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Editorial

Guiding policy towards zero leprosy: Challenges for modelling & economic evaluation

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae,* affecting the skin and peripheral nerves[1]. It can only be diagnosed based on clinical signs and symptoms, which appear on an average of five years (and sometimes even 20 yr) after the infection. If diagnosis is delayed or if the patient is left untreated, this can lead to physical disabilities. As a result, people affected by leprosy are often stigmatized and discriminated, leading to social exclusion, depression and economic loss. Fortunately, treatment with multidrug therapy can cure the patient and early diagnosis could prevent the patient from progressive and permanent disabilities.

Every year, awareness is raised for leprosy and the patients affected on World Leprosy Day, *i.e*. the last Sunday of January. Although great progress has been made in reducing the number of patients since the 1990s, still more than 200,000 new leprosy patients are diagnosed annually worldwide (in the last 10 yr), while many more go undiagnosed[2]. Of those diagnosed, 15,000 are children, indicating that transmission is ongoing. Leprosy is found in more than 120 countries[2], but it is very unevenly distributed between and within countries. In 2019, India alone was responsible for more than half of the annual new patients worldwide (114,000 new cases, of which almost 8000 children)[3]. Great variation in the distribution of leprosy also exists within India, with endemicities at State level ranging from below one to above 20/100,000 population[3].

In 2020, the World Health Organization launched the new Global Leprosy (Hansen's disease) Strategy 2021-2030 'Towards Zero Leprosy'[4]. Its long-term vision is to reach zero infection and disease, zero disability and zero stigma and discrimination. Ambitious global targets for 2030 have been set, including 70 per cent reduction in annual new cases detected, 90 per cent reduction in severe (grade-2) disability and 90 per cent reduction of new child cases. Given the trend of new cases of the past decade, it is evident that continuation of past and current leprosy control will not be sufficient to achieve these targets. A scale-up of leprosy-preventive treatment alongside active case detection is required. Post-exposure prophylaxis with a single dose of rifampicin is most promising as a preventive treatment[5]. However, alternative novel tools can be considered such as a leprosy-specific vaccine or new diagnostic tools to aid case detection.

The impact of policy changes on leprosy cannot be measured easily in the short term, because of its long incubation time and the backlog of undiagnosed cases. Therefore, questions remain about which preventive tools and strategies are most (cost)-effective to achieve the 2030 targets and in the end reach zero infection and disease. Mathematical modelling and economic analyses can help to answer these questions. In leprosy, several models have been developed and deployed to provide answers to some of the policy questions. These models have been mainly used to predict the future trends of leprosy incidence for different control scenarios[6]. To date, only the SIMCOLEP model, developed by Erasmus MC, modelled the impact of preventive interventions (*i.e*. post-exposure prophylaxis) on leprosy incidence and evaluated the potential benefit of novel tools, such as a new leprosy diagnostic to identify infected individuals who will progress to disease[7,8]. This modelling has highlighted the importance of earlier diagnosis and (preventive) treatment to reduce the number of undiagnosed leprosy cases, which can be more than twice the number of diagnosed cases[6].

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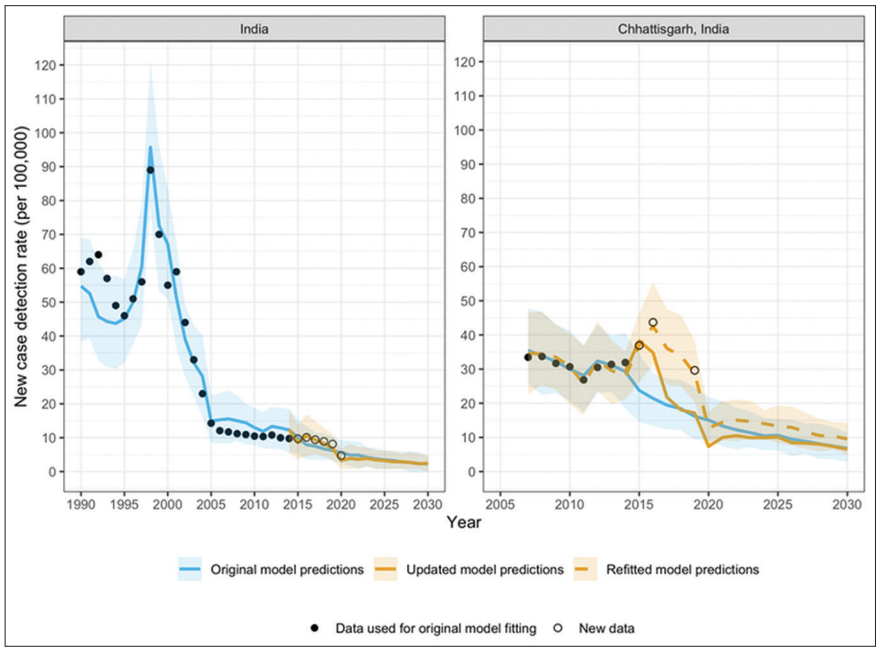

Figure. Predictions of leprosy incidence in India (left panel) and Chhattisgarh (right) until 2030. The blue line represents the original predictions based on the leprosy situation until 2014. The yellow line represents the updated model accounting for the leprosy case detection campaign from 2016 onwards and the underreporting due to COVID-19 in 2020. The dashed yellow line (right panel only) represents the refitted model: in addition to accounting for changes in leprosy control, disease processes (transmission rate and detection delays) were refitted. We assumed that underreporting due to COVID-19 impact only lasts until 2022. Predictions from 2023 onwards were based on the situation before COVID-19. *Source*: Refs 2,3,11. Original model predictions were modified from Ref 10. Part of panel 1 and panel 2 data were taken from Ref 10 with permission.

To ensure good modelling practice, mathematical modelling studies aimed to support policy, and intervention planning should follow guidelines as described by the five principles of the Neglected Tropical Disease Modelling Consortium[9]. These principles include (*i*) stakeholder engagement in the modelling process, (*ii*) complete model documentation, (*iii*) complete description of data used, (*iv*) communication of uncertainty in predictions, and (*v*) providing testable model outcomes. As an illustration of testable model outcomes, the Figure shows the new case detection rate (NCDR) of India as a whole and Chhattisgarh (high endemic State in India) as predicted by the SIMCOLEP model in 2015[10]. We have now compared these predictions with the actual observations in the following years. Predictions of the model (blue line) are clearly lower than the recent data of NCDR (from 2015 to 2020; open dots), and are thus more optimistic. This underestimation is more pronounced in Chhattisgarh. However, these model predictions were based on the leprosy situation in 2014 and could not account for unforeseen changes in policy such as the introduction of the leprosy case detection campaign in high-endemic States in India from 2016 onwards, which resulted in an increased number of new cases detected[11]. Similarly, it could not account for the impact of COVID-19, which resulted in under-reporting of new cases in 2020[2]. We have, therefore also updated these predictions in hindsight, accounting for the changes in leprosy control (yellow line). Model predictions for India matched the new observation well, but for Chhattisgarh, it remained too low. Further adaptations through refitting disease processes (*i.e*. transmission rate and detection delays) improved this (yellow dashed line). Eventually, updated predictions of 2030 remain similar to the original predictions. Nevertheless, it is a good practice to test model predictions, to increase confidence in the model, and, if necessary, to update predictions with new information about policy changes and new knowledge of disease processes.

The road to zero infection and disease requires extensive use of resources, while facing budget and resource constraints. Mathematical modelling can also aid to estimate future resources needed (*e.g*. the number of people requiring preventive treatment) over a given time horizon, including the opportunity to explore

the impact of health system constraints (*e.g*. limited capacity to deliver an intervention). This information is a crucial element for conducting economic evaluation of (new) policies and interventions but could also provide guidance for logistic planning of these policies and interventions.

Robust analysis of the health effects, costs and cost-effectiveness is important to support decision-making which can increase commitment to initiatives aimed to reach zero new leprosy cases and ensure value for money. To date, only limited information is available on the cost of leprosy and restricted to a few settings. An important step would be to conduct more studies on the cost of leprosy, especially in priority settings. These can provide insights on the (monetary) magnitude of the problem and help to guide the design and implementation of new policies and interventions. In addition, cost-effectiveness analyses (CEA) can determine the potential added value of these policies and interventions by comparing their costs and health effects. CEAs typically use metrics such as cost per case averted, morbidity averted and disability-adjusted life years (DALYs) averted. DALYs are a standardized measure of disease burden, which account for the years lost due to disability and the years of life lost. However, the usage of DALYs in leprosy is usually ignored because the currently used disability weights, which only cover health loss due to general disfigurement, do not sufficiently reflect the broader consequences of leprosy[12]. For DALYs to be a valuable metric, disability weights for leprosy should be revisited, covering leprosy-specific consequences including disfigurement and mental health.

CEAs should consider costs (and effects) that are directly relevant to a chosen perspective. The societal perspective is most common and incorporates both direct healthcare costs and indirect costs (*e.g*. productivity loss). Direct healthcare costs include all costs associated with the disease, such as clinic visits, diagnosis and treatment. Productivity costs may reflect the income missed due to inability to work or job loss as a result of leprosy disability or stigma. Also, an appropriate time horizon should be selected, which must be long enough to capture any impact of policies but at the same time does not go too far in the future (as predictions further in the future have greater uncertainty).

In conclusion, mathematical modelling has shown to be useful for understanding trends of leprosy incidence and evaluating the potential impact of interventions. However, to further support decision-making on the road to zero infections and zero new leprosy cases, complementary economic evaluation is crucial. Mapping of leprosy cost and revisiting leprosy disability weights are important steps to facilitate economic evaluation. There is a need for more cost and cost-effectiveness research for leprosy and leprosy interventions.

***Conflicts of Interest*:** None.

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