INTERNATIONAL JOURNAL OF LEPROSY Volume 39, Number 2
Printed in the U.S.A.

An Epidemiometric Approach for Planning and Evaluating Leprosy Control Activities[1]

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Mathematical models of diseases in populations, i.e., epidemiometric models, are not new. Such an approach was first used by Ross (9) for malaria in 1911, and later applied to tuberculosis by Reed and Frost at the Johns Hopkins School of Hygiene and Public Health (1, 5). Since then, epidemiometric models have been, or are presently being developed for a number of diseases, among them schistosomiasis (4), measles, hepatitis, trichomoniasis (3), cancer of the cervix, and a few others.

Lately, it has been realized that such models could possibly be applied to leprosy. This would prove invaluable, considering the urgent need for planning and evaluating large-scale mass campaigns presently carried on in many areas of the world. Building such a model involves three steps: (1) defining the fundamental quantities, or variables, used in the model, (2) deciding the rules of the game and possible transitions or flows, and (3) designing a way to measure and predict the outcome of the model as a function of the values taken by the variables, a process that requires solving equations.

In leprosy, the fundamental quantities we are using are various classes of people. These classes are shown in Table 1, which is adapted for leprosy from the model developed by Waaler *et al.* for tuberculosis (10, 11), with the major exception that no stage of infection without disease can be identified for leprosy. Criteria for delineating these classes must be agreed upon and standardized in such a manner that the classes are mutually exclusive and comparable in various subgroups of the population.

[1] Supported by an ELEP (European Federation of Anti-Leprosy Associations) research grant, contributed by the following associations: Amis du Père Damien, Amici dei Lebbrosi (Fondation Follereau Italie), Fondation Follereau France, Fondation Follereau Luxembourg, Ordre de Malte, Secours aux Lépreux (Fondation Follereau Canada).

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The number of classes can be extended *ad libitum*, to take into account sex, age, migration, type of treatment, etc. It is essential, however, to keep the model to a manageable level. The multiplication of classes will rapidly increase the complexity of the mathematics involved. However, a model which is too sophisticated tends to copy real life and is not a model any more. The problem is similar to the one met in epidemiologic studies when deciding on the amount of matching needed in controls or the number of factors to be adjusted in rates. There is an optimum between the efficiency of a method and its refinement.

Moreover, values will have to be given to these classes when the time comes to fit the model to observational data. We have, therefore, no choice but restricting the classes to the ones easily gathered from data routinely collected in the field. If possible, provision should be made for diagnostic misclassifications. Estimates of sensitivity and specificity of various case-finding and diagnostic methods could be calculated for the various classes whenever relevant.

The next steps consist of listing the possible transitions from one class to another, and weighing each of the transitions by its chance of occurrence. From now on we shall refer to the various classes as "states", and to the chances of occurrence as "transition probabilities". To list the transitions that are possible, we need a number of assumptions. In order to keep the model as realistic as possible, these are selected from what we know of the epidemiology of the disease. We could arbitrarily select the following assumptions:

1. Leprosy is developed only by exposure to leprosy patients (in other words, the leprosy patient constitutes the sole source of infection for leprosy).

2. The reservoir for leprosy is man only.
3. Leprosy may develop in either one of two ways: open leprosy (lepromatous and border-line) and closed leprosy (tuberculoid and indeterminate).
4. A tuberculoid patient may transform to the lepromatous type, whereas the reverse is not possible.
5. New-born children are free from leprosy.
6. Everybody is susceptible.
7. No cure occurs except with treatment.
8. Cured patients can relapse.

These assumptions, or rules, are quite restrictive and arbitrary. We deliberately ignore a number of situations, for example, the possible role of healthy or latent carriers (assumption 1), differential risk by exposure to lepromatous or tuberculoid patients (assumption 1), Wade's reversal reaction (assumption 4), immunologic and/or genetic mechanisms of resistance (assumption 6), and spontaneous healing of indeterminate or early tuberculoid cases (assumption 7).

The transitions which are possible between the various states can now be visualized in a flowgraph (Fig. 1). According to the assumptions, the following equations may be derived from Table 1 and Fig. 1.

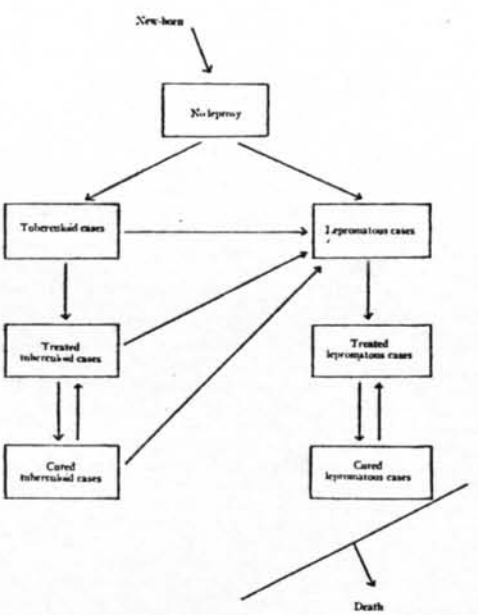

FIG. 1. Flowgraph of the various states of leprosy according to given assumptions.

$$T_{t+1} = T_t + T_{t/t+1} + RT_{t/t+1} - CT_{t/t+1} - B_{t/t+1} - DT_{t/t+1}$$

$$L_{t+1} = L_t + L_{t/t+1} + RL_{t/t+1} + B_{t/t+1} - CL_{t/t+1} - DL_{t/t+1}$$

$$H_{t+1} = N_{t/t+1} + CT_{t/t+1} + CL_{t/t+1} - RT_{t/t+1} - DM_{t/t+1} - RL_{t/t+1}$$

It should be noted that in Table 1 no special case is made for cured tuberculoid and cured lepromatous patients, whereas the relationship given above and the flowgraph make provisions for such classes. In the first case, the cured patients are assumed to return to the pool of the healthy. The decision for adopting one or the other of these models depends on the possibility of recognizing such states, i.e., on the follow-up data available.

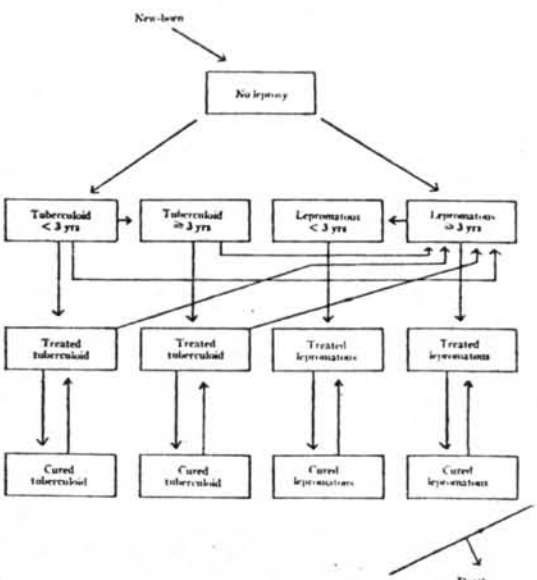

FIG. 2. Flowgraph of the various states of leprosy, taking into account time lag between onset and treatment.

The graph can be modified to take into account a number of additional data, such as sex, and treatment duration or lag time between case-finding and treatment (Fig. 2). The transition probabilities, i.e., the chance that an individual will stay in a given state during an interval of time, or go from one state to another, will be drawn from observational data in real life situations. In the simplified model given as an example, the following epidemiologic indices will be required: (a) incidence rate,

TABLE 1. *Leprosy. Initial and terminal states at times t and t + 1, and transient states.*

Time t	With no-leprosy H_t	With tuberculoid leprosy T_t	With lepromatous leprosy L_t	Total population P_t
Input time t to t + 1	New-born $N_{t/t+1}$ Treated tuberculoid cured $CT_{t/t+1}$ Treated lepromatous cured $CL_{t/t+1}$	New tuberculoid cases $T_{t/t+1}$ Relapsed tuberculoid $RT_{t/t+1}$	New lepromatous cases $L_{t/t+1}$ Relapse lepromatous $RL_{t/t+1}$ Tuberculoid cases having shifted to lepromatous (borderline transformation) $B_{t/t+1}$	New-born $N_{t/t+1}$
Output time t to t + 1	Deaths persons without leprosy $DH_{t/t+1}$ New tuberculoid cases $T_{t/t+1}$ New lepromatous cases $L_{t/t+1}$ Relapse tuberculoid $RT_{t/t+1}$ Relapse lepromatous $RL_{t/t+1}$	Deaths tuberculoid cases $DT_{t/t+1}$ Tuberculoid cured $CT_{t/t+1}$ Tuberculoid cases having shifted to lepromatous (borderline transformation) $B_{t/t+1}$	Deaths lepromatous cases $DL_{t/t+1}$ Lepromatous cured $CL_{t/t+1}$	Total deaths $D_{t/t+1}$
Time t + 1	With no-leprosy H_{t+1}	Tuberculoid cases T_{t+1}	Lepromatous cases L_{t+1}	Total population P_{t+1}

TABLE 2. *Transition probabilities (values drawn from observed epidemiologic rates).*

Incidence t/t + 1 I	$\frac{\text{Number of new cases } t/t+1}{\text{Population}}$	tuberculoid $T_{t/t+1}/P_t$ lepromatous $L_{t/t+1}/P_t$ total $(T_{t/t+1} + L_{t/t+1})/P_t$
Cure rate C	$\frac{\text{Number of cases cured } t/t+1}{\text{Cases}}$	tuberculoid $CT_{t/t+1}/T_t$ lepromatous $CL_{t/t+1}/L_t$ total $(CT_{t/t+1} + CL_{t/t+1})/(T_t + L_t)$
Death rate D	$\frac{\text{Number of deaths } t/t+1}{\text{Cases}}$	tuberculoid $DT_{t/t+1}/T_t$ (= case-fatality rate) lepromatous $DL_{t/t+1}/L_t$ (= case fatality rate) healthy $DH_{t/t+1}/H_t$
Relapse rate R	$\frac{\text{Number of cases}}{\text{Cured cases}}$	tuberculoid $RT_{t/t+1}/CT_{o/t}$ lepromatous $RL_{t/t+1}/CL_{o/t}$
Borderline rate B	$\frac{\text{Number of borderline shifts}}{\text{Tuberculoid cases}}$	$B_{t/t+1}/T_t$

(b) birth rate, (c) cure rate, (d) death rate, (e) relapse rate, and (f) border-line transformation rate (Table 2). These rates would have to be specific for disease-status, age, mode of treatment, attendance-characteristics to treatment, possibly sex, and, if relevant, type of leprosy.

Given the matrix of transition probabilities, it is then possible to develop a set of equations whose solution yields the subsequent state of the whole systems as a function of the initial state. A number of relationships will have to be drawn between these parameters. For example, the total incidence of cases during a period will be related with previous prevalence of lepromatous cases in the following manner:

$$(T_{i/i+1} + L_{i/i+1}) = f(L_{i-j})$$

The study of these functions will often require extensive and somewhat elaborate mathematics. This is typically a field for a pluri-disciplinary team-work approach. It is easy to see that such a model, if fitting the observational data, has a predictive value. It also can be developed into a simulation model, by introducing artificially modified variables: different treatment coverage, selective treatment according to age or type of leprosy, etc. For example, what would be the predicted value of prevalence after so many years if relapses were left untreated and coverage for lepromatous adults were increased to a given value? Any combination is possible as long as it is kept within the framework of the model. This is a leprosy campaign *in vitro*, which can be manipulated at will.

Last, it becomes possible to introduce economic data, in order to determine the optimal combinations of control measures according to cost and efficiency. The model thus can be used as a decision-model for more rational planning.

That such an approach can be successful is demonstrated by its use in tuberculosis ([2, 6, 7, 8,12]). That it could be realized for leprosy is another matter. A major difficulty is raised by our present inability to distinguish leprosy infection from leprosy disease. This faces us with the problem of dealing with a class of people affected with latent or incubating leprosy, who are definitely not at risk, but still are included for years in the no-leprosy class. Other difficulties stem from inaccuracy of statistical data and poor diagnostic criteria, among which are incompleteness of census, unspecified time lag between onset of disease and diagnosis, and confusion of criteria for clinical inactivity.

If we are to continue our drive for controlling leprosy through mass treatment of millions of patients over the world—and there is presently no other way—it seems high time to try such an approach. It could help to optimize our efforts if we could gain knowledge from past experience. An attempt to build such a model is under way, using for estimates the data from some large-scale leprosy campaigns carried on for over a decade.

SUMMARY

For the last twenty years policy in leprosy control has been based on the somewhat simplified assumption that efficient treatment of as many infectious patients as possible will ultimately result in decrease in the frequency of the disease to a point below an unspecified level at which transmission will be interrupted.

In the light of what is presently known regarding the epidemiology of leprosy, this is the only valid assumption for "doing things." It seems, however, that the time has come for evaluating the long-term effects of large-scale leprosy control activities. This could help in planning future activities.

Epidemiometric models, i.e., mathematical models of the dynamics of diseases in populations, have been developed for a number of infectious or parasitic diseases. Using available data from a large scale leprosy control program carried on for 16 years, an attempt is being made to develop an epidemiometric model for leprosy. Three kinds of models are considered, viz., descriptive, simulation and operational. The basic epidemiologic assumptions underlying the building of these models are reviewed. Several flow-graphs are proposed, taking into account the available data and need for simplification. The various

parameters used, chiefly prevalence, incidence, death rates, and recovery rates, and the equations relating these parameters, are discussed.

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