Volume 70, Number 1 (Suppl.)
Printed in the U.S.A.
(ISSN 0148-916X)

Epidemiology and Control

1. Introduction

Leprosy elimination was defined in 1991 as a prevalence smaller than one per 10,000 inhabitants. Underlying the elimination strategy was the hypothesis that, because leprosy patients are assumed to be the sole source of infection ([1]), early detection and treatment of the cases by MDT would reduce transmission of the organism. Once the prevalence fell below a certain level, incidence would be reduced; in the long term, the chain of transmission would be broken, and leprosy would disappear naturally ([2]).

It is now necessary to seek evidence to verify this hypothesis. Some important questions must be answered concerning the effectiveness of interventions to reduce transmission of *Mycobacterium leprae* and the sources of infection. Evidence concerning these issues will be reviewed here. The validity of several indicators for leprosy epidemiology and control will also be discussed.

2. Are Untreated MB Patients the Only Significant Source of Infection?

Untreated MB patients are most probably the most important source of transmission of *M. leprae*. Household contacts of multibacillary patients have been estimated to have a risk of developing leprosy 5–10 times greater than that of the general population ([3–5]), and a positive association exists between smear positivity and infectiousness. In low endemic situations, the relative risk associated with household contact could even be greater.

Several studies have shown that untreated MB patients excrete large quantities of *M. leprae* from the nose and mouth ([6–8]). However, many studies have suggested that untreated MB patients do not represent the sole source of infection. Household contacts of paucibacillary (PB) patients have also been shown to be at greater risk of developing the disease than are non-contacts ([3, 4]), although the risk is smaller than that to contacts of MB patients. It is possible that the PB patients are not themselves the source of transmission; rather, the household contact has had contact with some outside source of infection ([4]). Those who join the household of an MB patient after treatment has been started have been shown to be at lower risk than the contacts of untreated MB cases, but at greater risk than the general population. If MDT renders the index case noninfectious, it appears likely that the source of infection is not the index case directly, but the environment of the household ([9]).

Because, in many areas, the numbers of MB patients are very small, they may not represent the most important source of infection. There is increasing evidence that subclinical transmission may occur. Nasal excretion of *M. leprae* by subclinically infected individuals could be responsible for transmission, although this is not proven. DNA sequences apparently unique to *M. leprae* have been isolated on nasal swabs from many apparently healthy individuals residing in endemic areas ([10–15]), and large proportions of those who live in areas endemic for leprosy have been shown to demonstrate seropositivity against *M. leprae*-specific antigens ([11, 14–16]). Even in highly endemic countries, no history of close contact with a leprosy patient can be established for many patients ([4]), although a study carried out in one endemic village in Indonesia showed that some contact with a leprosy patient could be demonstrated for most incident cases ([5]).

Direct spread is certainly important, but infection may also be indirect ([17]). *M. leprae*, which have been said to be capable of survival outside the human body for as long as several months under favorable conditions ([18]), have also been found in the soil ([19, 20]), and insect-bites have also been said to be capable of transmitting the organism ([21]). This latter route of infection is probably not very efficient ([22]), but it cannot be completely dismissed as a possibility. The existence of extra-human, animal reservoirs of *M. leprae* has been demonstrated ([23–27]) but, with the possible exception of the nine-banded armadillo, there is

no evidence that these animals are of epidemiologic significance. *M. leprae*-specific DNA has been reported to be present in water, and the risk of leprosy was said to be correlated with the use of contaminated water for bathing and washing ([28]). Leprosy lesions following dog-bites ([29]), vaccinations and tattooing ([30]) have also been reported. Nude mice, the feet of which had been smeared with *M. leprae* and also pricked with contaminated thorns, developed leprosy lesions ([31]), and infection of wild armadillos through thorn pricks has also been suspected ([32]); such a route of infection cannot be completely excluded for humans. Finally, in some settings, the anatomical distribution of the lesions in patients with a single macule strongly suggests transcutaneous infection through wounds ([33]). Other studies of the anatomical distribution of lesions are not consistent with this hypothesis, but could be consistent with infections through insect-bites ([34]).

3. What Evidence Is There for the Effectiveness of Interventions to Stop Or Reduce the Incidence of Leprosy?

3.1 Impact of MDT on transmission

MDT greatly reduces the infectiousness of leprosy patients in a matter of a few days ([35]), a period of time much shorter than that required by dapsone monotherapy (approximately three months). Although incidence rates have been observed to have declined in many settings, evidence that MDT caused an acceleration of that decline is rare ([36–40]). In many places, the decline of incidence began before the introduction of MDT, or could be explained as well by other factors ([41–46]). In other settings, no decline of incidence has been observed, despite the routine administration of MDT to all newly detected patients for a number of years ([47–49]).

Several explanations can be advanced for the apparent lack of acceleration of a decline of incidence following the introduction of MDT:

- the long incubation period of leprosy;
- the increased case detection efforts; or
- detection too late to effect very much of a reduction of transmission ([50]).

3.2 Impact of other interventions

3.2.1 Immunoprophylaxis. In several randomized controlled trials that have been carried out, vaccination with BCG was shown to reduce the risk of developing leprosy ([51–56]). The level of protection varied among trials from 20 to 80%, for reasons that remain unclear. Repeated vaccination with BCG is capable of enhancing protection against leprosy ([54, 56]), and addition of heat-killed *M. leprae* (HKML) to BCG does not appear to increase the protection conferred by BCG alone ([54, 57]). However, this has not been true of all of the trials; in one trial in South India, the combination of BCG + HKML conferred protection that was almost double that conferred by BCG alone ([58]). Protection conferred by BCG appears greatest if the vaccine is administered before 15 years of age ([51, 54]). The ICRC vaccine was also shown to confer significant protection against leprosy ([58]). Current research suggests the possibility of producing vaccines for leprosy that are more effective ([59]).

3.2.2 Chemoprophylaxis. Chemoprophylaxis against leprosy has been studied in several trials. A systematic review and meta-analysis of these trials has shown that chemoprophylaxis based on dapsone or intra-muscular acedapsone conferred an overall protection against leprosy of about 60% ([60]). However, the protection appeared to wane over time after administration of the chemoprophylactic regimen. An uncontrolled trial with rifampicin administered in a single dose at a dosage of 25 mg per kg yielded an estimated protective efficacy of 35–40% ([61–63]). Finally, a program of chemoprophylaxis employing single doses of the combination rifampicin-ofloxacin-minocycline, was launched in the Federated States of Micronesia, Kiribati and the Republic of the Marshall Islands as part of their elimination program ([64]). Because this was not a controlled trial, but rather an attempt to prevent the disease in an entire population, it is difficult to draw conclusions regarding the degree of protection conferred by this chemoprophylaxis.

3.2.3 Other factors. Socio-economic conditions are thought to play an important role in leprosy, their improvement resulting in a decline of incidence. One of

the best demonstrations of such an influence was provided by a study of trends of incidence in mainland Japan and Okinawa ([65]). Although the factors contributing to this decline are not known, housing conditions, the number of persons per household or per room, and family-size are thought to have been most important. A study in Malawi found an inverse relationship between the number of years of schooling and the risk of leprosy, and good housing conditions were also associated with a decreased risk of leprosy ([66]). Nutritional factors could also influence individual susceptibility ([67, 68]).

4. What Are the Essential Indicators for Leprosy Epidemiology and Control?

Indicators are tools for measuring progress in achieving the objectives of a program. Ideally, these indicators should be valid (measure effectively what they are supposed to measure), simple, easy to measure and to interpret, responsive to changes, and give information that could be used to reorient activities. This section concerns the usefulness of a number of indicators often employed in leprosy control programs.

4.1. Prevalence

Prevalence should deal with the actual number of people in need of, or receiving chemotherapy. There were several reasons for choosing prevalence, and not incidence, as the indicator of elimination:

- the incidence of leprosy is not easy to measure employing routine reporting systems, which generate information only on case-detection;
- detection of new cases may correlate very poorly with incidence, because of operational changes in activities;
- because of the long incubation period, current incidence reflects transmission that had occurred several years earlier and, therefore, does not reflect the effectiveness of current anti-leprosy activity ([69]);
- it was hoped that reduction of prevalence to very low levels would lead, in time, to reduction of transmission of infection and, therefore, to reduction of incidence;
- the target of a prevalence of less than 1 in 10,000 at the national level and the target date of the end of the year 2000, although arbitrary, provided sufficient challenge to build political commitment and intensify activities ([70]).

However, prevalence possesses limitations as an indicator of elimination:

- the data collected refer in practice only to those who are registered for treatment. Undetected leprosy patients are not taken into account;
- it is directly dependent upon the duration of treatment;
- prevalence of registered cases is directly influenced by detection activities, and thus by operational factors.

4.2 Incidence

The annual incidence is the number of new cases of a disease that occur in a population in the course of a year. In theory, it represents the best estimate of the current risk of developing leprosy within the specified population. It also reflects the transmission pattern of *M. leprae* in the population during preceding years ([71]). However, it is very difficult to measure in practice: clear and undisputed criteria for the diagnosis of leprosy are required, and total populations must be examined at regular intervals. Even in an ideal situation, because some leprosy lesions are evanescent, the number of leprosy patients detected in a program depends upon the frequency at which the population is surveyed ([72, 73]). Even if incidence cannot be measured accurately, its trends can be estimated by a set of indicators.

4.3 New-case detection-rate

The rate at which new cases are detected is the most logical proxy-indicator of incidence. However, the new-case detection-rate poses some problems of interpretation:

- it is directly influenced by the intensity and frequency of detection activities and the quality of services;
- a number of newly detected cases may have developed leprosy several years earlier;
- at the same time, some people who develop symptoms will be detected only after a number of years, and thus will not be included in the current year's case detection rate.

In spite of these limitations, one may assume that trends of case detection reflect trends of incidence, on condition that there has been no important change of detection activities, including coverage, self-reporting behavior, diagnostic procedures and criteria ([74, 75]).

4.4 Proportion of newly detected patients with grade 2 impairment

This is a highly relevant indicator. The proportion of newly detected patients with impairments has been shown to be related to delay before detection ([50]). A large proportion of patients with deformity among newly detected patients indicates that these include old cases ([76]), whereas a small and stable proportion of new patients with impairments among the newly detected cases is a sign that the delay between onset of the disease and its diagnosis is stable, and that trends of case detection reflect trends of incidence ([77]). However, the validity of this indicator depends upon the thoroughness of the examination of the new patients at the time of detection.

4.5 Proportion of children

A large proportion of children among the newly detected patients is a sign of active and recent transmission of the infection. Thus, it is an important epidemiological indicator, even though the proportion can also be influenced by operational factors, such as active campaigns among specific subgroups of the population—school surveys, for example. As transmission of *M. leprae* decreases in a population, the proportion of children among the newly detected cases may also be expected to decrease. However, this is a slow process ([43, 46]). Therefore, it would be informative to monitor age-specific case-detection rates ([75]) or mean age at detection; this should increase in the situation of declining incidence.

4.6 Proportion of MB patients

This indicator is particularly difficult to interpret: the proportion of MB patients among newly detected patients differs from country to country, and is directly influenced by the criteria used for classification (bacteriological or clinical) and by detection efforts ([75]). Its usefulness for interpretation of trends of case-detection rates is also questionable: the proportion of MB patients among the newly detected cases has been shown both to increase and to decrease in situations of declining incidence ([78, 79]). However, as long as treatment differs for PB and MB patients, the proportion of MB patients will remain useful for estimating drug requirements. It may also be important to collect information on new smear-positive patients; this may be accomplished by the use of "sentinel" sites.

4.7 Treatment completion rate

This should be calculated, by cohort analysis, as the proportion of patients who have completed treatment among those expected to do so. As long as treatment differs for PB and MB patients, this indicator must be calculated separately for each type of patient.

4.8 Relapses

Although relapses appear to be very rare after MDT, it remains useful to monitor relapses at the program or country level. If a sizeable proportion of the patients starting treatment consists of relapses, the situation is worth investigating ([80]).

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