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# Disappearance of leprosy from Norway: an exploration of critical factors using an epidemiological modelling approach

Abraham Meima,[a] Lorentz M Irgens,[b] Gerrit J van Oortmarssen,[a] Jan H Richardus[a] and J Dik F Habbema[a]

**Background** By the middle of the 19th century, leprosy was a serious public health problem in Norway. By 1920, new cases only rarely occurred. This study aims to explain the disappearance of leprosy from Norway.

**Methods** Data from the National Leprosy Registry of Norway and population censuses were used. The patient data include year of birth, onset of disease, registration, hospital admission, death, and emigration. The Norwegian data were analysed using epidemiological models of disease transmission and control.

**Results** The time trend in leprosy new case detection in Norway can be reproduced adequately. The shift in new case detection towards older ages which occurred over time is accounted for by assuming that infected individuals may have a very long incubation period. The decline cannot 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 depends on assumptions made on build-up of contagiousness during the incubation period and waning of transmission opportunities due to rapid transmission to close contacts.

**Conclusion** The impact of isolation on interruption of transmission remains uncertain. This uncertainty also applies to contemporary leprosy control that mainly relies on chemotherapy treatment. Further research is needed to establish the impact of leprosy interventions on transmission.

**Keywords** Computer simulation, epidemiology, history, leprosy, Norway, patient isolation

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Founded in 1856, the National Leprosy Registry of Norway documents the fall of leprosy in Norway. By 1920, new cases were only rarely detected. On the basis of the registry, Irgens analysed the disappearance of leprosy from Norway.[1] Between 1856 and 1920, the new case detection rate steadily declined, whereas the ages of newly detected cases gradually but distinctly increased. The decline of leprosy coincided with changes in a number of factors which may influence the occurrence of leprosy and it has been shown to be associated with the policy of isolation of patients in hospitals which was implemented in Norway.[1] The decline took place long before effective anti-leprosy treatment became available.

Leprosy epidemiology is fraught with many uncertainties. In particular, knowledge on the relative contagiousness of different stages of leprosy is lacking. The uncertainties make it difficult to assess the impact of interventions on time trends in leprosy, especially when other factors influencing leprosy change simultaneously. Simulation models can help to organize knowledge and assumptions on diseases, and enable exploration of the occurrence of diseases in populations over time. This study uses a series of simulation models of leprosy transmission and control with the objective of further clarifying mechanisms underlying the Norwegian time trend data. The following questions are addressed:

- Can the decline in leprosy be simulated?
- Can the age-shift in new case detection over time be explained?

[a] Department of Public Health, Faculty of Medicine, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands.

[b] Medical Birth Registry of Norway, Locus of Registry-Based Epidemiology, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway.

Correspondence: Abraham Meima, Department of Public Health, Erasmus MC, University Medical Centre Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail: meima@mgz.fgg.eur.nl

- Can the contribution of isolation to the declining trend be assessed?

First, a statistical model is used, which does not include assumptions about leprosy or the fact that an infectious disease is addressed (curve fitting). Next, a simple standard infectious disease transmission model is applied which does not yet include age. These models only allow for exploration of the overall trend in new case detection. As a third step, models are introduced with an explicit age dimension in order to explain the shift in new case detection to older ages over time, as observed in Norway.[2] Differences in contagiousness before and after onset of clinical symptoms of leprosy influence the degree to which isolation can prevent leprosy transmission. Various model variants are therefore considered which make different assumptions on the transmission of *Mycobacterium leprae* in successive stages of leprosy. The age-specific models are implemented in the SIMLEP framework for modelling the transmission and control of leprosy.[3]

## Material

### History of leprosy and its control in Norway

An historical overview of leprosy research and control in Norway[4] indicates that leprosy was not regarded as a serious health problem by the Norwegian authorities prior to the 1820s. Censuses of leprosy sufferers in 1836, 1845 and 1852 each reported more new patients. Control measures were initiated following the 1852 census which reported 1782 patients. A Chief Medical Officer for Leprosy was appointed, and local measures were entrusted to District Health Officers. By Royal Decree in 1856, the National Leprosy Registry of Norway was founded. The first leprosy hospital in Norway, St George's in Bergen, probably dates back to the 15th century. In 1849, a leprosy research hospital was completed. Three additional hospitals were built in the period 1854–1861. The total capacity in 1861 was 930 beds. In 1873, the leprosy bacillus *M. leprae* was discovered at the research hospital, and it became recognized that leprosy is an infectious disease. It was suggested that transmission could be reduced by isolation of contagious individuals from the general community. The admission to hospitals was voluntary up to 1875. By legislation in 1877 and 1885, leprosy patients either had to be isolated in separate rooms in their homes, or had to be admitted to a hospital, if necessary with the help of the police.

### The National Leprosy Registry of Norway: patient data

The National Leprosy Registry was computerized in the 1970s, and consists of a district register and a hospital register. A detailed description of the database is available.[1] The database includes information on birth, onset of disease as recalled by the patient, registration, admission to hospital, death, and emigration. Years of birth and onset of disease are available for 98% and 94% of patients, respectively. The year of detection refers to the first entry in either the district register or the hospital register. It is known for all registry patients. Nearly 60% of registry patients had at least one hospital admission recorded, and 72% of these admissions were permanent. We will use the term isolation to refer to the first hospital admission of a patient. For 96% of registry patients, the year of either death or emigration is available.

### Trends in case detection

The registry contains information on 8231 patients, including 213 patients who were admitted to a hospital before the founding of the registry in 1856. The secular trend before 1856 is uncertain. Annual numbers of patients detected during 1856–1920 and corresponding case detection rates are given in Table 1. In 1856, many patients were detected (1796). This reflects the registration of a backlog of prevalent leprosy cases. The declining trend in new case detection rate accelerated over time and was on average about 7% per year during 1861–1920. Only 27 patients were detected after 1920.

The age distribution of cases detected during the period 1856–1920 is given in Table 2. The proportion of children is low. A shift towards older ages is observed after 1876: the percentage of newly detected cases of ages $\geqslant 35$ increased steadily from 49% for 1876–1885 to 66% for 1901–1920. Demographic data[5] show that the age structure of the Norwegian population hardly changed between 1856 and 1920.

### Times between onset, detection, isolation and emigration or death

Table 3 gives the mean times between onset and detection, between onset and isolation, emigration or death, and between

**Table 1** New leprosy case detection in Norway, 1856–1920

| Period | Population (person-years) | No. detected[a] | Detection rate per 100 000 person-years |
|---|---|---|---|
| 1856–1860 | 7 671 135 | 2833[b] | 36.9 |
| 1861–1865 | 8 199 131 | 1146 | 14.0 |
| 1866–1870 | 8 597 373 | 1034 | 12.0 |
| 1871–1875 | 8 828 299 | 797 | 9.0 |
| 1876–1880 | 9 326 248 | 692 | 7.4 |
| 1881–1885 | 9 620 933 | 428 | 4.4 |
| 1886–1890 | 9 859 632 | 358 | 3.6 |
| 1891–1900 | 20 958 385 | 411 | 2.0 |
| 1901–1910 | 23 095 413 | 220 | 1.0 |
| 1911–1920 | 24 997 694 | 72 | 0.3 |
| **Total** | | 7991 | |

[a] Out of the 8231 registry patients, 213 were detected before 1856, and 27 after 1920.

[b] 1796 cases were detected in the first year of the National Leprosy Registry, 1856.

**Table 2** Age distribution of newly detected leprosy cases in Norway, 1856–1920

| | Contribution of age groups to total new case detection (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Period** | 0–14 | 15–24 | 25–34 | 35–44 | 45–59 | 60+ | **Total no. detected** |
| 1856–1860 | 5% | 18% | 26% | 25% | 12% | 14% | 2833 |
| 1861–1865 | 8% | 21% | 24% | 20% | 15% | 13% | 1146 |
| 1866–1875 | 8% | 23% | 24% | 18% | 16% | 12% | 1831 |
| 1876–1885 | 5% | 21% | 24% | 18% | 18% | 13% | 1120 |
| 1886–1900 | 6% | 18% | 20% | 16% | 18% | 21% | 769 |
| 1901–1920 | 3% | 13% | 18% | 17% | 19% | 30% | 292 |
| Total | 6% | 20% | 24% | 21% | 15% | 15% | 7991 |

**Table 3** Time from onset to events for leprosy patients, according to year of onset of disease, Norway, 1800–1920

| | | Mean time (in years) | | |
|---|---|---|---|---|
| **Year of onset** | **No.**[a] | Onset to detection (1) | Onset to isolation, death or migration (2) | Onset to death or emigration (3) |
| <1851[b] | 1088 | 12.2 | 18.6 | 22.0 |
| 1851–1855[b] | 1201 | 3.8 | 9.4 | 12.9 |
| 1856–1860 | 1154 | 2.8 | 8.0 | 12.7 |
| 1861–1865 | 1009 | 2.7 | 7.3 | 11.8 |
| 1866–1870 | 996 | 2.8 | 7.0 | 11.7 |
| 1871–1875 | 716 | 3.2 | 6.9 | 12.3 |
| 1876–1885 | 865 | 3.2 | 6.4 | 12.1 |
| 1886–1900 | 551 | 3.5 | 6.1 | 11.9 |
| 1901–1920 | 160 | 3.2 | 6.2 | 13.0 |

[a] Concerns 7740 of the 8231 registry patients. For the remaining 491 patients, the year of onset was after 1920 for 14 patients, and not available for 477 patients.

[b] High values for mean times between events due to founding of registry in 1856, see text.

onset and emigration or death (intervals 1–3). The longer intervals for patients with onset of disease before 1856 are due to length bias in registration: apart from the 213 early hospital admissions, the registry only includes those patients that survived up to the founding of the registry in 1856. The delay in case detection (interval 1) was somewhat shorter in the first 15 years of the registry as compared to later years. Interval 2 gives an indication of the period during which symptomatic leprosy cases can transmit *M. leprae* under the assumptions that the first isolation is permanent, and that isolated patients stop contributing to transmission. The mean length of this period decreased initially due to an increase in the proportion of patients who were isolated, and was rather stable during 1876–1920. Since only 1% of the patients emigrated, the time between onset and emigration or death (interval 3) reflects the life expectancy at onset of leprosy. A clear trend is not visible. The additional time during which leprosy cases could transmit *M. leprae* when isolation would not affect transmission is reflected in the difference between the intervals 2 and 3, which is smaller in early as compared to later years (about 3.5–5 years between 1851–1870 versus about 6 years for 1876–1920).

# Methods

## Models

Three modelling approaches are used: statistical curve fitting, a transmission model without age-dimension, and age-specific transmission models.

### Statistical curve fitting

To fit the observed trend in case detection, a regression model that does not involve any assumptions about leprosy is used. Inspired by visual inspection, the log-transforms of the new case detection rates $D(t)$ with time $t$, $\ln(D(t))$, are fitted by a quadratic regression model, $\ln(D(t)) = \ln(D_0) - a(t - t_0)^2$, with three free parameters time $t_0$ (year in which the quadratic function starts to decline), $D_0$ (the detection rate at time $t_0$) and $a$ (the strength of the quadratic decline in the log-transformed rates). This model is implemented in Excel.

### Simple transmission model without age-dimension

The transmission model without age-dimension, shown in Figure 1, is also implemented in Excel. The in-flux of newborns in the SUSCEPTIBLE compartment is determined by a crude birth rate. Upon becoming infected, susceptible individuals move to ASYMPTOMATIC infection. A rate reflecting the length of the incubation period governs the transition from ASYMPTOMATIC infection to SYMPTOMATIC leprosy, i.e. the onset of clinical symptoms. The transition from SYMPTOMATIC to DETECTED reflects detection of leprosy. Detected patients who emigrate, die from leprosy or are isolated move to WITHDRAWN. The rates that describe the transitions to DETECTED and WITHDRAWN are referred to as 'registration rate' and 'withdrawal rate', respectively. All compartments are subject to death from other causes. Emigration rates as reported for the general population in Norway[5] are applied to the compartments SUSCEPTIBLE and ASYMPTOMATIC infection, which will contain most individuals.

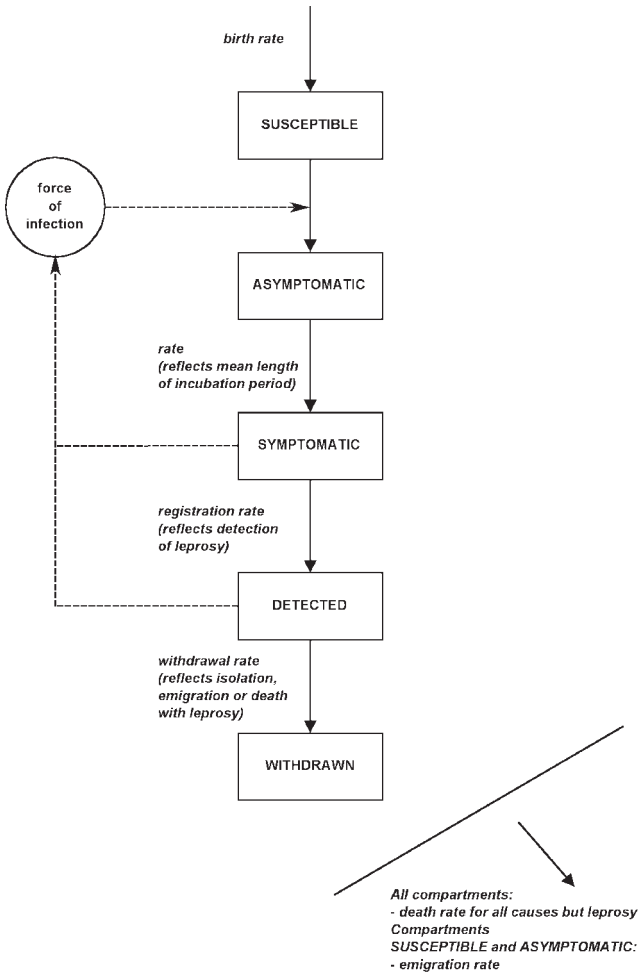


**Figure 1** The transmission model.

Transmission is caused by individuals in the compartments SYMPTOMATIC and DETECTED. A transmission parameter represents the level of their contagiousness. Downward trends in leprosy can be the consequence of leprosy control, but may also have other causes, such as improvement of general living conditions. These autonomous factors are accounted for by assuming that the initial transmission parameter $\beta_0$ decreases by a constant annual reduction factor $\Delta\beta$ from a certain time $t_0$ onwards. The resulting transmission parameter $\beta(t)$ at time $t$ beyond $t_0$ thus equals $\beta_0(1 - \Delta\beta)^{t-t_0}$. The fraction of individuals in the SUSCEPTIBLE compartment that become infected in a time step $\Delta t$ is calculated as $FOI \times \Delta t$, with force of infection $FOI$ equal to $\beta(t)\,(SYM + DET)/N$ ($SYM$, $DET$ = number of individuals in SYMPTOMATIC and DETECTED, respectively; $N$ = population size).

A policy of isolation causes detected individuals to move faster from DETECTED to WITHDRAWN. This results in lower forces of infection. Anti-leprosy treatment of patients is not considered because it only became available long after the end of the study period.

## Age-specific models

An age-specific version of the simple transmission model with age-specific death rates and emigration rates is considered first (Model I). Starting from this model, a series of models is explored. These models are implemented in the SIMLEP framework for modelling the transmission and control of leprosy, which was adapted to allow for emigration. SIMLEP uses a different time distribution for the duration of the incubation period to the simple transmission model (see below). A detailed description and discussion of the SIMLEP modelling framework has been provided before.[3]

## Directly estimated model parameters

Parameters of the simple transmission model and of the corresponding age-specific Model I are estimated as follows.

### *Birth, death and emigration*

The birth rate and the crude and age-specific death rates for the middle decade 1881–1890 of the period 1851–1920[5] are used in all simulations. The birth rate and crude death rate are 30.8 and 17.1 per 1000 population, respectively. The total and age-specific emigration rates vary over time and were derived from data that are available from 1836 onwards.[5,6]

### *Incubation period*

The simple transmission model uses a constant transition rate based on a mean length of the incubation period of 11.0 years. The age-specific models use a time distribution with a mean duration of 8.6 years and less variation (five-phase Erlang distribution[3]). The mean durations of the incubation period have been estimated from war veteran data.[7]

### *Registration rates*

These rates are derived from the observed mean times between onset of clinical symptoms and detection (Table 1: column 2), adjusted for death from all causes. The corresponding mean sojourn times in SYMPTOMATIC from the year 1857 onwards are given in Table 4 (the period before 1857 is addressed under 'Fitting the Norwegian leprosy trend data').

### *Withdrawal rates*

The withdrawal rate $w$ is based on the sojourn time distribution which minimizes the difference (using the Kolmogorov-Smirnov criterion) between:

(1) the distribution of the recorded times between onset and isolation, emigration or death, and

**Table 4** Mean sojourn times in the SYMPTOMATIC and DETECTED disease stages, according to year of onset of disease

| | Mean sojourn time (in years) | | |
|---|---|---|---|
| | | In DETECTED: | In DETECTED: |
| **Year of onset** | In SYMPTOMATIC | With isolation policy | Without isolation policy |
| 1857–1860 | 2.9 | 3.8 | 10.1 |
| 1861–1870 | 2.9 | 2.9 | 10.2 |
| 1871–1875 | from 2.9 to 3.5 | from 2.9 to 1.7 | from 10.2 to 9.0 |
| 1876–1920 | 3.5 | 1.7 | 9.0 |

(2) the distribution of the total time in SYMPTOMATIC and DETECTED that results from subsequent application of the registration rate and this withdrawal rate $w$ itself.

To investigate the impact of isolation, withdrawal rates are also estimated from the recorded times between onset and emigration or death only. All withdrawal rates are corrected for death from other causes. The corresponding sojourn times in DETECTED are given in Table 4.

## Age-specific model: variants

Starting from Model I, variants involving assumptions about the following six aspects of transmission and of course of infection and disease (A1–A6) are explored.

***A1 Geographical heterogeneity in exposure***

In Norway, 98% of leprosy cases with onset between 1851 and 1920 originated from the counties in West and North Norway. The percentage of the Norwegian population living in these counties was stable at about 47%.[1] Model I assumes homogeneous exposure of the susceptible population. The alternative assumption is that 53% of newborns will never be exposed to *M. leprae*.

***A2 Genetic heterogeneity***

Leprosy infection has been considered to be far more common than clinical leprosy.[7,8] The extent to which genetic factors influence the outcome of infection with *M. leprae* is as yet unknown.[9] Model I assumes that every infection leads to clinical disease. The alternative assumptions are that 45% and 90% of individuals self-heal from infection without developing clinical disease. It is assumed that individuals who self-heal after becoming infected will not be re-infected and have immunity from ever developing clinical leprosy disease.

***A3 Waning of transmission opportunities***

Close contact with a leprosy patient, in their own household or through neighbours and social contacts, may be important for leprosy transmission. Since a contagious individual may infect close contacts rapidly, opportunities to transmit *M. leprae* may decrease with longer duration of disease. Model I neglects this possibility. In three alternative assumptions, it is assumed that the contribution of individuals with SYMPTOMATIC leprosy to transmission gradually decreases after onset of clinical symptoms, being halved every 2, 4 and 8 years, respectively.

***A4 Build-up of contagiousness during ASYMPTOMATIC infection***

Model I assumes that contagiousness of leprosy requires the presence of clinical symptoms, but this may not necessarily be true.[10] The alternative assumption is that contagiousness builds up gradually from zero immediately after infection to the maximum level at onset of clinical symptoms.

***A5 Age at maximum exposure***

In Model I, exposure to *M. leprae* is assumed to be independent of age. SIMLEP offers the provision of specifying that exposure gradually increases from zero at birth to a maximum level from a certain age onwards. The alternative assumptions are that maximum exposure is reached at the ages of 1, 2,..., 10 years.

***A6 Tail of the incubation period***

The war veteran data on incubation periods involve small numbers of patients and only relate to adults becoming infected.[7] The maximum time span available for diagnosis after leaving for service abroad was about 25 years for the vast majority of the veterans.[11–13] It has been suggested that manifestation of disease can be due to a mechanism similar to endogenous reactivation in tuberculosis (i.e. the manifestation is due to bacilli that were acquired earlier in life, and which persisted as dormant bacilli within the body).[8] This is not considered in Model I. The alternative assumption is that the distribution of the incubation period is a mix of a distribution with a mean of 8.5 years (as in Model I) and an essentially lifelong distribution (mean of 50 years) that expresses endogenous reactivation (two five-phase Erlang distributions).

## Fitting the Norwegian leprosy trend data

All models are fitted to the Norwegian trend data. For each model, the values for the 'free' parameters are determined that minimize the difference between the observed and the estimated numbers of newly detected cases in successive time periods. The three free parameters for the quadratic model are $a$, $D_0$ and $t_0$. The three free parameters for the transmission models are:

- $\beta_0$: the initial value of transmission parameter $\beta$,
- $\Delta\beta$: the annual proportional decrease in the transmission parameter which reflects 'autonomous decline' (i.e. secular decline due to factors other than isolation),
- $t_0$: the year in which the autonomous decline starts.

Age-specific models that involve assumption A6 have a fourth free parameter:

- the fraction of newly infected individuals with a mean of 50 years for the time distribution of the incubation period.

Simulations with the transmission models start in the year 1830 from a stable epidemiological situation, which is calculated on the basis of the model parameters (including the free parameter $\beta_0$). The decline in the simulated new case detection rates over time depends on changes in both registration and withdrawal rates (Table 4), and on the strength of the autonomous decline.

We quantify the free parameters of the quadratic model and the simple transmission model by fitting these models to the data on total new case detection from the period 1856–1920, using Excel's solver utility. The observed numbers of new cases $O_i$ are given in Table 1. The model-generated new case detection rates are combined with the sizes of the Norwegian population for deriving the estimated numbers of newly detected cases $E_i$. The fit is evaluated as the weighted sum of the squared differences between observed and estimated numbers of cases for the nine time periods from 1861 onwards, (Table 1):

$$D_1 = \sum_{i=1}^{9} (E_i - O_i)^2 / E_i \qquad (1)$$

The age-specific Model I and variants with assumptions from A1 to A6 are quantified using the Nelder & Mead Simplex optimization method.[14] Observed numbers $O_{i,j}$ of cases detected in time period $i$ and age group $j$ follow from Table 2 (five time periods, six age groups). Estimated numbers $E_{i,j}$ again follow from simulated new case detection rates and Norwegian population

data, and the weighted sum of the squared differences for evaluating age-specific models is calculated as:

$$D_2 = \sum_{i=1}^{5} \sum_{j=1}^{6} (E_{i,j} - O_{i,j})^2 / E_{i,j} \quad (2)$$

First, Model I is fitted to the age-specific Norwegian trend data. Subsequently, a forward stepwise procedure is applied which with each step adds a new assumption from A1 to A6 to Model I. In each step, the assumption that is added is the one that gives the largest improvement in the goodness-of-fit score $D_2$. The stop criterion is a less than 10% improvement in $D_2$. The resulting model will be referred to as Model II.

### The period before 1856

Case detection data before 1856 are very incomplete. The completeness of detection efforts in 1856 is not exactly known. Therefore, data from 1860 onwards are used to fit the models. We only marginally considered the early years, as follows. We assumed a detection delay of 12 years before 1856, and 90% detection of SYMPTOMATIC cases in 1856. Model quantifications are only rejected when the estimated and observed number of newly detected cases in 1856–1860 differ by more than 10%.

### Impact of isolation

The impact of isolation is estimated using Model II by comparing the average annual decline $d_{tot}$ as calculated from the simulated new case detection rates for 1861 and 1920, with results of a simulation which ignores the isolation policy by only using withdrawal rates that refer to emigration and death (Table 4). The average annual decline over 1861–1920 for this simulation, $d_{sec}$, is due to other factors than isolation (autonomous decline). The simulated contribution of isolation to the decline is estimated as $(d_{tot} - d_{sec})/d_{tot}$.

In a sensitivity analysis of the impact of isolation, extensions to Model II are considered with assumptions from A1 to A6 that were not yet included due to the stop criterion in the forward stepwise procedure. Only those assumptions are selected for which the goodness-of-fit score $D_2$ of Model II does not decrease by more than 10%. The impact of isolation is also determined for these variants.

## Results

### Trend in total new case detection

The new case detection data of Table 1 are more or less equally well fitted by the quadratic model, the simple transmission model and the corresponding age-specific version (Model I). The goodness-of-fit scores equal 17, 17 and 22, respectively (Table 5). Statistically significant differences ($P < 0.05$) between data and model results are observed for the consecutive periods 1876–1880 (estimates lower than data) and 1881–1885 (estimates higher than data). The less good fit for Model I is entirely attributable to these two periods. For the decade 1876–1885 as a whole, estimated total new case detection deviates by less than 1% from the Norwegian data for all three models.

The decline in new case detection rate in Norway accelerated over time. The quadratic model estimates an increase in decline from 4.5% during 1861–1880 to 9.2% during 1901–1920 (Figure 2). The simple transmission model and the age-specific Model I estimate that both the overall decline and the autonomous decline in transmission started in the 1860s. The fit of the age-specific Model I worsens considerably when the start of the autonomous decline is postulated to occur before 1855.

### Age-specific trend in new case detection

The fit of Model I to the age-specific Norwegian trend data from Table 2 is poor. Too many child cases are estimated for all time periods considered, and also too few cases of ages ⩾60 for 1896–1900 and 1901–1920. The reason for the latter finding is that Model I fails to reproduce the observed shift in new case detection towards older ages: the estimated percentage of new cases of ages ⩾35 only increases by 2% between 1876–1885 and 1901–1920 (Model I: 48% versus 50%; data: 49% versus 66%). The child case group and the failure to reproduce the age shift together account for more than 60% of the goodness-of-fit score of Model I, which equals 204 (Table 5).

The largest improvement of the fit is obtained by extending Model I with assumption A5: the goodness-of-fit score halves by assuming that maximum exposure is reached at age 4, due to much better estimates for the child case group (Model I + A5). First adding assumption A6 also leads to a major

**Table 5** Start of autonomous decline and goodness-of-fit score for the fit of different model variants against Norwegian leprosy new case detection data, 1856–1920

| Model[a] | Start of autonomous decline | Goodness-of-fit score |
|---|---|---|
| **Evaluation: trend in total new case detection** | | |
| Quadratic regression model | n.a. | 17 |
| Simple transmission model | 1863 | 17 |
| Model I | 1868 | 22 |
| **Evaluation: age-specific trend in new case detection** | | |
| Model I | 1861 | 204 |
| Model I + A5[b] | 1866 | 104 |
| Model I + A5 + A6 | 1867 | 79 |
| Model I + A2 + A5 + A6[c] | 1866 | 66 |
| Model II = Model I + A1 + A2 + A5 + A6 | 1865 | 60 |

[a] A1: Geographical heterogeneity in exposure; A2: Genetic heterogeneity; A5: Age at maximum exposure; A6: Tail of the incubation period.

[b] With age at which maximum exposure is reached: 4 years (A5).

[c] With percentage of new infections that self-heal without manifestation of clinical disease: 90% (A2).

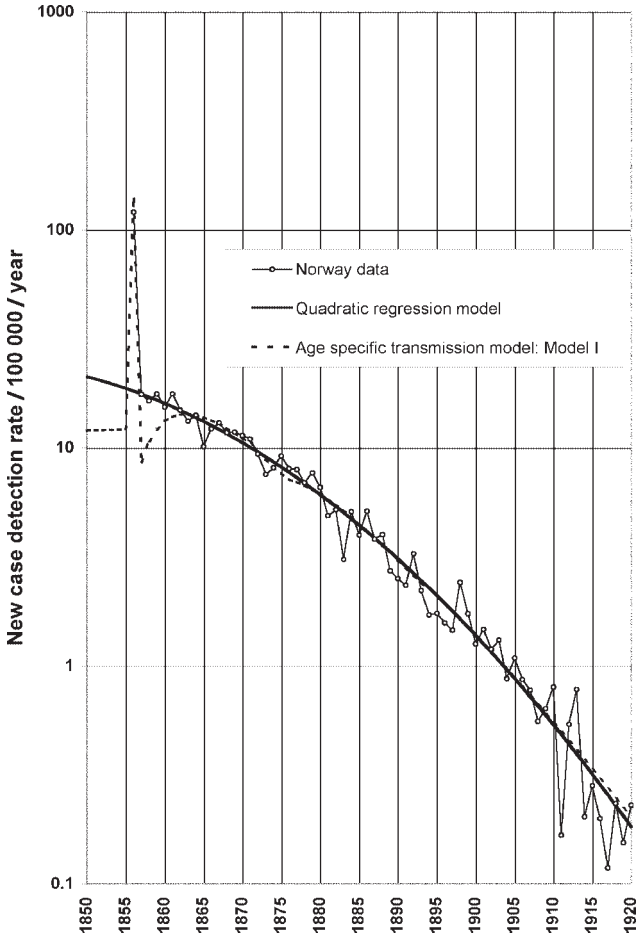


**Figure 2** Trend in total new case detection rate: comparison between observed data and estimates by the quadratic regression model for log-transformed new case detection and by the first age-specific transmission model (Model I), Norway, 1856–1920

improvement: assuming a long tail for the distribution of the incubation period results in a satisfactory reproduction of the age shift and a goodness-of-fit score of 145 (Model I + A6).

Table 5 shows that stepwise extension of Model I with A5 and A6 reduces the goodness-of-fit score to 79. By adding the assumptions A2 (genetic heterogeneity with 90% self-healing infections) and A1 (geographical heterogeneity in exposure) in the next two steps, the score further improves to 60. The resulting model is denoted as Model II (= Model I + A1 + A2 + A5 + A6). The fitting results for Model II are as follows: the autonomous decline in transmission starts in 1865, and 9.7% of newly infected individuals have a long incubation period (mean duration of 50 years) which causes ages at detection to increase with time. No substantial further improvement is achieved by adding the remaining assumptions A3 and A4.

Table 6 and Figure 3 compare age-specific new case detection as simulated by Model II with the observed Norwegian data. No important systematic under- or overestimation of child cases (ages 0–14) occurs. The shift in new case detection towards older ages over time is reproduced well: the estimated percentage of new cases of ages ⩾35 increases from 50% for 1876–1885 to 65% for 1901–1920 (data: 49% to 66%). Statistically significant differences between estimated and observed numbers of newly detected cases are observed in 4 out of the 30 cells of Table 6. These differences are largely due to fluctuations in observed new case detection rates with age which are not well understood: from 1861 to 1885, the rates were highest for the age group 25–34, and lower for the age group 45–59 than for those of ages ⩾60 (Figure 3). These fluctuations are also largely responsible for the difference in the age specific fits of Model II itself and the earlier Model I + A5 + A6 which includes the two assumptions that influence the goodness-of-fit most. The importance of this difference is not clear, and some caution in the comparative judgement of these two models is indicated.

## Role of isolation

The contribution of isolation to the simulated decline in new case detection rate over 1861–1920 is 60% for Model II, and 68% for the earlier Model I + A5 + A6 which excludes geographical and genetic heterogeneity. Seven new models result from extending Model II with the remaining assumptions regarding waning of transmission opportunities (A3) and build-up of contagiousness during the incubation period (A4) (Table 7). Since the fits do not worsen by more than 10%, these new models are all included in the sensitivity analysis for investigating the role of isolation. Table 7 shows that the contribution of isolation strongly depends on the precise assumptions made: it varies between almost no impact (3%) and 39% (Model II: 60%). The contribution decreases with more rapid waning of transmission opportunities (A3) and/or with build-up of contagiousness during the incubation period (A4). This is not surprising because less transmission can be prevented through isolation under these assumptions, which necessitates a stronger autonomous decline that starts earlier

**Table 6** Age-specific new case detection: comparison between estimates by the age-specific Model II and observed data, Norway, 1861–1920

| | New case detection: difference (%) between estimated (*E*) and observed (*O*) numbers by age[a] | | | | | |
|---|---|---|---|---|---|---|
| **Period** | 0–14 | 15–24 | 25–34 | 35–44 | 45–59 | 60+ |
| 1861–1865 | 17% | 11% | –11% | –13% | 4% | –8% |
| 1866–1875 | 2% | 8% | –13%* | –4% | 15%** | 0% |
| 1876–1885 | 13% | 7% | –13%* | –14% | 12% | 7% |
| 1886–1900 | –34%* | 1% | 0% | 4% | 12% | –11% |
| 1901–1920 | 27% | 18% | –9% | –14% | 16% | –9% |

[a] Differences calculated as $(E - O)/E$.

* $P < 0.05$, ** $P < 0.01$.

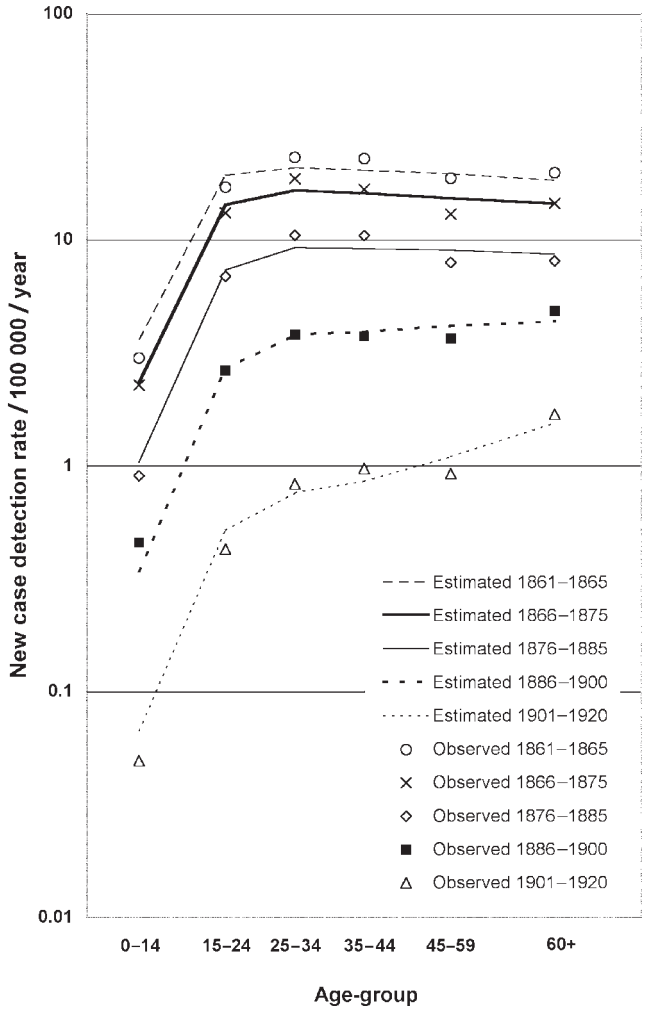


**Figure 3** Trend in age-specific new case detection rate: comparison between observed data and estimates by the age-specific Model II

**Table 7** Sensitivity analysis: estimated contribution of isolation to the total decline in new case detection rate for Model II and variants of Model II, Norway, 1861–1920

| Half-value time for transmission opportunities[a] | Contribution of isolation to decline | |
|---|---|---|
| | Build-up[b]: no | Build-up[b]: yes |
| Infinite[c] | 60%[d] | 36% |
| 8 years | 39% | 17% |
| 4 years | 27% | 9% |
| 2 years | 14% | 3% |

[a] Reflects waning of transmission opportunities due to rapid transmission to close contacts (A3).

[b] Build-up of contagiousness during ASYMPTOMATIC infection: yes or no (A4).

[c] No waning of transmission opportunities.

[d] Estimated contribution of isolation for Model II.

in order to arrive at good fits of the data. The start of the autonomous decline varies from 1846 to 1857 for the seven new models (Model II: 1865).

# Discussion

The disappearance of leprosy in Norway has been analysed by epidemiological models that explain both the time trend in total new case detection and the shift towards older ages. Various model variants are capable of explaining the data, but the estimated impact of isolation varies widely between these variants.

## Reproduction of the Norwegian trend data

The quadratic regression model fits the accelerating decline in total new case detection well but it does not provide insight into the mechanisms (including the isolation policy) which may have governed the declining leprosy trend. A simple transmission model also produces this acceleration. Its age-specific version has two problems: too many child cases are predicted, and the shift in new case detection towards older age groups is missed.

The problem with detection rates in children is solved by letting the exposure to *M. leprae* gradually increase from zero at birth to a maximum level that is reached in young childhood. We are aware that this assumption is rather arbitrary. International data on age-specific new case detection rates vary. Peaks in the age group 10–20 have been observed several times.[7] A study from Bangladesh shows a peak in the new case detection rate for ages 10–14 in females, while rates continue to rise in males until age 25.[15] In Norway, new case detection rates are highest for the age group 25–34 during the first few decades of the study period (Figure 3). Causes that may underlie this variation include the role of intra-household transmission and the duration of the incubation period which appears to be related to the type of leprosy[7] (the frequency of lepromatous leprosy was always high in Norway[1]). In addition, the extent of natural immunity, factors related to gender, endemicity levels of leprosy, and operational factors (case detection methods) may be relevant.

Different explanations are possible for the observed shift in new case detection towards older age groups. Firstly, detection may have been delayed longer, however, no important increase in the detection delay was found in the registry data. Secondly, case detection at older ages is limited by the decreasing number of remaining susceptibles when transmission is high. A decrease in transmission will lead to an increase in the number of susceptibles at older ages, and thus to an increase in infection rate at older ages. However, leprosy transmission was quite low even at the start of the study period, and the susceptibles constitute the largest part of the population throughout the study period.

The third explanation relates to the incubation period. The fraction of new cases with long incubation periods will increase over time with decreasing transmission levels, which will cause ages at detection to go up. The variance in the time distribution of the incubation period should be sufficiently large to reproduce the observed age shift. We reproduce this age shift by adding a long tail to the baseline incubation time distribution (Figure 3). According to this distribution, 7% of all incubating individuals has an incubation period of at least 25 years. This percentage is still compatible with further analyses of the war veteran study which showed that the follow-up period did not exceed 25 years for the vast majority of the war veterans.[7,11–13] The long incubation periods are consistent with the suggestion that reactivation of bacilli that were acquired earlier in life, and

which persisted as dormant bacilli within the body (endogenous reactivation), may play a role in the manifestation of leprosy disease.[8]

Due to the transmission cycle, detected numbers of cases in subsequent time periods are interdependent. In addition, sizeable fluctuations in observed numbers of detected cases occur over time and with age which are difficult to explain. Therefore, we considered a formal $\chi^2$ test overkill, and restricted ourselves to comparative analysis of the various models and their fits. The SIMLEP model framework which has been used for the age-specific models is limited in possibilities for varying model assumptions. More freedom to vary model parameters could potentially result in much lower values of the age-specific goodness-of-fit score.

### Role of the isolation policy

The isolation regime in Norway was relatively mild: hospital patients had full freedom of movement, but had to spend the night in hospital.[4] An earlier epidemiological analysis[1] showed that the *degree of isolation*, a measure reflecting how often and long patients were hospitalized, was associated with relative falls in leprosy incidence rates between subsequent decades in different counties. Both the degree of isolation and the decline in incidence rate increased over time.

Our study shows that the model variants that are compatible with the observed age-specific trend data lead to a broad range of estimates for the contribution of isolation to the decline (from 3% to 60%). The impossibility of measuring contagiousness is an important cause of this broad range. The estimated contribution of isolation to the decline was lower when much of the transmission was assumed to occur before the onset of symptoms. Discussions are ongoing on who is responsible for leprosy transmission. Cree *et al.*[10] suggest that infection from 'subclinical sources' may be more important than infection from symptomatic cases. There is even evidence from Norway and from other countries suggesting existence of environmental sources of infection in addition to human sources.[16,17]

The estimate for the role of isolation also became lower when transmission opportunities were assumed to wane during the infectious period. Whether and to what extent waning really occurs is not known. It is more likely to occur if close contact with a patient is important for the transmission of leprosy. Family clustering of patients was observed in Norway despite incomplete information.[1] By also considering neighbour and social contacts, a recent study of an Indonesian village showed that close contact may be more important for transmission than is commonly believed: out of 101 cases newly detected over a period of 25 years, 78% could be associated with other patients[18] (household contact: 28%, neighbours and neighbours of neighbours: 36%, social contacts: 15%). The suggestion that many individuals who become infected with leprosy do not develop clinical leprosy disease[7,8] further supports hypothesizing waning of transmission opportunities.

The model from which the sensitivity analysis for the role of isolation started, Model II, assumes geographical and genetic heterogeneity. The estimated contribution of isolation to the decline was somewhat higher when these heterogeneities were ignored (68% versus 60%). In endemic areas, individuals not developing leprosy through endogenous reactivation may well have shorter incubation periods than the war veteran data[7] suggest. Shorter incubation periods reduce the turnaround time of the transmission cycle, thus increasing the estimated impact of isolation on reported trends. The estimated contribution of isolation indeed increases from 60% to 67%, when a mean duration of 6 instead of 8.5 years is used for the incubation period in Model II (a similar fit is realized, and the long tail is maintained). Smaller means resulted in too rapid declines in new case detection rate in the first few decades of the study period.

More complex models could be considered. For instance, we do not distinguish between different types of leprosy disease. Also, we do not take gender differences into account. Undoubtedly, adding complexity would lead to other estimates of the contribution of isolation to the decline. However, such additions would not tackle the problem of measuring contagiousness, and the uncertainty regarding the role of isolation will remain. Therefore, further complexity would not add to the insights gained through the present analysis.

### Other contributing factors

We represented the way transmission may be influenced over time by factors other than isolation simply by a constant annual reduction factor. The earlier epidemiological study identifies several such factors.[1] These include nutritional conditions, a rise in tuberculosis, and selective emigration to overseas countries. At farm level, the occurrence of leprosy is shown to be associated with a low production of oats and milk. No doubt, nutritional conditions greatly improved during the second half of the 19th century.[1] This is in line with a historical analysis of the Norwegian economy by Bergh *et al.*[19] which shows growth in the production per capita from 1830 onwards after centuries of economic stagnation. This growth continued virtually without interruption for the next 150 years. Thus, the Norwegian population may, due to improved nutritional conditions, have been rendered more resistant to infections with *M. leprae*,[1] which may have originated from environmental sources.[16] Morbidity rates of tuberculosis, which may protect against leprosy,[7] either by immunization or by competing risk, increased in Norway until beyond the turn of the 19th century.[1] The increase was relatively high in the coastal counties (leprosy was particularly frequent in the coastal counties). Emigration heavily influenced the Norwegian demography.[20] It was particularly frequent in areas, and in age and sex groups, with high leprosy incidence rates. The assumptions made on emigration in this study hardly affect estimated impacts of isolation. We could, however, not exclude whether *selective* emigration would affect estimates on the impact of isolation.

### Relevance for contemporary leprosy control

The estimated impact of isolation strongly depends on assumptions made about leprosy transmission. The results also have a modern interpretation, because both isolation and anti-leprosy treatment of patients, which became available long after leprosy had disappeared from Norway, prevent leprosy transmission. Nowadays, early case detection followed by chemotherapy (multidrug therapy: MDT) forms the mainstay of leprosy control. It is unclear to what extent present day control influences leprosy trends in populations. Currently, we are performing a model-based scenario analysis to predict plausible leprosy trends up to 2020 and the influence of present-day control. The

scenario predictions are complicated by the same factors that we encountered in the evaluation of the decline of leprosy in Norway. A logical next step in our approach would be a model-based analysis of long-term trends in geographical areas with comparable general conditions, but with different well-documented leprosy control policies. Such data would enable further clarification of the forces driving leprosy trends, but unfortunately they are not readily available. Epidemiological studies which apply modern diagnostics and address different hypotheses on leprosy transmission (e.g. refs 10,17,18) may improve knowledge on leprosy transmission. Further development, testing and application of various diagnostic tools is required, including serological tests and tests using skin reagents for detection of subclinical and early clinical leprosy, DNA amplification for detection of carriage of *M. leprae* in nasal swabs, and DNA fingerprinting to distinguish between different strains of *M. leprae*. Improved knowledge about the contagiousness of individuals and the process of leprosy transmission would greatly improve the conditions for evaluation of the impact of interventions such as early case finding in combination with chemotherapy treatment, vaccination strategies, and chemoprophylaxis of close contacts of leprosy patients.

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KEY MESSAGES

- Between 1850 and 1920, leprosy disappeared from Norway.
- The extent to which the Norwegian policy of isolation of leprosy patients has contributed to the decline through interruption of the transmission of leprosy is uncertain.
- Estimates of the impact of isolation depend strongly on assumptions about occurrence of transmission during the incubation period and about the importance of close contacts in transmission.
- Evaluation of contemporary leprosy control through chemotherapy is confronted with the same uncertainties about leprosy transmission.

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