

# The future incidence of leprosy: a scenario analysis

Abraham Meima,<sup>1</sup> W. Cairns S. Smith,<sup>2</sup> Gerrit J. van Oortmarssen,<sup>1</sup> Jan H. Richardus,<sup>1</sup> & J. Dik F. Habbema<sup>1</sup>

**Objective** To investigate the impact of the current strategy for the elimination of leprosy on its incidence and to assess the consequences of failure to sustain this strategy.

**Methods** Scenarios for assessing the impact of the elimination strategy were implemented in a computer simulation program. The scenarios reflected the assumptions made regarding contagiousness, transmission and bacille Calmette–Guérin (BCG) vaccination. The trend in case detection rate for the main countries in which leprosy was endemic during 1985–98 was fitted, and incidence up to 2020 was projected.

**Findings** Owing to the gradual shortening of delays in detection up to 1998, and because of the low relapse rate that occurs with multidrug treatment MDT, incidence is predicted to decrease beyond 2000 in all scenarios. The annual decline was a few per cent 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%.

**Conclusion** The elimination strategy reduces transmission, but the decline may be slow. Relaxation of control after 2005 is unjustified given the uncertainty about the rate of decline and the adverse effects of longer delays in detection. A long-term strategy for leprosy control should be adopted.

**Keywords** Leprosy/diagnosis/drug therapy/epidemiology; Drug therapy, Combination; BCG vaccine; Treatment outcome; Incidence; Forecasting; Computer simulation; Models, Theoretical (*source: MeSH, NLM*).

**Mots clés** Lèpre/diagnostic/chimiothérapie/épidémiologie; Polychimiothérapie; Vaccin BCG; Evaluation résultats traitement; Resultado del tratamiento; Incidence; Préviation; Simulation ordinateur; Modèle théorique (*source: MeSH, INSERM*).

**Palabras clave** Lepra/diagnóstico/quimioterapia/epidemiología; Quimioterapia combinada; Vacuna BCG; Resultado del tratamiento; Simulación por computador; Incidencia; Predicción; Modelos teóricos (*fuentes: DeCS, BIREME*).

Arabic

Bulletin of the World Health Organization 2004;82:373-380.

Voir page 378 le résumé en français. En la página 379 figura un resumen en español.

## Introduction

The mainstay of current leprosy control is early detection and treatment with multidrug therapy (MDT). The number of patients receiving treatment declined after implementation of MDT because its period of treatment is shorter than that for dapsone monotherapy. At the same time, the annual number of new leprosy cases increased (1). These contrasting trends result from changes in control programmes, and the impact of MDT-based control on transmission is unknown.

MDT was introduced in 1982 because of the emergence of resistance to dapsone monotherapy (2). Relapse rates are low (3). MDT has improved the image of leprosy as a curable disease and has led to increases in the commitment of national health services to finding and treating leprosy patients (4, 5). In 1991 optimism about the impact of MDT led the World Health Assembly (WHA) to pass a resolution to “eliminate leprosy as a public health problem” by the year 2000. This elimination target led to intensive case-finding campaigns, called “leprosy elimination campaigns” in the late 1990s. The WHA resolution has therefore indirectly caused the increase in global case detection.

The elimination target was defined as a prevalence of less than one person per 10 000 population registered for treatment by the year 2000 (6–8). During that year, the number of patients registered for treatment worldwide fell below the target level (9). This achievement was largely the result of two operational factors: the duration of treatment was shortened, and patients not in need of treatment, but possibly with disabilities, were removed from registries (10, 11). This elimination target differs from the concept of “elimination of an infectious disease”, which is defined as the absence of incident cases in a defined geographical area (12).

In order to reach the elimination target in all countries by the end of 2005, WHO formulated a strategy based on early case detection and MDT, called “the final push” (13). This strategy is intended to “reduce the leprosy burden to very low levels, and therefore liberate resources to address other health priorities in the community”. In response, the editor of *Leprosy Review* pointed out that there is no evidence that reaching the target will reduce transmission, and expressed serious concerns regarding the fulfilment of future demands to control leprosy (11).

<sup>1</sup> Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 1738, 3000 DR Rotterdam, Netherlands. Correspondence should be sent to Mr A. Meima at this address (email: a.meima@erasmusmc.nl).

<sup>2</sup> Department of Public Health, Medical School, University of Aberdeen, Aberdeen, Scotland.

Ref. No. 03-003632

(Submitted: 03 April 03 – Final revised version received: 03 November 03 – Accepted: 05 November 03)

An assumption underlying the elimination strategy is that MDT will reduce transmission through reducing the number of contagious individuals in the community, but evidence to support this assumption is lacking (14–16). Data to evaluate the impact of MDT are not readily available for several reasons. Because leprosy has a long and variable incubation period (17), decreases in transmission only gradually become evident. Also, declines in case detection may have other causes, such as bacille Calmette–Guérin (BCG) vaccination. BCG vaccination is used against tuberculosis, but appears to afford greater protection against leprosy (18). Variability in control efforts further complicates the interpretation of trend data.

How much transmission a control strategy can prevent depends on two unresolved issues. Is the incubation period contagious, and, are close contacts of a patient infected rapidly? This article describes scenarios based on certain assumptions regarding earliness of case detection, the above-mentioned unresolved issues and BCG vaccination. These scenarios were explored using the epidemiological modelling framework known as SIMLEP which was designed for assessing and predicting trends in leprosy (19). For each scenario, the trends in incidence and case detection up to 2020 were projected. By comparing the projections, the impact of the current MDT-based elimination strategy could be explored. An analysis of the sensitivity of the projections for uncertainties in leprosy epidemiology was undertaken. Finally, the consequences of relaxation of the elimination strategy beyond 2005 were predicted.

## Methods

SIMLEP distinguishes states to describe the course of leprosy infection and disease. Changes in these states are determined by epidemiological parameters. The parameter values and a set of mathematical equations determine how an epidemiological situation, i.e. the proportions of the total population within the various states, evolves over time.

Different models can be specified within SIMLEP. The essential features of the model used in this study are as follows. The number of births is based on a birth rate applied to the general population. Neonates are susceptible to leprosy and susceptible individuals can become infected as a result of transmission. New infections self-heal, or progress either to contagious disease which does not self-heal, or to non-contagious disease which self-heals (i.e. the patient becomes free from bacteria). Self-healing is a well-recognized phenomenon (17, 20, 21). The appearance of the first clinical symptom denotes the onset of disease, or incidence. A transmission parameter reflects the contagiousness of individuals with contagious disease. SIMLEP considers two interventions: (early) case detection followed by chemotherapy, and BCG vaccination, together with the associated states “on treatment” and “vaccinated”, respectively. The time between onset of disease and case detection, or detection delay, reflects the length of time for which an individual with contagious disease can transmit *Mycobacterium leprae*, and can be varied in SIMLEP. Further assumptions regarding transmission and interventions are varied in the scenario analysis. SIMLEP is age-specific. A life table governs mortality.

Appendix A (web version only, available at: <http://www.who.int/bulletin>) gives more details on the model used (including a graphical representation), and provides the quantification of the parameters. A detailed description of SIMLEP is provided elsewhere (19). SIMLEP is conceptually similar to models for tuberculosis (22, 23).

## Transmission of leprosy

Two gaps in knowledge were found to be critical in a SIMLEP-based investigation of the role of control in the disappearance of leprosy from Norway (24).

*Does contagiousness build up during the incubation period of leprosy?* Contagiousness does not necessarily require the presence of clinical symptoms. Two possibilities were considered; the first is that there is no contagiousness during the incubation period, and the second, that there is gradual build-up of contagiousness during this period. The level of contagiousness is assumed to be constant after onset of disease.

*Do opportunities to transmit *M. leprae* decrease over time?* Because close contacts, who are the people most at risk, may be infected rapidly, the opportunities to transmit *M. leprae* may decrease over time. In addition to no decrease, this study considered half-value times for transmission opportunities of 2, 4 and 8 years. The decrease starts at onset of disease.

## Leprosy control

The value assigned to the detection delay reflects earliness of case detection. In SIMLEP, chemotherapy is assumed to start immediately following case detection, and to stop contagiousness instantaneously, because both dapsone and MDT render patients non-contagious quickly (25). In the scenario analysis, dapsone is used from the start of the simulations in 1960, and MDT from 1990 onwards. The main differences between dapsone and MDT are the duration of treatment and the risk of relapse after treatment.

Trends in the detection delay were based on information recalled by patients from areas with good control (26–31). Our assumptions on delay are as follows. The average detection delay gradually decreased from an initial period of 12 years (no control) to 6 years in 1990, reflecting the gradual establishment of control programmes. Subsequently, the average delay decreased to a constant 4 years for 1992–96, corresponding to the intensification of control after the 1991 WHA resolution (32). Next, following the initiation of leprosy elimination campaigns (33) the average delay decreased further to 2 years in 1998. For the future, we considered two possibilities. The first is that the delay remains constant until 2020. The second is that the average delay gradually increases from 2 to 4 years between 2006 and 2009, and remains constant thereafter reflecting failure to sustain early case detection.

The protective efficacy of BCG against leprosy is well established, although the reported efficacy varies widely (18). The policy in most developing countries is to vaccinate only very young children (34). Country data on immunization coverage are disseminated by WHO (35). Two policies were considered: no vaccination at all, and, vaccination of infants starting in 1975 with an initial coverage of 5%, increasing to 80% in 1990, and to 95% in 1999 and later years. In SIMLEP, BCG is assumed to reduce the chance of an individual becoming infected. A non-waning protective efficacy of 50% was assumed.

## Scenarios: procedure

The alternative assumptions regarding contagiousness during incubation of disease, waning of transmission opportunities and BCG vaccination resulted in 16 ( $2 \times 4 \times 2$ ) scenarios: eight without BCG and eight with BCG. Each scenario was fitted to a reference case detection rate (CDR) during 1985–98. The CDR trends since 1985 are described elsewhere (1) using reported information (36–42). Reference CDRs are calculated as the

average of the CDRs of the countries that satisfied two criteria, namely that at least 2000 cases were detected in 1998, and that figures on the number of cases detected had been reported throughout 1985–95. Fourteen countries satisfied these criteria: Bangladesh, Brazil, China, Ethiopia, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Philippines, Sudan and Viet Nam. The reference CDR increased from 1.3 per 10 000 total population per year in 1985 to 2.3 per 10 000 in 1998, which corresponds to an average annual increase of 4.6% (Fig. 1). The increase was the result of the intensification of control following the WHA elimination resolution, and of leprosy elimination campaigns.

In the scenario simulations, the postulated reductions in the detection delay may first induce increases in CDR (see Results). On the other hand, these reductions imply that contagious cases are detected earlier and earlier. This may bring about reductions in transmission, and after a time lag due to the incubation period and detection delay, also to reductions in incidence and CDR.

The reference trend is fitted by varying SIMLEP's transmission parameter for the level of contagiousness of individuals with contagious disease (19). The best fit of a scenario is obtained by minimizing the sum of the squared differences between the simulated CDR and reference CDR between 1985 and 1998. After fitting, projections of the incidence and CDR until 2020 were made (see above).

### Sensitivity analysis: procedure

Leprosy epidemiology is fraught with uncertainty, and a sensitivity analysis was carried out to account for this. The following seven parameters are varied one by one: percentage of infected

individuals who do not develop disease, duration of the incubation period, percentage of new cases who develop contagious disease, self-healing rate for non-contagious self-healing disease, trend in detection delay, duration of dapsone monotherapy and relapse rate after dapsone.

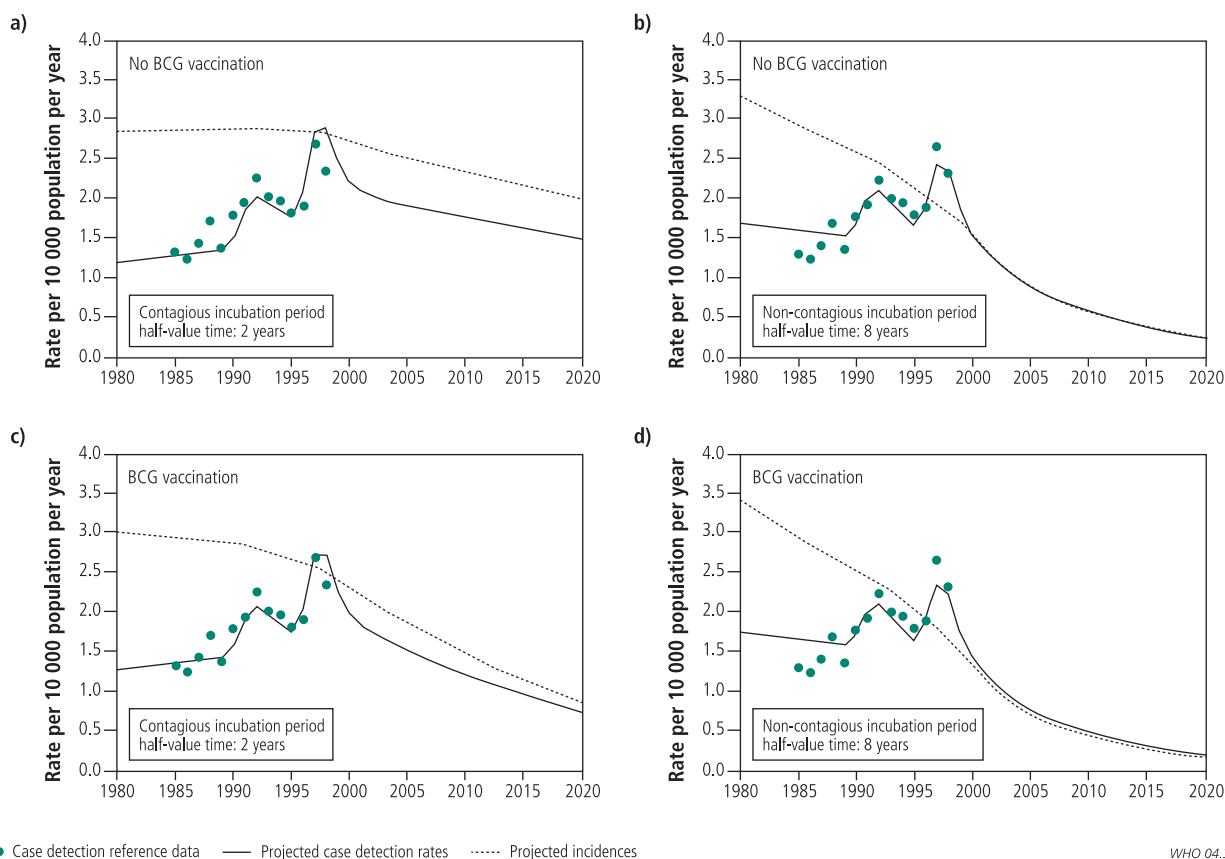
For each new parameter value, the eight scenarios with BCG were again fitted to the CDR reference trend. Projections are made under the assumption that early case-finding and treatment are sustained until 2020 (i.e. a constant detection delay of 2 years is used). Results were compared with those obtained with the baseline assumptions. Tables A2 and A3 in Appendix A specify the parameter values used in the sensitivity analysis (web version only, available at: <http://www.who.int/bulletin>).

## Results

### Scenarios without BCG vaccination

Fig. 1a) shows the simulated CDR and the incidence for the scenario in which leprosy is most difficult to control; i.e. the disease is contagious during the incubation period and opportunities for transmission wane fast. The simulated CDR roughly follows the reference data, suggesting that the trend in the observed, seemingly capricious, CDR can be explained by reductions in detection delays. These reductions were associated with the removal of backlogs in case detection and ceased in 1998, which explains the peak and subsequent drop in simulated CDR. The simulated CDR then started to follow the trend in the incidence because the detection delay was not reduced further. Relative to the incidence, the simulated CDR beyond 2000 was higher than in the 1980s because fewer patients with non-contagious

Fig. 1. Trends in incidence and case detection rate in the study



● Case detection reference data — Projected case detection rates ..... Projected incidences

WHO 04.35

leprosy self-healed before detection. The incidence was constant until 1995, and the average decrease in incidence predicted between 2000 and 2020 is 1.6% per year.

Fig. 1b) depicts a scenario in which leprosy is easier to control; i.e. there is no transmission during the incubation period and transmission opportunities wane slowly. Before 1990, the incidence had already decreased. Nevertheless, the simulated CDR again increased in the 1990s due to the reductions in detection delays. The trend in the incidence determines the trend in simulated CDR beyond 2000, as in the previous scenario. The projected average annual decline in incidence during 2000–20 is 8.3%.

In six of the eight scenarios without BCG, the CDR increased during 1985–98, with a difference from the 4.6% annual increase in the reference trend of less than 50% (Table 1). These increases coincided with incidences in the same period that were either stable, or decreased by up to 3.6% annually. As expected, the decline in incidence beyond 2000 is faster when the incubation period is not contagious, and when the transmission opportunities wane more slowly. The projected decline in incidence accelerates after 2000 in all scenarios because detection delays became shorter in the 1990s, and also because few relapses occur after MDT. For the six scenarios, the average annual decline in incidence projected for 2000–20 ranges from 1.6% to 8.3% (corresponding range for the time needed to halve the incidence: from 8 to 43 years). The two remaining scenarios assumed that transmission opportunities do not wane over time and show a stable CDR (annual changes: between –1% and 1%), which conflicts with the reference trend.

### Scenarios with BCG vaccination

The addition of BCG vaccination had a small impact up to 2000, because only infants are vaccinated and coverages were initially low. Therefore, no important changes were noted in the fit of the reference trend and in the decline in incidence during the reference period 1985–98 (Table 1). BCG vaccination is projected

to enhance the annual decline in incidence during 2000–20 by a few per cent, with a resulting range for the annual decline in incidence from 4.9% to 10.0% for the six scenarios with a good fit. The time required to halve the incidence varies from 7 to 14 years. The scenarios with the least and most favourable projections (see Figs 1c) and 1d)), have 57% and 39% lower incidences in 2020 than in the corresponding scenarios without BCG.

### Scenarios without sustained early case detection and treatment

The consequences of an increase in the detection delay after 2005 are shown in Fig. 2a) and Fig. 2b). Initially, the CDR decreases considerably because detection is postponed and more self-healing cases will go undetected. However, the prolonged delay also implies increased transmission which, after some delay due to the incubation period, results in a slower decrease of the incidence. The consequences of failure to sustain early case detection are similar for the other scenarios.

### Sensitivity analysis

Of the seven parameters varied in the sensitivity analysis (see Appendix A, Table A3: web version only, available at: <http://www.who.int/bulletin>), only two — the length of the incubation period and the trend in detection delay — led to a substantial change in the annual decline in incidence beyond 2000. In all other cases, the annual declines are very close to the baseline value (maximum difference, 1%).

Halving the length of the incubation period leads to a faster decrease in the incidence because shorter incubation periods imply shorter transmission cycles. The effect is greater for the unfavourable scenarios; the decline in incidence beyond 2000 is up to 4% higher. Of the four scenarios with a good fit to the reference trend, the highest annual decline in incidence beyond 2000 is 10.4% (baseline, 10.0%). Doubling the incubation period has the reverse effect of slowing the declines in incidence.

Table 1. Trend in case detection rate (CDR) and in incidence for the 16 scenarios<sup>a</sup>

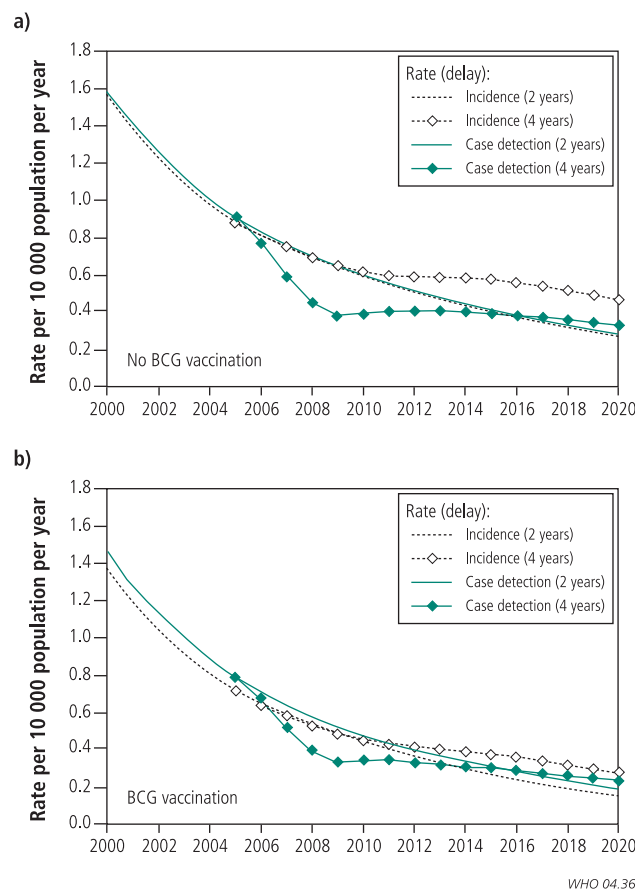
Incubation period contagious?		Yes				No			
		No <sup>b</sup>	8	4	2	No <sup>b</sup>	8	4	2
Without BCG vaccination	Fit of trend in case detection rate 1985–98	Poor	Good	Good	<b>Good<sup>c</sup></b>	Poor	<b>Good<sup>c</sup></b>	Good	Good
	Annual decrease in incidence 1985–98	5.5%	2.4%	1.1%	<b>0.1%</b>	6.4%	<b>3.6%</b>	2.0%	0.5%
	Annual decrease in incidence 2000–20	8.9%	5.2%	3.3%	<b>1.6%</b>	10.6%	<b>8.3%</b>	6.6%	4.3%
With BCG vaccination	Fit of trend in case detection rate 1985–98	Poor	Good	Good	<b>Good<sup>c</sup></b>	Poor	<b>Good<sup>c</sup></b>	Good	Good
	Annual decrease in incidence 1985–98	6.5%	3.5%	2.3%	<b>1.4%</b>	7.2%	<b>4.4%</b>	3.0%	1.5%
	Annual decrease in incidence 2000–20	10.9%	7.9%	6.3%	<b>4.9%</b>	11.9%	<b>10.0%</b>	8.5%	6.5%

<sup>a</sup> A trend in CDR between 1985 and 1998 is scored as “Good” when the scenario has a CDR increase that differs at most by 50% from the 4.6% annual increase in the CDR reference data (i.e. between 2.3% and 6.9%), and is otherwise scored as “Poor”. The four scenarios in which no waning of transmission opportunities occurs show either no increase in CDR or an average annual increase below 2.3%.

<sup>b</sup> Transmission opportunities do not decrease over time.

<sup>c</sup> The scenarios with trends indicated in bold type are the subject of Fig. 1.

Fig. 2. **Effect on leprosy incidence and case detection if failing to sustain early case detection beyond 2005.** Impact on incidence and case detection rate of increasing detection delay from 2 years to 4 years over the period 2006–09 is shown for scenarios in Fig. 1b) and Fig. 1d) (no transmission during the incubation period and half-value time for transmission opportunities of 8 years)



Two alternative trends for detection delay up to 1998 were considered: one with decreases in delay that were greater than in the baseline delay trend, and the other with smaller decreases. Of the scenarios with larger decreases in delay, three give a good fit to the reference trend, whereas six of the scenarios with the baseline delay trend had a good fit. This is because with larger decreases, initial delays in detection are longer and detection backlogs larger, which led to greater increases in simulated CDR during the reference period 1985–98. When compared to the baseline, the decrease in incidence beyond 2000 — when the detection delay has ceased to be longer — is predicted to be somewhat faster (maximum increase, 1.6%). The greatest annual decline was 11.8% (half-value time, 6 years) for the three “good” scenarios, which is the highest decline among all scenarios with a good fit. The maximum annual decline is a little higher (13.5%; half-value time, 5 years), when the five scenarios with a poor fit are also considered. Faster declines were not obtained in this study. The scenarios in which smaller decreases in detection delay before 1998 were assumed had a slower decline in incidence beyond 2000 relative to the baseline.

## Discussion

This study addressed two questions: what is the impact of early case detection and MDT treatment on the transmission and

incidence of leprosy, and what are the consequences of failing to sustain early case detection?

Early case detection and treatment led to a reduced incidence of leprosy in all scenarios. The time required to halve the incidence was 7 years in the most optimistic scenario with BCG vaccination. Slightly faster declines were obtained in the sensitivity analysis. However, much slower declines were found to be possible; half-value times of 14 years with BCG and 43 years without BCG cannot be excluded. A detailed analysis of the predictions indicates that ensuring early detection of contagious patients is the key factor in reducing transmission. Treatment with MDT instead of dapsone monotherapy is also beneficial, because of the lower relapse rates after MDT.

## Consequences of not sustaining early case detection

Sustained early case detection is essential for maintaining decreases in transmission and incidence: the predicted decrease slows down when the detection delay increases after 2005. Keeping detection delays short will be more difficult when leprosy incidence decreases, because both the general population and health workers will become less experienced in recognizing symptoms of leprosy.

Leprosy is a public health problem because of the disabilities it causes. There may be three million people worldwide with disabilities caused by leprosy (43). It has been argued that early detection could prevent the development of disabilities in more than three-quarters of patients (44). Early case detection is therefore also important for prevention of leprosy morbidity.

## Trend in detection delay

For most scenarios, the shortening of the detection delay after 1990 resulted in a good fit of the historical trend for the average case detection rate in countries for which data were available throughout 1985–98. The incidence of leprosy in the “good” scenarios decreased by at most 4.4% per year in this period (Table 1: half value time 15 years). The simulations show that where such declines occur, intensified control may induce a temporary increase in case detection (Figs 1b) and 1d)). In recognition of the limited empirical basis for quantifying the detection delay, two additional delay trends were considered in the sensitivity analysis. The impact on incidence predictions was found to be small: detection delays before 2000 did not influence incidence trends far beyond 2000. It could be argued that the 2-year delay used from 1998 onwards is somewhat optimistic (28, 30, 45, 46); longer delays would lead to less optimistic predictions about future declines in incidence.

## Historical case-detection data

The simulated CDRs increased for more than a decade until 1998, after which control activities were not intensified further. The increase was possible because the simulated CDRs were substantially lower than the incidences in 1985 (Fig. 1). The increase in the historical CDR also lasted more than a decade. Cumulative new cases detected in 1992–98 exceeded those detected in 1985–91 by at least 50% in eight of the 14 countries for which historical data on CDRs were available (1). This indicates that the differences between case detection and incidences must indeed have been substantial.

Information on detection of new cases worldwide is incomplete. Aggregate information is available from 1985 onwards for a group of 33 countries in which leprosy is endemic. Throughout

1994–98, at least 97% of cases detected globally were detected in these 33 countries (global figures were not available before 1994) (1). India detected at least 75% of the cases in this group throughout 1985–98. The other 13 countries in this study accounted for at least 75% of the remaining cases detected. Thus, the majority of the world leprosy problem was concentrated in the 14 countries that detected at least 2000 cases in 1998 and for which historical CDR data were available throughout 1985–98.

The figures reported from some countries may be incomplete or contain inaccuracies, and may have been influenced by overdiagnosis and re-registration of previously treated patients (39). Nevertheless, the data used in this analysis were the best available. To compensate for limitations in the quality of the data, the CDR increase was allowed to deviate by 50% from the increase in the historical CDR over 1985–98 while scoring simulated trends as “good”. The historical trend in CDR reflects an average pattern of case detection trends, and only in some cases is it representative of the trend in individual countries. However, the robustness of the predicted declines in incidence beyond 2000 has already been indicated. Given the historical trend towards an increase in CDR, autonomous decreases in transmission (e.g. due to socioeconomic improvement) were not considered.

India was counted as one country in the construction of the historical trend. The CDR in India was quite stable over 1985–98. For each of the three trends in detection delay, the scenarios were also fitted to India alone for the baseline assumptions: this resulted in slower declines in incidence beyond 2000.

### Impact of BCG vaccination

The scenario analysis suggests that BCG vaccination is important in reducing the incidence of leprosy, yet for various reasons its impact remains uncertain. BCG vaccination is ignored in half of the scenarios, which is equivalent to making the pessimistic assumption that BCG does not protect against leprosy. The remaining scenarios incorporated optimistic assumptions about the efficacy and coverage of BCG vaccination. Fifty per cent lifelong protective efficacy was assumed. In randomized trials, the protection afforded ranged from 20% to 80%, with low values reported in India (18, 47). The assumed trend in coverage is optimistic when compared with data disseminated by WHO (35). Thus, the impact of BCG vaccination may have been overestimated in this analysis.

### Reasons for variability in predicted incidence trends

The scenarios differ in their assumptions regarding two important unknowns, namely, transmission during the incubation period and waning of transmission opportunities due to rapid transmission to close contacts. These unknowns have led to great uncertainty as to the part played by the policy of isolating patients in the disappearance of leprosy from Norway (24). Basic and epidemiological research on transmission is required to improve our understanding of the impact of any strategy for controlling leprosy.

### Extrapolation to global case detection

In 2000, 720 000 new cases of leprosy were detected worldwide (1). 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 will be detected up to 2010 and 2020 is 5 million and 7.5 million, respectively. In the most optimistic prediction, obtained with larger decreases in the detection delay than in the baseline trend (11.8% annual decline in incidence), the number of cases detected would be 4 million in 2010 and 5 million in 2020.

### Conclusion

The scenario analysis demonstrates that the present leprosy elimination strategy will reduce transmission, although the decline may be slow. Early case detection is the key factor in the success of the strategy. The uncertainties about the rate of decline and the adverse effects of longer detection delays imply that relaxation of leprosy control following the end of the “final push” period in 2005, when the target of elimination of leprosy as a public health problem is set to be achieved in all countries, is unjustified. A long-term strategy for leprosy control should be adopted. ■

### Acknowledgements

The financial support from Netherlands Leprosy Relief which made it possible to conduct this study is gratefully acknowledged.

**Conflicts of interest:** none declared.

## Résumé

### Incidence future de la lèpre : analyse de scénarios

**Objectif** Etudier l'impact de la stratégie actuelle d'élimination de la lèpre sur l'incidence de la maladie et évaluer les conséquences qu'aurait l'incapacité à maintenir cette stratégie dans le temps.

**Méthodes** Un programme de simulation informatisé a permis d'appliquer plusieurs scénarios pour évaluer l'impact de la stratégie d'élimination. Les scénarios correspondaient aux hypothèses retenues concernant la contagiosité, la transmission et la vaccination par le BCG. Après avoir pris en compte la tendance du dépistage des cas pour les principaux pays d'endémie entre 1985 et 1998, on a établi des projections de l'incidence jusqu'en 2020.

**Résultats** Du fait que les cas ont été repérés de plus en plus tôt jusqu'en 1998 et grâce au faible taux de rechute associé à

la polychimiothérapie, on prévoit un recul de l'incidence après 2000, quel que soit le scénario. Le recul annuel était un peu plus élevé en pourcentage lorsque des hypothèses favorables étaient retenues concernant la protection et la couverture de la vaccination par le BCG. D'une façon générale, la réduction prévue des taux d'incidence se situait chaque année entre 2 % et 12 %.

**Conclusion** La stratégie d'élimination permet de faire reculer la transmission mais le recul risque d'être lent. Un relâchement des contrôles ne se justifie pas après 2005 étant donné les incertitudes qui entourent le taux de réduction et les effets qu'aurait des retards plus marqués dans le dépistage des cas. Il faudrait adopter une stratégie à long terme pour la lutte antilépreuse.

## Resumen

**Incidencia de la lepra en el futuro: análisis de escenarios**

**Objetivo** Investigar la repercusión de la actual estrategia de eliminación de la lepra en su incidencia, y evaluar qué ocurriría si no se mantuviera esa estrategia.

**Métodos** Mediante un programa informático se simularon distintos escenarios para evaluar el impacto de la estrategia de eliminación. Los escenarios incorporaban las hipótesis asumidas respecto a la infecciosidad, la transmisión y la vacunación con bacilo de Calmette-Guèrin (BCG). Tras ajustar la tendencia de la tasa de detección de casos para los principales países con lepra endémica durante los años 1985-1998, se procedió a proyectar la incidencia hasta 2020.

**Resultados** Debido al progresivo acortamiento de los intervalos de detección hasta 1998, y debido también a la baja tasa de recaídas que se produce con el tratamiento multimedicamentoso

(TMM), se prevé que la incidencia disminuirá a partir de 2000 en todos los escenarios. La disminución anual fue ligeramente mayor - algunos puntos porcentuales - cuando se asumieron hipótesis favorables respecto a la protección y la cobertura con vacuna BCG. En términos generales, la disminución anual predicha de las tasas de incidencia osciló entre un 2% y un 12%.

**Conclusión** La estrategia de eliminación reduce la transmisión, pero la disminución suele ser lenta. La relajación del control con posterioridad a 2005 no está justificada, dada la incertidumbre acerca de la tasa de disminución y de los efectos adversos de los mayores retrasos en la detección. Es preciso adoptar una estrategia a largo plazo para el control de la lepra.

## Arabic

## References

- Meima A, Richardus JH, Habbema JD. Trends in leprosy case detection worldwide since 1985. *Leprosy Review* 2004;75:19-33.
- Ji BH. Drug resistance in leprosy — a review. *Leprosy Review* 1985;56:265-78.
- Visschedijk J, van de Broek J, Eggens H, Lever P, van Beers S, Klatser P. *Mycobacterium leprae* — millennium resistant! Leprosy control on the threshold of a new era. *Tropical Medicine and International Health* 2000;5:388-99.
- Noordeen SK. Elimination of leprosy as a public health problem: progress and prospects. *Bulletin of the World Health Organization* 1995;73:1-6.
- Noordeen SK. Eliminating leprosy as a public health problem — is the optimism justified? *World Health Forum* 1996;17:109-44. [Erratum published in *World Health Forum* 1996;17:426.]
- World Health Assembly. *Elimination of leprosy: resolution of the 44th World Health Assembly*. Geneva: World Health Organization; 1991 (Resolution No. WHA 44.9).
- A guide to leprosy control*. Second edition. Geneva: World Health Organization; 1988.
- WHO Expert Committee on Leprosy. Seventh report*. Geneva: World Health Organization; 1998 (WHO Technical Report Series, No. 874).
- World Health Organization. Leprosy — global situation. *Weekly Epidemiological Record* 2002;77:1-8.
- Fine PE. Reflections on the elimination of leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases* 1992;60:71-80.
- Lockwood DN. Leprosy elimination — a virtual phenomenon or a reality? *BMJ* 2002;324:1516-8.
- Dowdle WR. The principles of disease elimination and eradication. *Bulletin of the World Health Organization* 1998; 76 Suppl 2:22-5.
- The final push towards elimination of leprosy: strategic plan 2000–2005*. Geneva: World Health Organization; 2000.
- Meima A, Gupte MD, van Oortmarssen GJ, Habbema JD. Trends in leprosy case detection rates. *International Journal of Leprosy and Other Mycobacterial Diseases* 1997;65:305-19.
- Fine PE, Warndorff DK. Leprosy by the year 2000 — what is being eliminated? *Leprosy Review* 1997;68:201-2.
- Smith WC. We need to know what is happening to the incidence of leprosy. *Leprosy Review* 1997;68:195-200.
- Fine PE. Leprosy: the epidemiology of a slow bacterium. *Epidemiologic Reviews* 1982;4:161-88.
- Fine PE, Smith PG. Vaccination against leprosy — the view from 1996. *Leprosy Review* 1996;67:249-52.
- Meima A, Gupte MD, van Oortmarssen GJ, Habbema JD. SIMLEP: a simulation model for leprosy transmission and control. *International Journal of Leprosy and Other Mycobacterial Diseases* 1999;67:215-36.
- Browne SG. Self-healing leprosy: report on 2749 patients. *Leprosy Review* 1974;45:104-11.
- Sirumban P, Kumar A, Neelan PN. Healing time in untreated paucibacillary leprosy: a cross-sectional study. *International Journal of Leprosy and Other Mycobacterial Diseases* 1988;56:223-7.
- Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *Lancet* 1998;352:1886-91.
- Murray CJL, Salomon JA. Modeling the impact of global tuberculosis control strategies. *Proceedings of the National Academy of Sciences USA* 1998;95:13881-6.
- Meima A, Irgens LM, Van Oortmarssen GJ, Richardus JH, Habbema JD. Disappearance of leprosy from Norway: an exploration of critical factors using an epidemiological modelling approach. *International Journal of Epidemiology* 2002;31:991-1000.
- Waters MF. The treatment of leprosy. *Tubercle* 1983;64:221-32.

26. Smith TC, Richardus JH. Leprosy trends in northern Thailand: 1951-1990. *Southeast Asian Journal of Tropical Medicine and Public Health* 1993;24:3-10.
27. Li HY, Pan YL, Wang Y. Leprosy control in Shandong Province, China, 1955-1983; some epidemiological features. *International Journal of Leprosy and Other Mycobacterial Diseases* 1985;53:79-85.
28. World Health Organization. Progress towards the elimination of leprosy as a public health problem. Part I. *Weekly Epidemiological Record* 1995;70:177-82.
29. Li HY, Weng XM, Li T, Zheng DY, Mao ZM, Ran SP, et al. Long-term effect of leprosy control in two Prefectures of China, 1955-1993. *International Journal of Leprosy and Other Mycobacterial Diseases* 1995;63:213-21.
30. Meima A, Saunderson PR, Gebre S, Desta K, van Oortmarssen GJ, Habbema JD. Factors associated with impairments in new leprosy patients: the AMFES cohort. *Leprosy Review* 1999;70:189-203.
31. Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1978-1995. I. Overview of the study. *International Journal of Leprosy and Other Mycobacterial Diseases* 1998;66:149-58.
32. Noordeen SK. Eliminating leprosy as a public health problem; why the optimism is justified. *International Journal of Leprosy and Other Mycobacterial Diseases* 1995;63:559-66.
33. World Health Organization. Trends in leprosy detection. *Weekly Epidemiological Record* 1998;73:169-75.
34. World Health Organization. BCG in immunization programmes. *Weekly Epidemiological Record* 2001;76:33-9.
35. World Health Organization. *Vaccination, immunization and biologicals*. Coverage time series. Geneva: World Health Organization. Available from: URL: <http://www.who.int/vaccines-surveillance/StatsAndGraphs.htm>.
36. *Progress towards the elimination of leprosy. Reports from major endemic countries*. New Delhi: International Conference on the Elimination of Leprosy; 11-13 October 1996.
37. World Health Organization. Progress towards leprosy elimination. *Weekly Epidemiological Record* 1997;72:165-72.
38. World Health Organization. Progress towards leprosy elimination. *Weekly Epidemiological Record* 1998;3:153-60.
39. World Health Organization. Global leprosy situation, September 1999. *Weekly Epidemiological Record* 1999;74:313-6.
40. Dharmshaktu NS, Barkakaty BN, Patnaik PK, Arif MA. Progress towards elimination of leprosy as a public health problem in India and role of modified leprosy elimination campaign. *Leprosy Review* 1999;70:430-9.
41. World Bank. The 2001 World Development Indicators CD ROM. Washington: The World Bank; 2001.
42. World Health Organization. Leprosy — global situation. *Weekly Epidemiological Record* 2000;75:226-31.
43. Report of the International Leprosy Association Technical Forum. Paris, France, 22-28 February 2002. *International Journal of Leprosy and Other Mycobacterial Diseases* 2002;70 1 Suppl:S1-62.
44. Richardus JH, Finlay KM, Croft RP, Smith WC. Nerve function impairment in leprosy at diagnosis and at completion of MDT: a retrospective cohort study of 786 patients in Bangladesh. *Leprosy Review* 1996;67:297-305.
45. Wittenhorst B, Vree ML, Ten Ham PB, Velema JP. The National Leprosy Control Programme of Zimbabwe a data analysis, 1983-1992. *Leprosy Review* 1998;69:46-56.
46. Chen XS, Li WZ, Jiang C, Ye GY. Leprosy in China: epidemiological trends between 1949 and 1998. *Bulletin of the World Health Organization* 2001;79:306-12.
47. Gupte MD. South India immunoprophylaxis trial against leprosy: relevance of findings in the context of leprosy trends. *International Journal of Leprosy and Other Mycobacterial Diseases* 2001;69 Suppl:S10-3.

## Appendix A

This appendix details the quantification of the SIMLEP model and provides the values for the parameters used in the sensitivity analysis. A detailed description of the SIMLEP modelling framework has appeared elsewhere (1). The information underlying the reference trend for the case detection rate (CDR) that is used in the scenario analysis is also summarized.

### Model and parameter quantifications

Fig. A1 shows the structure of the SIMLEP model. The transitions between compartments are governed by transition rates, i.e. by exponential probability distributions, unless otherwise indicated (see also (1)). Table A1 and Table A2 list the quantification of the model parameters. Additional information and its sources are given below.

### Demographic data

Demographic data for India for 1987, which is close to the middle year of the simulation period, 1960–2020, are used for the birth rate and age-specific death rates (2).

### Asymptomatic infection

A high percentage (90%) of newly-infected individuals are assumed to self-heal without developing any clinical symptoms of leprosy, because leprosy infection is considered to be far more common than leprosy disease (3, 4).

The episode of asymptomatic infection represents the time until self-healing for infected individuals who do not develop disease, and the incubation period for those who develop non-contagious self-healing disease or contagious disease which does not self-heal. These forms of disease are referred to below as PB leprosy (paucibacillary leprosy) and MB leprosy (multibacillary leprosy). The median values of the duration of the incubation periods of PB leprosy (3.5 years) and MB leprosy (10 years) are based on data collected from studies on veterans from non-endemic areas who contracted leprosy after serving in endemic areas (reported minimum and maximum estimates for the median incubation period for veterans with PB leprosy: 2 and 5 years, respectively, and for MB leprosy 8 and 12 years, respectively) (3). For those people who did not develop the disease,

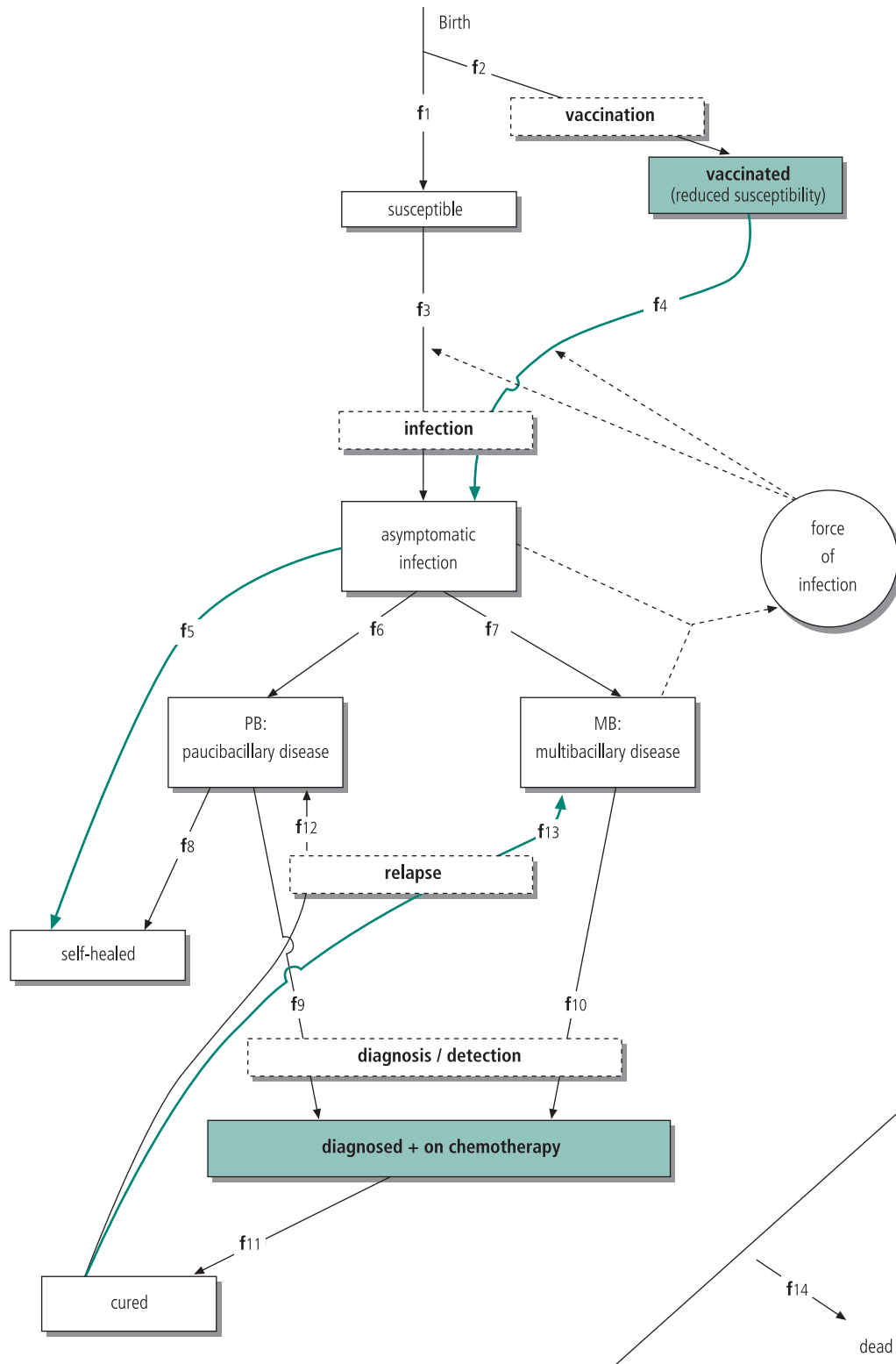
Table A1. Parameter values used in the scenario analysis<sup>a</sup>

Input parameter	Flows	Value(s)
<b>Demographic data</b>		
Birth rate per 1000 total population per year	<i>f1, f2</i>	32.2
Age-specific death rates (based on Indian life table)	<i>f14</i>	see text
<b>Asymptomatic infection</b>		
Percentage of newly-infected individuals not developing leprosy disease	<i>f5</i>	90%
Median duration of asymptomatic infection (Erlang distribution; years)		
– for those not developing leprosy disease	<i>f5</i>	3.5
– for those developing paucibacillary disease	<i>f6</i>	3.5
– for those developing multibacillary disease	<i>f7</i>	10
<b>Disease and transmission</b>		
Percentage of new cases who develop		
– paucibacillary disease	<i>f6</i>	80%
– multibacillary disease	<i>f7</i>	20%
Self-healing rate for paucibacillary disease per year	<i>f8</i>	22.4%
Build-up of contagiousness while incubating for multibacillary disease	<i>f3, f4</i>	<u>no, yes</u>
Half-value times for waning of transmission opportunities (years)	<i>f3, f4</i>	<u>none<sup>b</sup>, 2, 4, 8</u>
<b>BCG vaccination at birth: different scenarios</b>		
Application	<i>f1, f2</i>	<u>no, yes</u>
Coverage	<i>f1, f2</i>	see text
Protective efficacy	<i>f4</i>	50% lifelong
<b>Case detection and chemotherapy treatment</b>		
Mean delay in case detection	<i>f9, f10</i>	see text, Table A2
Mean duration of treatment (years) and drug regimen		
– 1960–89: dapsone monotherapy	<i>f11</i>	9
– 1990–99: multidrug treatment	<i>f11</i>	0.8
– 2000–20: multidrug treatment	<i>f11</i>	0.6
Relapse rate per year		
– after dapsone monotherapy cure	<i>f12, f13</i>	1.5%
– after multidrug therapy cure	<i>f12, f13</i>	0.1%
Proportion of relapsing patients who relapse after either therapy to:		
– paucibacillary disease	<i>f12, f13</i>	10%
– multibacillary disease	<i>f12, f13</i>	90%

<sup>a</sup> Flows refer to Fig. A1. Underlined values refer to assumptions that have been varied in the 16 scenarios.

<sup>b</sup> Transmission opportunities do not wane over time.

Fig. A1. Structure of the SIMLEP model as used in the scenario analysis



WHO 04.37

the length of time until self-healing was equal to the duration of the incubation period for PB leprosy.

### Untreated disease and transmission

The incidence of leprosy is based on a ratio of PB to MB disease of 4:1. For PB disease, a self-healing rate of 22.4% per year is

assumed in accordance with Sirumban et al. (5). The ratio of PB leprosy to MB leprosy in new case detection depends on the PB to MB ratio for incidence, on the self-healing rate of PB leprosy, and on delays in detection and diagnosis. The reported ratios vary widely between the different regions of the world (see e.g. (3)).

Table A2. Time trends over 1960–2020 for the mean detection delay

	Mean detection delay (years)				
	1960–90 Decrease	1990–92 Decrease	1992–96 Constant	1996–98 Decrease	1998–2020 Constant
Trend with small decreases in delay	from 8 to 4	from 4 to 3	3	from 3 to 2	2
Baseline trend in delay	from 12 to 6	from 6 to 4	4	from 4 to 2	2
Trend with large decreases in delay	from 16 to 8	from 8 to 5	5	from 5 to 2	2

Knowledge on the extent of contagiousness and transmission of leprosy is limited. In the scenario analysis, MB leprosy is assumed to be contagious, and in half of the scenarios considered, individuals incubating MB disease are assumed to gradually build up contagiousness. The possibility that patients with PB leprosy and those incubating it are also contagious was not explored. This is because the issue of contagiousness of patients with PB leprosy was considered to be much less important in assessing the possible impact of interventions on transmission than the question of when (which may also be before the onset of disease) transmission takes place.

It is not known whether the opportunities for an individual to transmit *Mycobacterium leprae* decrease over time. Such a decrease is plausible because close contacts, who are at a high risk of contracting leprosy (6), may be infected rapidly. In the scenario analysis, in addition to no decrease, half-value times for transmission opportunities for diseased individuals of 2, 4 and 8 years were considered.

### BCG vaccination at birth

In most developing countries, bacille Calmette–Guérin (BCG) vaccination is given in very early childhood (7). BCG vaccination was ignored in half of the scenarios (“no vaccination at all”), which is equivalent to the pessimistic assumption that BCG does not protect against leprosy. In the other half of the scenarios, optimistic assumptions about BCG were made. A policy of vaccination of infants was assumed, starting in 1975 with an initial coverage of 5%, increasing to 80% in 1990, and to 95% in 1999 and all subsequent years. These figures are optimistic when compared to the coverages reported by Member States to WHO (8). Randomized controlled trials have shown that the protective efficacy of BCG against leprosy ranges from 20% to 80% (9). The protective efficacy was quite low in Asia, particularly in India where most patients with leprosy are detected (10–12), and it is not known whether the protective efficacy decreases with age. The optimistic assumption of a lifelong 50% efficacy was made.

### Case detection and chemotherapy

The delay in detection has a skewed distribution (13). Therefore, SIMLEP uses a convolution of two exponential probability distributions for the length of the detection delay (13). A trend in mean detection delay was defined using historical information based on recall by patients from areas in which leprosy control is well organized (13–18).

The historical trend is summarized in Table A2 (baseline trend in delay). The mean detection delay gradually decreases from an initial 12 years (“no control”) to 6 years in 1990, reflecting the gradual establishment of leprosy control programmes. Subsequently, the mean delay decreases to a constant 4 years for

1992–96, corresponding to the intensification of control after the 1991 WHA resolution regarding leprosy elimination (19). The mean delay then decreases to 2 years in 1998, following the initiation of “leprosy elimination campaigns” (20).

In the predictions for the future, two possibilities were considered. The first was that the detection delay remains constant at 2 years until 2020. The second possibility was that the mean detection delay gradually increases from 2 to 4 years between 2006 and 2009, remaining constant thereafter, which reflects possible failure to sustain early case detection and treatment beyond 2005.

The duration of treatment is governed by a single exponential probability distribution for all patients. In the scenario analysis, treatment between 1960 and 1989 was by dapsone monotherapy and, from 1990 onwards, by multidrug therapy (MDT). The choice of a mean duration of dapsone treatment of 9 years was somewhat arbitrary: dapsone was usually prescribed for 5 years for patients with tuberculoid leprosy and for 20 years or for life for patients with lepromatous leprosy (21). The prescribed duration of MDT treatment has changed several times, but has always been much shorter than dapsone treatment (22–24). The assumed mean duration of MDT treatment (all patients) was less than 1 year (see Table A1).

In SIMLEP, the relapse rates after treatment cure are equal for PB and MB leprosy, and are constant over time. A relapse rate after dapsone monotherapy of 1.5% per year was chosen, based on the data of Becx Bleumink who reported a relapse rate of 0.7% for PB leprosy and 2.5% for MB leprosy (under the assumption that equal numbers of new cases of PB and MB leprosy are detected, the 1.5% rate for all patients and the separate 0.7% and 2.5% rates for PB leprosy and MB leprosy give the same cumulative proportion of relapsed cases after 25 years) (25). The reported rates of relapse after dapsone monotherapy vary widely (see, for example, (25–32)). Programmes conducted in the field have reported much lower relapse rates after MDT (6). A relapse rate for PB and MB patients of 0.1% per year following MDT was used. Using the data of Smith et al. (33), 10% of patients with relapses present with PB leprosy, and the remaining 90% with MB leprosy.

### Sensitivity analysis

Table A2 and Table A3 list the different values of the parameters that were used in the sensitivity analysis. Birth rate and age-specific death rates were not varied in the sensitivity analysis. Also, no variation was made in the mean duration of MDT (changes will not affect simulation results), the relapse rate after cure with MDT (this rate is too low to affect simulation results), or in the proportion of those patients who relapse to MB disease (baseline value, 90%; the majority of patients who relapse would be expected to have leprosy of the MB type).

Table A3. Alternative quantifications in the sensitivity analysis

Parameter changes	Flows	Value(s)
Percentage of newly-infected individuals not developing disease	f5	0%
Median duration of incubation period (years) <sup>a</sup>	f6, f7	halved: PB <sup>b</sup> : 1.75, MB <sup>c</sup> 5 doubled: PB: 7, MB 20
Percentage of new cases who develop MB disease	f6, f7	halved: 10% doubled: 40%
Self-healing rate for PB disease per year	f8	halved: 11.2% doubled: 44.8%
Trend in mean delay in case detection	f9, f10	small decreases in delay large decreases in delay
Mean duration of dapsone monotherapy (years)	f11	halved: 4.5 doubled: 18
Relapse rate per year after dapsone monotherapy cure	f12, f13	halved: 0.75% doubled: 3.0%

<sup>a</sup> Median durations of 1.75 and 7 years were also used for the period of asymptomatic infection for subjects who did not develop disease (flow f5). The duration of this period had no effect on the scenario predictions.

<sup>b</sup> PB = paucibacillary.

<sup>c</sup> MB = multibacillary.

### Values of parameters that are varied

The values of the baseline parameters are given in Table A1 and Table A2. For most of the parameters, the baseline values were halved and doubled for the scenario analysis (Table A3). The exceptions were the percentage of newly detected cases who do not develop leprosy disease (Table A3) and the trend in detection delay (Table A2). The baseline assumption is that 90% of newly-infected individuals self-heal without ever displaying any clinical symptom of leprosy. The contrasting assumption is that all newly-infected individuals will develop leprosy disease. In the baseline trend in detection delay, the mean delay decreased by 2 years between 1990 and 1992, and by a further 2 years between 1996 and 1998 (Table A2). By contrast, for the trend with small decreases in the delay, the mean delay decreases twice by 1 year and, in the trend with large decreases, twice by 3 years. The mean delay of 2 years from 1998 onwards, which corresponds to a median delay of 1.5 years, was used in all three trends for the detection delay.

### Reference data for case detection rate

The reference CDR during 1985–95 was calculated as the average of the CDRs of the 14 countries in which at least 2000 cases were detected in 1998, and for which detection figures at country level were reported throughout 1985–95. The trends in CDR since 1985 are described elsewhere (34) on the basis of the reported information (35–41). The CDRs per 10 000 total population for the year 1998 and the average annual increases in CDR between 1985 and 1998, derived from the CDRs for these 2 years for the 14 countries are as follows: Bangladesh (1.0; +5.3%), Brazil (2.5; +4.5%), China (0.02; –7.8%), Ethiopia (0.7; –3.6%), Guinea (5.2; +21.8%), India (6.5; +0.3%), Indonesia (0.9; +4.5%), Madagascar (6.1; +9.0%), Mozambique (2.2; +9.2%), Myanmar (3.1; +4.3%), Nepal (3.0; –0.2%), Philippines (0.5; +6.6%), Sudan (0.7; +26.0%) and Viet Nam (0.3; –1.6%). The reference CDR increased from 1.3 per 10 000 total population per year in 1985 to 2.3 in 1998 (average annual increase, 4.6%).

### References

1. Meima A, Gupte MD, van Oortmarssen GJ, Habbema JD. SIMLEP: a simulation model for leprosy transmission and control. *International Journal of Leprosy and Other Mycobacterial Diseases* 1999;67:215–36.
2. Foundation for Research in Health Systems. *Health Monitor*. Pune, India: The Foundation; 1993. p.10, p. 21.
3. Fine PE. Leprosy: the epidemiology of a slow bacterium [review]. *Epidemiologic Reviews* 1982;4:161–88.
4. Noordeen SK. The epidemiology of leprosy. In: Hastings RC, editor. *Leprosy*. Edinburgh: Churchill Livingstone; 1985. p. 15–30.
5. Sirumban P, Kumar A, Neelan PN. Healing time in untreated paucibacillary leprosy: a cross-sectional study. *International Journal of Leprosy and Other Mycobacterial Diseases* 1988;56:223–7.
6. Report of the International Leprosy Association Technical Forum. Paris, France, 22–28 February 2002. *International Journal of Leprosy and Other Mycobacterial Diseases* 2002;70 Suppl:S1–62.
7. World Health Organization. BCG in immunization programmes. *Weekly Epidemiological Record* 2001;76:33–9.
8. World Health Organization. Vaccination, immunization and biologicals. Coverage time series. Geneva: World Health Organization. Available from: URL: <http://www.who.int/vaccines-surveillance/StatsAndGraphs.htm>
9. Fine PE, Smith PG. Vaccination against leprosy – the view from 1996 [editorial]. *Leprosy Review* 1996;67:249–52.
10. Lwin K, Sundaresan T, Gyi MM, Bechelli LM, Tamondong C, Garbajosa PG, et al. BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma. *Bulletin of the World Health Organization* 1985;63:1069–78.
11. Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa S, Balasubramanyam RLJdB, et al. Comparative vaccine trial in South India. *Indian Journal of Leprosy* 1998;70:369–88.
12. Gupte MD. South India immunoprophylaxis trial against leprosy: relevance of findings in the context of leprosy trends. *International Journal of Leprosy and Other Mycobacterial Diseases* 2001;69 Suppl:S10–S13.
13. Meima A, Saunderson PR, Gebre S, Desta K, van Oortmarssen GJ, Habbema JD. Factors associated with impairments in new leprosy patients: the AMFES cohort. *Leprosy Review* 1999;70:189–203.
14. Smith TC, Richardus JH. Leprosy trends in northern Thailand: 1951–1990. *Southeast Asian Journal of Tropical Medicine and Public Health* 1993;24:3–10.
15. Li HY, Pan YL, Wang Y. Leprosy control in Shandong Province, China, 1955–1983; some epidemiological features. *International Journal of Leprosy and Other Mycobacterial Diseases* 1985;53:79–85.
16. World Health Organization. Progress towards the elimination of leprosy as a public health problem. Part I. *Weekly Epidemiological Record* 1995;70:177–82.

17. Li HY, Weng XM, Li T, Zheng DY, Mao ZM, Ran SP, et al. Long-term effect of leprosy control in two Prefectures of China, 1955-1993. *International Journal of Leprosy and Other Mycobacterial Diseases* 1995;63:213-21.
18. Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1978-1995. I. Overview of the study. *International Journal of Leprosy and Other Mycobacterial Diseases* 1998;66:149-58.
19. Noordeen SK. Eliminating leprosy as a public health problem; why the optimism is justified [editorial]. *International Journal of Leprosy and Other Mycobacterial Diseases* 1995;63:559-66.
20. World Health Organization. Trends in leprosy detection. *Weekly Epidemiological Record* 1998;73:169-75.
21. Waters MF. The treatment of leprosy. *Tubercle* 1983;64:221-32.
22. World Health Organization. *Chemotherapy of leprosy for control programmes*. WHO Technical Report Series, No. 675. Geneva: World Health Organization; 1982.
23. WHO Study Group. *Chemotherapy of leprosy*. Geneva: World Health Organization; 1994 (WHO Technical Report Series, No. 847).
24. WHO Expert Committee on Leprosy. *Seventh Report*. Geneva: World Health Organization; 1998 (WHO Technical Report Series, No. 874).
25. Becx-Bleumink M. Relapses in leprosy patients after release from dapsone monotherapy; experience in the leprosy control program of the all Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *International Journal of Leprosy and Other Mycobacterial Diseases* 1992;60:161-72.
26. Noordeen SK. Relapse in lepromatous leprosy. *Leprosy Review* 1971;42:43-8.
27. Jesudasan K, Christian M, Bradley D. Relapse rates among nonlepromatous patients released from control. *International Journal of Leprosy and Other Mycobacterial Diseases* 1984;52:304-10.
28. Waters MF, Rees RJ, Laing AB, Khoo Kah F, Meade TW, Parikshak N, et al. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Leprosy Review* 1986;57:101-9.
29. Cartel JL, Naudillon Y, Remy JC, Grosset JH. Contribution of relapses to total infection sources of leprosy in Guadeloupe. *Leprosy Review* 1987;58:339-48.
30. Cartel JL, Boutin JP, Spiegel A, Plichart R, Roux JF. Longitudinal study on relapses of leprosy in Polynesian multibacillary patients on dapsone monotherapy between 1946 and 1970. *Leprosy Review* 1991;62:186-92.
31. Pandian TD, Muliylil J, Vellut C. Risk of relapse among non-lepromatous patients released from treatment after dapsone monotherapy. *Leprosy Review* 1991;62:288-96.
32. Li HY. Problems of leprosy relapse in China. *International Journal of Leprosy and Other Mycobacterial Diseases* 1993;61:1-7.
33. Smith TC, Richardus JH. Relapse rates in patients treated with dapsone monotherapy and combinations of dapsone and thiambutosine, thiacetazone, isoniazid and streptomycin in the pre-MDT era. *International Journal of Leprosy and Other Mycobacterial Diseases* 1994;62:353-8.
34. Meima A, Richardus JH, Habbema JD. Trends in leprosy case detection worldwide since 1985. *Leprosy Review* 2004;75:19-33.
35. Progress towards the elimination of leprosy. Reports from major endemic countries. International Conference on the Elimination of Leprosy. New Delhi, India: 11-13 October 1996.
36. World Health Organization. Progress towards leprosy elimination. *Weekly Epidemiological Record* 1997;72:165-72.
37. World Health Organization. Progress towards leprosy elimination. *Weekly Epidemiological Record* 1998;73:153-60.
38. World Health Organization. Global leprosy situation, September 1999. *Weekly Epidemiological Record* 1999;74:313-6.
39. Dharmshaktu NS, Barkakaty BN, Patnaik PK, Arif MA. Progress towards elimination of leprosy as a public health problem in India and role of modified leprosy elimination campaign. *Leprosy Review* 1999;70:430-9.
40. World Health Organization. Leprosy — global situation. *Weekly Epidemiological Record* 2000;75:226-31.
41. The World Bank. The 2001 World Development Indicators CD ROM. Washington: The World Bank; 2001.