Global Partnership for
Zero Leprosy

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Research Agenda Working Group
Subgroup on Epidemiologic Modeling and Socioeconomic Research

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Background

Epidemiologic modeling can play a key role in supporting efforts to reach zero transmission and zero disability of leprosy. It is an efficient and powerful tool for quantifying transmission patterns and for predicting future trends in leprosy detection and the potential impact of existing and novel interventions (1). Transmission dynamics of leprosy are inherently nonlinear. Apart from host factors, an individual's risk for developing leprosy is determined by the number of cases in an area and the infectiousness of cases among their contacts. The number of newly detected cases is determined by past exposure of the individual to *M.leprae*. Moreover, leprosy is known for its long incubation time and delayed diagnosis due to difficulties in diagnosis and fear of stigma (2,3). As a result, measuring the impact of changes in policy can be difficult because the impact of current changes may not be seen in the short run. Epidemiologic modeling can help to identify long-term impact of policy changes and optimal (endgame) strategies (1).

At the same time, an investment case should be built to inform (local) policy makers and other donors on the importance of investing in new tools and strategies aimed for achieving zero leprosy. As the road to zero leprosy requires extensive use of resources, the decision to commit to zero leprosy initiatives should be based on a robust analysis of the benefits, risks, and costs to ensure value for money—especially in less developed settings (4). To guide this process, an eradication investment case (EIC) for leprosy is recommended (5). Such a framework would provide a systematic inventory of what is needed to achieve zero leprosy along with information about the challenges, risks, and sustainability of an initiative. An EIC is particularly appropriate for diseases such as leprosy that have a high socioeconomic burden and for which multiple interventions exist or are being developed. The EIC framework has been recently tailored to the context of leprosy by Tiwari and Richardus (6), who outlined the following key domains:

- Disease burden and elimination
- Current state of the leprosy program and recent technical advances
- Available and new tools and their scope in interrupting transmission
- Future requirements during and after transmission interruption
- Biological and technical feasibility of transmission interruption
- Socioeconomic burden and public goods obtainable
- Financing leprosy elimination
- Health systems and their capacity

A leprosy EIC would help to determine whether zero leprosy is feasible, the capacity of the initiative to monitor and evaluate control programs, the most promising interventions for achieving that goal, and the long-term consequences of the interventions. It also includes an assessment of the health-system changes required in leprosy-endemic countries (3).

In formulating their research agenda, the Subgroup on Epidemiologic Modeling and Socioeconomic Research of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group reviewed recent modeling work on leprosy and socioeconomic research and identified important key questions that support efforts to reach zero leprosy and contribute to the development of a leprosy EIC.

Current Knowledge and Key Questions

Previous modeling work on leprosy has mainly focused on predicting future leprosy trends and evaluating the impact of various interventions. A leprosy EIC does not exist yet, but a recent literature review has identified current knowledge and key information gaps on constructing a leprosy EIC (6). An overview of the key findings from this systematic review was published separately (3) and is presented in the Box below.

Panel: Key findings of a systematic review on constructing a leprosy elimination investment case

A 2016 systematic review[98] identified a number of factors that should be considered when developing a case for investing in the elimination of leprosy. The findings listed below, adapted from that review, are grouped under eight headings, in accordance with an internationally recognised guide on preparing disease eradication investment cases.[99]

Disease burden and elimination

- The proportion of newly detected leprosy cases in children younger than 15 years reflects the degree to which *Mycobacterium leprae* transmission is occurring.
- The proportion of patients with grade 2 disability (visible deformity or damage) reflects the degree to which a health system is achieving early detection and prompt treatment of patients.
- Many leprosy cases escape detection by health systems.[2]

Current state of the leprosy programme and recent technical advances

- The new PCR test is capable of detecting the leprosy bacillus and its resistance to drugs,[100] but its application is limited.
- The *M leprae*-specific anti-PGL-I antibody test has limited applicability, because it is only reliably positive in multibacillary cases.[101]

Available and new tools and their scope in interrupting transmission

- Tracing contacts of index leprosy patients can detect new cases more effectively than population-based approaches but faces operational and ethical challenges.[12]
- Contact tracing followed by administration of chemoprophylaxis, BCG vaccination, or both is currently the most promising approach to halting *M leprae* transmission.

Future requirements during and after transmission interruption

- Linking leprosy elimination efforts with programmes working on other neglected tropical diseases ensures the sustainability, efficacy, and financial resilience needed to reach the WHO leprosy elimination goal.[2,25]

Biological and technical feasibility of transmission interruption

- Genome-based technology will probably facilitate the development of leprosy vaccines and diagnostic tests.[102]

Socioeconomic burden and public goods obtainable

- The disability-adjusted life-year is not a reliable indicator of the leprosy disease burden.[103,104]
- Leprosy is one of many neglected tropical diseases associated with poverty.[105]

Financing leprosy elimination

- Information about the costs of provision of leprosy services is scarce.

Health systems and their capacity

- Integration of a leprosy programme into the general health system reduces the level of anti-leprosy stigma in a country.
- Community-based rehabilitation is effective in integrated programmes but is used in few health systems.[106,107]

To develop a leprosy EIC, input is mainly required from epidemiologic modeling and socio-economic research. However, developments in research outlined by other subgroups of the GPZL Research Agenda Working Group (i.e., Diagnostics, Vaccines, PEP, and Operational Research) are also crucial.

The key findings and knowledge gaps in the field identified by the Subgroup on Epidemiologic Modeling and Socioeconomic Research are summarized below.

Epidemiologic Modeling

Feasibility of Global Interruption of Leprosy Transmission

Interruption of leprosy transmission is unfeasible within two decades without additional efforts and new interventions (7,8). A next step would be to provide a realistic time frame upon which zero leprosy and zero disability can be reached. This information would also be relevant when developing a leprosy EIC. As zero leprosy has not been formally defined yet, modeling studies can assess various definitions, such as achieving zero new (child) cases or sustained zero new leprosy cases. Moreover, modeling studies could also assess the time frames for reaching intermediate targets.

- *Key questions:*
    - What would be a realistic time frame to achieve global interruption of transmission?
    - How long should programs be continued to achieve zero leprosy?
    - How should zero leprosy be defined?

Potential Impact of New Strategies and Tools

Universally, studies have highlighted the need for earlier diagnosis and treatment of leprosy, preferably in the asymptomatic stage, in order to substantially reduce the new case detection rate (NCDR) (9-11). Innovative ways to prevent leprosy include administering post-exposure prophylaxis (PEP) to contacts of newly diagnosed leprosy patients and providing earlier diagnosis through screening with diagnostic tools. A modeling study on leprosy in Pará State in Brazil showed that administering a single dose of rifampicin (SDR) to household contacts, in addition to current controls, would lower the NCDR by 40% (12). Another study showed that the use of a diagnostic test to detect subclinical leprosy cases could be a crucial step for interrupting transmission (9). In high endemic settings, the use of a population survey as a testing strategy with a diagnostic is preferred over household contact testing. Another strategy to consider is poverty reduction (13). In Brazil and Mexico, research is being done on cash transfers in relation with diseases, including leprosy, with promising results (14,15). Also, integrated strategies can be explored (16). For example, joint detection of tuberculosis (TB) and leprosy could be considered in some areas (17), with BCG treatment also effective in patients with leprosy. Another example is the use of skin camps for several neglected tropical diseases (NTDs).

- *Key questions:*
    - What is the potential long-term impact of available and new tools such as vaccines and diagnostics and their scope in interrupting transmission?
    - Which interventions are most promising?
    - Which strategy would yield the highest impact on transmission (both in terms of reduction in incidence and in time until lower infection levels are reached)?
    - How can modeling of the impact of poverty reduction on leprosy best be done?

Geographical Variation and Population at Risk

- ***Geographical variation***

  Current incidence trends show the geographical variability of leprosy. This is also evident in the predictions from modeling studies. Regions with lower incidence of leprosy are predicted to reach the 10 per 100,000 threshold within a few years, whereas those with higher incidence are predicted, with current interventions, to have only a small chance of reaching this threshold within 20 years (7). This pattern is true at the national scale (e.g., India, Brazil, and Indonesia compared to other affected countries) and at a sub-national level (e.g., among Brazilian states) (7,8), and might be true of smaller spatial scales. Also, differences in breakdown between multi-bacillary and paucibacillary infections may impact the infection reservoirs and thus transmission.

- *Key questions:*
  - To what extent does the impact of interventions differ among geographical regions?
  - Should interventions be tailored to specific endemicity levels, and, if so, how?
  - In which areas is zero leprosy feasible in a relatively short time span?
  - How should zoonotic transmission in the Americas be measured?

- ***Population at risk***
  The size of the population at risk for leprosy may determine the size of the problem and therefore could be used for advocacy, awareness raising, and program-planning activities. However, the population at risk in the context of leprosy is not defined or estimated yet because of several challenges in making such an estimate. A modeling study is ongoing to estimate the number of people needing PEP, as a proxy of the population at risk, in order to substantially reduce the newly detected cases.
  - *Key questions:*
    - How should we define population at risk?
    - What is the estimated population at risk?

Impact of Other Epidemiological Risk Factors for Transmission
Geographical variation could be dependent on (as yet) largely understudied risk factors, including environmental reservoirs and host factors that may predispose an individual to multibacillary infection (2). Potential host factors include undernutrition and comorbidities/co-infections (18). These risk factors could be identified through meta-analyses, accompanied by observational studies or trials.

- *Key questions:*
  - Which epidemiological risk factors are relevant?
  - How do we incorporate these types of risk factors into a model?

End-game Scenarios
No research has been conducted in this area. Endgame scenarios might already be considered in several regions in the world that report a very low number of new annual cases. These areas may serve as a blue print for others when they will reach this point. Using modeling, we can identify what is needed to achieve zero leprosy and what possible post-zero leprosy scenarios may look like.

- *Key questions:*
  - What is needed to achieve and sustain zero leprosy?
  - What are possible scenarios for a post-zero leprosy era?

Testing Hypotheses
In the past, modeling has been used to explore the likelihood of certain hypotheses in the absence of empirical evidence. A good example is a study that assessed multiple hypotheses of susceptibility mechanisms in leprosy (genetic vs. non-genetic) (19). Epidemiologic modeling can be used to assess various hypotheses on issues such as transmission dynamics, migration, and/or drug resistance. Such studies may overlap with the research agendas prioritized by other subgroups of the GPZL Research Agenda Working Group and should align with those agendas.

- *Key questions:*
  - What efforts are needed to assess hypotheses regarding transmission dynamics?
  - What is the impact of migration on leprosy trends?
  - If drug resistance becomes a problem, how would that affect the course of leprosy incidence?

Economic Research

Available Tools and Their Economic Feasibility

Cost effectiveness and cost-benefit analyses are essential for identifying the best possible leprosy control strategy for a specific country or region. Two cost-effectiveness studies have been published: one on case detection strategies and one on chemoprophylaxis (20,21). Currently, a modeling study on the cost-effectiveness of PEP taking into account future benefits is ongoing. To determine if an investment is sound, a cost-benefit analysis comparing the total expected cost of each option against their total expected benefits is recommended.

- *Key questions:*
  - What is the cost-effectiveness of current and new tools?
  - What are the results from cost-benefit analyses conducted in different settings (health system contexts)?

Socioeconomic Burden of Leprosy

- ***Disease burden***

  Estimates on the burden of disease due to leprosy rely on disability weights that underestimate the actual disadvantages resulting from leprosy. First, there is a need to identify leprosy-associated disability (social and mental issues are not considered currently), followed by a re-estimate of disability weights for endemic counties or WHO regions. The burden in children, including the impact of the disease on school dropout, lifelong stigma, and mental health, should also be considered.
  - *Key questions:*
    - What efforts are needed to estimate disability and assess disability weights of leprosy?
    - What efforts are needed to estimate the burden of morbidity due to leprosy and other NTDs or other diseases that share cross-cutting issues with leprosy?
- ***Socioeconomic risk factors of leprosy***

  Socioeconomic risk factors of leprosy include the length of time in poverty, level of education, and socioeconomic status of the family; nutritional factors; water, sanitation, and hygiene factors; housing conditions; and the presence of coinfection(s). Previous and ongoing studies have focused on several of these risk factors for transmission (related to hotspots). However, studies to determine the importance of each risk factor are still needed. This evidence may also contribute to epidemiologic modeling.
  - *Key questions:*
    - *What are the relevant socioeconomic risk factors of leprosy?*
    - *What is the potential impact of each risk factor?*
- ***Monetizing socioeconomic burden of leprosy and associated illness***

  The social burden of leprosy is hardly estimated but is important for leprosy prevention efforts due to high social negative impact. The prevalence of social consequences and public expenditure on social welfare (directly and indirectly related to leprosy) remain unknown. Also, an analysis of the likely effect of leprosy on economic productivity at the household and population levels and on social participation is unknown. Willingness-to-pay studies are needed to quantify/monetize the impact of social consequences (discrete choice experiment).
  - *Key questions:*
    - *What is impact of leprosy on economic productivity?*
    - *What is the impact of leprosy on social participation?*

– *What is the estimated impact of social consequences due to leprosy*?

Financial and Cost Analysis of Leprosy and Associated Illness

- ***Cost analysis of leprosy and associated illness:***
  A study has been published estimating the out-of-pocket expenditures for leprosy households (21). Direct and indirect household expenditure on leprosy was estimated to be on average $5.40–$6.50 and $8.70–$12, respectively. More such studies are needed from various countries to estimate the total societal cost of leprosy care.
  - *Key question:*
    - What is the out-of-pocket expenditure on leprosy for affected households and individuals in different settings?
- ***Financial analysis of (global) leprosy programs***
  The 2015 WHO report on investing to overcome the global impact of NTDs estimated that the investment in leprosy services would be on average $37 million annually (22) [22]. This includes costs for contact tracing, treatment, and care. It is important for health systems to facilitate sustained leprosy control activities. However, with low numbers of leprosy cases, this may become difficult due to financial and human resource constraints and diminishing ability to diagnose leprosy. A recent study has also assessed the leprosy costs in two primary health settings in India (23) [23].
  - *Key questions:*
    - *What efforts are needed to develop a systematic method to estimate gross expenditure per country?*
    - *What is the gross total expenditure on leprosy per country/region?*

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