General introduction

1. Introduction to leprosy

Leprosy as a disease

Leprosy or Hansen's Disease (HD) is an ancient disease that still causes suffering to human beings. It is a chronic infection caused by *Mycobacterium leprae*. The incubation time of leprosy is long, with averages of around 5-7 years [1]. Individuals in the subclinical phase are suspected as the main sources of transmission of *M. leprae,* as they remain undetected and untreated. [2]. The bacteria can damage the peripheral nerves and cause anaesthetic discoloured patches on the skin [3]. Delay or absence of treatment causes deformity of face and limbs that can become permanent in nature. Socially, leprosy brings stigma and discrimination, which deteriorate the mental health and quality of life of patients and family members [4].

Symptoms, diagnosis, classification, and treatment

Leprosy is diagnosed based on clinical signs and symptoms, along with establishing the presence of the typical acid-fast bacteria (AFB) of *M. leprae* in slit skin smears (SSS) or skin biopsies. Subclinical leprosy cannot yet be detected reliably due to the absence of a suitable diagnostic test [2]. A case of leprosy is defined as an individual who has one of the following cardinal signs of leprosy, but who has not received a full course of multidrug therapy (MDT) for the type of leprosy identified: 1) A definite loss of sensation in a pale (hypopigmented) or reddish skin patch; 2) A thickened or enlarged peripheral nerve with a loss of sensation and/or weakness in the muscles supplied by the nerve; and 3) The presence of AFB in a SSS [5].

Leprosy has a spectrum of disease manifestations depending primarily on the immunological response of the host. The Ridley-Jopling classification divides the disease into the following categories: Tuberculoid (TT), Borderline Tuberculoid (BT), mid-Borderline (BB), Borderline Lepromatous (BL), and Lepromatous (LL). Specific (cell-mediated) immunity against *M. leprae* is decreasing from TT to LL leprosy, and the bacterial load consequently inversely increased along the spectrum towards LL leprosy. This classification system requires expert clinical and pathological investigation, including a count of the bacterial load in a SSS or skin biopsy, and is currently mainly used in research [6]. For control programmes, the World Health Organization (WHO) introduced a simplified classification system by counting the number of skin lesions. It classifies leprosy into paucibacillary (PB) single-lesion leprosy, PB leprosy 2-5 skin lesions, and multibacillary (MB) leprosy (more than five skin lesions) [7].

Current treatment of leprosy consists of MDT, which is a combination of rifampicin, clofazimine and dapsone. A combination of all three drugs is used to treat MB leprosy

patients, whereas the combination of rifampicin and dapsone is used to treat PB leprosy. Prescription recommendations have evolved over the years, and the latest recommendation is to treat PB for 6 months and MB for 12 months with all three drugs.[8]

Transmission

In general, experts believe that spread is mainly through droplet infection among humans [9]. Since *M. leprae* cannot be cultured in vitro, many characteristics of the bacterium, including the transmission mechanism, remain unclear. Other than humans, bacteria have reservoirs in the environment and in animals (e.g. armadillo and squirrel), but their contribution to transmission is considered insignificant [9, 10].

Risk factors for leprosy

Individuals who have prolonged contact with a (MB) leprosy patient are most at risk of acquiring leprosy. These individuals can be family members, neighbours, or social contacts. Family members of leprosy patients living in the same house are highly exposed to the bacteria, therefore, their risk is also higher than the neighbours and social contacts [11]. Susceptibility to leprosy is partly determined genetically, and it has been observed that blood-related relatives have a higher risk than relatives that are not blood-related [12]. Leprosy is common in the age group of 16-49 years, which is also the most productive phase of life [12]. Next, poverty is an important determinant of leprosy [13]. Poverty is often accompanied by poor nutritional status, which in turn can affect immunity. Food shortage has been found to be associated with leprosy [14, 15]. Once having leprosy, stigma, discrimination or physical disability reduces the chance of earning livelihood, which in turn leads to further poverty [16].

2. Leprosy epidemiology

Global leprosy burden

Figure 1 shows the global trend of leprosy new case detection from 1985-2018. The global annual new leprosy case detection started increasing in the year 1995 and peaked around 2000 due to intensive active case finding in endemic countries to achieve the WHO ‘elimination as public health problem’ target set to be achieved in the year 2000. Elimination as public health problem was defined as a reduction of leprosy prevalence to less than 1:10,000 population. Intensified case detection efforts continued for several more years, but the steep decrease in case detection after 2001 is attributed primarily to discontinuation of active case finding in leprosy control programmes after achieving ‘elimination of leprosy’. After 2005, the new case detection rate has remained fairly stable to date, indicating that transmission of *M. leprae* is continuing unabated.

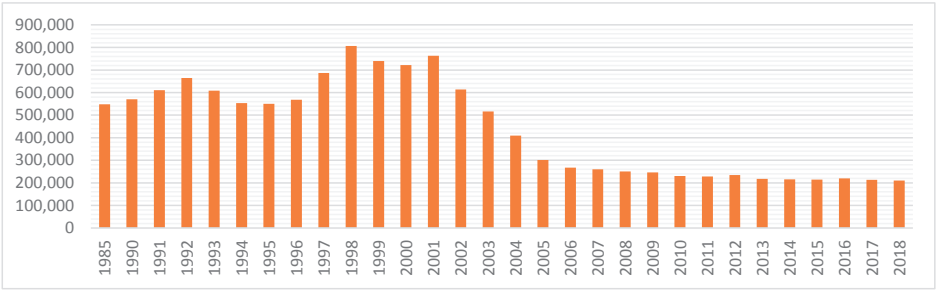

Figure 1. Global trends in leprosy new case detection, 1985–2018
Source: Weekly Epidemiological Reports, WHO

In the year 2018, 159 countries reported 208,619 new cases of leprosy [17]. WHO has prioritised 23 countries with the highest number of new leprosy cases per year. These countries are in Asia, Africa and Latin America (Figure 2). The top three countries are India, Brazil and Indonesia, which account for 80% of the global new caseload.

Leprosy burden in terms of disability

The WHO leprosy disability grading system grades patients according to the presence of disabilities of the eyes, hands and feet. For hands and feet Grade 0 means no anaesthesia and no visible impairment; Grade 1 signifies anaesthesia present, but no visible impairment; and Grade 2 indicates that visible impairment is present. For eyes the grading is as follows: Grade 0 no eye problem due to leprosy and no evidence of visual loss; Grade 1 eye problems due to leprosy present, but vision not severely affected as a result; and Grade 2 indicates severe visual impairment (vision worse than 6/60; inability to count fingers at 6 meters) and also includes lagophthalmos, iridocyclitis and corneal opacities. The highest grade of disability of any of these body sites is used as an overall indicator of the disability status of a person with leprosy. Leprosy-related Grade 2 Disability (G2D) is usually reported as the proportion of people with G2D among leprosy cases newly diagnosed in a specific year.

In 2018, new cases with G2D were 5.4% (n=11,323) of the global new cases. Further, leprosy contributed 31,500 (21,500- 44,600) years lived with disability (YLDs) to the global burden of disease [18]. As the mortality in leprosy is negligible, YLDs can also be seen as disability-adjusted life years (DALYs).

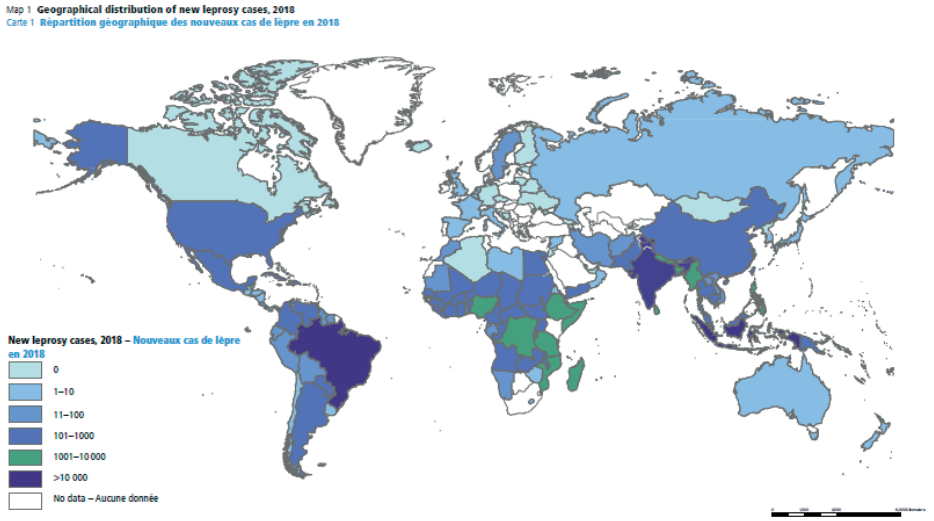

Figure 2. Geographical distribution of new leprosy cases, 2018
Source: Weekly Epidemiological Reports 2019, WHO

Leprosy burden and control in India

India declared leprosy elimination in the year 2005, but still detects more than 100,000 new cases each year, which is around 60% of the global burden. In 2017-18, India detected 126,164 new cases, among those 4,552 (3.6%) had G2D.[19] In 2016-17, new cases were 135,485, among those MB cases were 67,160 (49.57%), female 53,072 (39.17%), children 11,792 (8.7%) and G2D 5,245 (3.87%), respectively [20]. The new case detection and prevalence trend showed that leprosy transmission in India is continuing unabated (figure 3). The leprosy epidemic is concentrated and confined to pockets which have a high burden. There are around 80 districts (12% of all districts in India) which have an annual new case detection rate of over 20 new cases per 100,000 population, and 22 districts (3% of all districts) reported more than 50 new cases per 100,000 population [20].

Leprosy elimination is mainly the responsibility of the public-funded National Leprosy Eradication Program (NLEP). Early detection and treatment are the backbone of the national programme, which is largely integrated into general health care. The leprosy services include surveys, treatment, referral, complication management, rehabilitation, counselling, health promotion, data collection and reporting. However, not all services have the same priority and the local public health system focuses mainly on treatment and referral. Leprosy complication management is performed in tertiary hospitals, of

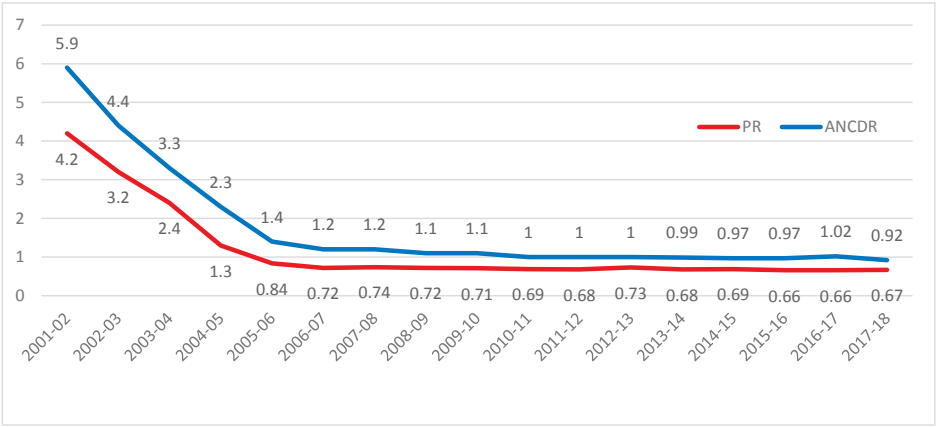

Figure 3. Trends in Annual New Case Detection Rate (ANCDR) and Prevalence Rate (PR) in India
Note: ANCDR is per 100,000 population and PR is per 10,000 population

which there are few and often located remotely. Active case finding surveys are also not done consistently in all areas, and depend on the motivation of local authorities and available resources. There is also an extensive network of philanthropic and non-governmental organisations (NGO's) that support national programme activities.

3. Leprosy control and interventions

Historic and current control strategies

Between 1980 and 2000, the focus in leprosy control was on the provision of MDT to eligible leprosy patients. The underlying assumption at the time was that timely treatment of all cases, especially MB, would also interrupt transmission of *M. leprae* in the community. This evidently was not the case indicated by the stagnation of the new case detection rate after 2005. After 2000, the focus in leprosy control shifted to prevention of leprosy and disability through early detection. The last WHO Strategy (2016–2020) aimed to further reduce the local burden and avert disabilities, especially among children. The target was to have zero visible disability in children diagnosed with leprosy and <1 per million in newly diagnosed leprosy patients. It also called for renewed political commitment and enhanced coordination among partners, while highlighting the importance of research and improved data collection and analysis [21]. Endemic countries were asked to include strategic interventions in their national programmes such as contact tracing, screening, interventions against stigmatization and discrimination [21]. The actual uptake of guidelines is unknown, but countries included contact tracing indicators in their reporting. Particularly, India started a door-to-door case detection campaign, which claimed to reach 320 million people and detected 34,000 new cases in high endemic pockets in 149 districts across 19 states by 2016 [22, 23].

Past leprosy control strategies have not led to clear interruption of transmission of *M. leprae*, as indicated in Figure 1, with stagnating new case detection (incidence) rates since 2005. This poses a major challenge for leprosy control and necessitating the development of novel preventive interventions such as immunoprophylaxis (vaccines) and chemoprophylaxis.

Leprosy vaccines

Efforts to develop leprosy vaccines have been made since the 1960s. The first in line is the Bacillus Calmette–Guérin (BCG) vaccine, which was originally developed to protect against tuberculosis (TB). It was found that it also offers protection against leprosy [24]. The role of BGC in leprosy prevention was confirmed, but a meta-analysis showed that the protective effect was limited to 26% (95% CI: 14-37%) [25]. Other leprosy vaccines were developed in the due course, but their superiority over BCG is unclear as to date none have been tested at population scale [26]. A promising candidate is the *Mycobacterium indicus pranii* (MIP) vaccine, which was developed in India and recently tested in the field, but no scientific publications are available yet on its effectiveness to protect against leprosy. In 2019, a trial with the MIP vaccine was reported in Kanpur Dehat, Uttar Pradesh, spanning 272 villages with a population of 420,832. Around 24,060 close contacts of leprosy patients were either vaccinated or given a placebo [27]. Finally, a specific leprosy vaccine (LepVax) is under development, which is reported to be effective in pre-exposure and post-exposure prophylaxis of *M. leprae* infection in animals [28]. In 2018, LepVax passed the Phase I safety studies in the USA, and field trials are expected to start soon [29].

Post-exposure prophylaxis

To interrupt transmission, the alternative preventive approach is chemoprophylaxis. In the 1960s and 1970s, trials were carried out in Uganda and India with dapsone administered as chemoprophylaxis [30-34], subsequently followed by trials with acedapsone in India [35, 36]. Meta-analysis indicated an overall reduction of the risk of developing leprosy among contacts of up to 50%.[37] In 1988, a chemoprophylaxis study with single-dose rifampicin (SDR) was implemented in the southern Marquesas Islands. This was a non-controlled trial, which after 10 years suggested the effectiveness of SDR of 35-40% [38-40]. Due to the high leprosy incidence rate in the Pacific islands, chemoprophylaxis programmes were also done in the Federated States of Micronesia, Kiribati, and the Republic of the Marshall Islands in the mid-1990s [41]. The combination of rifampicin-ofloxacin-minocycline (ROM) was given to adults and rifampicin only to children under 15 years of age [42]. By 1999, a substantial reduction in case detection rates was observed, but recent figures indicate that this reduction was not sustained. In 2000, a chemoprophylaxis intervention study with rifampicin was started on five

highly endemic Indonesian islands [43, 44]. Two types of intervention strategies were compared with a control group. The blanket (complete population) group included three islands on which prophylaxis was given to all eligible persons. The contact group included an island on which prophylaxis was given to all eligible contacts of all known and newly diagnosed leprosy patients. The control group was the population of an island on which no chemoprophylaxis was offered. This study showed that population-based chemoprophylaxis was associated with a reduced leprosy incidence in the first 3 years after implementation. The answer to the need for a more rigorous trial to determine the preventive efficacy of SDR as post-exposure chemoprophylaxis was the COLEP study in Bangladesh, a single-centre, double-blind, cluster randomized, placebo-controlled trial. SDR given to contacts of patients with newly diagnosed leprosy resulted in an overall reduction in incidence of leprosy of 57% [45]. The effect of SDR depended on contact level (highest in contact groups with lowest a priori risk for leprosy), and on the BCG vaccination status of the contact [46]. If the contact had received BCG as part of a childhood vaccination programme (as established by the presence of a BCG scar), the protective effect of SDR was 80%. In 2018, based on the available evidence, the WHO included a recommendation to implement chemoprophylaxis with SDR in their Guidelines for the Diagnosis, Treatment and Prevention of Leprosy [8].

4. The LPEP program

Based on available evidence from trials, a multi-country study was initiated on implementing PEP with SDR in routine leprosy control programmes. This study was called the Leprosy Post-Exposure Prophylaxis (LPEP) program, which was conducted between 2015-18 in India, Nepal, Indonesia, Myanmar, Sri Lanka Tanzania and Brazil [47]. The programme carried out different case detection methods such as retrospective contact tracing, prospective contact screening and self-screening approach.

The objective was to assess the feasibility of integrating contact tracing and SDR into routine leprosy programmes in different settings. The healthy contacts of leprosy patients were listed, screened and given SDR. Collectively, LPEP program enrolled 9,186 index patients, screened 174,782 (97.2%) contacts and administered SDR to 151,928 (86.9%) contacts. The Indian LPEP project enrolled 1,643 index cases (18% of the LPEP programme), screened 42,333 contacts (24% of the LPEP programme) and administered SDR to 30,295 (20% of the LPEP programme and 71.5% of the total screened in the Indian project). It was concluded that SDR is safe and can be integrated into different leprosy control programmes with minimal additional efforts once contact tracing has been established. PEP with SDR is generally well accepted by index patients, their contacts and the health workforce.

5. Economic evaluation

Economic evaluation is a common practice in health care, especially in the area of prevention programmes, diagnostics, treatment interventions, and the organization of health care. Popular economic evaluation methods are cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. The cost-benefit analysis estimates the benefits and costs in monetary units and enables to compare results between projects of different sectors [48]. However, it excludes the population not participating in the labour force, and converts social benefits into monitory units. In healthcare, the preferred methodology is cost-effectiveness or cost-utility analysis, which examines cost and benefits as health outcomes, such as cases prevented or the quality/disability-adjusted life years, in one or more interventions. The cost should have a perspective, either that of a health system or societal. The health system perspective only accounts for the cost of intervention delivery whereas societal perspective is comprehensive by also accounting indirect costs such as out-of-pocket expenditure or wage loss by patients. Cost-effectiveness/utility analysis aims to maximise health effects with the available resources and guide policy by comparing potential alternative approaches [49]. The cost-effectiveness analysis is widely used to guide advising policy in HIV, TB and other neglected tropical diseases [50], but not sufficiently applied in leprosy.

Comparison between interventions is possible because all the health gains are converted to the same measurement unit, i.e., quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). Particularly, DALYs are preferred over QALYs for diseases prevalent in developing countries, including leprosy [51]. In 1993, the DALYs were first introduced in the global burden of disease (GBD) study to quantify and compare the burden of diseases, injuries and risk factors.

DALY = year of life lost due to premature death (YLL) + year of life lived with disability (YLD)
YLD = disease prevalence estimates * disability weights

The centre of DALYs calculation is the disability weight assigned to a disease by a group of experts, based on their opinion of the disease burden for an individual. The DALYs were appreciated because it provides some basis for comparison, but are also criticised as it may not necessarily reflect the patient's perspective. However, in the later editions of the GBD studies, it is claimed that the disability weights estimation made more realistic, but the exact process remains unclear.

The DALYs are not commonly used in leprosy because the currently assigned disability weights are very low, i.e., grade I disability = 0.011 (0.005-0.021) and grade II disability = 0.067 (0.044-0.096) [18]. The disability weights are low because experts considered only two sequelae (disability) as the complications of leprosy. Skin lesions, nerve

involvement and reactions are not considered as sequelae, implying that a leprosy patient is equal to a healthy person if he has no disability. Because of low disability weights, leprosy is even neglected in the neglected tropical diseases, which portraits that leprosy is no more a priority. As a result, the funding for leprosy has continuously decreased over time because funding agencies rely mainly on DALYs to prioritise funds.

There is a need to develop an investment case for leprosy elimination that can inform on the investment and benefit of leprosy elimination. An investment case is needed for advocating the investments needed in leprosy elimination because the economic burden of leprosy is high, and which is not shown in DALYs due to the above mentioned methodological limitations. Leprosy is known for causing stigma, discrimination, and mental health problems more than any other disease, which increases its economic burden. Investment case concepts were first applied to justify the introduction of a vaccine for eradication of a disease [52]. The investment case comprises largely the health economic evidence; especially cost-effectiveness analysis, which guides the decision to scaling-up interventions. As all effective interventions are necessary not cost-effective; the investment case thoroughly examines all aspects of investment and yield of an intervention. A government may choose to invest to eliminate a disease, even if it not cost-effective in the short term.

6. Gaps and research priorities

Since 2005, leprosy research and funding has declined, which is also a reason for limited health economic evidence in leprosy. Moreover, due to linkage with poverty, leprosy imposes a substantial economic burden, but such estimates are not available that can bring leprosy under the umbrella of poverty elimination. As leprosy is slowly moving towards elimination, active case finding, early detection, and post-exposure prophylaxis with SDR need to be intensified in national leprosy programmes. This needs resources for which an investment case is needed to inform funding agencies on the value of the investment, return benefit, and duration of the commitment.

7. Aim and research questions

The main objective of this thesis is to study the health economic aspect of leprosy prevention. This includes the cost-effectiveness analysis of post-exposure prophylaxis (PEP) in leprosy with single-dose rifampicin (SDR). We aim to provide crucial information on the elements of an investment case for leprosy elimination. Our study focusses on India, the country with the highest leprosy burden in the world.

The specific research questions are:

1. How do investment case concepts apply to leprosy elimination?

2. Can post-exposure prophylaxis with SDR be implemented into a national leprosy control programme?
3. What is the cost-effectiveness of SDR?

8. Outline of this thesis

In **Chapter 2**, we applied the concepts of an investment case in leprosy and adapted the investment case framework for leprosy. The literature on leprosy was systematically reviewed to identify useful information for the investment case. Further, we identified the information gaps and recommended studies, mainly cost-effectiveness analysis.

Chapter 3 is a protocol which explains the objective, definitions and operating procedures of LPEP program in multiple countries.

In **chapter 4**, as a baseline, we document the epidemiological and programmatic situations before and in the first year of the LPEP program. We documented LPEP adjustments along with the national programme in three countries including India.

In **chapter 5**, we estimated the patients' household expenditure on leprosy outpatient services in LPEP and non-LPEP settings. These estimates are important to estimate the economic burden of leprosy.

In **chapter 6**, we calculated the economic cost of leprosy services at primary care level between LPEP and non-LPEP setting. These estimates inform about the financial burden on the public health system that can be reduced by preventing leprosy.

In **chapter 7**, we estimated the cost-effectiveness of leprosy prevention through SDR that is desired for its scale-up. The cost-effectiveness was compared between SDR and no SDR using the SIMCOLEP mathematical model.

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