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Simulation of Vaccination and Resistance in Leprosy Using an Epidemiometric Model[1]

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Epidemiometric models are useful tools for studying the dynamics of diseases in populations. Classical examples are the models developed for tuberculosis ([11, 13]).

Such a model was initially developed for leprosy by Lechat, *et al.* ([8]). It has proved useful to predict incidence trends and to simulate various control measures (case holding, early detection, segregation, vaccination) over several decades ([7, 9]). This model, however, did not take into account age- and sex-specific incidence rates.

This paper presents a new version of the model which makes provision for age and sex differential rates according to the type of disease. More realistic parameters are also introduced for death rates, population structure, and rates of natural growth. This new version of the model has been used to simulate the effects on incidence of various types of vaccines and of drug resistance.

METHODS

The model supposes that a case of leprosy originates exclusively from another case of the disease. Individuals with subclinical infection or a conjectural animal reservoir are assumed to play no role in the transmission. Additional simplifications are made, such as no migration, universal susceptibility to the disease, and equal risk of exposure for every individual. Under such conditions, the prevalence at any given time will govern the incidence in subsequent years, depending on the time lag between infection and onset of clinical disease.

Provision is also made in the model for various classes of infective patients, according to type of disease and duration of treatment.

The dynamics is regulated by three types of equations: a) equations of level, which at the beginning of each annual period state the number of individuals (stock) in each class; b) equations of flow, which give the number of individuals transferring from one class to another in a year; and c) auxiliary equations, which determine the importance of the flow according to the duration spent in each state.

The parameters used in both the initial model and this new version were calculated from actual data collected in the Polambakam leprosy control area, South India, on 35,200 patients detected and treated between 1955 and 1970. During this period, the mode of detection and treatment regimens were kept constant in the study area. They were based on early case finding (75% of the patients supposedly detected within one year of onset) followed by dapsone monotherapy. The respective potential for transmission of the various classes of patients and the presumed delay between infection and onset of disease (latency period) were estimated from these data using a least-square method.

The structure of the new model consists of nine different states, with 70 classes of age for each sex, 15 years for the maximal duration of the disease, and 1 to 8 years for the latency period (Fig. 1). Three additional states are included in order to simulate vaccination and resistance. The total number of classes is 25,200.

The assumptions regarding the natural history of the disease and the definitions describing its various stages are identical to those used in the initial model reported previously ([8]). The parameters for infectivity

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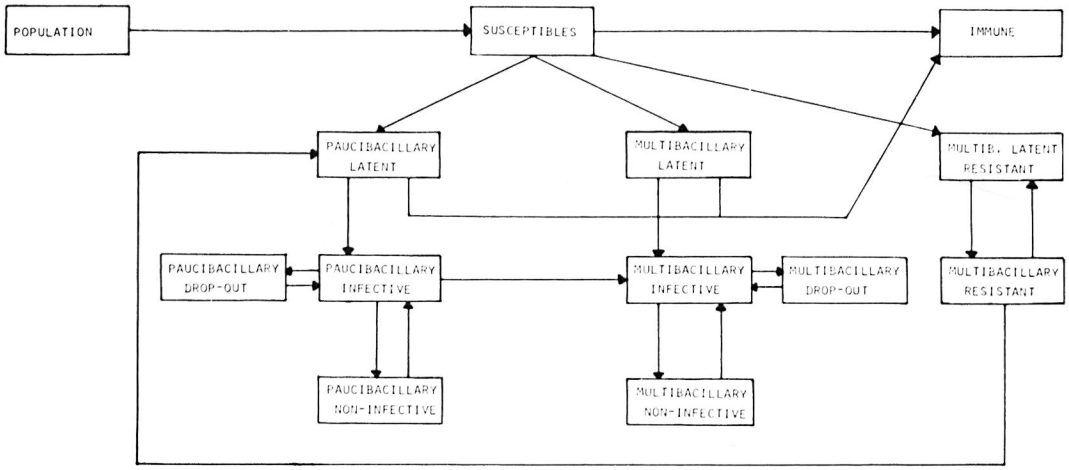

FIG. 1. Flow chart of the model.

and distribution of the latency period have been reproduced from the initial model. The terms "lepromatous" and "tuberculoid" have been replaced, respectively, by "multibacillary" and "paucibacillary."

The demographic parameters are as follows: a) The age and sex structure of the population were obtained from the "Census of India, Madras area" (1961). The five-year structure of the population was transformed into a one-year structure, according to Sprague interpolators matrices ([14]); b) death rates were reproduced from Coale-Demeny's mortality tables, Family West ([4]); and c) fertility was taken from Cassen and Dyson's "New Population Projections for India" ([3]).

Two sets of parameters are required by the model, i.e., a) prevalence in each state per year, and b) rates of transition per year according to the duration spent in each state. These parameters were carried over from the initial model with the following modifications: a) all rates were made age-, sex-, and type-specific, based on analysis of the data collected during the 16-year observation period; b) rates of relapses in multibacillary and paucibacillary cases were derived from observations which have been partly published elsewhere ([12]); c) the distributions of time spent in each state were smoothed on 100 years in order to cancel ergodicity; d) the probabilities of transitions from one state to another were recalculated using a life-table method.

Vaccination was simulated in two ways, which correspond to two, different postulated mechanisms for protection ([2]). According to the first mechanism, the vaccine is assumed to have an immunoprophylactic effect, i.e., it prevents infection in exposed individuals while it does not confer protection against the later development of the disease in those already infected. This is conceptually similar to the effect expected from the armadillo vaccine now being contemplated. The vaccine is administered once to the whole or to part of the population irrespective of age or sex. This process is simulated by creating an immune state into which individuals are transferred from the "susceptible" state once they are vaccinated.

In the second mechanism, the vaccine is supposed to have an immunotherapeutic effect. It will prevent individuals already infected from developing an overt disease, while it will confer no protection against infection. It is similar to the effect expected from the mixture of killed *M. leprae* and BCG now being tested in various parts of the world ([2]). The vaccine is administered once to the whole or to part of the population. Its effect is simulated by transferring individuals from the so-called latent state into an immune state.

Resistance was simulated by creating a state where multibacillary patients are entered. Input to this state is regulated by two types of transactions:

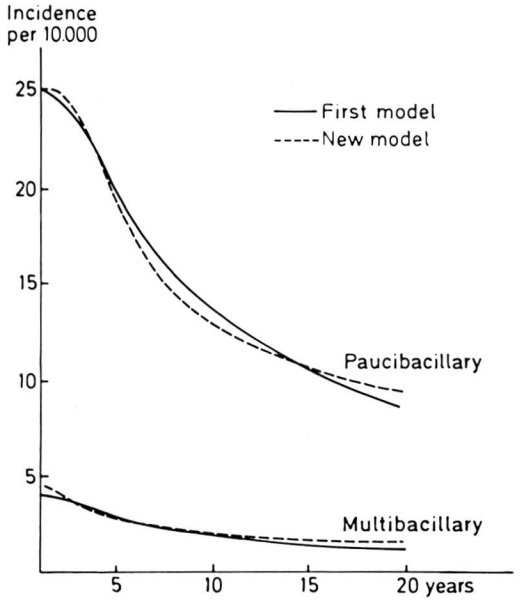

FIG. 2. Prediction of incidence by type of leprosy over 20 years with the two models.

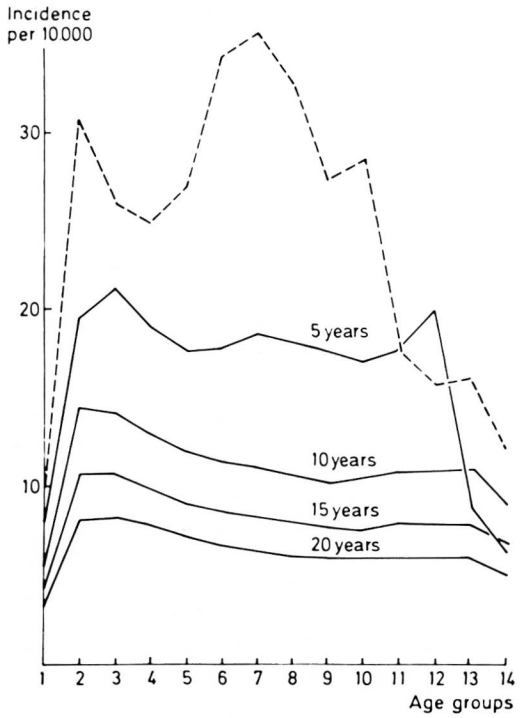

FIG. 3. Prediction of incidence for paucibacillary leprosy over 20 years by 14 age groups (age-specific incidence rates introduced in the model).

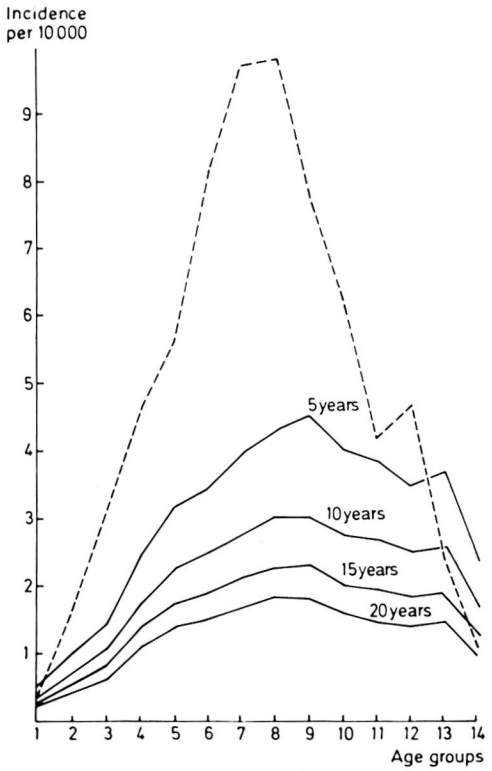

FIG. 4. Prediction of incidence for multibacillary leprosy over 20 years by 14 age groups (age-specific incidence rates introduced in the model).

a) secondary resistance: The appropriate way to simulate resistance should be by using a life-table approach, the probability of developing resistance depending on the number of years of treatment. No data being available on the annual incidence of resistance, an alternative approach was used. Each year, a constant proportion of multibacillary patients having completed four years of treatment regain the infective capacity of new patients, staying in this state thereafter for life. Assuming that, in actual conditions, resistance may emerge with equal probability between the 5th and the 14th year of treatment, the annual incidence is taken as 1:10 of this figure.

b) primary resistance: The number of new patients with resistance each year depends on the total prevalence of resistant patients.

RESULTS

Crude and specific incidences. Predictions of incidence by type of the disease were compared in the initial and in the pres-

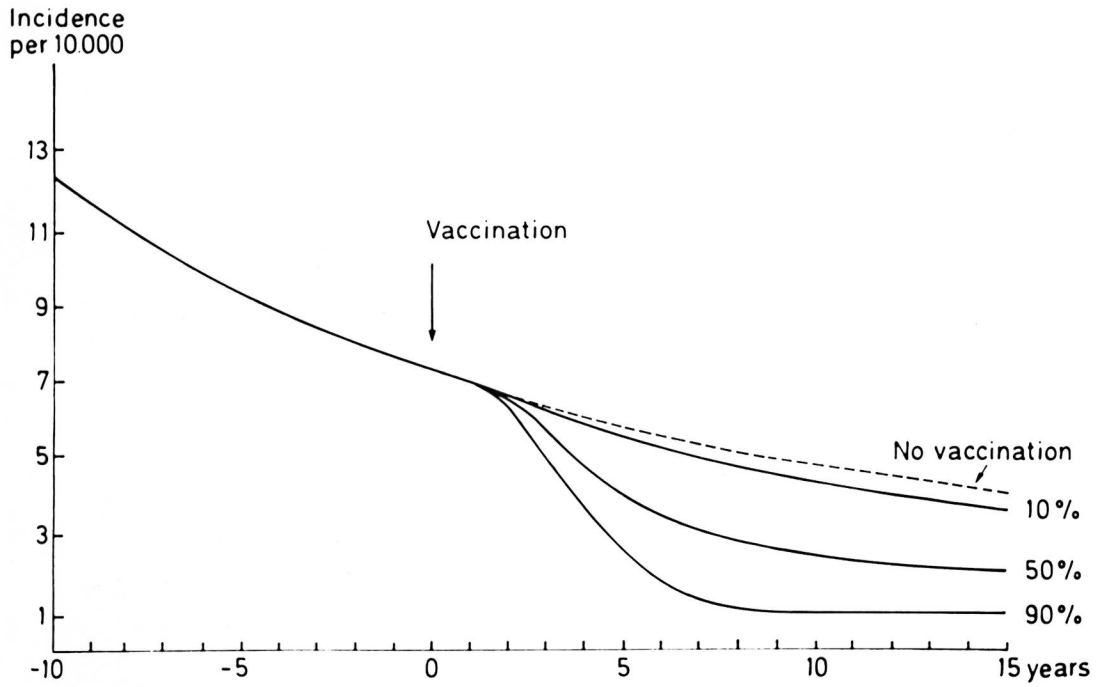

FIG. 5. Prediction of incidence for both types of leprosy with an immunoprophylactic vaccine covering 10–50–90% of the population.

ent models. Over a 20-year period, the trends of the crude incidence rates are similar in the two models (Fig. 2).

Age-specific incidence rates for paucibacillary leprosy show a characteristic bimodal distribution at the beginning of the simulation, which reflects the data introduced in the model based on actual observations in the study population (M. F. Lechat, unpublished data) (Fig. 3). The two peaks of age-specific incidences are blurring off with time. The mean age of onset for the paucibacillary cases is stable (from 25.2 years at the first year of simulation to 25.5 years after 20 years). The proportion of children among the new paucibacillary cases is stable (from 33% to 35% after 20 years). In multibacillary leprosy, incidence shows its single peak in the 35–44-year group throughout the simulation period (Fig. 4). The mean age of onset remains stable (31.0 years at the first year to 32.4 years after 20 years).

Vaccination. Three coverages of vaccinations were simulated, the proportion of the vaccinated population being relatively 10%, 50%, and 90%.

The effect of an immunoprophylactic vaccine starts to manifest itself after two years, which corresponds to the mean latent period (delay between infection and onset of disease) as introduced in the model. It stabilizes after a few years, reflecting the arrival of unvaccinated cohorts through birth (Fig. 5).

By contrast, the effect of an immunotherapeutic vaccine is immediate, bringing a considerable decline in incidence. After a couple of years, the effect is waning, due to new susceptibles having contracted infection in the meantime (Fig. 6).

Resistance. The prevalence of multibacillary patients with resistance increases with time. It represents the accumulation of patients with secondary resistance plus the new patients they have contaminated (primary resistance) minus the deaths. With a 3% incidence of secondary resistance per year, the prevalence of resistance among the multibacillary patients reaches some 26% 15 years after the appearance of the phenomenon (Fig. 7).

Conversely, the effect on incidence of an increasing reservoir of infective patients can be calculated for different rates of resistance.

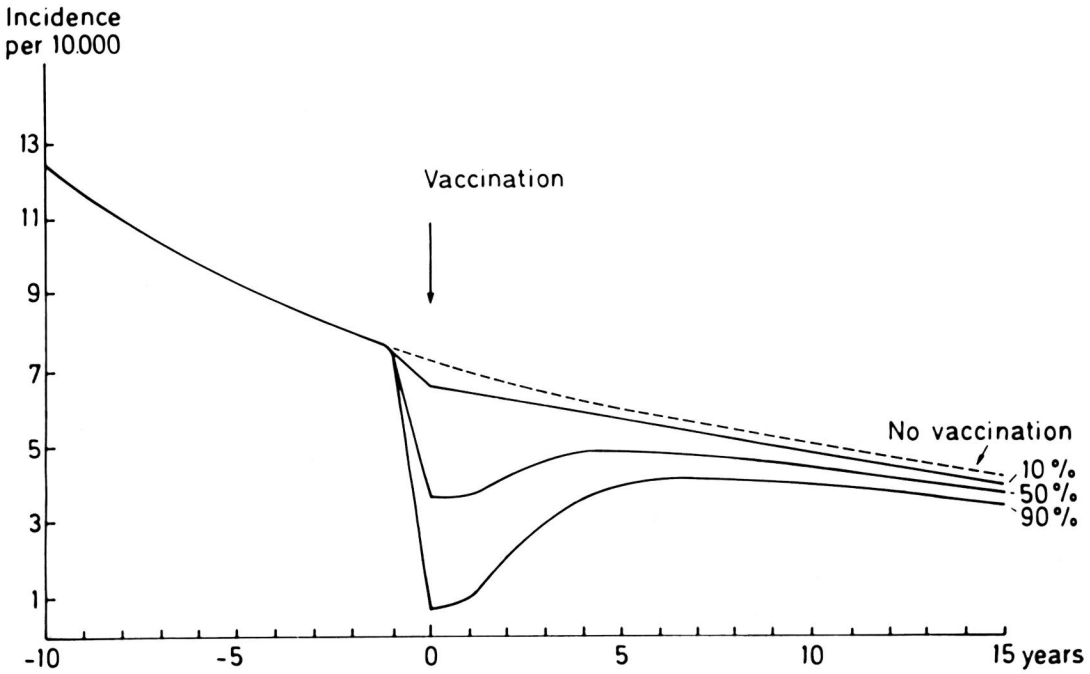

FIG. 6. Prediction of incidence for both types of leprosy with an immunotherapeutic vaccine covering 10–50–90% of the population.

With secondary resistance at a rate of 1% per year, the decline in incidence reaches a plateau after the 31th year. With 2% and 3% incidence rates of resistance per year, the declining trend of incidence is reversed, respectively, after 23 and 18 years (Fig. 8).

DISCUSSION AND CONCLUSIONS

Incidence rates predicted with either of the models show similar trends over a 20-year period. With a control strategy based, at the time, on early case finding and complete coverage with dapsone monotherapy, incidence is reduced by one half in some nine years. This similarity of results suggests that the model is rather insensitive to changes in the age-dependent parameters, at least in the first 20 years of simulation. The conclusions drawn from the first model are therefore strengthened.

Comparing the two possible mechanisms of vaccination, immunotherapy has only a short-term effect. While an immunoprophylactic vaccine is supposed to protect for life against infection, immunotherapy is effective only in that group of the population which is already infected.

In the model, the distribution of the delays between infection and onset of the disease ranges from 1–8 years, with an average of 2.2 and 4 years in the multibacillary and paucibacillary patients, respectively. It follows that under these assumptions regarding the duration of the latency period, immunotherapy will have no effect whatever after eight years.

It is fully recognized that these estimates of the latency period may raise serious objections. According to present concepts regarding the pathogenesis of leprosy, incubation should be longer in multibacillary than in paucibacillary patients. Observations in United States' veterans from the Second World War confirm this concept ([5]). On the other hand, in highly endemic countries, where the entire population may be considered as exposed at a young age, the distribution of age-specific incidence rates suggests a much longer incubation period than generally accepted ([6, 10]). The statistical method used (least squares) for estimating the latency period has yielded values providing the best fit to the observed trends of incidence in the study area. These estimates

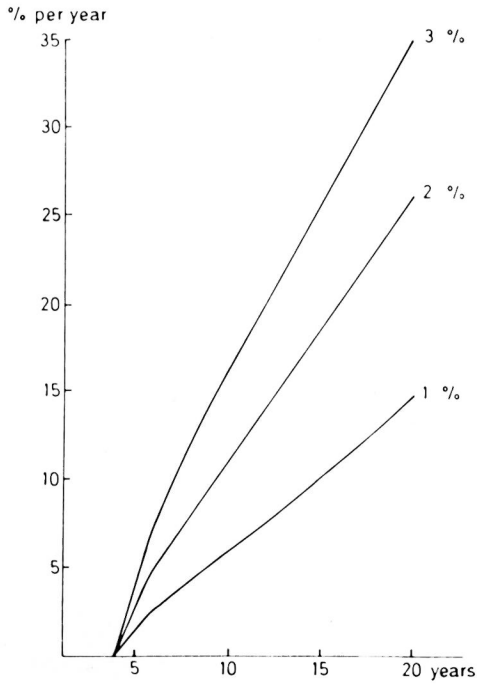

FIG. 7. Prediction of the prevalence of drug resistance (primary, secondary) among the multibacillary patients according to incidence of secondary drug resistance.

were therefore accepted as the best possible approximation.

An immunotherapeutic vaccine would be much more effective than indicated in the model if the latency period is longer than it has been assumed. Its effect could even be considerable if, as suggested by immunoepidemiological studies ([1]), the majority of the exposed population is indeed infected.

The simulation of the effects of the two types of vaccines are important in terms of cost. An immunoprophylactic vaccine with a lasting effect will need to be administered once, and thereafter only to cohorts of infants. An immunotherapeutic vaccine will have to be repeated after a few years to all individuals potentially incubating the disease.

The model can be used to test the effects of drug resistance. At the moment, however, due to the lack of actual data on the incidence of resistance, arbitrary values have to be entered. Although secondary resistance may affect a large number of multibacillary patients, the effects on incidence are rather slow to become manifest. With 3% resistance per year, the decline in inci-

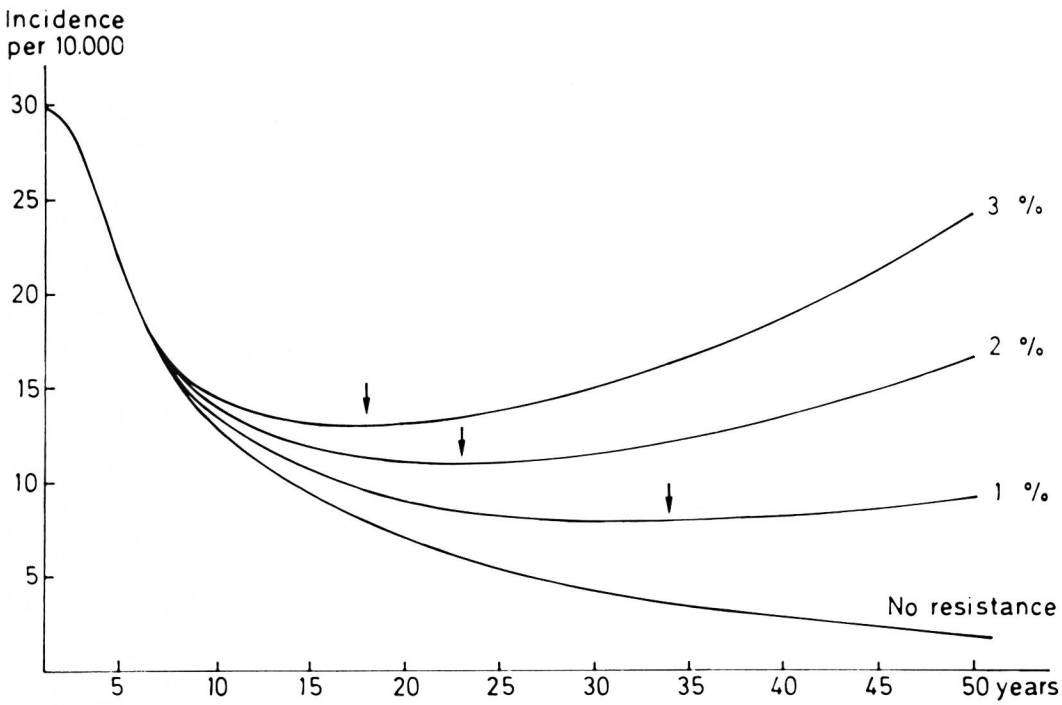

FIG. 8. Prediction of incidence for both types of leprosy with 1–2–3% secondary drug resistance.

dence is reversed after 18 years. The importance of the phenomenon clearly calls for the collection of more accurate data on the incidence of resistance in cohorts of patients according to duration of treatment. These results demonstrate, however, the potential importance of resistance which, in the long run, could jeopardize the success of leprosy control. It stresses the need for a rapid implementation of multiple drug therapy.

SUMMARY

Epidemiometric models are useful in studying disease dynamics in populations. Such a model was developed for leprosy and proved useful, but did not take into account age- and sex-specific incidence rates. This paper presents a new version of the model which makes provisions for age and sex differential rates according to the type of leprosy and which includes more realistic parameters for death rates, population variations, and natural growth rates. This new version of the epidemiometric model was used to simulate the effects of various vaccines and drug resistance on the incidence of leprosy in a population.

RESUMEN

Los modelos epidemiométricos son útiles en el estudio poblacional de la dinámica de enfermedades. Uno de estos modelos se desarrolló y aplicó en el estudio de la lepra demostrando su utilidad pero no tomó en cuenta la incidencia de la enfermedad en función de la edad y sexo. Este trabajo presenta una nueva versión del modelo en la que se toman en cuenta estos parámetros en función del tipo de lepra y la cual incluye consideraciones más realistas sobre tasas de mortalidad, variaciones poblacionales, y tasas de crecimiento natural. Esta nueva versión del modelo epidemiométrico se usó para simular los efectos de varias vacunas y la resistencia a drogas sobre la incidencia de lepra en una población.

RÉSUMÉ

Les modèles épidémiométriques sont utiles pour étudier la dynamique des maladies dans des populations. Un tel modèle a déja été développé antérieurement pour la lèpre et s'est révélé fort utile. Néanmoins, ce modèle ne prenait pas en compte les taux d'incidence spécifiques pour l'âge et le sexe. On présente ici une nouvelle version du modèle qui prend en considération les taux spécifiques pour l'âge et le sexe, selon le type de lèpre. Ce modèle fait également appel à des paramètres plus réalistes pour les taux de décès, les fluctuations de la population, et les taux de croissance naturelle. Cette nouvelle version du modèle épidémiométrique a été utilisée pour simuler l'effet de différents types de vaccins, et l'influence que peut jouer la résistance médicamenteuse, sur l'incidence de la lèpre dans une population.

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