The impact of leprosy control on the transmission of *M. leprae*: is elimination being attained?

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Summary In 1991 the World Health Assembly decided to ‘eliminate leprosy as a public health problem’ by the year 2000. Elimination was defined as reducing the global prevalence of the disease to less than 1 case per 10,000. In 2000 the World Health Organization (WHO) announced that elimination was reached globally.

Conventionally control of disease is defined as the reduction of disease burden to a locally acceptable level. Elimination of disease is defined as the reduction to zero of the incidence in a defined geographical area, and eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent. In leprosy however, WHO limited elimination to control instead of transmission, by using prevalence instead of incidence of disease.

Leprosy statistics usually report on prevalence and new case detection. Prevalence is linked to length of treatment, which has changed over time. Trends in new case detection rates only reflect trends in incidence rates when no changes occur in case detection, but in the past 25 years case detection in leprosy has been determined strongly by operational factors.

For the leprosy elimination strategy it was assumed that MDT would reduce transmission of *M. leprae*, but there is no convincing evidence for this. Data for evaluating the impact of MDT on transmission are not readily available because leprosy has a long incubation period. Also declines in case detection may have other causes, such as BCG vaccination. Mathematical modelling of the transmission and control of leprosy showed that the elimination strategy reduces transmission slowly, with a predicted annual decline in incidence ranging from 2% to 12%. Early case finding was the key factor to attain this decline. Future projections of the global leprosy burden indicated that 5 million new cases would arise between 2000 and 2020, and that in 2020 there would be 1 million people with WHO grade 2 disability.

It is concluded that substantial progress has been made to control leprosy, but when elimination of disease is defined as the reduction to zero of the incidence, leprosy is definitely not eliminated. To attain elimination of leprosy it is necessary to find effective interventions to interrupt transmission of *M. leprae* and practical diagnostic...
tools to detect levels of infection that can lead to transmission. This requires extensive research in the areas of epidemiology and microbiology.

Introduction

Leprosy is a disease with which mankind has been struggling for thousands of years. It causes severe disfigurement in many cases and has been subject to strong social stigma around the world. It was shown to be an infectious disease when Armauer Hansen in 1872 in Norway identified the causative agent *Mycobacterium leprae*. With the discovery of dapsone in the 1940s a cure became available for leprosy, but patients needed to take this drug for life. Evolving resistance to dapsone stimulated the search for new anti-leprosy drugs, and clofazimine and rifampicin were introduced in the 1960s and 1970s. To avoid drug resistance, a combination of all three drugs in the form of multi-drug therapy (MDT) was recommended by a World Health Organization (WHO) Expert Committee in 1981. MDT could be taken for a limited period of time (initially up to 24 months for multibacillary cases), but was introduced slowly because of the cost and the lack of a clear strategy to control the disease. The 44th World Health Assembly in 1991 passed a resolution to ‘eliminate leprosy as a public health problem’ by the year 2000. Elimination was defined as reducing the global prevalence of the disease to less than 1 case per 10,000. At the Assembly, WHO was given the mandate to develop an elimination strategy, based on increasing the geographical coverage of MDT and patients’ accessibility to the treatment. Intensive ‘elimination campaigns’ were held in many endemic countries and in 2000 WHO announced that elimination was reached globally, i.e. a world prevalence of less than 600,000 leprosy patients. WHO then introduced the ‘Strategic Plan for the Elimination of Leprosy 2000–2005’. By the end of 2005 all but six countries (Brazil, Democratic Republic of the Congo, Madagascar, Mozambique, Nepal and Tanzania) reported a prevalence of less than 1 per 10,000. For the period 2006–2010 the WHO introduced the ‘Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities’ to address the remaining challenges in providing services for leprosy patients under conditions of low prevalence. The emphasis remains on providing MDT, and WHO states that this strategy should ensure that gains made by the elimination strategy will be sustained and that the disease burden will continue to reduce over the coming years. Simultaneously, the six countries are encouraged to reach the elimination goal. WHO recognises that new and cost-effective tools will be needed to embark on a strategy to eradicate the disease and that the necessary tools are not available at present.

Without doubt enormous progress has been made in leprosy control since the introduction of MDT. But how do we interpret this achievement in terms of impact on the transmission of *M. leprae*? Elimination in infectious disease control conventionally assumes interruption of transmission, but what evidence is available that this is indeed happening? In this review we discuss ways in which the impact of leprosy control can be measured and, in the absence of diagnostic tools for sub-clinical infection, how the effect of control on transmission can be estimated and what the result is of these estimations. Finally, we discuss briefly the knowledge needed to attain elimination of leprosy.
Defining and measuring control, elimination and eradication

The principles of disease elimination and eradication have been clearly described by Dowdle in the Bulletin of the WHO in 1998. Control of disease is defined as the reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. Elimination of disease is defined as the reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required. Similarly, elimination of infection is defined as a reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required. Finally, eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as the result of deliberate efforts; intervention measures are no longer needed. Dowdle also adds the term ‘extinction’, in which the specific infectious agent no longer exists in nature or in the laboratory. In leprosy however, WHO limited elimination to control instead of transmission, by using prevalence instead of incidence of disease.

Three indicators are of primary importance to attain eradication: 1) an effective intervention is available to interrupt transmission of the agent; 2) practical diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to transmission; and 3) humans are essential for the life-cycle of the agent, which has no other vertebrate reservoir and does not amplify in the environment.

There are no suitable tests for detecting sub-clinical mycobacterial infections reliably, including M. leprae. Assessment of the results of leprosy control depends on information about disease and not infection. Available disease statistics, as for instance those reported on the global leprosy situation by WHO, are expressed in terms of prevalence and new case detection. Disease prevalence in leprosy is measured by counting all patients receiving MDT at a given time and expressing this as a ratio using the population as the denominator (in leprosy traditionally per 10,000). Prevalence figures are therefore proportionally linked to length of treatment. Trends in prevalence have been strongly determined over the years by shortening of treatment duration. Halving the length of treatment, for instance, for patients with multibacillary (MB) leprosy from 24 to 12 months, halved the prevalence rate for that group. Also, paucibacillary (PB) patients who received their 6-month course early in the calendar year are not registered since only patients registered on the 31st of December are counted for that year. New case detection is not affected by duration of treatment. Trends in new case detection rates reflect trends in incidence rates, provided that no significant changes occur in case detection efforts, self-reporting behaviour, or diagnostic procedures or criteria. In the past 25 years however, case detection has been determined in many countries by operational factors such as expanding of control activities during the elimination drive leading up to 2000 and decreased activities afterwards. Operational influence is particularly visible in India, where new case detection dropped by 75% from 559,938 in 2000 to 139,252 in 2006. At the same time the proportion of new cases with WHO grade 2 disability increased by 38% between 2004 and 2007, from 1.6% to 2.2%. This increase suggests less active case finding. Also the drop in new case detection of 24% in Brazil from 2004 to 2005 is attributed primarily to operational change rather than reflecting a genuine trend. Such dramatic drops within a short period of time are not credible biologically because of the long incubation period of leprosy and the absence of an instantaneously implemented high-coverage preventive intervention such as vaccination in the decade preceding the sudden drop in case detection.
Apart from prevalence and new case detection (as possible proxy for incidence) rates, other relevant indicators have been introduced to describe the impact of leprosy control. These are the proportion of MB leprosy cases, the proportion of females, the proportion of children, and the proportion of cases with grade 2 disabilities found among newly detected cases. These indicators reflect the burden of disease in terms of morbidity (disability), programme quality, and possibly transmission (a high proportion of children with leprosy is seen as an indicator for ongoing transmission of \textit{M. leprae}).

The leprosy elimination confusion

Contrary to the principles of disease elimination, WHO defined leprosy elimination in terms of reduction of the prevalence of the disease to less than 1 case per 10,000, which is basically the definition of a control target. The WHO goal was to eliminate leprosy 'as a public health problem' and not as a disease, and certainly not to eliminate the agent \textit{M. leprae}. The term 'leprosy elimination' was apparently considered to have a stronger appeal than the term 'leprosy control' to motivate governments and the general public to intensify leprosy control, in effect 'branding' the term to sell the WHO strategy internationally.\textsuperscript{10} Nevertheless, the expectation existed that reduction in prevalence through expanding MDT coverage would eventually also lead to reduction in incidence of the disease,\textsuperscript{11} and ultimately to elimination in terms of zero incidence of the disease.

An important assumption underlying the WHO leprosy elimination strategy was that MDT would reduce transmission of \textit{M. leprae} through a reduction of the number of contagious individuals in the community.\textsuperscript{12} Unfortunately, there is no convincing evidence for this hypothesis.\textsuperscript{13–16} Data for evaluating the impact of MDT on transmission are not readily available for several reasons. Leprosy has a long and variable incubation period, ranging from 2 to 20 years, and decreases in transmission only gradually become apparent.\textsuperscript{17} Also declines in case detection may have other causes, such as bacille Calmette-Guérin (BCG) vaccination against tuberculosis. BCG vaccination has been implemented in many countries and is known to afford protection against leprosy as well.\textsuperscript{18} Finally, as mentioned above, variability in control efforts further complicates the interpretation of trend data.

In 1997, a systematic review of the trends in leprosy incidence was published by Meima \textit{et al.}\textsuperscript{13} The study investigated trends in new case detection rates up to 1993 in 16 selected leprosy-endemic areas in the Pacific, Asia, Africa and Latin America. The observed downward trends in 10 areas could not be attributed to reduced control activities or changed diagnostic criteria. A general acceleration of downward trends in the new case detection rate after the introduction of MDT had not occurred. In a more recent study, trend analysis of leprosy new case detection between 1985 and 2000 at various levels of geographical aggregation showed no general decline in case detection at global level up to 2000.\textsuperscript{5} Where these kinds of trend analyses help clarify and interpret reported leprosy statistics, they add little to insight of the incidence of leprosy, the transmission of \textit{M. leprae}, and the contribution of control to these trends.

Modelling disease incidence

With limited diagnostic tools to detect infection with \textit{M. leprae}, other methods are necessary to estimate trends in incidence and transmission. A computer programme has been developed for
modelling the transmission and control of leprosy (SIMLEP), which can be used to project epidemiological trends over time, producing output on indicators such as prevalence, incidence and case detection rates of leprosy. In SIMLEP, health states have been defined that represent immunological conditions and stages of *M. leprae* infection and disease, including natural immunity, asymptomatic infection, type distribution of new cases, delay between onset of disease and start of chemotherapy, and mechanisms for *M. leprae* transmission. SIMLEP can be used to improve the understanding of observed leprosy trends, for example, in relation to early detection campaigns and the use of MDT, by exploring which combinations of assumptions can explain these trends. In addition, SIMLEP allows for scenario analysis in which the effects of control strategies combining different interventions can be simulated and evaluated.

SIMLEP was applied to explain the disappearance of leprosy from Norway between 1856 and 1920. The time trend in leprosy new case detection in Norway was reproduced adequately. The shift in new case detection towards older ages that occurred over time was accounted for by assuming that infected individuals may have a very long incubation period. The decline could not be explained fully by the Norwegian policy of isolation of patients: an autonomous decrease in transmission, reflecting improvements in for instance living conditions, must also be assumed. The estimated contribution of the isolation policy to the decline in new case detection very much depended on assumptions made on build-up of contagiousness during the incubation period and waning of transmission opportunities due to rapid transmission to close contacts. It was concluded that the impact of isolation on interruption of transmission remains uncertain, and that this uncertainty also applies to contemporary leprosy control that relies mainly on MDT.

The SIMLEP model was also applied in a scenario analysis investigating the impact of the current strategy for the elimination of leprosy on its incidence, and assessing the consequences of failure to sustain this strategy. The scenarios reflected the assumptions made regarding contagiousness, transmission and BCG vaccination. The trend in case detection rate for the main countries in which leprosy was endemic during 1985–1998 was fitted, and incidence up to 2020 was projected. It was found that owing to the gradual shortening of delays in detection up to 1998, and because of the low relapse rate that occurs with MDT, incidence is predicted to decrease beyond 2000 in all scenarios. The annual decline was a few percent higher when favourable assumptions were made about protection and coverage of BCG vaccination. Overall, the predicted annual decline in incidences ranged from 2% to 12%. It was concluded that the elimination strategy reduces transmission, but the decline may be slow. Early case finding is the key factor in the success of the strategy. Relaxation of control after 2005 was considered to be unjustified given the uncertainty about the rate of decline and the adverse effects of longer delays in detection. The advice was that a long-term strategy for leprosy control should be adopted.

Figure 1 shows the effect of failure to sustain early case detection beyond 2005 on leprosy incidence and case detection. The impact on incidence rate and case detection rate of an increase in the detection delay from 2 to 4 years between 2006 and 2009 is shown for a scenario with (A) and without (B) BCG vaccination in the population.

The modelling studies highlighted that the assessment of how much transmission a control strategy is able to prevent depends on two unresolved questions: is the incubation period contagious, and how rapid are close contacts of leprosy patients infected? As long as these two questions remain unanswered, it will be difficult to estimate the impact of control strategies on the transmission of *M. leprae* on resulting disease incidence.
Prediction of future trends in leprosy

Based on previous and current trends in case detection, predictions have been made using the SIMLEP modelling framework of the future leprosy case detection and prevalence of WHO grade 2 disability.

In 2000, 720,000 new cases of leprosy were detected worldwide. In an intermediate scenario with BCG vaccination, it would take about 10 years to halve the incidence. If population growth is ignored, extrapolation of this rate of reduction to case detection would imply that 360,000 cases would be detected worldwide in 2010 and 180,000 in 2020.
The cumulative number of new patients who would be detected up to 2010 and 2020 is 5 and 7.5 million, respectively. In the most optimistic prediction, obtained with larger decreases in the detection delay than the baseline trend (11.8% annual decline in incidence), the number of cases detected would be 4 million by 2010 and 5 million by 2020.21

The prevalence of people with WHO grade 2 disability decreases much slower than leprosy incidence and case detection. Therefore a substantial number of people will live with impairment and will need support, training in self-care and other prevention of disability interventions in the next decades. A prediction of the future prevalence of WHO grade 2 disability was made by calculating the survival of existing and new impaired individuals. Assuming an annual decline in the new case detection rate of 12% and 6% WHO grade 2 disability among newly detected cases, it was calculated that the prevalence of WHO grade 2 disability in 2010 and 2020 would be 1.2 million and 0.9 million, respectively.22

Discussion

More than 13 million cases were detected and treated with MDT between 1982 and 2002.23 The WHO leprosy elimination strategy has succeeded in mobilising governments to intensify leprosy control activities in their countries and highly effective antibiotic treatment (i.e. MDT) has been delivered worldwide. There is increased awareness in endemic countries about the disease and that it can be cured, helping people to seek treatment early, and fewer newly detected cases have disabilities. Nevertheless, many new cases are still detected yearly and future projections of the global leprosy burden indicate that at least 5 million new cases will arise between 2000 – the year of leprosy ‘elimination’ – and 2020. Also, by 2020 there will still be approximately 1 million people with WHO grade 2 disability caused by leprosy.

Taking into account the substantial decrease in disease prevalence and related morbidity, it can be argued that control of leprosy disease has been achieved in many endemic countries in terms of reducing the burden to an acceptable (i.e. manageable) level as result of deliberate efforts. Achieving control implies that continued intervention measures are required to maintain the reduction. There are indications that the leprosy incidence has come down in a number of countries, but it is not clear to what extent this can be attributed to control, and in particular MDT. Many countries already had downward trends before the systematic introduction of MDT, and these trends are probably explained by more general factors such as increased socio-economic conditions.20 When elimination of disease is defined as the reduction to zero of the incidence, leprosy is definitely not eliminated!24,25

What is needed to attain elimination of leprosy in future, if at all possible? First of all an effective intervention is needed to interrupt the transmission of *M. leprae*. BCG vaccination does not offer full protection and in the absence of another more specific vaccination against the bacillus other strategies need to be developed, such as preventive treatment (chemoprophylaxis) of sub-clinically infected people at risk of developing leprosy.26,27 This necessitates better understanding of the transmission of *M. leprae*, for which practical diagnostic tools are still lacking to detect levels of infection that can lead to transmission.28,29 In addition, the question of the existence and relevance of possible non-human or environmental reservoirs for *M. leprae* needs to be resolved.30,31 Although appropriate genomic-based technologies exist or are under development, they are not yet readily available to address the unresolved issues of transmission of and infection with *M. leprae*. This requires extensive research efforts in the areas of epidemiology and microbiology.32,33
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