
	b	9 mo.	23 mo.	0.70
Case IV	a	6 mo.	59 mo.	0.46
	b	9 mo.	59 mo.	0.50

Table 2: Period epidemiologic indices at pre-immunization equilibrium and at post-immunization equilibrium for four sets of immunization programs

		Case I		Case II		Case III		Case IV	
	Baseline	a	b	a	b	a	b	a	b
Annual incidence per 1,000 population	38	8	10	20	23	15	17	10	10
Annual incidence per 1,000 children 0-4 yrs.	178	31	42	79	93	52	68	39	42
Share of cases 0-4 yrs. in 0-8 month-olds	.088	.088	.091	.091	.092	.099	.101	.091	.091
Case-fatality rate	.045	.040	.043	.038	.040	.035	.038	.040	.043
Case-fatality rate 0-4 yrs.	.051	.054	.054	.053	.053	.052	.052	.053	.054
Case deaths per infant death	.078	.018	.021	.040	.046	.029	.039	.021	.021
Case deaths per toddler death	.49	.15	.18	.28	.32	.20	.26	.17	.18

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