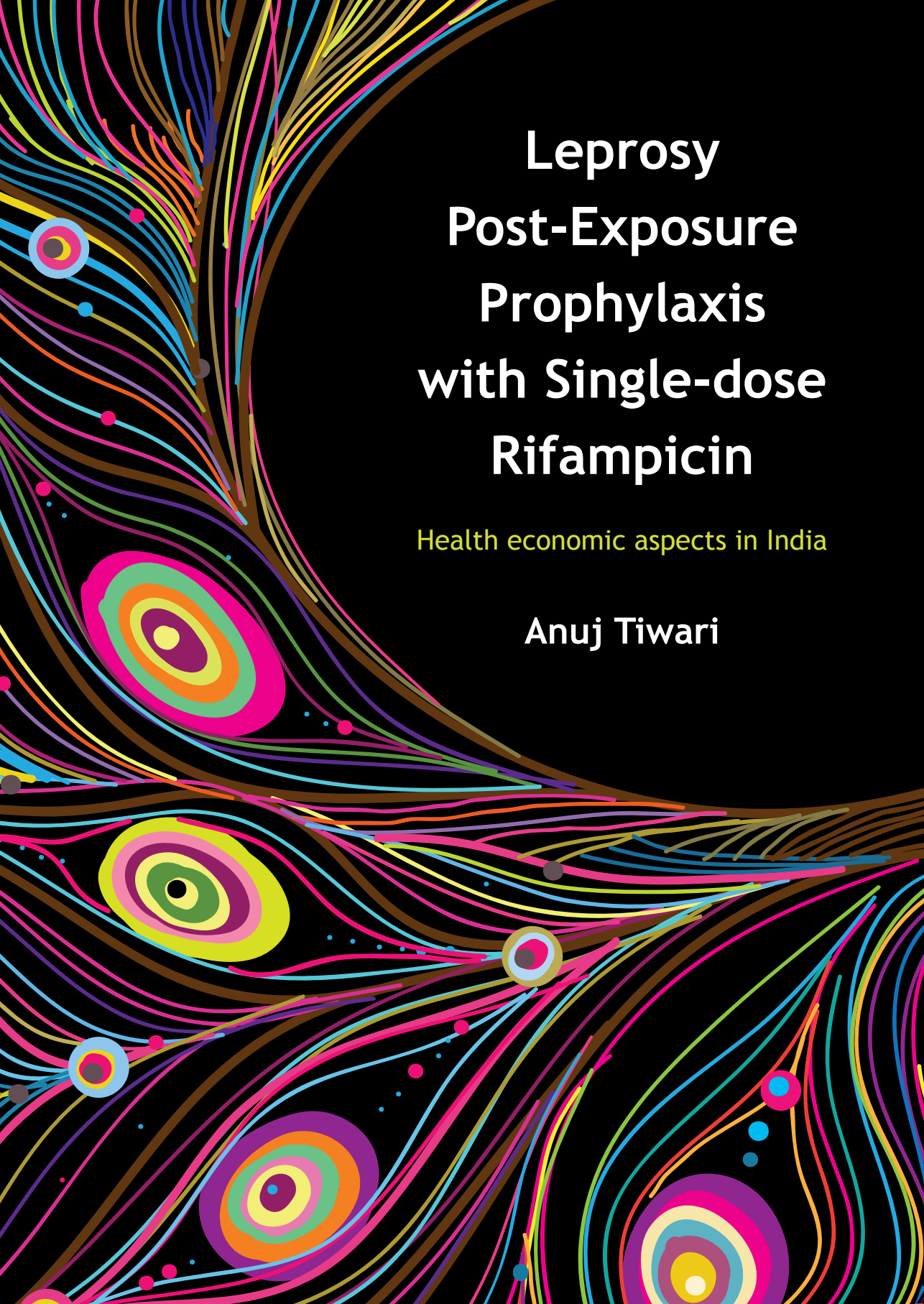

Leprosy Post-Exposure Prophylaxis with Single-dose Rifampicin

Health economic aspects in India

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Lepra post-expositie profylaxis met enkel-dosis rifampicine
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CONTENTS

1 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.

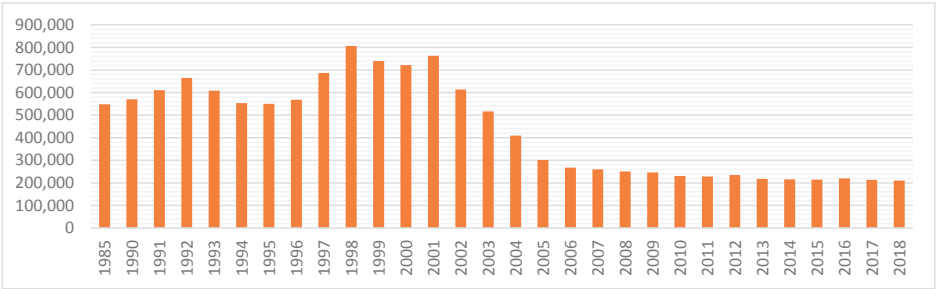

Figure 1. Global trends in leprosy new case detection, 1985–2018
Source: Weekly Epidemiological Reports, WHO

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).

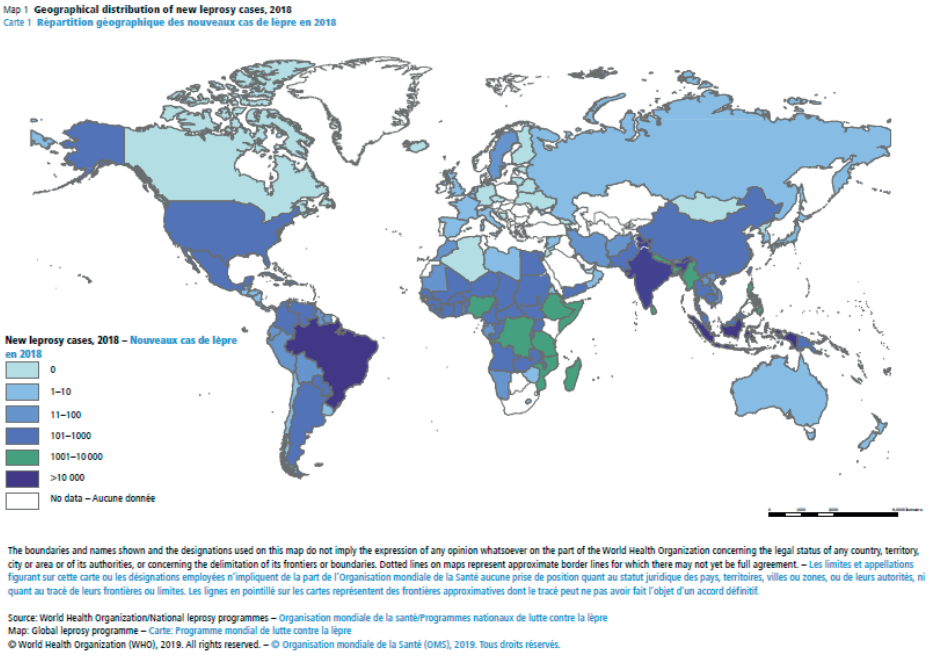

Figure 2. Geographical distribution of new leprosy cases, 2018
Source: Weekly Epidemiological Reports 2019, WHO

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

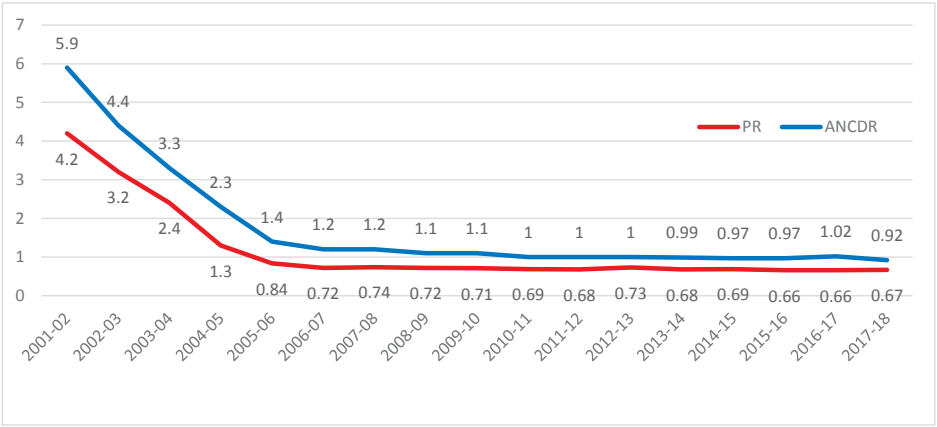

Figure 3. Trends in Annual New Case Detection Rate (ANCDR) and Prevalence Rate (PR) in India
Note: ANCDR is per 100,000 population and PR is per 10,000 population

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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Description: Illustration of Lord Dhanvantari, God of Ayurveda and health, ancient India. Sanskrit 172.

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2 Investment case concepts in leprosy elimination: A systematic review

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ABSTRACT

Introduction

Leprosy continues to be a global public health problem, but draws less attention because 'prevalence based elimination' has been misinterpreted as eradication. The ongoing transmission of *M. leprae* has renewed interest in complete elimination. The aim of our study is to review systematically the literature regarding the elimination of leprosy, and to assess this information on its applicability for defining a Leprosy Elimination Investment Case (LEIC) based on Eradication Investment Case guidelines.

Methods

A literature search was conducted using the MeSH subheadings and synonyms of leprosy. A total of 1007 articles were considered and 112 were included in the final selection. The search focused on the literature covering leprosy elimination and its public health aspects. The LEIC framework was adapted from an existing "Guide to Preparing an Eradication Investment Case".

Results

The LEIC framework provided 11 topics under which information was synthesized from the literature. The fields were categorised under sections: 1) Proposed investment; 2) Rationale for investing; 3) Issues to consider when moving from control to eradication; 4) Management and governance. Scanty quantitative data are available for developing a LEIC, particularly regarding disease burden, and new interventions that could contribute to elimination are not yet applied routinely.

Discussion

For monitoring global elimination, it is necessary to measure disease burden comprehensively, and contact centred preventive interventions should be part of a global elimination strategy. The biological and technical feasibility of elimination is not certain and advanced microbiological and operational research is necessary to understand transmission better. The current WHO road map for leprosy elimination is too vague and needs further structuring through a thoroughly prepared LEIC.

INTRODUCTION

Leprosy, an infectious disease caused by the bacterium *Mycobacterium leprae*, continues to be a public health problem in many areas of the world, with 213,899 new cases detected globally in 2014, representing a new case detection rate (NCDR) of 3·78 per 100,000 population [1]. This rate has remained fairly stable over the past years [2]. Leprosy has a low mortality rate, but is characterized by chronic complications in the form of disability and social stigma. Moreover, its association with poverty increases its propensity to financial impoverishment [3]. Regardless, leprosy has to compete with other public health priorities and is given less attention by health authorities than in the past. An important reason is that leprosy was declared eliminated as public health problem at global level in the year 2000, with the reduction of prevalence to less than 1 per 10,000 (world) population. This 'prevalence based elimination' has been misinterpreted as absolute eradication, and 'reduced case load' as 'low disease burden'[4]. The stagnation in the decrease of the NCDR in leprosy, with its underlying implication that transmission of *M. leprae* is not being interrupted, has led to renewed interest in reaching elimination of the disease. Recently, the World Health Organization (WHO) has formulated a roadmap for 17 neglected tropical diseases, including leprosy, to reduce their global impact. The targets for leprosy are (1) global interruption of transmission or elimination by 2020, and (2) reduction of Grade-2 disabilities in newly detected cases to below 1 per million population at global level by 2020 [5].

Disease elimination is a resource intensive exercise. Especially in resource poor settings careful examination is required to ensure value for money. Investors want to know the social gain and advantage of a long term effort of elimination, before committing sustainable support. Thus, the decision should be evidence based, clearly outlining liabilities against achievements [6]. Inadequate information may hamper the elimination initiative by causing delay or introducing systemic errors. For example, the World Health Assembly resolution of 1991 to eliminate leprosy globally by the year 2000 as a public health problem was based on arbitrary figures, and the elimination plan was not formulated explicitly [4]. The target was reached officially at global level in 2000. Subsequently, the WHO decided to use this elimination target even at national level of endemic countries, which took another 5 years to achieve [7]. Such requirements for decision making have recently led to the development of the 'Eradication Investment Case (EIC)' concept. This concept was first used by vaccine initiatives and later developed into a systematic methodology for the global management of infectious diseases [8].

The EIC concept was elaborated on by a working group at the 7th Ernst Strungmann Forum meeting in 2010, and a guide was published for preparing such EIC [9]. An EIC is

defined as 'a body of data upon which evaluations will be based and investment commitments made when new eradication initiatives are established' [6]. As a next step to disease modelling and economic analysis, the investment case additionally informs on the challenges, risk and sustainability of an initiative, based on the actual context of the disease. Now modelling and cost effectiveness analysis come under the larger umbrella of investment. Basically, it is an exercise that generates a set of triangulating evidences, leading to a conclusion regarding the prospect of an elimination or eradication initiative.

Conventionally, control of disease is defined as the reduction of disease burden to a locally acceptable level. Elimination of disease is defined as the reduction to zero of the incidence in a defined geographical area, and eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent [10]. In leprosy however, the WHO limited elimination to control (prevalence below 1 per 10,000 population) instead of transmission, by using prevalence instead of incidence of disease [10]. This has led to confusion in the discussion about targets in leprosy regarding control and elimination, which is reflected in the scientific literature. The aim of our study is to (1) systematically review the literature on information regarding the elimination of leprosy (either defined as prevalence or incidence based elimination), and (2) to assess the existing information on its applicability for defining a Leprosy Elimination Investment Case (LEIC) according to the existing guidelines for an EIC. In this way, we intend to provide a baseline of information for building a LEIC, and identify information gaps in order to guide a future research agenda and to highlight topics that need further exploration.

METHODOLOGY

Search Strategy

We conducted a literature search in June 2015, using a combination of MeSH subheadings and synonyms of leprosy. The search targeted studies on leprosy elimination, control programme and epidemiology. We searched the following databases: Embase, Medline (Ovid), Web-of-science, Scopus, Cinahl (ebsco), Cochrane, Pubmed publisher, ProQuest, Scielo, and Google scholar. The databases and search terms are listed in Table 1.

We used the following selection criteria:

- Studies using the terms elimination and/or control at least once
- Studies addressing public health aspects of leprosy
- Global, regional and national level studies

Table 1. Database and search builder used for search strategy

Database	Search Builder
Embase.com	(leprosy/exp OR 'leprosy control'/exp OR 'leprosy epidemiology'/exp OR (lepros* OR lepra OR Hansen*):ab,ti) AND ('disease elimination'/exp OR (eliminat* OR eradicat*))
Medline (Ovid)	(exp leprosy/ OR (lepros* OR lepra OR Hansen*).ab,ti.) AND ("Disease Eradication"/ OR (eliminat* OR eradicat*))
Cochrane	((lepros* OR lepra OR Hansen*):ab,ti) AND ((eliminat* OR eradicat*))
Web-of-science	TS=(((lepros* OR lepra OR Hansen*)) AND ((eliminat* OR eradicat*)))
Scopus	TITLE-ABS-KEY(((lepros* OR lepra OR Hansen*)) AND ((eliminat* OR eradicat*)))
Cinahl (ebsco)	(MH leprosy+ OR (lepros* OR lepra OR Hansen*)) AND (MH "Disease Eradication+" OR (eliminat* OR eradicat*))
Pubmed publisher	(leprosy[mh] OR (lepros*[tiab] OR lepra OR Hansen*[tiab])) AND ("Disease Eradication"[mh] OR (eliminat*[tiab] OR eradicat*[tiab])) AND publisher[sb]
Google scholar	Leprosy eliminate|eradicate|elimination|eradication|eliminated|eradicated
Scielo	Leprosy AND (eliminat* OR eradicat*)
ProQuest	(ti(Leprosy) OR ab(Leprosy)) AND (ti(eliminat* OR eradicat*) OR ab(eliminat* OR eradicat*))

Exclusion Criteria:

- Studies published before the year 2000
- Studies on clinical research and (other) Neglected Tropical Diseases (NTDs)
- Study information not relevant to the LEIC framework

The search resulted into 984 records after removal of duplicates, which were considered for review. Due to high relevance to the topic, another 23 important records (reports and research articles) were included on expert's recommendation. Next, the studies published prior to the year 2000 were rejected, because elimination of leprosy as a public health problem (prevalence elimination) was claimed in that year [11]. The focus of our study is on elimination in terms of reduction of incidence and interruption of transmission of *M. leprae*. Thus, we considered pre-2000 strategies as outdated. This led to the rejection of 259 records.

Further, studies based purely on clinical research and other NTDs than leprosy were rejected. This led to the rejection of 392 studies based on title scanning. Another 154 studies were rejected after reading the abstract, because they appeared not relevant to our topic. This lead to 202 full papers that were fully read and of these 90 were rejected due to lack of data relevant to the framework. The remaining 112 papers were used for data abstraction and cited in the references of this study. Figure 1 gives the flow chart of the process.

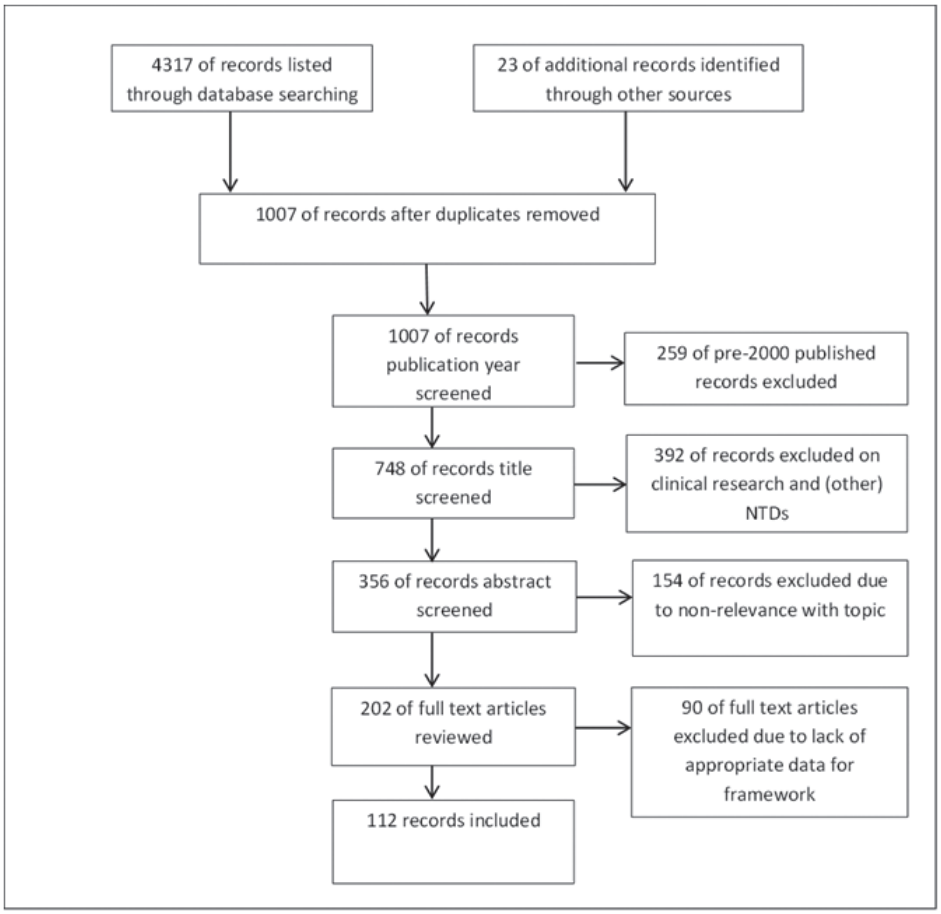

Figure 1: Flow chart of the literature review

Data Abstraction and Study Characteristics

One author (AT) extracted the relevant data (e.g. type of study design, interventions, and outcome measures) from the eligible studies, and the second author (JHR) checked the data. The authors were not blinded to the names of the study authors, journal or institutions. Many studies were discussion papers; focusing on elimination, programme evaluation and epidemiology. Other studies were research articles and reports. However, there were no restrictions on the type of study searched.

Conceptual Framework for Analysing the Selected Literature

The investment case framework for this paper was adapted from the 'Guide to Preparing an Eradication Investment Case"[9]. The report informs that the guidelines are generic and can be taken as a starting point. Moreover, it recommends to customise

and adapt according to the disease and context. The guide has four sections, which are further divided into sub-sections (Table 2, 1st and 2nd column).

The first section focuses on disease context and background preparation for the investment case. The second section is dedicated to the 'Rationale for Investing'. We considered it as a main body that focuses on the scientific evidence one should consider for a convincing case. The third section, 'Issues to Consider when Moving from Control to Eradication' guides towards the possible challenges and alternative plans for management. The last section 'Management and Governance' focuses on operational and

Table 2: Study framework derived from "Guide to Preparing an Eradication Investment Case (2011)"

Section		Subsection	Study framework (based on the section & subsection of the Guide*)
I	The proposed investment	a. The disease and its global health significance	Disease burden and elimination
		b. Current state of control efforts	Current state of the leprosy program and recent technical advancements
		c. How can eradication be achieved?	Available and new tools and their scope in elimination
		d. Post-eradication scenarios	Future requirements during and after elimination
II	Rationale for investing	a. Biological and technical feasibility	Biological and technical feasibility of elimination
		b. Health, social, and economic burden of disease	Socioeconomic burden and public goods obtainable
		c. Assessment of total costs	Financing leprosy elimination
		d. Cost-effectiveness and cost-benefit analyses	
		e. Public goods obtainable through eradication	Socioeconomic burden and public goods obtainable
		f. Strengthening health systems	Health systems and its capacity
III	Issues to consider when moving from control to eradication	a. Stakeholder involvement	Partnership, governance and demand for elimination
		b. Challenges, risks, and constraints	Future requirements during and after elimination
		c. Critical risks and risk management plan	Risks involved moving from control to elimination
IV	Management and governance	a. Partnerships and governance	Partnership, governance and demand for elimination
		b. Critical milestones and monitoring	Disease burden and elimination
		c. Operational research plan	Elimination plan/framework
		d. Evaluating impacts on health systems	Health systems and its capacity

*Walker DG, Lupp J (2011) Guide for preparing an eradication investment case. Available at http://eic-guidelines.org

management aspects. The guide can be used to build a case from any stage i.e. from control to eradication of a disease. As leprosy already attained control, a few headings were not relevant and excluded from the framework for this paper. Further, we merged related subheadings to derive common headings, relevant and convenient for leprosy, e.g. 'Assessment of total costs' and 'Cost-effectiveness and cost-benefit analyses' were merged into 'Financing of leprosy elimination'. We covered all the headings and the majority of sub-headings of the original guide under the topics listed in in the 3rd column of Table 2. The selected literature will be discussed under these headings.

RESULTS

Disease Burden and Elimination

Leprosy cases were reported by 121 countries from five WHO regions in 2014. South-East Asia was the highest contributor with 72% of the reported cases, followed by the Americas (16%), Africa (9%), Western Pacific (2%), and Eastern Mediterranean (1%). Moreover, the number of new cases reduced only marginally in South-East Asia between 2006 (174,118) and 2014 (154,834) [1]. India reported the highest number of new cases in 2014 (125,785; 62% of the global burden) followed by Brazil (31,064) and Indonesia (17,025) [1]. In leprosy, several indicators are used routinely by the WHO to report on the burden of disease: registered prevalence rate, new case detection rate (NCDR), and percentage among new cases of multibacillary (MB) leprosy, females, children (under 15 years), and grade-2 disability [1]. The NCDR is considered to be a more consistent indicator than the prevalence rate. Contrary to the prevalence rate, the NCDR is less sensitive to the operational factors that have changed over time, such as the definition of a leprosy case (which is linked to the duration of treatment), frequency of updating the records, and changes in the WHO leprosy classification system [12-15]. For example, the prevalence of leprosy was almost halved when the duration of treatment with MDT for MB patients was reduced from 24 to 12 months in 1985-2001 [11]. Because the prevalence rate in leprosy only refers to cases under treatment (on average less than 1 year), it does not represent at all the true disease burden, which includes lasting disability and stigmatization in many patients after release from MDT treatment [16]. The percentage of new cases with MB leprosy represents the possible force of infection in the community, because this group is considered to contribute most to the transmission of *M. leprae*. Also, this is the group that is most at risk for complications and lasting disability [17]. Females are a vulnerable group in many countries and have a higher risk of disability due to delay in detection [18, 19]. Globally, females contributed to 38% of new cases in 2014. The Americas show a higher proportion of females among new leprosy cases (44%) compared to South-East Asia (37%) and the Eastern Mediterranean

region (36%) [1, 20]. These differences may be explained partially by sociocultural circumstances regarding the position of women in some countries, hindering their health seeking behavior due to fear of rejection and/or limited access to health care. The NCDR of children younger than 15 years of age is important because it is considered as a proxy of ongoing transmission, in that the average incubation time in children is necessarily shorter than in adults and therefore reflects recent transmission. of *M. leprae* better than in adults, who may have acquired the infection many years ago [21].

Box 1 Key results of Literature Review.

Disease burden and elimination
- The NCDR of children younger than 15 years of age is a proxy of recent transmission, as average incubation time in children is shorter than in adults [21]
- Grade-2 disability reflects the efficiency of a health system in early detection and treatment
- A high number of leprosy cases are undetected and not reported by the health systems [22]. If these cases are accounted for the burden estimates will increase substantially

Current state of the leprosy programme and recent technical advancements
- The WHO target to reduce grade-2 disabilities by at least 35% at the end of 2015 [24], compared to 2010 is unrealistic
- Polymerase Chain Reaction (PCR) is an advanced technique, capable of early detection of *M. leprae* and to finding drug resistance [12, 26], but its application is limited
- *M. leprae* specific phenolic glycolipid (PGL)-1 antibody test has limited applicability, as this test is only positive in the MB spectrum of disease [27]

Available and new tools and their scope in elimination
- Contact tracing has advantage over intensified population-based detection approaches, but operational and ethical challenges need to be accounted for during implementation [29]
- Contact tracing, followed by chemoprophylaxis and/or vaccination with BCG or leprosy specific vaccines is currently the most promising tool for elimination

Future requirements during and after elimination
- Linking leprosy with other NTDs ensures sustainability through programmatic and financial efficiency [22]
- The relationship between poverty and leprosy needs clarification [56]

Biological and technical feasibility of elimination
- Genome based technology is promising for the development of vaccines and diagnostic tests [47]

Socioeconomic burden and public goods obtainable
- DALY is a problematic indicator to describe the burden of leprosy disease [70, 71]
- Leprosy belongs to the portfolio of diseases associated with poverty [16]

Financing leprosy elimination
- Information on costs of providing leprosy services is limited

Health systems and its capacity
- Integration into the general health care system has been shown to decrease the level of stigma [87]
- Community based rehabilitation (CBR) is found to be effective in integrated settings, but its activities are limited in most health systems [95, 96]

Finally, another important indicator is Grade-2 disability. Grade-2 disability is defined as visible deformity or damage present on the hands and feet; severe visual impairment,

lagophthalmos, iridocyclitis, or corneal opacities [7]. An efficient health system can prevent disability through early detection, treatment and care. Thus, it reflects the efficiency of a health system, including service delivery.

Apart from the approximately 200,000 leprosy cases that are reported annually, without a clear sign of a rapid decrease, there are also undetected and untreated cases of leprosy, which further threaten elimination, as they act as a hidden reservoir of the infection. Modeling suggests that a large number of such cases escape detection by the health systems [22]. Furthermore, Kumar et al. reported that the observed trend of increasing MB ratio in India (from 25·9% in 1994 to 45·2% in 2005) is the result of early cases of leprosy being missed [17]. If undetected cases would be included in the reported count, the leprosy burden would increase significantly.

Box 2 Key information gaps.

- No information is available on the total disability burden of all individuals who have had leprosy in the past
- Quality and effectiveness of various national programmes are unknown as routine data do not contain such information [78]
- None of the studies have given a structured elimination plan or framework, which is a gap to be filled while building an investment case for leprosy
- Knowledge on transmission of *M. leprae* is limited [102]
- Operational research is required to assess the feasibility of chemoprophylaxis in different settings [33, 34]

Box 3 Key recommendations.

- Monitor global elimination through short-term (epidemiological) and long-term (socioeconomic) indicators
- Implement active case finding strategies, especially in countries or areas where the disease has clustered over a long time
- Commission health economic studies on societal cost of leprosy, including economic profiling of the population
- In health economic studies, broaden the focus from DALYs to socioeconomic impoverishment and disability due to leprosy
- The leprosy elimination investment case should be built on the development agenda, including poverty reduction and education under its umbrella
- Reconstructive surgery is cost-effective [57], therefore scale this up in routine national leprosy programmes
- The burden of psychiatric illness should not be ignored while estimating the economic burden for LEIC
- Replace paper based reporting by an electronic Health Management Information System (HMIS) platform for quality data [93]
- Detailed literature reviews could be performed taking the various elements of the LEIC framework as starting point

Current State of the Leprosy Programme and Recent Technical Advancements

The current WHO leprosy control strategy is termed 'Enhanced Global Strategy for Further Reducing the Disease Burden Due to Leprosy: 2011–2015' [23]. The emphasis is on disability reduction, while ensuring that the quality of services is not compromised so that every person affected by leprosy has easy access to diagnosis and free treatment with MDT, and that sustainable activities are carried out and quality services provided within an integrated set-up that includes an effective referral network to manage leprosy-related complications effectively. This strategy has an ambitious target to reduce Grade-2 disabilities by at least 35% at the end of 2015, compared to 2010 [24]. However, complete lack of progress has been registered so far on this indicator [1]. The London Declaration on Neglected Tropical Diseases was launched in 2012 and supports the agenda of the WHO 2020 roadmap to eradicate NTDs. The targets for leprosy are global interruption of transmission or elimination by 2020, and reduction of grade-2 disabilities in newly detected cases to below 1 per million population at global level by 2020 [22, 25].

The diagnosis of leprosy is since long based on clinical criteria only. A person has leprosy in the presence of one of the following cardinal signs: skin lesion consistent with leprosy and with definite sensory loss, with or without thickened nerves, and/or a positive skin smear. Rod-shaped, red-stained (acid-fast) leprosy bacilli, which are diagnostic of the disease, may be seen in the smears taken from the affected skin when examined under a microscope after Ziehl-Neelsen staining. Skin smears however, are not performed routinely any more in many countries. Polymerase Chain Reaction (PCR) is an advanced technique that can be applied to the early detection of *M. leprae* and to finding drug resistance [12, 26]. PCR is quick, accurate and does not require bacterial culture, but its application in the field is still limited. *M. leprae* specific phenolic glycolipid (PGL)-1 antibody testing has been available for many years, but this test is only positive in patients in the MB spectrum of the disease [27]. There have been advances in the development of serological tests, e.g. through ELISA techniques and applying other markers than PGL-1 [27], but their advantage above PGL-1 serology remains questionable.

Available and New Tools and Their Scope in Elimination

The basic intervention strategy in leprosy control is still the provision of MDT, given to newly found leprosy cases. Preventive interventions, other than awareness raising and health education activities, are not routinely available. It has long been argued that elimination of leprosy cannot be achieved by a strategy based on MDT alone and that new tools and technologies are needed to attain this goal [10]. Intensified, population-based approaches to case detection are no longer considered cost-effective and a new

approach is indicated that is appropriate to the current epidemiological situation. New cases are relatively rare even in endemic countries, health care resources are scarce with many competing health care demands, and leprosy control activities are difficult to sustain within integrated programmes.

The main risk of exposure to leprosy is in close contacts of new, untreated cases and the risk of exposure to leprosy in the general community is very low. An increasing proportion of new cases will be from household contacts [28]. Thus, contact tracing is beneficial but operational and ethical challenges need to be accounted for during implementation [29]. In the past years, progress has been made in the areas of chemoprophylaxis and immunoprophylaxis (vaccination) to prevent leprosy, and these interventions have focused primarily on contacts of leprosy patients [30-32]. Chemoprophylaxis with single dose rifampicin is shown to be cost effective, but further research is required to assess its operational feasibility [33, 34]. Vaccines have a role in interrupting transmission in the long term, but are expensive and operationally challenging. Targeting seropositive household contacts who are at greater risk of developing leprosy could be an efficient strategy [35, 36]. The combination of contact tracing, followed by chemoprophylaxis and/or vaccination with BCG or leprosy specific vaccine is currently the most promising tool for elimination.

An important additional component of a successful contact-based preventive strategy is the availability of reliable and simple diagnostic tests to establish both disease and infection. Clinical diagnosis of leprosy is dependent on the recognition of disease signs and symptoms and can thus only be established once the disease has become manifest. Available tests based on antibody responses to PGL-1 are only effective for detecting infection in MB patients, and do not predict the development of disease in subclinical cases accurately [37, 38]. It would be invaluable for control purposes to establish whether leprosy contacts are infected with *M. leprae* and, more importantly, whether they are likely to develop leprosy disease. In that case they could receive prophylactic treatment. The challenge is to produce tests based on immunological biomarkers that distinguish individuals controlling bacterial replication from those developing disease [39]. Currently extensive work is ongoing in this area to develop specific T-cell diagnostic tests and examine their validity and applicability in the field [40-42]. Results of such test or combination of tests could determine the choice of intervention given to the contact (e.g. MDT, chemoprophylaxis and/or immunoprophylaxis). Modeling studies have shown that all three interventions (detection of subclinical infection and treatment, chemoprophylaxis and BCG vaccination) when applied consistently to household contacts of leprosy patients, will lower the incidence of disease in the population [43].

Future Requirements During and After Elimination

Leprosy in future should not stand in isolation, but be linked with other NTDs. Collaboration will draw attention to the collective burden of disease and enhance sustainability through programmatic and financial efficiency [22]. In the elimination phase, efforts should be employed to maintain and where necessary restore the clinical expertise in the system [14]. There are still many uncertainties and difficulties in the field of leprosy and it is recommended to boost research in the areas of diagnosis, treatment, prevention, reactions, prevention of disability, stigma and rehabilitation [44]. Early diagnosis of disease and nerve function impairment, and the management of leprosy reactions and subsequent physical, psychological, and social complications are also important areas of research [19, 45]. Investment is needed for new drug discovery, due to the threat of drug resistance [46, 47]. Furthermore, a strong surveillance system is required to monitor new case detection, drug resistance and relapse [48]. New technologies should be developed in the area of e-health and social media, such as the use of a quantitative rapid diagnostic test for MB leprosy using smart phone technology, as was recently reported [49]. Three studies have been reported on the advantages of using GPS technology and recommend its integration into routine programmes for better planning and service delivery [50-52]. Operational research is an urgent need regarding optimal implementation of immunoprophylaxis and chemoprophylaxis [18, 44]. The acceptability of these interventions should be explored in different settings for generalized results [53]. Periodic sample surveys are important to assess the actual burden of disease and other indicators [54]. Treatment discontinuation is a common problem due to poor socioeconomic conditions and needs appropriate response from the health system [55]. Finally, more economic analysis studies are required to establish the relationship between poverty and leprosy [56]. Especially, cost-effectiveness analyses on leprosy (and leprosy related disability) are scarce and are required for policy development and annual planning [57]. They can help identify sustainable activities in the phase of elimination.

Biological and Technical Feasibility of Elimination

Feasibility of elimination is a well discussed topic, and experts share both positive and negative views. Leprosy has a long incubation period, ranging from 6 months to 20 years. Furthermore, a large number of asymptomatic carriers act as reservoir and may spread infection to new hosts [12, 27]. It has been shown in endemic areas that around 5% of the population are nasal carriers of *M. leprae* DNA [11, 14]. It has also been pointed out that cases of histoid leprosy (a rare and often unrecognised form of MB disease) can act as a reservoir [58]. Unfortunately, knowledge on transmission of *M. leprae* is limited because in vitro bacterial culture is not possible [27]. Moreover, a recent systematic review concluded that available literature is not conclusive of the

transmission mechanism, and multiple modes of transmission are possible [59]. The organism can be dormant for a long time, and survive outside the human body. There are non-human vectors, notable armadillos in the southern states of the USA [60]. Environmental factors are also suspected to play a role in leprosy transmission [61]. Studies in endemic regions have indicated soil as a possible reservoir for the bacteria [18, 62]. Some experts believe that due to the above mentioned reasons, MDT-based strategies alone cannot lead to elimination. The suggestion is to consider leprosy as a chronic disease and focus on sustaining control rather than pursuing elimination [16, 63] Smith & Richardus argue that as long as the epidemiological and microbiological features of *M. leprae* are not sufficiently clear, a scientific case for elimination or eradication cannot be justified [64]. Thus, the recommendation is to accelerate microbiological research to understand the transmission abilities of the bacterium [65]. The most exciting scientific advancement has been the sequencing of the genome of *M. leprae*. Genome-based technology has the potential to solve the many uncertainties regarding transmission through strain typing and molecular epidemiology, and enhance the development of vaccines and diagnostic tests, which increases the prospects of elimination in future [47].

Socioeconomic Burden and Public Goods Obtainable

Leprosy affects the peripheral nervous system and in the absence of timely treatment this leads to irreversible neuropathy in a considerable proportion of cases. This in turn leads to secondary impairments, such as wounds caused by burns or pressure on the sole of the foot, contractures of fingers and toes and visual impairment. These impairments can finally lead to limitations in activities of daily living and/or restrictions in social participation [66]. Leprosy is thereby a leading cause of preventable disability in many endemic countries. The number and percentage of new cases globally with Grade-2 disability has been fairly stable between 2007 (14,403; 5·58%) and 2014 (14,110; 6·59%). Furthermore, there is no information available on the total disability burden of all individuals who have had leprosy in the past. In 2009, the WHO estimated that over three million people worldwide are living with leprosy generated disability [23]. A modeling study estimated that the global Grade-2 disability burden will reach 1 million in 2020 [10]. The stable number of new cases with Grade-2 disability is leading to a relative increase of people living with disability [67].

Disability Adjusted Life Years (DALYs) is a standardised measure to compare the disability burden among diseases. This measure is useful for establishing (cost) effectiveness of interventions for preventing illness or alleviating disease burden and has been widely used, also for estimating the burden of NTDs, including leprosy. DALY is the sum of years of life lost (YLL) plus years lost due to disability (YLD). Mortality in leprosy is not

an important issue; few people die from leprosy [68]. Therefore, the DALY in leprosy is derived primarily from YLD, which is the number of incident cases times disability weight times the average duration of the case until remission or death (in years). The average disability weight attributed to leprosy WHO Disability Grades 1 and 2 is 0·1528 [69]. In comparison, the disability weight for blindness is 0·600. It is however, very difficult to measure disability caused by leprosy and its duration accurately. Disability often starts insidiously at a relatively early age and can develop gradually over time. DALY is therefore a problematic indicator to describe the burden of leprosy disease [70, 71]. Alternatively, Rao et al. developed a method to calculate the loss of productive working life years, but this is not yet widely accepted due to lack of comparability with all other diseases [72].

Field evidence suggests a close association between leprosy and poverty. Socioeconomic improvement and high coverage of BCG vaccination has contributed significantly to the reduction of transmission and disease burden [73, 74]. This was also the experience in Europe, where leprosy was eliminated during a time of increasing living standards, even before the discovering of the biological nature of the bacteria and the availability of antibiotic treatment [75]. Low socioeconomic status and leprosy are commonly observed at both individual and community level [3]. It has therefore been advocated to include leprosy in the portfolio of diseases associated with poverty [16]. Disability leads to financial impoverishment due to loss of work opportunity, forcing people further into poverty. Stigma also reduces work opportunity [18]. Leprosy remains one of the most stigmatized diseases [76]. Stigma not only affects the patient with leprosy, but also family members. Thus, the burden is higher than presumed [77]. Furthermore, adverse legislation defending discrimination continues to exist in some countries [78].

National programmes often focus only on achieving coverage and treatment targets, and neglect stigma and poverty reduction activities. Indicators on socioeconomic improvement or rehabilitation are not a part of routine or periodical surveillance under national programmes. Thus, there is little information about socioeconomic progress made due to leprosy control activities. The existing evidence suggests that leprosy affected people (especially the disabled) continue to contribute to the economic burden of the disease [79]. The socioeconomic consequences of leprosy are a reduced quality of life and high burden of mental illness among patients and family members [45]. The mental health of leprosy affected people is significantly poorer than the general population and those affected by other skin diseases [80]. The results of mental health problems are (self) stigmatisation, low education, ongoing physical deformities through lack of self-care, and a lower annual income [81]. We could not identify any socioeconomic studies that predict or evaluate the overall public goods obtainable through leprosy elimination or

control. However, studies demonstrated that poverty reduction initiatives (conditional cash transfer) and strengthening primary health care has a role in decreasing leprosy transmission [74, 82].

Financing Leprosy Elimination

Leprosy programmes are currently facing financial difficulties due to the reduction of international funds and commitment [78]. The integration of leprosy into the general health system increases domestic programme funding and the responsibility of local governments [83]. Information on costs of providing leprosy services is limited. We have not encountered any peer reviewed costing study that estimates the complete cost of delivering leprosy services, nationally or globally. However, a recent WHO report 'Invest to overcome the global impact of NTD 2015' targets an investment of about US$ 37 million (US$ 32–42 million) on average each year during 2015–2030, required for contact tracing, treatment and care. Furthermore, it predicts that investment targets will decrease slowly over time, from US$ 52 million (US$ 45–58 million) in 2015 to US$ 30 million (US$ 25–34 million) by 2030 [84]. However, the methodology of calculating cost in this report is not clear. A recent costing study estimated the household costs of leprosy reactions in rural India and concluded that the economic burden on households affected by leprosy reactions is significant [85]. Socioeconomic assessment is not part of routine monitoring, nor is periodic surveillance. With limited financial resources, socioeconomic data can help in targeting the aid to those who require it most. Also, this will help in assessing the economic burden of leprosy and establishing its association with poverty [86].

Health Systems and its Capacity

The integration of leprosy programmes into the general health care system of endemic countries is a significant development. It is a positive step towards sustaining leprosy control activities after the declaration of elimination as a public health problem [16]. Furthermore, integration into the general health care system has been shown to decrease the level of stigma as compared to the vertical approach [87].

With a low leprosy incidence, it is difficult for health systems to do active case finding due to financial and human resource constraints [88]. This leads to weak monitoring of drug resistance and relapse cases [89]. Post integration, India reports issues such as weak monitoring, increase of hidden cases, and declining adherence rates [90, 91]. Another study from India reports human resource training, MDT supply and referral management as integration issues [92]. Furthermore, experience from Indonesia indicates that human resource unavailability has a negative effect on data quality. The interrupted availability of human resources resulted into a large amount of missing

data, impeding active case finding [93]. A study in Bangladesh reported higher new case estimates after comparing the data of a sample survey with that of the routine leprosy control programme [12]. Moreover, routine data do not contain information on the quality or effectiveness of the implementation, which is a gap [78]. The private sector data do not contribute to the global estimates. As the private sector serves large urban populations in some countries, the missing numbers could be significant [89, 94]. Rehabilitation is another neglected component in most health systems. Community based rehabilitation (CBR) is found to be effective in integrated settings, but its activities are limited [95, 96]. Awareness activities remain important in the post elimination era, when programmes depend largely on passive case finding [97]. Moreover, innovative information and communication techniques should be employed in creating awareness [98]. Finally, geographic information systems (GIS) are very helpful in planning and service delivery, but its uptake in national programmes is poor [50].

Partnership, Governance and Demand for Elimination

The primary responsibility for leprosy control is with national governments, which may have a national programme manager for leprosy or co-ordination and supervision of leprosy services within a department of disease control, communicable disease control, or NTDs. Governments are supported by a number of stakeholders such as the WHO, international NGOs such as the International Federation of Anti-Leprosy Associations (ILEP), local NGOs, as well as organizations of people affected by leprosy, and professional associations such as the International Leprosy Association (ILA). Novartis and Novartis Foundation support programmes and innovation as well as providing all MDT drugs free of cost.

There is currently a demand for eradication of leprosy, together with a number of other NTDs, and a willingness to co-operate at the global level. The London Declaration (2012) affirms the global demand to eradicate leprosy along with other NTDs [25]. Leprosy is classified as NTD by the WHO, but none of the studies included in our literature search discuss this topic in particular. The declaration vows to accelerate progress to achieve 2020 WHO targets and provides yearly updates on progress made [25]. Further, it focuses on enhancing drug donation, supply of multidrug therapies, research & development, collaboration and partnership.

Risks Involved Moving from Control to Elimination

Sustaining leprosy activities after declaration of elimination is a challenge. A reduced case load limits the clinical exposure and leads to loss of knowledge and expertise [4, 78, 99]. This increases the risk of detection delay and wrong diagnosis, affecting adversely the incidence of nerve function impairment and disability. Premature dec-

laration of elimination induces a passive attitude amongst researchers, policy makers and health providers, and makes the programme lethargic [11, 100]. Further, research is badly affected in such a condition, due to reduced funding [14, 100]. The field of leprosy is no more an attractive area to work in and leprosy workers face uncertainty in their career [101]. In addition, programme policies are changed without considering the local situation, which yields inefficiency. An example from India describes that a policy shift from active to passive case finding is not practical [89]. Low level of community awareness and high social stigma prevents individuals from reporting voluntarily.

Elimination Plan/Framework

None of the studies in our literature search have given a structured elimination plan or framework, which is a gap to be filled while building an investment case for leprosy. However, a published symposium report on transmission knowledge listed current gaps and proposed areas of investigation in a systematic manner. It concludes that prospective long-term studies are needed to understand the transmission of *M. leprae* [102]. Further, the recommendations in this paper can be helpful in designing a framework or plan for elimination. Sufficient evidence exists in support of chemoprophylaxis. It is recommended that active contact tracing, followed by chemoprophylaxis and/or immunoprophylaxis in contacts should be a part of a global policy [16, 103]. Next, informal education and communication activities should continue even after elimination. Similarly, investment in infrastructure and human resources should not stop in the current phase of transition from control (prevalence based) to incidence based elimination [104, 105]. The programme should rely on active case finding, as the disease is not yet eliminated [106]. Innovative financial mechanisms should be explored to bridge the funding gap [78, 107]. Advocacy needs to be aggressive for generating global demand for elimination. Furthermore, NGO partnerships and linkages are desired for organised and co-ordinated efforts in national programmes [63]. Finally, Lockwood et al. suggested focusing on sustaining activities and preventing disability. The future of leprosy programmes lies in rehabilitation because the number of people with leprosy related disability appears to be increasing. Furthermore, health systems should be strengthened to manage leprosy reactions [16]. The capacity to manage reactions by general health care staff can be developed by repeated training and community awareness [22].

DISCUSSION

Leprosy can cause chronic complications, even after completion of treatment with MDT. Thus, the disease burden of leprosy has both a short-term and long-term perspective. Short-term indicators are important to monitor epidemiological progress of disease

control, while long-term indicators are needed to capture socioeconomic improvement. For the purpose of monitoring global elimination, it is necessary to measure disease burden comprehensively through a balance between both type of indicators. Furthermore, missing (undetected or wrongly diagnosed) leprosy cases are unchecked sources of transmission that frustrate elimination planning due to underestimation of the burden. In order to achieve elimination, it is necessary to implement active case finding strategies, especially in countries or areas where the disease has clustered over a long time.

There has been substantial progress in the field of chemoprophylaxis and immunoprophylaxis, which are now considered as promising tools for elimination, focusing on (close) contacts of leprosy patients. There is a growing body of evidence in support of these interventions to be the part of a global elimination strategy. However, elimination also needs innovative field friendly diagnostics that can early detect sub-clinical infection, such as cellular immunological tests, which are still in development [27, 108]. Our review shows that literature on the biological and technical feasibility of elimination is not conclusive. Advanced microbiological and operational research methods are necessary to better understand the transmission and ecology of the leprosy bacteria [22].

DALYs as indicator has failed to describe accurately the disability burden of leprosy. On the basis of our literature review we recommend to broaden the focus from DALYs to socioeconomic impoverishment and disability due to leprosy. Although the relationship between leprosy and poverty has been discussed extensively, no correlation has been shown between a country's GDP and leprosy new case detection [56]. We agree that such a macroeconomic analysis is desirable but not compulsory, especially when a disease has attained control. A significant disease burden (in a proportion to the total population) is essential for such an analysis, which is not the case now in leprosy. Thus, we recommend conducting health economic studies on societal cost of leprosy, including economic profiling of the population. Moreover, the leprosy elimination investment case should be built on the development agenda, including poverty reduction and education under its umbrella. Evidence should be gathered to forecast the monetary and non-monetary impact of leprosy elimination on the Millennium Development Goals (MDGs) i.e. poverty and education [16].

Our literature review shows that evidence on health systems is sufficient and supportive of building a leprosy elimination investment case. The health systems should collectively focus on socioeconomic aspects (stigma, disability and poverty). Stigma is an ongoing problem in leprosy and its assessment remains relevant in guiding programme policies [109]. Repetitive training of the health workers on stigma is important [109]. Next,

reconstructive surgery is a cost-effective way of reducing the disability and financial burden of leprosy [57]. We therefore recommend scaling up reconstructive surgery in routine national leprosy programmes. Psychiatric care for leprosy patients and their families is usually not available in the general health care system. Mental illness is not even considered as a sequel, and services are not available in national programmes. Our study indicates that when estimating the economic burden for a LEIC, the burden of psychiatric illness should not be ignored.

Some health systems are facing operational challenges in managing leprosy routine services [98]. Experience sharing between countries is an effective way of solving common problems. These experiences should be evidence based, i.e. built on a body of data. A good first step would be to replace paper based reporting by an electronic Health Management Information System (HMIS) platform for quality data [93]. Public Private Partnership (PPP) is an effective strategy to strengthen the referral network, which is often a weak point of health systems [110]. Private providers are the first point of contact for many patients, who are often missing from national programme records [108], thus an effective PPP policy is highly desired for national programmes to achieve universal coverage. The risk of leprosy expertise erosion is well documented, while moving from control to elimination. The health system should retain leprosy specialist services, which has decreased after integration [111].

Nsagha et al. published a literature review in 2011 on the topic of leprosy elimination [62]. Their study identified publications on the leprosy elimination strategy (as a public health problem) by using three keywords, i.e. leprosy, elimination and 2000. Their search resulted in 63 studies and a total of 64 studies were cited in their reference section. Contrary to this study, our search is a systematic literature review, using MeSH terms for our search. In addition, we have used the LEIC framework to describe our results. Furthermore, our search included only studies from the year 2000 onwards, which is not the case with Nsagha et al. Ten studies are commonly cited and many findings and recommendations of both the studies match.

In addition to our current literature review, which has the elimination of leprosy as starting point, further literature reviews could be performed taking the various elements of the LEIC framework as starting point, e.g. DALY and leprosy, health systems and leprosy. This would doubtlessly produce a wealth of further data to inform a LEIC, but this was beyond the scope of the current study. We therefore recommend conducting separate literature reviews on each element of the LEIC framework proposed in our study.

CONCLUSION

We conclude that the current WHO road map for leprosy elimination is vague and needs further structuring by producing a systematic inventory of what is needed at different levels and in a realistic timeframe to achieve incidence-based elimination (i.e. interruption of transmission of *M. leprae*). As part of a LEIC, research studies should be assigned to identify and justify the items of the inventory in detail. Furthermore, the elimination targets should be backed by scientific evidence and framed after detailed consultation with prominent stakeholders in the field of leprosy [112]. The declaration of elimination in the year 2000 based on arbitrary targets, has translated into greater loss than benefit with the current stagnation in new case detection, reduced resources and political commitment, knowledge and expertise. A thoroughly prepared LEIC can avoid such pitfall.

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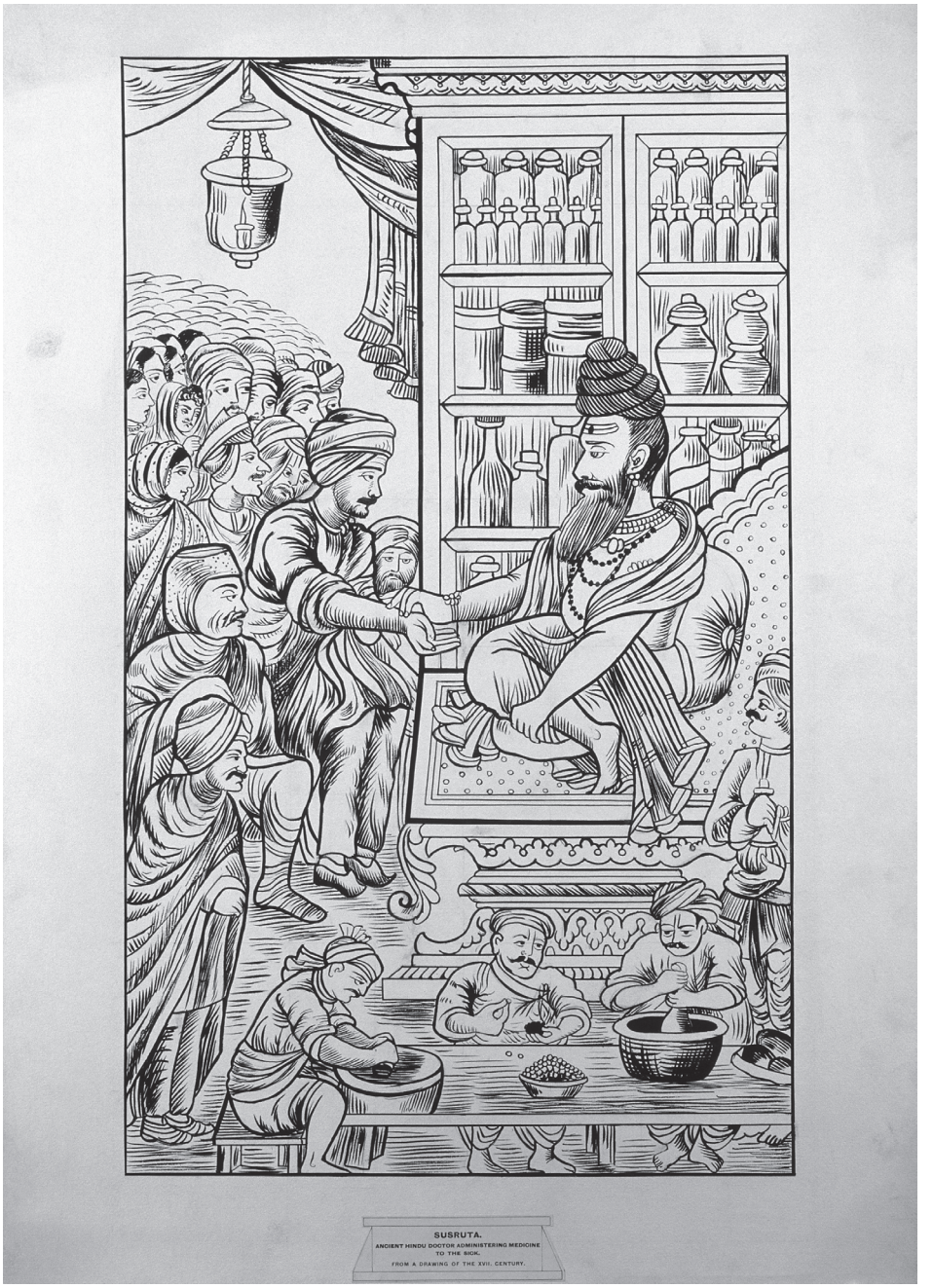

Description: Sushruta (c. 7th or 6th century BCE) was a physician in ancient India known today as the "Father of Indian Medicine" and "Father of Plastic Surgery" for inventing and developing surgical procedures. His work on the subject, the Sushruta Samhita (Sushruta's Compendium) is considered the oldest text in the world on plastic surgery. Source: https://www.ancient.eu/sushruta/

Picture credit: Wellcome Collection, London

3 Leprosy Post-Exposure Prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin

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ABSTRACT

Introduction

The reported number of new leprosy patients has barely changed in recent years. Thus, additional approaches or modifications to the current standard of passive case detection are needed to interrupt leprosy transmission. Large-scale clinical trials with single dose rifampicin (SDR) given as post-exposure prophylaxis (PEP) to contacts of newly diagnosed patients with leprosy have shown a 50–60% reduction of the risk of developing leprosy over the following 2 years. To accelerate the uptake of this evidence and introduction of PEP into national leprosy programmes, data on the effectiveness, impact and feasibility of contact tracing and PEP for leprosy are required. The leprosy post-exposure prophylaxis (LPEP) programme was designed to obtain those data.

Methods and analysis

The LPEP programme evaluates feasibility, effectiveness and impact of PEP with SDR in pilot areas situated in several leprosy endemic countries: India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania. Complementary sites are located in Brazil and Cambodia. From 2015 to 2018, contact persons of patients with leprosy are traced, screened for symptoms and assessed for eligibility to receive SDR. The intervention is implemented by the national leprosy programmes, tailored to local conditions and capacities, and relying on available human and material resources. It is coordinated on the ground with the help of the in-country partners of the International Federation of Anti-Leprosy Associations (ILEP). A robust data collection and reporting system is established in the pilot areas with regular monitoring and quality control, contributing to the strengthening of the national surveillance systems to become more action-oriented.

Ethics and dissemination

Ethical approval has been obtained from the relevant ethics committees in the countries. Results and lessons learnt from the LPEP programme will be published in peer-reviewed journals and should provide important evidence and guidance for national and global policymakers to strengthen current leprosy elimination strategies.

INTRODUCTION

Over the past 30 years, the prevalence of diagnosed leprosy cases has declined by 95%, from 5.2 million in 1985 to <200,000 in 2015 [1, 2]. This remarkable reduction has often been cited as a major public health success. Indeed, in 2000, the WHO's goal to eliminate leprosy as a public health problem, defined as a prevalence of <1 leprosy patient per 10 000 population, was officially reached [3]. This contributed to a sharp decline in official interest for leprosy in most endemic countries, and a significant reduction in financial support for national programmes that manifested itself in reduced case finding and diagnosis efforts [4-7]. The reduction of the recorded prevalence can be attributed to the widespread availability of free multidrug therapy (MDT), along with a shortening of the standard treatment [8]. The reported annual number of new cases has plateaued at 200,000–250,000 globally in the past decade; with 213 899 new diagnoses reported in 2015 [1, 2]. This stagnation, and the fact that still about 10% of the new diagnoses occur in children, suggests ongoing leprosy transmission [4-7], while the continuing detection of patients with advanced disease indicates serious diagnostic delays [7]. As a result, alternative control strategies are needed to interrupt transmission of Mycobacterium leprae and accelerate case detection.

The main risk factor for leprosy is prolonged close contact with an infectious patient [9]. Early case detection and prompt treatment with MDT are the cornerstones of the WHO recommendations for leprosy control [10, 11] but solid evidence exists that post-exposure prophylaxis (PEP) with single dose rifampicin (SDR) can reduce the risk of contacts to develop leprosy by 50–60% over the 2 years following SDR administration [12-15]. Chemoprophylaxis has already been used in the 60s and 70s when weekly dapsone for 2–3 years was tested, an approach that proved too cumbersome to become widely implemented [16-21]. Other trials used acedapsone every 10 weeks for 7 months [22, 23]. A meta-analysis of the dapsone studies showed their superiority over placebo with an overall reduction of the leprosy new case detection rate (NCDR) of 40% in contacts [16, 17, 20], while the NCDR reduction of acedapsone prophylaxis was 51% [13, 22, 23]. In 1988, SDR chemoprophylaxis (25 mg/ kg) was first studied in the Southern Marquesas Islands in a non-controlled trial [24, 25]. A follow-up survey 10 years later suggested a 70% effectiveness of chemoprophylaxis. However, over the same period a 50% reduction in the NCDR was observed in the non-treated population of French Polynesia. Therefore, the true effectiveness of SDR may have been 35–40% [26]. In the mid-1990s, chemoprophylaxis was introduced on different Pacific islands where the leprosy NCDR had remained very high [27]. Over two cycles, with a 1-year interval, 70% of the population was screened for leprosy and treated prophylactically. Healthy adults received rifampicin, ofloxacin and minocycline (ROM), while children under 15 years

received SDR [28]. In 1999, a substantial reduction in the NCDR was observed [27]. Recent data indicate that transmission is ongoing [29]. In 2000, a study using rifampicin only was initiated on five highly endemic Indonesian islands [14]. The population was screened before the intervention and subsequently once a year for 3 years; two doses of rifampicin were administered to asymptomatic inhabitants with a 3.5 months interval, either in a 'blanket' approach where SDR was given to the entire population, or a 'contact' strategy in which SDR was only given to eligible household and neighbour contacts of patients with leprosy. The NCDR on the control island was 39/10,000. After 3 years, the cumulative NCDR in the blanket group was significantly lower (about 3 times), whereas no difference was found between the control group and the islands where SDR was given to contacts only [14].

The COLEP trial in Bangladesh was a single-centre, double-blind, cluster-randomised, placebo-controlled study designed to determine the effectiveness of SDR in contacts and to identify the characteristics of contact groups most at risk of developing clinical leprosy [30]. The overall risk reduction for contacts during the first 2 years after SDR administration was 57%. There was no further risk reduction beyond the 2 years [12] and thereafter[31]. The overall number needed to treat to prevent a single diagnosis of leprosy among contacts was 265 after 2 years and 297 after 4 years [12]. The protective effect of SDR was highest in contact groups with the lowest a priori risk for leprosy: non-blood-related contacts, contacts of index patients with paucibacillary leprosy and social contacts [12]. Importantly, childhood vaccination with Bacillus Calmette-Guérin (BCG) also had a protective effect of nearly 60%, and previously immunised contacts appeared to benefit from an 80% protective effect [32].

Considering all available evidence, it appears that chemoprophylaxis should target defined contact groups, but under certain conditions, mass administration may be warranted. High NCDRs, difficult geographical accessibility, insufficient availability health-care services or a high level of stigma are reasons to prefer mass administration to targeted PEP [13]. Two international expert meetings hosted by the Novartis Foundation in 2013 and 2014 and including physicians, epidemiologists and public health professionals, concluded that contact tracing followed by PEP for asymptomatic contacts has the potential to offer a degree of protection, across diverse settings, comparable to that reported in controlled trials [1, 33].

To accelerate the translation of the existing evidence into policy and motivate endemic countries to introduce chemoprophylaxis into their routine leprosy activities, the LPEP programme was designed. It aims to demonstrate the effectiveness and impact on case detection rates of contact tracing and screening combined with SDR PEP under routine

programme conditions, across a diversity of health systems, national leprosy programmes and geographical characteristics, and to determine operational parameters.

Objectives

The LPEP programme aims to assess contact tracing and administration of SDR PEP implemented by national leprosy programmes with regard to:

1. Impact on the new case detection rate, measured through strengthened surveillance and reporting systems
2. Feasibility in diverse routine programme settings

The LPEP programme provides a comprehensive package, including systematic contact tracing and screening for early case detection and PEP administration for asymptomatic contacts (figure 1). In addition, the programme also promotes capacity building for frontline leprosy workers to strengthen screening and diagnosis, and for surveillance system managers to improve data collection and reporting.

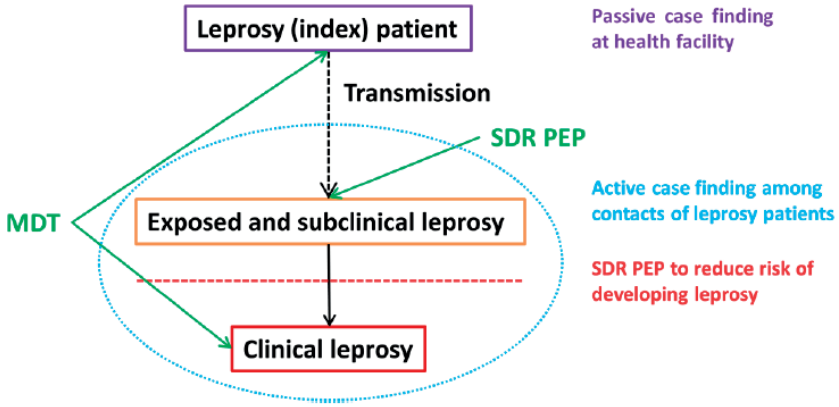

Figure 1: Conceptual framework of the impact of the LPEP programme on the transmission of Mycobacterium leprae. LPEP, leprosy post-exposure prophylaxis; MDT, multidrug therapy; SDR PEP, single dose rifampicin post-exposure prophylaxis.

METHODS

Study Coordination

A steering committee of leprosy experts, policymakers, academic researchers, people affected by leprosy and the project partners (International Federation of Anti-Leprosy Associations (ILEP) members, national leprosy programmes and the Novartis Foundation) oversees the programme, advises on strategic and operational matters, establishes the dissemination strategy and reviews programme publications. The Novartis Foundation

provides the overall coordination of the LPEP programme and ensures financial support. LPEP country protocol development, programme management and implementation at national level are handled by the national leprosy programmes supported by the respective ILEP partners. The Swiss Tropical and Public Health Institute (Swiss TPH) and the Erasmus University Medical Center (Erasmus MC) support the local programme protocol development, provide training and assist with the strengthening of surveillance systems operated by the national programmes. They further monitor adherence to protocol and data quality, coordinate data analysis and facilitate the dissemination of the study results. All in-country activities of the academic partners are closely coordinated with, and supported by, the respective ILEP partner and the national programme (figure 2). An annual meeting facilitates progress and review and exchange among the partners.

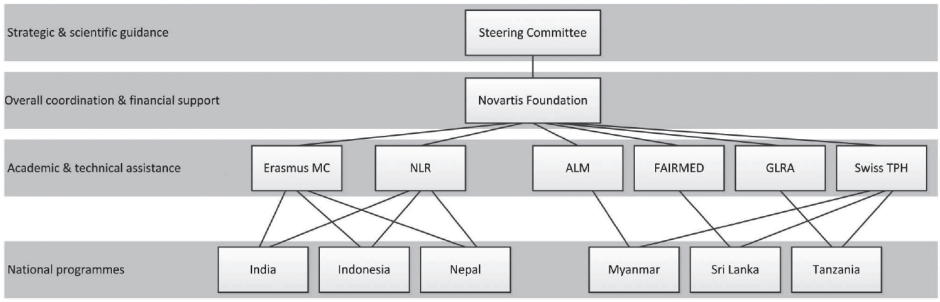

Figure 2: Governance structure of the LPEP programme. ALM, American Leprosy Mission; Erasmus MC, Erasmus Medical Center; GLRA, German Leprosy and Tuberculosis Relief Association; ILEP, International Federation of Anti-Leprosy Associations; LPEP, leprosy post-exposure prophylaxis; NLR, Netherlands Leprosy Relief; Swiss TPH, Swiss Tropical and Public Health Institute.

Study areas

Participation in the LPEP programme was open to countries meeting the following criteria: (1) subnational administrative units (e.g., districts) with a high NCDR, relatively easy access and a functioning leprosy control infrastructure, (2) capacity for routine contact tracing and screening in the local leprosy programme, (3) declared interest from the Ministry of Health and (4) commitment and resources to continue contact tracing and PEP after the conclusion of the LPEP programme. When selecting the countries, diversity in terms of geography and leprosy programme organisation was taken into account. Table 1 presents key leprosy indicators at baseline in the selected LPEP sites in India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania. Additional pilot sites are located in Brazil and Cambodia.

Table 1. Key leprosy-related indicators in the areas where the LPEP programme is implemented (baseline as of 2013)

Country	India	Indonesia		Myanmar			Nepal	Sri Lanka			Tanzania		
Sub-national area	Dadra & Nagar Haveli Union Territory	Sumenep District	Maluku Tenggara Barat (Lingat village)	Nyan-ung-U District	Mying-yan District	Tharyar-waddy District	Jhapa District	Mo-rang Dis-trict	Parsa District	Kalutara District	Puttalam District	Ki-lombero District	Li-wale Dis-trict	Nanyum-bu District
Population (in thousands)	374	1,059	1.9	738	976	1,110	813	965	601	1,200	800	401	95	159
NCDR (per 10,000)	9.8	4.5	NA*	1.0	0.8	1.0	2.7	2.3	2.0	1.4	1.2	1.8	5.8	6.7
New cases of MB leprosy (%)	23.1	75.8	NA*	68.9	75.3	67.5	57.2	47.8	NA	36.4	60.9	76.1	78.2	58.5
New cases with G2D (%)	0.0	9.5	NA*	6.8	19.5	14.9	2.2	7.1	1.6	5.5	13.0	NA	1.8	6.6
New cases (%)														
- Females	59.2	48.0	NA*	47.3	37.7	34.2	38.0	38.6	NA	44.2	41.3	NA	49.1	51.9
- Children	26.1	10.9	NA*	2.7	3.9	7.0	4.8	11.7	8.9	6.7	9.8	1.4	1.8	8.5

*no data due to absence of leprosy services in this isolated village, but a visiting health worker from district level reported 30 suspected patients with leprosy.

G2D: grade 2 disability; MB: multibacillary; NA: not available; NCDR: New Case Detection Rate;

Study design

In agreement with its objectives; the LPEP programme is implemented under routine conditions rather than as a clinical trial. A general study protocol was prepared and served as the basis for the elaboration of national LPEP protocols tailored to the realities of each country. Patients with leprosy diagnosed <2 years prior to the start of the field work (retrospective index patients) and patients diagnosed during the programme period (3 years prospective index patients) are eligible for inclusion. These index patients have to meet the following inclusion criteria: (1) confirmed leprosy diagnosis and being on MDT treatment for at least 4 weeks, (2) residency in an LPEP pilot area, (3) one or more contacts (as defined by the local definition of contacts, see table 2) and (4) willingness to disclose their disease status to the targeted contacts. All traced contacts are screened for signs of leprosy. Exclusion criteria for SDR administration are: (1) refusal to give informed consent, (2) age <2 or 6 years (country specific age ranges are applied, see table 2), (3) pregnancy (PEP can be given after delivery), (4) rifampicin use in the past 2 years (e.g., for tuberculosis (TB) or leprosy treatment, or preventively as a contact of another index patient), (5) history of liver or renal disorders (e.g., jaundice), (6) leprosy disease, (7) signs and/or symptoms of leprosy until negative diagnosis, (8) signs and/or symptoms of TB until negative diagnosis (patients having any of the following symptoms are referred for full TB assessment: cough for more than 2 weeks, night sweats, unexplained cough for more than 2 weeks, night sweats, unexplained fever, weight loss) and (9) known allergy to fever, weight loss) and (9) known allergy to rifampicin.

Table 2 presents the study modalities in the different countries. Leprosy services are integrated into primary healthcare services in all LPEP countries, with passive case detection as the core strategy of the routine leprosy programmes combined with contact tracing in all countries except Tanzania (see online supplementary annex 2). Focal persons for diagnosis of leprosy vary from non-clinician health professionals in Indonesia, Myanmar and Nepal, to trained clinicians in India, Sri Lanka and Tanzania. Notably, contact tracing, screening and diagnosis are all performed by different functions and persons in Sri Lanka, demanding particularly robust communication and information systems.

In most study areas the LPEP programme targets specific contact groups. Owing to high prevalence, its difficult access and the closed character of the community, a blanket approach is applied in a village on the Indonesian Selaru Island (Lingat) where all inhabitants are screened and PEP is administered to all asymptomatic individuals.

Table 2. LPEP modalities in the participating countries

Activities	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania
Routine contact tracing in the national programme	HH and neighbours	HH and neighbours	HH	HH and neighbours	not systematic	none
Contact definition in LPEP	HH members, neighbours and class fellows	HH members and neighbours	HH members and neighbours	HH members and neighbours	HH members	HH members
Estimated number of contacts per index patient	20	50	20	30	5	5
Screening period for LPEP	Retrospective contact tracing starting in 2013	Contact tracing starting in 2015	Retrospective contact tracing starting in 2014	Retrospective contact tracing starting in 2014	Retrospective contact tracing starting in 2015	Retrospective contact tracing starting in 2014
Responsible for contact tracing	Accredited Social Health Activist, Para Medical Worker, multipurpose health worker	Village midwife	Midwives, Public Health Supervisor 2 (PHS2) or Junior Leprosy Worker (JLW), supported by (Assistant) leprosy inspector (LI)	Leprosy focal person and female Community Health Volunteer (CHV)	Public Health Inspector (PHI)	Trained voluntary health worker (VHW)
Responsible for contact screening	Para medical worker and multipurpose health worker	Self-screening; Leprosy health worker at PHC and Village midwife	Midwives, PHS2 or JLW; supported by (Assistant) LI	Leprosy focal person and female CHV	Medical Officer of Health (MOH)	VHW
Responsible for diagnosis	Doctor at PHC	Leprosy health worker at PHC	Midwives, PHS2 or JLW; supported by (Assistant) LI	Leprosy focal person / doctor	Dermatologist	Clinician
Responsible for SDR administration	Para medical worker and multipurpose health worker	Leprosy health worker at PHC	Midwives, PHS2 or JLW; supported by (Assistant) LI	Leprosy focal person and female CHV	MOH	VHW
Minimum Age for SDR	2	2	2	2	6	6
Level of data entry	At district level	At district level	At national level	At district level	At district level	At district level

Sample size calculation

To establish a decreasing trend in the NCDR of 10–15% per year in every LPEP country, with sufficient statistical power (p=0.05), a logistic regression model suggests the enrolment of between 175 (decrease of 15% in NCDR) and 400 (decrease of 10% in NCDR) new index patients per year.

Data collection and monitoring

The data collection and reporting solutions for LPEP were developed or adapted by the technical partners in close collaboration with the national leprosy programmes and the in-country ILEP partners. To ensure the seamless integration of the LPEP programme into the national leprosy control programmes, existing data collection and reporting systems were assessed. The aim was to use the available structures wherever feasible and thereby to minimise duplication of data collection efforts between national programmes and LPEP. Supplementary LPEP forms were then developed to capture the not-routinely collected data. The minimally required LPEP indicators are listed in online supplementary annex 1. Sociodemographic information, leprosy classification and disability grade, disease history (mode of detection, start of treatment) and previous rifampicin use (apart from MDT) are recorded for all index patients. For contacts, data collection captures sociodemographic characteristics, relationship to the index patient, contact category (household, neighbour, social), BCG vaccination scar, outcome of the screening (signs of leprosy or TB) and SDR exclusion criteria. In addition, referrals and adverse events (AEs) following SDR PEP are documented (see Ethics section).

A programme-specific database is offered to participating countries but any locally developed database that fits the programme requirements is also accepted. For example in Sri Lanka, a locally developed MySQL database is used. Data entry is carried out continuously, either at national or district level; and database copies are regularly shared with the technical and ILEP partners for verification and interim analyses. Feasibility will be evaluated in terms of coverage (proportion of contacts traced, screened and receiving PEP, if eligible), required resources and coordination efforts. Effectiveness will be measured as the impact of the LPEP programme on the NCDR of the pilot areas.

In addition to the routine surveillance and programme- specific monitoring of the national programme, twice yearly monitoring visits are conducted by the technical and in-country ILEP partners to monitor protocol adherence, resolve operational questions and evaluate the quality of procedures and data. Data collection and monitoring will be maintained for 3 years.

Ethics

An expert meeting, involving both tuberculosis and leprosy experts, focused on the potential risk of promoting rifampicin resistance through the use of SDR in leprosy control. It concluded that current evidence suggests that the risk of emerging rifampicin resistance in *M. tuberculosis* is minimal, and that the benefit of reducing the leprosy NCDR largely outweighs that risk [34].

The national leprosy programmes submitted the country-specific LPEP protocol and data collection instruments for review and approval to the relevant ethics committees. There was no need for ethical clearance in Indonesia as the country has already integrated the principle of PEP into its routine leprosy programme in several districts. In each of the participating countries, a designated national expert from the Ministry of Health acts as the principal investigator for the LPEP programme.

Informed consent is obtained from all index patients and contacts, either written or verbally, depending on local practices for comparable studies and as approved by the ethical committee. It contains information on possible side effects of SDR (ie, influenza-like syndromes and discolouration of urine) and details of how a leprosy expert can be contacted in case of AEs or other concerns. AEs are reported following national pharmacovigilance guidelines and using the LPEP AE Form, while referred for proper follow-up.

DISCUSSION

The WHO global strategy for leprosy control 2011–2015 called for increased investments in operational research to support the overall aims of the global leprosy control programme, and to evaluate novel and promising interventions [10, 11]. Being an essential building block of various disease control and outbreak containment programmes, contact tracing and chemoprophylaxis have been identified as key factors to sustainably reduce the number of new patients and move towards *M. leprae* transmission interruption. The LPEP programme is designed to answer key questions regarding the implementation of chemoprophylaxis for leprosy control and to provide evidence for the feasibility and impact of contact tracing and PEP on the NCDR across a range of different health systems and levels of leprosy endemicity.

The LPEP programme is accompanied by ancillary studies. The cost-effectiveness study aims to measure the local costs associated with contact tracing and PEP and compare those to the costs of routine case detection and treatment. The acceptability and perception studies focus on knowledge and understanding of leprosy in communities where

LPEP is implemented, on attitudes and behaviour towards persons affected by leprosy, and views of the proposed intervention among different stakeholders.

In Brazil and Cambodia, similar approaches, complementing the evidence from the LPEP programme, are tested. In Brazil, the government-funded 'PEP-Hans' project explores the administration of chemoprophylaxis and immunoprophylaxis (SDR and BCG), to about 20 contacts per index patient. PEP-Hans is implemented in 16 municipalities of Mato Grosso, Pernambuco and Tocantins states, and covers index patients diagnosed from 2015 to 2017. An estimated 850 index patients with 17,000 contacts will be included each year. The inclusion and exclusion criteria for SDR and BCG are aligned with the LPEP programme, as are the main variables for impact evaluation. Chemoprophylaxis and immunoprophylaxis cannot be co-administered since there is a minimum waiting time of 24 hours for BCG after SDR, and of 30 days for SDR after BCG. In Cambodia, the administration of SDR to household and neighbour contacts is evaluated within the 'Retrospective Active Case Finding' project started in 2011. Given the relatively low Finding' project started in 2011. Given the relatively low number of new patients with leprosy diagnosed in this country, the contacts of all patients diagnosed in an operational district since 2011 are traced, screened and managed in a single 'drive'. This approach is repeated until all 31 high-priority operational districts have been covered. The project is implemented by a consortium involving the National Leprosy Elimination Programme, CIOMAL (International Committee of the Order of Malta for Leprosy Relief) and the Novartis Foundation.

Outlook

After 3 years of SDR administration to contacts of patients with leprosy, the full impact and feasibility of the intervention will start to emerge in 2019. Data will be analysed at country level, and pooled analyses will be conducted as far as differences in the epidemiology and set-up of national leprosy programmes allow.

The LPEP programme will help to translate the existing evidence on SDR PEP for reducing the risk of developing leprosy among contacts of patients with leprosy into routine action by providing solid data from a range of settings and conditions, established by national leprosy control programmes themselves. Participating countries will be in a good position to fully integrate contact tracing and SDR PEP into their national leprosy control strategies and expand the activities to additional areas in the country.

Dissemination of the results and lessons learnt from the LPEP programme will be carried out through publication in open access journals, as well as through reports and conference abstracts and presentations. The data will provide crucial guidance for Ministries

of Health of all leprosy endemic countries interested in applying a similar approach. The results of the LPEP programme will also be of great value for global policymakers when deciding on resource allocation for the interruption of *M. leprae* transmission.

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ANNEXURES

Annex 1 Individual data to be collected and reported for (A) index patients and (B) contacts.

(A) Data collected for index patients

indicator	Comment
Name	For local reference, not to be entered/transmitted to international partners.
Unique patient ID/ Registration number	Provides a unique identifier for each index case, allowing its unambiguous identification across documents and time.
LPEP ID	Consists of Country/district/health facility acronym and number followed by the registration number.
Country	Basic administrative information.
District	Basic administrative information.
Health facility	Basic administrative information.
Age	Basic demographic information about the index case.
Gender	Basic demographic information about the index case.
Address / location	Collect level of detail as appropriate to the setting, e.g. village name
LPEP contact ID	To identify previous SDR treatment (from contact database)
Date of diagnosis	General information on treatment.
Disease classification at time of diagnosis	According to WHO definition into MB/PB as general information on clinical presentation.
Disability grade at time of diagnosis	0/1/2 as general information on clinical presentation.
Mode of case discovery/ detection	Contact screening, voluntary, mass screening, referred
Received rifampicin within the last 2 years	Includes rifampicin from LPEP project, TB treatment etc.
Consent to leprosy status disclosure and participation in the study	On separate information sheet to document informed consent to study participation, including disclosure of leprosy diagnosis to contacts.
Reason for missing contact screening activities	To explain lack of contacts in contact screening database (having no contacts indicated, living outside LPEP area, home inaccessible).
List of potential contacts as reported by the patient	Identifying information for all potential contacts as provided by the index case. This information will provide the basis for contact tracing.

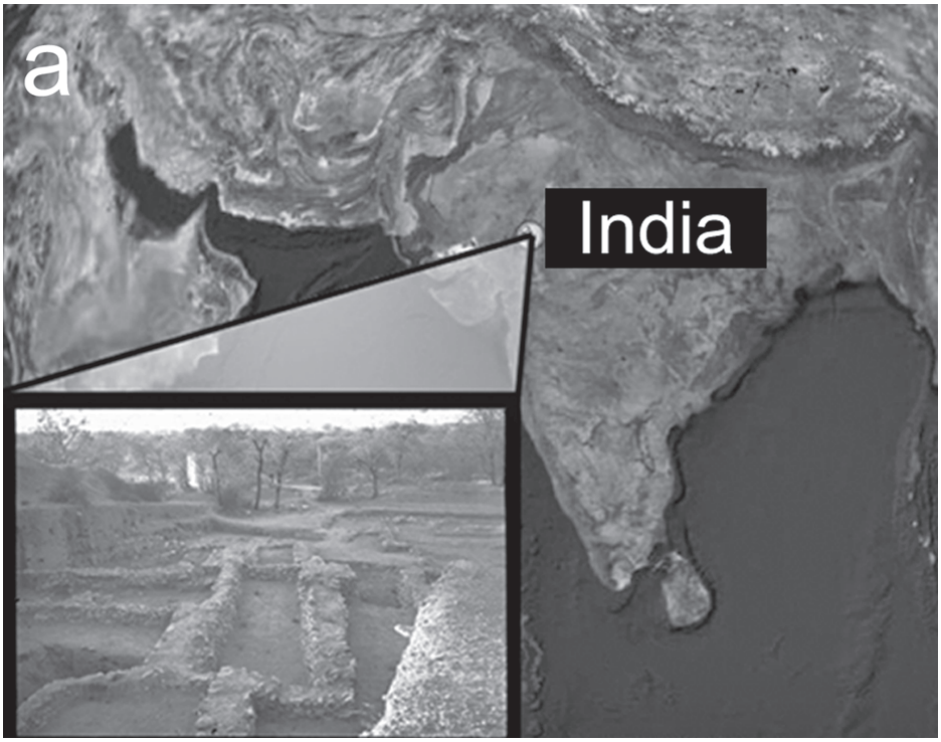
(B) Data collected for contacts

Indicator	Comment
Name	For local reference, not to be entered/transmitted to international partners.
Unique contact ID/ Registration number	Provides a unique identifier for the contact. The LPEP contact registration number consists of the index case registration number and an extension (number C01, C02, …).
LPEP ID	Consists of Country/district/health facility acronym and number followed by the registration number.
Country	ID (India), IN (Indonesia), LK (Sri Lanka), MM (Myanmar), NP (Nepal), TZ (Tanzania).
District	Basic administrative information.
Health facility	Basic administrative information.
Date of screening	General information on tracing and screening.
Present / absent at time of screening	Availability of contact to be screened.
Consent of contact to screening and LPEP	To document informed consent to study participation, including screening and LPEP, if eligible.
Age	General information about the contact.
Gender	General information about the contact.
Address (if other than patient) / location	General information about the contact.
Distance code	Household contact, neighbour, social contact as general information about the contact.
Relationship code	Degree of (blood) relationship to determine influence of genetic distance (Brother or sister; brother or sister in law; child; son or daughter in law; spouse; not related; other relative; parent; parent in law).
Outcome of screening	Rationale for further actions (Leprosy diagnosed, suspicion of leprosy and confirmation required, no signs of leprosy). In case of suspicion: outcome of confirmation (leprosy diagnosed, no signs of leprosy) to be obtained from referral registry
Exclusion criteria for SDR (if screening negative for leprosy)	Reason for not delivering LPEP among screening negative participants (No LPEP informed consent, pregnancy, previous rifampicin (e.g. for TB), age <2 years (or as applied in country), liver or renal disease, LPEP received as leprosy contact, rifampicin allergy, possible TB).
BCG vaccination	Scar or vaccination card entry present; no scar or vaccination card entry
SDR dose (if LPEP provided)	Dose in mg (150, 300, 450, 600)

Annex 2 Differences in set-up of national leprosy programmes between the LPEP countries

Country	Name programme	Structure leprosy service	Case detection	Contact tracing	Data collection	ILEP Partner
India	NLEP	Integrated into general health system	Active and passive	Routine HH and neighbours contact tracing	Individual at sub-centre level, then aggregated (paper based)	NLR, GLRA
Indonesia	NLCP	Integrated into general health system	Mainly passive	Routine HH and neighbours contact tracing; integrated SDR since 2012 in three districts	Individual at sub-centre level, then aggregated (paper based)	NLR
Myanmar	NLCP	Integrated into general health system	Mainly passive	Systematic screening of HH contacts at 2 and 5 years	Limited individual data at national level (paper-based)	ALM
Nepal	NLCP	Integrated into general health system	Mainly passive	Routine HH and neighbours contact tracing	Individual at health-post level, then aggregated (paper-based)	NLR
Sri Lanka	ALC	Integrated into general health system	Active and passive	Systematic screening of HH contacts started	Full individual case data at national level (paper-based; start of electronic reporting)	FAIRMED
Tanzania	NTLP	Integrated into general health system	Mainly passive	Planned to be introduced	Individual at district level, then aggregated (paper-based)	GLRA

Abbreviations: ALC: Anti Leprosy Campaign ; ALM: American Leprosy Mission; GLRA; German Leprosy and Tuberculosis Relief Association; HH: Household; ILEP: International Federation of Anti-Leprosy Associations; NLCP: National Leprosy Control Programme; NLEP: National Leprosy Eradication Programme; NLR: Netherlands Leprosy Relief; NTLP: National Tuberculosis and Leprosy Programme; SDR: single dose rifampicin



Description: Ancient Skeletal Evidence for Leprosy in India (2000 B.C.) The excavation site in Balathal, India. Source: Robbins G et. al (2009), PLOS ONE

4 Introducing Leprosy Post-Exposure Prophylaxis into the Health Systems of India, Nepal and Indonesia: A case study

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ABSTRACT

Introduction

Leprosy has a wide range of clinical and socio-economic consequences. India, Indonesia and Nepal contribute significantly to the global leprosy burden. After integration, the health systems are pivotal in leprosy service delivery. The Leprosy Post Exposure Prophylaxis (LPEP) program is ongoing to investigate the feasibility of providing single dose rifampicin (SDR) as post-exposure prophylaxis (PEP) to the contacts of leprosy cases in various health systems. We aim to compare national leprosy control programs, and adapted LPEP strategies in India, Nepal and Indonesia. The purpose is to establish a baseline of the health system's situation and document the subsequent adjustment of LPEP, which will provide the context for interpreting the LPEP results in future.

Methods

The study followed the multiple-case study design with single units of analysis. The data collection methods were direct observation, in-depth interviews and desk review. The study was divided into two phases, i.e. review of national leprosy programs and description of the LPEP program. The comparative analysis was performed using the WHO health system frameworks (2007).

Results

In all countries leprosy services including contact tracing is integrated into the health systems. The LPEP program is fully integrated into the established national leprosy programs, with SDR and increased documentation, which need major additions to standard procedures. PEP administration was widely perceived as well manageable, but the additional LPEP data collection was reported to increase workload in the first year.

Conclusions

The findings of our study led to the recommendation that field-based leprosy research programs should keep health systems in focus. The national leprosy programs are diverse in terms of organizational hierarchy, human resource quantity and capacity. We conclude that PEP can be integrated into different health systems without major structural and personal changes, but provisions are necessary for the additional monitoring requirements.

INTRODUCTION

Leprosy is an infectious disease, predominantly affecting peripheral nerves and the skin. It leads to a wide range of clinical symptoms, eventually resulting in disfigurement and disability if left untreated [1]. Additionally, the disease has severe socioeconomic consequences such as stigma and poverty, which may impact the patients and their families lifelong [2, 3]. The WHO calls to globally interrupt leprosy transmission and reduce grade-2 disabilities in newly detected cases to below 1 per million population by 2020 [4]. However, current progress indicates that these targets are difficult to achieve [5, 6]. In the year 2014, a total of 213,899 new cases were detected with a rate of 3.78 cases per 100,000 population. Southeast Asia accounted for 72% of the global new case load. India was the largest contributor (58.8%), followed by Brazil (14.5%) and Indonesia (8%). Nepal identified 3,046 new cases in 2014, which is around 2% of the total Southeast Asia burden [5]. Hence, India, Indonesia and Nepal are important contributors to the global burden of leprosy despite established and relatively well-resourced control programs, and elimination of leprosy (zero incidence) needs alternative control strategies.

After integration, the general health systems are pivotal for leprosy service delivery. A health system is defined as "the combination of resources, organization, financing and management that culminate in the delivery of health services to the population." [7]. Early case detection and subsequent treatment with multi-drug therapy (MDT) are the key strategies to reduce the disease burden [8, 9]. Health systems however, do not appear to be efficient in detecting cases early, as the grade 2 disability rate remained stable (between 0.23 to 0.25 per 100,000 population) over the last 10 years [5]. Furthermore, the stagnation in the new case detection rate (NCDR) and relatively high child case rates in many countries indicate that transmission of Mycobacterium leprae, the causative agent of leprosy, is ongoing and that current methods, including MDT, are insufficient to break transmission [10, 11]. The transmission of the M. leprae bacteria is complex poorly understood [12, 13]. Also, it has been argued that leprosy programs are not implemented properly [6, 14], and needs to be improved [15, 16].

There is sufficient evidence that chemoprophylaxis with Single Dose Rifampicin (SDR) is efficacious in reducing the risk of developing leprosy among contacts of leprosy patients [17, 18]. It has thus been recommended to assess the effectiveness of SDR in different field settings [19]. Therefore, the Leprosy Post-Exposure Prophylaxis (LPEP) program was initiated by different stakeholders in close collaboration with the ministries of health of eight countries - India, Nepal, Indonesia, Myanmar, Sri Lanka, Tanzania, Brazil and Cambodia. LPEP activities started in 2014 for a duration of three years. The objec-

tive of LPEP is to assess the impact on the new case detection rate, measured through strengthened surveillance and reporting systems and its feasibility in diverse routine programme settings. The program has three prime components: Contact tracing; screening; and SDR administration. It is designed to complement and be integrated into the national leprosy control programs, rather than operating vertically. Moreover, it aims to contribute to the strengthening of the general health care systems by providing support in human resources, training and program monitoring.

The primary objective of this work is to compare national leprosy control programs and adapted LPEP strategies in India, Nepal and Indonesia. The secondary objective is to summarize the lessons learned during the first year of implementation.

METHODS

LPEP program sites

In India, the program is operating in the union territory (UT) of Dadra and Nagar Haveli (DNH), situated in the west of India between the state of Gujarat and Maharashtra. Nepal is implementing the program in the tarai (plains) districts of Jhapa, Morang and Parsa. All three districts share boundaries with India. In Indonesia LPEP is implemented in Sumenep district, which is a regency of East Java province, situated on the eastern end of Madura Island. All intervention areas are high leprosy endemic and have been selected based on the recommendations of the respective ministry of health (Table 1).

Table 1. Demographic, geographical and epidemiological profile (2015-16) of the LPEP program sites

Country (2015-16)	**India**	**Nepal**			**Indonesia**
Sub-national area	Dadra & Nagar Haveli, UT	Jhapa District	Morang District	Parsa District	Sumenep District
Population	427,462	887,023	1,044,071	660,249	1,059,000
Area (km2)	491	1,606	1,855	1,353	1,998
New cases detection rate (NCDR/100,000)	99.4	20.97	19.3	16.56	43.3
Percent new cases of MB leprosy	26.5	60.75	49.0	41.44	76.3
Percent new cases with DGII	1.8	2.69	1	NA	5.5
Percent new cases:					
- Females	57.8	46.24	44	25.22	46.2
- Children	23.2	3.76	8.9	5.40	6.5

UT: Union Territory; NA: Information not available; NCDR: New Case Detection Rate; MB: Multi Bacillary; DGII: Disability Grade II

Study design

The study followed the multiple-case study design with single units of analysis [20]. The case study methodology was selected because it was suitable for the objective of the research, i.e. comparing LPEP (case) in the context of the national leprosy control programs. Furthermore, the selected methodology enables exploratory analysis by using data from multiple sources. The study aims to cover a broader range of complex field conditions that have a role in developing LPEP strategies in each country.

Data collection

We collected quantitative and qualitative data. The data collection methods were direct observations (facility and service delivery), interviews (open-ended and semi-structured conversations) with the staff at various levels, and desk review. The type of information (online and printed) reviewed were peer reviewed publication, department reports, and other program documents such as guidelines, training manuals and annual report.

The study was divided into two phases (Table 2). In the first phase, we reviewed the national leprosy control programs in the three countries. The first set of data was collected through desk review, followed by a field visit in each country between April 2015 and January 2016. The desk review aimed to identify documents describing the standard operating procedures and policies of the national leprosy programs, whereas the objectives of the field visits were to interview staff and observe on-site activities. During field visits, we collected relevant documents that were not available online. The staff at the national, provincial and field level were interviewed to assess perceived reasons behind current epidemiological trends, and to describe their routine practices and associated challenges. An additional file shows this in more detail [see Additional file 1]. Furthermore, we verified the standard operating procedures and data trends published by the national programs during interviews. The first phase data were then used to assess and compare the different national programs and describe a baseline for LPEP.

In the second phase, we reviewed the LPEP activities at study site level, i.e. UT of Dadra and Nagar Haveli in India, Morang and Jhapa districts of Nepal, and Sumenep district of Indonesia. We visited each country twice between April and November 2015, after the inception of LPEP. The data collection methods were identical with the ones used in the first phase. Quantitative data were mainly related to the program coverage. The qualitative data were collected on the LPEP implementation practices. We focused on the difference between planned and actual implementation [21]. The health staff were interviewed to describe LPEP practices for various activities such as SDR distribution,

contact tracing, screening, recording and reporting. The focus was on the coordination and integration of activities with the national leprosy programs. Finally, respondents were asked about the challenges faced during the pilot. A special focus was on the anticipated integration of PEP into the national programs.

Table 2. Details of the data collection methods, data type and sources

Data Collection Method	Type of data and sources	Nature
Phase I: National Leprosy Programs		
Desk review	Secondary data from scientific papers, archival records and document on national leprosy control programs	Quantitative data on the epidemiology and performance of the programs.
		Qualitative data on the SOP and policies
Direct observation	Primary data	Qualitative observations of the activities such as contact tracing, treatment rehabilitation, etc.
Interviews	Primary data	Qualitative data on explanations of epidemiological trends, routine functioning, challenges and solutions
Phase II: LPEP Program		
Desk review	Secondary data on LPEP service delivery from MIS	Quantitative data on the coverage of services
Direct observation	Primary data	Qualitative observations of the LPEP activities such as screening, SDR distribution and recording & reporting
Interviews	Primary data	Qualitative data on LPEP routine functioning, challenges and solutions

SOP: Standard Operating Procedures; MIS: Monitoring Information System

Data analyses

The national leprosy control programs are part of the general health care system, and LPEP is integrated into it. Therefore, we adopted the WHO health system framework [22, 23] to outline the main components of the health system, as presented in Figure 1.

These components were elaborated by the common emerging themes, identified from the primary and secondary data from the first phase and second phase.

We used the epidemiological (quantitative) data to assess the leprosy situation and the (qualitative) data on implementation to depict the program and LPEP project functioning respectively. The qualitative data on standard operating procedures and actual implementation were verified to minimize bias and assess similar patterns.

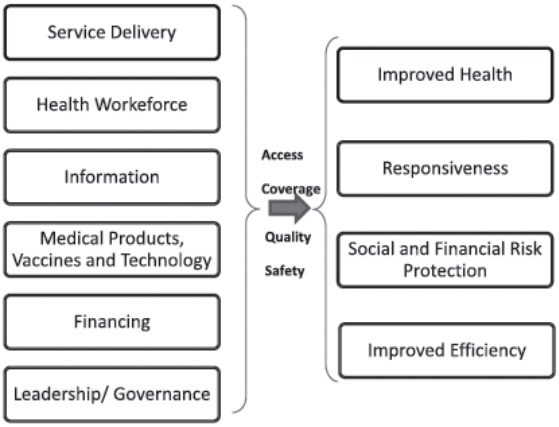

Figure 1. The WHO health system building blocks framework (2007)

RESULTS

National Leprosy Control Programs

The general health care system is based on a three-tier structure in all reviewed LPEP countries, i.e., national, provincial and district level (Figure 2). The Indian leprosy program is called the National Leprosy Elimination Program (NLEP), whereas the Nepal and Indonesian programs are indicated as National Leprosy Control Program (NLCP). An additional file lists the official leprosy control/elimination strategies [see Additional file 2]. The leprosy control programs are operational throughout the countries, however, special attention is given to the high endemic areas. Case detection is mainly passive, although India and Indonesia reported instances of outreach leprosy activities, integrated or non-integrated with other diseases.

The periodicity and focus of such activities (only in high endemic areas) is not fixed, and varies depending on the local situation and available means. Contact tracing was already a part of all reviewed leprosy programs before LPEP, but in practice only household contacts were covered in all three countries. The programs in Nepal and Indonesia depend largely on the paramedical staff located on the peripheries. The role of doctors is limited to the confirmation of unclear cases and management of complicated cases at higher levels. The presence and support of volunteers is strongest in India as compared to the other countries. Volunteers are actively engaged in information dissemination, suspect identification, and monitoring treatment adherence. The comparative details of national programs are listed in Table 3.

Figure 2. Organogram of the Health Services in India, Nepal and Indonesia

Table 3. Description of National Leprosy Control / Elimination Programs in India, Nepal and Indonesia based on WHO framework

WHO Framework	Themes	NLEP India	NLCP Nepal	NLCP Indonesia
Service Delivery	Coverage (Prevalence) 2014	88,833 cases registered and treated (Source: Global leprosy update 2014)	2,382 cases registered and treated (Source: Global leprosy update 2014)	19,949 cases registered and treated (Source: Global leprosy update 2014)
	Infrastructure	153,655 Sub Center; 25,308 PHCs; 5,396 CHCs (Source: Rural Health Statistics 2015, India)	208 PHCs; 1,559 HPs; 2,643 SHP (Source: Annual Report 2013-14, Dept. of Health, Nepal)	3,395 HCs with IPD and 6,345 HCs with only OPD (Source: Jumlah Puskesmas 2015, Indonesia)
	Activities	Case detection is mainly passive with few periodic active outreach	Case detection is mainly passive	Case detection is mainly passive with few periodic active outreach
		Routine household contact tracing	Routine household contact tracing	Routine household contact tracing; integrated SDR since 2012 in two districts
		Suspect identification & their adherence is checked by volunteers (ASHA) at field level	Suspect identification & their adherence is checked by volunteers (FCHV) at field level	Suspect identification & their adherence is checked by paramedical staff (village midwife)
		Contact screening by paramedical staff (PMW/ANM) at sub-center	Contact screening by paramedical staff (Leprosy Focal Person) at Health Post	Contact screening by paramedics staff (Leprosy officer) at HC
		Confirmation diagnosis by doctor at PHC and higher	Confirmation diagnosis by Leprosy focal person / doctor at Health Post and higher	Confirmation diagnosis by Leprosy officer at HC and doctor at higher level
	Process	Refer Figure 3		
	MDT supply (Source: Interviews)	No stock out situation reported at peripheral level	Seldom stock out situation reported for a very short period at peripheral level	A major stock out situation reported in 2016 at peripheral level
Health Workforce	Staff	General health care staff. High epidemic PHCs have additional staff	General health care staff	General health care staff
	Leprosy Training	10624 Doctors, 24,255 Paramedics and 104011 volunteers trained on leprosy (Source: NLEP Progress Report 2014-15)	150 health worker trained on leprosy. (Source: Annual Report 2013-14, Dept. of Health, Nepal)	120 Doctors, 516 leprosy staff trained on leprosy in 2014 (Source: Subdit Kusta 2014, Indonesia)

Table 3. (*continued*)

WHO Framework	Themes	NLEP India	NLCP Nepal	NLCP Indonesia
Information	Indicators	Standard set of indicators as per WHO	Standard set of indicators as per WHO	Standard set of indicators as per WHO
	Data Management	Individual at sub-center level, then aggregated.	Individual at health-post level, then aggregated. General MIS electronic entry at district level but limited leprosy indicators.	Individual at sub-center level, then aggregated
	Supervision & Monitoring	CLD State Leprosy Office & District Leprosy Officer	CLD, Regional Health Directorate and District Health / Public Health officer	Department of Leprosy & Yaws (central), Provincial Leprosy Office and District Health Office
	Reporting	Monthly, quarterly and Annually. Bottom-up at all levels	Monthly, quarterly and Annually. Bottom-up at all levels	Monthly, quarterly and Annually. Bottom-up at all levels
Innovation	New initiatives	Developed *M.w* vaccine	NA	NA
Financing	Budget	NLEP total budget decreased by 9.8% from 2014-15 to 2015-16 (Source: MoHFW, Outcome Budget 2014-15 & 2015-16)	NLCP recurrent budget (released) was increased by 58% from 2012-13 to 2013-14 (Source: Annual Report Dept. of Health, 2012-13 & 2013-14)	NA
	Funding	CLD and State Leprosy Office	Ministry of Health and Population	Sub-directorate Leprosy & Yaws and District Health Office
	OOPs in leprosy	No evidence		
	Periodicity of funds (Source: Interviews)	Sometimes delay in salary disbursement at peripheral level or case reimbursements to ASHA	Sometimes delay in salary disbursement at peripheral level or case reimbursements to FCHV	Mostly on time
Governance	National Strategy	Strategy focus on decentralization of leprosy services. For more information, refer additional file 1	Strategy focus on disability and rehabilitation. For more information, refer additional file 1	Strategy focus on early detection. For more information, refer additional file 1
	Organization structure	Figure 2		
	Integration	Integrated into general health system	Integrated into general health system	Integrated into general health system

ANM Auxiliary Nurse Midwife, ASHA Accredited Social Health Activist, CHC Community Health Center, CLD Central Leprosy Division, FCHV Female Community Health Volunteer, HC Health Center, HP Health Post, LFP Leprosy Focal Person, MPW Multipurpose Worker, NA Not Available, PHC Primary Health Center, PMW Para Medical Worker, SHP Sub-Health Post

The overall implementation process and the coordination between different staff levels is comparable in the three countries (Figure 3).

Service delivery is integrated into the general health care system in all three countries. However, central leprosy divisions have an extensive role in planning, funding and monitoring. The Indonesian health system is the most decentralized in terms of higher

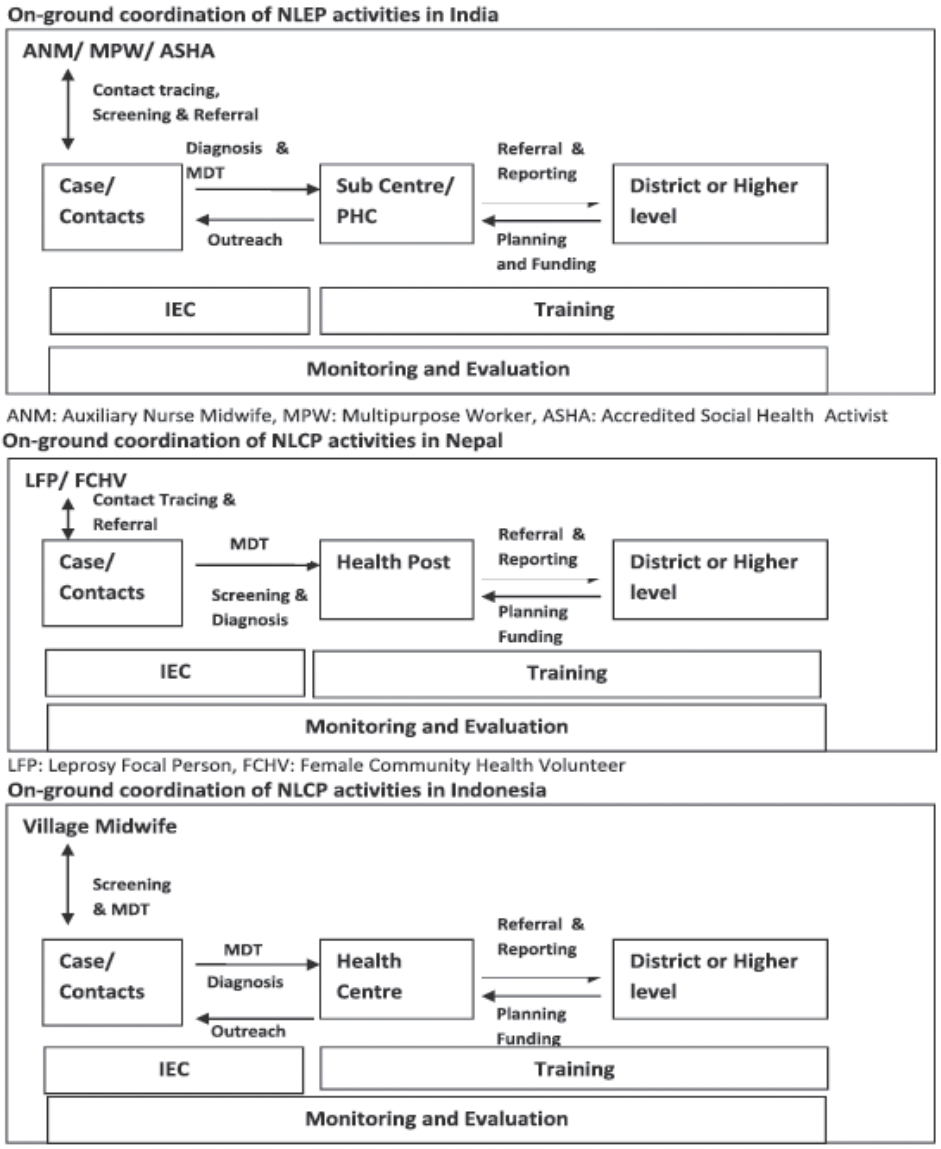

Figure 3. Diagram illustrating the implementation process under the National Leprosy Control / Elimination Programs in India, Nepal and Indonesia

autonomy of districts in planning and allocating funds between diseases or activities. Next, MDT supply is based on the demand, i.e. case load of health facilities. Mostly the supply chain is smooth, but short periods of out-of-stock instances were reported from peripheral centres in Nepal. The general health care staff are involved in the implementation of the leprosy program, but in India high endemic districts occasionally receive top-up human resource budgets under the NLEP. In all countries training is the shared responsibility of provincial and district health departments. The recording and reporting includes all the indicators prescribed by WHO to estimate the burden [5, 8, 9]. Other reported indicators are on coverage of services, which varies between countries due to difference in activities. Nepal has developed an electronic database portal named WeBLeRS, capable of individual level data entry. Unfortunately, WeBLeRS is only used in a limited number of high endemic districts. Remaining countries are recording individual data on paper which remains at the field level. Subsequently, the aggregated data is reported to higher levels. Supervision and reporting follow the same structure and periodicity in all the three countries (Figure 3 and 4).

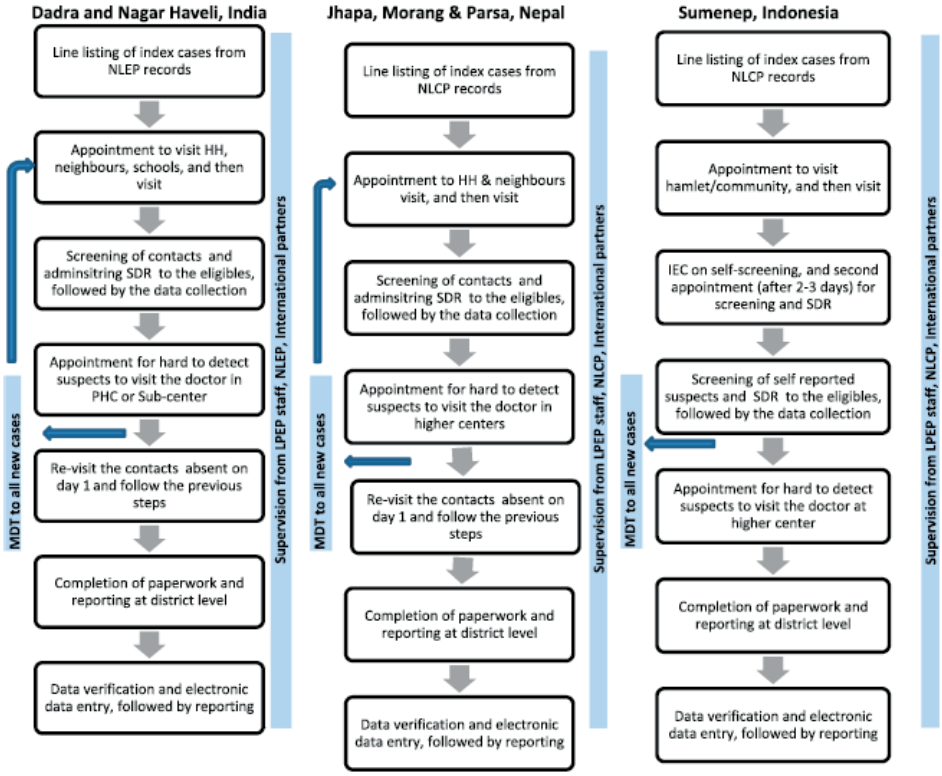

Figure 4. Flow chart of LPEP activities in India, Nepal and Indonesia

LPEP Inception and Target Population

The LPEP field activities started in March 2015 in India, covering retrospective cases and contacts of the last two years. In Nepal, LPEP was slightly delayed due to the earthquake on 25 April 2015, therefore field implementation started in May 2015, covering retrospective cases and contact of the last one year. In Indonesia LPEP field implementation started in January 2015, with no target to cover retrospective cases. Instead, all leprosy cases diagnosed since January 1st 2015 are aimed to be covered, excluding the cases of 8 health centres, located on the remote islands of that regency in Indonesia. These islands are hard to reach and accessibility is limited.

LPEP Implementation Comparison

The LPEP service delivery in all three countries is fully integrated into the general health care systems. Indonesia is practicing extended contact tracing using self-screening, whereas in India and Nepal the contacts are screened by paramedical staff. In the case of self-screening, the first field visit is dedicated to Information Education and Communication (IEC) on self-screening, followed by a second field visit (after 2-3 days) for investigation of self-reported suspects and SDR administration (Figure 4).

In India, contacts are defined as Household, Neighbours and Social contacts (only school class fellows), whereas in Nepal and Indonesia only Household and Neighbours contacts are included. The minimum age to provide SDR is 2 years in all the three countries. Common activities include line listing, contact tracing, screening, SDR administration, recording, reporting and monitoring (Figure 4). Rifampicin is procured by the local Department of Health in all the three countries. LPEP appointed staff in India are LPEP supervisor (n=1) and research assistants (n=4). The Nepal program is supported by a LPEP manager (n=1) and district supervisors (n=3), whereas Indonesia appointed only a LPEP manager (n=1). The staff dedicate their full time to conduct training, supervision, assistance and reporting. All LPEP staff were trained in Training of Trainers (ToT) just before the program field implementation. Two types of trainings were imparted in all three countries, i.e. operational training and data management training. The LPEP data is collected on paper forms in the field, and reported to district level where electronic data entry takes place. A similar Microsoft Access database is used in all three countries, which collects demographic, epidemiological, clinical and coverage indicators. The supervision and monitoring structure is similar in all countries. Furthermore, Indonesia distributes IEC hand fans and packed drinking water during leprosy activities. The NGO funds are reported to be disbursed on time, however the government disbursements are aligned with the national program's schedule. The comparative details of LPEP are listed in Table 4.

Table 4. Description of LPEP country programs in India, Nepal and Indonesia based on WHO framework

WHO Framework	Themes	LPEP Dadra and Nagar Haveli, India	LPEP Morang, Jhapa and Parsa, Nepal	LPEP Sumenep, Indonesia
Service Delivery	Average coverage (2015-16)	SDR coverage is average 22 contacts per index case	SDR coverage is average 23 contacts per index case	SDR coverage is average 33 contacts per index case
	Infrastructure	General health care system	General health care system	General health care system
	Activities	Line listing of HH, Neighbours and social contacts	Contact tracing of HH and Neighbours	Contact tracing of HH and Neighbours
		HH, neighbours and school visits by volunteers (ASHA) and paramedics (ANM/ PMW)	HH and neighbours visits by volunteers (FCHV) and paramedics (LFP)	Community gathering by village midwife and paramedics (LO)
		Individual screening of contacts by paramedics	Individual screening of contacts by paramedics	Self-screening and then re-screening of the suspects by paramedics
		SDR distribution immediately after screening	SDR distribution immediately after screening	SDR distribution after 2-3 days of IEC on self-screening
		Onsite data collection (paper forms)	Onsite data collection (paper forms)	Onsite data collection (paper forms)
	Process	Refer figure 4	Refer figure 4	Refer figure 4
	SDR supply	Rifampicin is procured by Dept. of Health in al dosages. Syrups available	Rifampicin is procured by Dept. of Health in all dosage. Syrups not available	Rifampicin is procured by Dept. of Health in all dosage. Syrups not available
Health Workforce	Staff	General health care staff + LPEP Supervisor (1) and Research assistants (4)	General health care staff, + LPEP Manager (1) and District supervisors (3)	General health care staff + LPEP manager (1)
	Training	LPEP operations and data management training to the staff before inception	LPEP operations and data management training to the staff before inception	LPEP operations and data management training to the staff before inception

Table 4. (*continued*)

WHO Framework	Themes	LPEP Dadra and Nagar Haveli, India	LPEP Morang, Jhapa and Parsa, Nepal	LPEP Sumenep, Indonesia
Information	Indicators	Demographic, Epidemiology, Clinical and coverage indicators	Demographic, Epidemiology, Clinical and coverage indicators	Demographic, Epidemiology, Clinical and coverage indicators
	Data Management	Electronic data entry at district level by RAs in standard database (similar in all countries)	Electronic data entry at district level by SAs in standard database (similar in all countries)	Electronic data entry at district level by DLO in standard database (similar in all countries)
	Supervision	Filed supervision by LPEP staff (daily bases), National program (periodic), International partners (twice a year)	Filed supervision by LPEP staff (daily bases), National program (periodic), International partners (twice a year)	Filed supervision by LPEP staff (daily bases), National program (periodic), International partners (twice a year)
	Reporting	Monthly, quarterly and Annually. Bottom-up at all levels	Monthly, quarterly and Annually. Bottom-up at all levels	Monthly, quarterly and Annually. Bottom-up at all levels
Innovation	Initiatives	Rifampicin available in syrup for pediatric cases	No initiatives identified	Hand fan with leprosy and self-screening information.
Financing	Funding	Majorly Govt. funds. NGO funding only for LPEP staff, monitoring and trainings	Majorly Govt. funds. NGO funding only for LPEP staff, monitoring and trainings	Majorly Govt. funds. NGO funding only for LPEP staff, monitoring and trainings
	Funds disbursement	On time disbursement of NGO funds. The government funds disbursement depends on national program's status	On time disbursement of NGO funds. The government funds disbursement depends on national program's status	On time disbursement of NGO funds. The government funds disbursement depends on national program's status
Governance	Strategy	Extended contact tracing, including social contacts (school children)	Extended contact tracing	Extended contact tracing with self-screening
	Integration	Integrated into general health system	Integrated into general health system	Integrated into general health system

ANM Auxiliary Nurse Midwife, ASHA Accredited Social Health Activist, DLO District Leprosy Officer, FCHV Female Community Health Volunteer, HH Household, IEC Information Education Communication, LFP Leprosy Focal, LO Leprosy Officer, NGO Non-governmental Organization, PMW Multipurpose Worker, RA Research Assistant, SA Statistical Assistant, SDR Single Dose of Rifampicin

Challenges in the first year of implementation

The initial months of the program field work were characterized by intense activities, due to the recruitment of retrospective leprosy cases. The country programs have been implemented by the general health care staff, after striking a balance between LPEP and other disease programs. The most common problem reported by the staff was the additional data collection work load (especially, filling of consent forms of cases and contacts) due to the research nature of the program. Next, not all contacts are present on the screening day, therefore health staff need to visit 2-3 times to achieve optimal coverage. Participation of male contacts is lower compared to females because they are more often out of the home to work. According to the field staff, refusals are more common in urban areas than rural areas, probably due to stigma, therefore more efforts reported to be deployed in urban areas to explain the program and the significance of SDR. A particular challenge is that houses are often dark while good light is required for screening, but females cannot be screened in the open.

DISCUSSION

The general health care system is the covering umbrella of leprosy services, thus we emphasize that all field-based leprosy research should be aligned with the local health system realities. The above statement is more relevant in a post global elimination scenario, when resources are reduced, but the pressure is high to deliver pragmatic results [24]. Correspondingly, feasibility also depends on the capacity of the health systems to accommodate new interventions. Systematic and sustained health system strengthening is important. Continuous and coordinated efforts are needed from various components (including disease specific programs) of a health system [25, 26]. For example, the coordination between leprosy and TB departments is desired to collectively deal with the risk of rifampicin resistance and to ensure proper follow-up of suspected TB cases identified in the frame of leprosy screening [27, 28]. Furthermore, leprosy service delivery also experiences common limitations of a weak health system such as poor accessibility, availability, affordability and quality [29-31]. Despite that the cross cutting evidence on leprosy and health systems is limited. As an exception, integration of vertical leprosy programs into the general health care system is a well-documented topic [32]. Most of the experiences however, are in the form of commentaries on individual cases. We recommend to synthesize the available literature on integration in a systemic way to highlight the differences and derive a framework, which can be further developed into a standardize tool to measure the level of integration. This is relevant because leprosy programs are partially integrated in many countries and such a tool can help in measuring performance over time. Further, the framework can be applied to other vertical programs.

The London Declaration recommends to increase funding for leprosy and other Neglected Tropical Diseases (NTDs) [4]. However, funding continues to decline, e.g. the total budget of NLEP India was decreased by 9.8% from 2014 to 2016 [33, 34]. Besides public funding, national leprosy programs should also promote inclusion of their services into other financial risk protection schemes [35]. In many high epidemic countries, state run insurance schemes are operational [36]. The leprosy programs should strive for a high coverage of their target population under such schemes, as leprosy poses a high financial risk [37].

Our study showed that the national leprosy programs as part of the health systems are diversified in the three countries, based on organizational hierarchy, human resource quantity and capacity. Further, the compatibility between LPEP and national programs is high, as the existing contact tracing system (including infrastructure and staff) is retained and strengthened. As a result, contact tracing is intensified, but needs to be maintained after LPEP program completion. The ownership of the program lies with the government, and their active involvement increases the chances of integration of SDR into national policies, if the results are promising. The LPEP program has introduced simple but important innovations such as digital information system.

As a limitation, this study summarised the national leprosy programs mainly based on the secondary data. The primary data was collected only at LPEP sites (high endemic), which are small geographical units in the countries. There is a possibility of variation in the activities or intensity of national leprosy programs in other parts of the countries, especially low or medium endemic area.

CONCLUSIONS

We conclude that LPEP approaches can be integrated into different health systems without major structural and personal changes, but provisions are necessary for the additional monitoring needs. In the first year LPEP faced some challenges, but the program overcame these because of the committed attitude of the health care staff and officials. Intensive supervision and training developed the human resource capacity to implement similar programs in the future.

The London Declaration highlighted that strong and committed health systems are essential to achieve the 2020 targets for leprosy and other NTDs [4]. Therefore, all actions at the local or international level should contribute to health system strengthening [25]. Evidence suggests that integration strengthens the general health care systems

and also enhances the efficiency and sustainability of the disease specific activities if applied properly [31, 38]. Based on the above principles, LPEP was designed and successfully started its operations in coordination with the respective national programs. The next course of action is to apply the findings of this study, while assessing the impact of LPEP in future.

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ANNEXURES

Additional file 1: Staff Interview Questionnaire for Phase I and II

Staff Interview Questionnaire

Phase (Tick)	Country	Designation	Date
- I (National Program - II (LPEP)	- India - Nepal - Indonesia		

Instructions:
Phase I- Verify the standard operating procedures and data trends published by the national leprosy programs through below questions.
Phase II- Probe the difference between planned and actual implementation of LPEP and alignment with national leprosy program

Q1. What is the current epidemiological trend of leprosy in your area?

Q2. What is the reason for current epidemiological trend of leprosy in your area?

Q3. Please describe the National Leprosy Program (I)/ integrated LPEP practices (II) in your area?

Q4. Please describe the associated challenges with National Leprosy Program (I)/ integrated LPEP practices (II) in your area?

Q5. Please suggest the strategies to overcome said challenges?

Additional file 2: The national strategies on leprosy control/elimination adopted by India, Nepal and Indonesia

NLEP, India	NLCP, Nepal	NLCP, Indonesia
Early diagnosis & prompt MDT, through routine and special efforts	Early new case detection and their timely and complete management	Early new case detection through active case finding (since 2004)
Early detection & complete treatment of new leprosy cases.	Quality leprosy services in an integrated setup by qualified health workers	Provide quality leprosy services, including rehabilitation services , integrated with primary health care and referral
Carrying out house hold contact survey in detection of Multibacillary (MB) & child cases.	Prevention of leprosy associated impairment and disability	Focus on Information, Education & Communication (IEC)
Decentralized integrated leprosy services through General Health Care system.	Rehabilitation of people affected by leprosy, including medical and community based rehabilitation	Focus on Disability Prevention & Medical Rehabilitation (DPMR) services
Involvement of Accredited Social Health Activists (ASHAs) in the detection & complete treatment of Leprosy cases for leprosy work	Reduce stigma and discrimination through advocacy, social mobilization and IEC activities and address gender equality and social inclusion	Incorporation of innovative methods to decrease transmission
Strengthening of Disability Prevention & Medical Rehabilitation (DPMR) services.	Strengthen referral centers for complications management	
Information, Education & Communication (IEC) activities in the community to improve self-reporting to Primary Health Centre (PHC) and reduction of stigma.	Meaningful involvement of people affected by leprosy in leprosy services, and address human right issues	
Intensive monitoring and supervision at Primary Health Centre/Community Health Centre.	Promote and conduct operational researches/studies	
	Monitoring, supportive supervision including onsite coaching, surveillance and evaluation to ensure/strengthen quality leprosy services	
	Strengthen partnership, co-operation and coordination with local government, external development partners, civil society and community based organizations.	

OUTCASTES (A BEGGING LEPER AND PARIAH DOGS)

Description: Illustration of a begging leper and pariah dogs, to give an example of Kipling's 'Outcastes' and showing relationships between people and animals in India.

Picture credit: Wellcome Collection, London

5 Household expenditure on leprosy outpatient services in the Indian health system: A comparative study

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Mohammad Arif
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ABSTRACT

Introduction

Leprosy is a major public health problem in many low and middle income countries, especially in India, and contributes considerably to the global burden of the disease. Leprosy and poverty are closely associated, and therefore the economic burden of leprosy is a concern. However, evidence on patient's expenditure is scarce. In this study, we estimate the expenditure in primary care (outpatient) by leprosy households in two different public health settings.

Methods

We performed a cross-sectional study, comparing the Union Territory of Dadra and Nagar Haveli with the Umbergaon block of Valsad, Gujrat, India. A household (HH) survey was conducted between May and October, 2016. We calculated direct and indirect expenditure by zero inflated negative binomial and negative binomial regression.

Results

The sampled households were comparable on socioeconomic indicators. The mean direct expenditure was USD 6.5 (95% CI: 2.4-17.9) in Dadra and Nagar Haveli and USD 5.4 (95% CI: 3.8-7.9) per visit in Umbergaon. The mean indirect expenditure was USD 8.7 (95% CI: 7.2-10.6) in Dadra and Nagar Haveli and USD 12.4 (95% CI: 7.0-21.9) in Umbergaon. The age of the leprosy patients and type of health facilities were the major predictors of total expenditure on leprosy primary care. The higher the age, the higher the expenditure at both sites. The private facilities are more expensive than the government facilities at both sites. If the public health system is enhanced, government facilities are the first preference for patients.

Conclusions

An enhanced public health system reduces the patient's expenditure and improves the health seeking behaviour. We recommend investing in health system strengthening to reduce the economic burden of leprosy.

INTRODUCTION

Leprosy is caused by *Mycobacterium leprae*, affecting the peripheral skin, nerve and nasal mucosa [1]. The adverse impact of leprosy on human lives is serious due to nerve function impairment and disabilities. Moreover, the early manifestation of disability in the form of sensory loss of hands or feet, often fails to seize attention of clinicians and patients, resulting into detection delay and further transmission of *M. leprae* [2, 3]. Therefore, the annual new case detection rate (NCDR) of leprosy is stagnant since many years [4]. The expectation to permanently eradicate leprosy, also referred as zero transmission [5] is now reflected into new WHO targets i.e. zero grade 2 disabilities among children, and new cases with grade 2 disability <1 case/million population [6]. However, the targets are difficult to achieve in the near future [7, 8], which means that leprosy will keep on imposing burden in many endemic countries.

Leprosy and poor socioeconomic status are in a vicious cycle, characterized by inequality [9-11], poor education [12], poverty [13, 14], stigma, etc. [15, 16]. A broad spectrum of evidence confirms the strength of the relationship between leprosy and poverty [17-21]. Evidence from Bangladesh shows that leprosy affected households have a poor nutritional level due to lower food expenditure per capita and household food stocks. This in fact increases the risk of acquiring leprosy in healthy household members [22]. Another study revealed that "people affected by leprosy are less likely to be stigmatized because of leprosy impairments than for their incapacity to contribute to family/community finances" [23]. Furthermore, leprosy incidence is high in the productive age group, resulting in long term financial loss [17]. Therefore, we suspect that the economic burden of leprosy is higher than perceived so far.

Household expenditure represents the patient's perspective and is critical in estimating the economic burden. It is now routinely done across diseases [24], revealing underlying expenditure like income loss, which can sometimes be significant. Unfortunately, the cost evidence in leprosy is limited [25]. A literature search on PubMed using a broad search builder with 'leprosy' as MeSH term and 'economics' as sub-MeSH heading (year 2001 onwards), resulted in 51 records. Only 6 records presented some cost estimates: three studies focused on a particular event (ENL reaction and ulceration) in hospital settings [26-28]; two cost-effectiveness analysis (CEA) studies on provider's perspective [29, 30]; and one study on human resource cost of a project [31]. No study was found exclusively on primary care in a general public health setting, covering the patient's perspective.

Leprosy is a chronic infectious disease with long treatment duration, therefore needs long term care and support, mainly in an outpatient setting. Therefore, the primary objective of our study is to estimate the expenditure in primary (outpatient) care incurred by leprosy patients in two different health system settings in India. The secondary objective is to compare the effect of the health systems on consumer behaviour and practices. The results will help in understanding the economic burden of leprosy in primary care, and eventually contribute in building an investment case for leprosy elimination [25].

METHODS

Ethics Statement

The study was conducted under the Leprosy Post Exposure Prophylaxis (LPEP) program, approved in India by the Institutional Human Ethics Committees of the National Institute of Epidemiology (NIE/IHEC201407-01). Written informed consent was received from the respondents and necessary permission was taken from the concerned departments.

Background of LPEP in India

India contributes almost 60% to the global leprosy burden [4]. The LPEP program was launched in March 2015 in the Union Territory of Dadra and Nagar Haveli (DNH), located on the western coast of India. The program aims to assess impact and feasibility of contact tracing and administration of single dose of rifampicin (SDR) to asymptomatic contacts of leprosy cases. LPEP is implemented by the National Leprosy Elimination Program (NLEP) of India [32].

Study design

The study followed a cross-sectional design, where a cohort from the Union Territory of DNH was compared with a cohort from Umbergaon block of Valsad district, Gujarat, India. A union territory is an administrative division, ruled directly by the federal government, whereas a block is the smallest administrative unit under a district. The cohorts were leprosy cases detected between April 2015 and March, 2016. A sample of 120 participants from each group was selected randomly from the annual leprosy case detection list. In the financial year of 2015-16, DNH reported 425 and Umbergaon reported 287 cases.

Study sites

DNH and Umbergaon share boundaries and are comparable with regard to demographic, epidemiological, and socioeconomic indicators (Table 1), but not to public health facilities due to the different governmental arrangement (see below).

Table 1. Comparison of Dadra and Nagar Haveli and Umbergaon with regard to demography, epidemiology, socioeconomics factors, and public health facilities.

Indicators	DNH	Umbergaon
Demographic & Socioeconomic indicators (Census 2011)		
Number of households (HH)	76,121	54,814
Population	343,709	261,204
Rural population	53.27%	68.74%
Females (per 1000 males)	774	933
Literacy	76.24%	69.53%
Schedule tribes#	51.95%	51.32%
Total working population	45.73%	40.40%
Epidemiology (2015-16)		
Leprosy screened population	388,613	371,731
New cases detected	425	287
NCDR* (per 100,000 per year)	109.36	77.21
New child cases (age < 15 years)	23.29%	16.03%
New female cases	57.88%	61.67%
Prevalence rate (per 10,000 per year)	6.77	3.81
Grade II disability in new cases	3.3%	2.44%
PB/MB** ratio	2.76	3.15
Public Health Infrastructure (2015-16)		
Area (sq. km)	491	343
Primary health centres (PHC)	15	10
Sub-centres	50	64
Average population screened for leprosy by health centre	25,907	37,173

#The Scheduled Castes (SCs) and Scheduled Tribes (STs) are various officially designated groups of historically disadvantaged indigenous people in India. * NCDR: new case detection rate; ** PB: Paucibacillary; MB: Multibacillary

Both study sites are mainly tribal areas, but there is a remarkable difference in the public health system of both sites. The public health system in DNH is enhanced because it falls directly under the federal government by bypassing provincial bureaucracy, and receives a higher health budget per capita [33-35] than the provinces. In comparison to DNH, Umbergaon has more PHCs per population covered; the average population screened for leprosy by a Primary Health Center (PHC) in Umbergaon was 43% more than DNH PHC (Table 1). The actual screening (active and passive) coverage was reported to be very high in both sites, approximating the total population of these areas. In the year

2015-16, the leprosy program performed two active case detection surveys in both sites. Currently both sites fall under the Leprosy Case Detection Campaign (LCDC), which was launched in early 2016 under the NLEP [36]. Furthermore, the population screened by Umbergaon PHCs is far more than the public health norms for tribal PHCs, i.e. 86% more in Umbergaon and 26% in DNH [37]. Typically, a PHC should cover a population of 20,000 in hilly, tribal, or difficult areas and 30,000 populations in plain areas [37]. Both sites provide free of charge leprosy outpatient department (OPD) services at all public health facilities, but the health systems vary with regard to infrastructure, availability, accessibility, and quality of services.

Data Collection and analysis

A household survey was conducted between June and October, 2016 by means of a structured questionnaire. The data were collected by two experienced staff members, post-graduates in public health. The patient, or head of the household, or most knowledgeable person in the household was asked to report on patient demographics, HH socioeconomic status, accessibility of health services, treatment seeking history and OPD expenditure. Respondents were asked to report on the last three OPD visits, either in a public or private facility, in the last 6 months. The database was created in Excel. The analysis included only those patients who mentioned at least 1 OPD visit out of 3.

The costs were categorized as direct and indirect expenditure. The direct part included the expenditure on consultation, investigations and medicines & supplies. The indirect part constituted expenditure on transport, food, and days lost during illness of the patient and attendant. We calculated the transportation expenditure by multiplying to-and-fro distance from house to the nearest health facility, using the government transportation rate [38]. The wage loss was analysed by means of the human capital approach [39]. The wage losses for patients and attendants per illness episode were calculated by using government minimum wage rates [40]. There were 20 (8%) patients who paid at least 1 OPD visit, but failed to report any loss of productive days. For these, we imputed half a day wage loss per visit under the assumption that at least half a day (4 hours) is required to travel and avail services for each illness episode. But attendant's productive day loss could be zero, as not all patients required attendants. We reported separately the days lost by child patients (age < 16 years) as 'school days lost', but while calculating indirect expenditure, all patients and attendants were assumed to be 16 years and older. The results are presented in US dollars (USD) using the conversion rate of INR 67 for 1 dollar for the year 2016 [41]. The analyzed expenditure was exclusively of outpatient services.

Data modelling

In order to answer our objectives, i.e. expenditure and patient's health seeking behaviour differences in DNH and Umbergaon, we used an integrated analytical approach. The data distribution was evaluated by observing normality plots. The distribution of the direct expenditure variables were not normally distributed due to abundance of zeros and highly skewed for non-zero values, which is common in cost data [42]. The indirect expenditure variables were skewed, but not zero inflated. We compared four different distribution models, i.e. Poisson, negative binomial, zero inflated Poisson, and zero inflated negative binomial distribution [43]. The 'zero inflated negative binomial regression' was selected for direct expenditure variables, and 'negative binomial regression' for indirect and total expenditure variables. We estimated the mean expenditure for each variable, followed by association measurement between expenditure and patient's household characteristics. Only significant ($p < 0.05$) variables were modelled together for multivariate regression analysis (Generalized Linear Model). The magnitude of total expenditure was compared against the individual's monthly income. The total per visit expenditure was defined catastrophic for an individual, if it exceeded 10% of the quarterly income [44, 45]. We assumed that at least one visit to the health centre in a quarter is necessary for regular check-up of leprosy. However as per NLEP norms, patients should visit the health center every month, which rarely happens. In practice, monthly MDT is delivered by staff at the patient's doorstep and health facility visits occur only during severe illnesses to avoid any wage loss.

RESULTS

A total of 240 patient households (120 in each group) were approached to capture their characteristics and OPD visit details in the last 6 months. The area-wise household characteristics are summarized in Table 2. The mean age (DNH: 25, Umbergaon: 24) showed a young and comparable population in both sites. The average monthly income (DNH: USD 81, Umbergaon: USD 97), expenditure (DNH: USD 73, Umbergaon: USD 83) and saving (DNH: USD 1 Umbergaon: USD 1) per earning member showed a poor economic status in both sites. The respondents differed prominently on characteristics such as distance to the nearest health facility, type of housing, OPD frequency and type of facility visited. Paucibacillary (PB) leprosy was more prevalent in both sites than multibacillary (MB) leprosy. Collectively in the three visits, 69% of the respondents in Umbergaon and 14% of the respondents in DNH had not paid any visit, and were therefore dropped for further analysis.

Table 2. Socioeconomic characteristics of patient households in DNH and Umbergaon.

	DNH (N=120)		Umbergaon (N=120)		p
	Mean (USD)	95% CI	Mean (USD)	95% CI	
Age (years)	24.7	22.0-27.7	23.6	17.9-31.1	0.58
HH size	6.0	5.6-6.4	5.4	4.7-6.3	0.03
Number of earning members	1.5	1.3-1.7	1.6	1.1-2.3	0.41
Monthly income per earning member in HH in INR	5,456 (81)	5,144-5,787	6,503 (97)	5,642-7,495	0.00
Monthly expenditure per earning member in HH in INR	4,890 (73)	4,566-5,238	5,591 (83)	4,736-6,601	0.01
Monthly savings per earning member in HH in INR	74 (1)	41-133	87 (1)	47-161	0.71
Distance of nearest health facility (km)	5.1	4.6-5.6	9	8.0-9.9	0.00
	N	%	N	%	p
Sex: Female	73	60.8	70	58.3	0.69
Occupation: Not Earning*	87	72.5	67	55.8	0.01
Leprosy type: PB	104	86.7	92	76.7	0.05
Type of housing: Concrete predominant**	95	79.2	68	56.7	0.00
OPD frequency (Max 3. duration last 6 months)					
0	17	14.2	83	69.2	0.00
1	77	64.2	25	20.8	
2	24	20.0	11	9.2	
3	2	1.7	1	0.8	
Type of OPD facility (last 3 visits in 6 months)					
No visit	17	14.2	83	69.2	0.00
Only government	97	80.8	14	11.7	
Both	4	3.3	5	4.2	
Only private	2	1.7	18	15.0	

*Not earning in comparison to earning, includes unemployed, children, housewives
** In comparison to mud predominant houses

The three visits expenditure was aggregated to obtain an average per visit. The details of direct and indirect expenditure are shown in Table 3. DNH and Umbergaon were comparable on demographic and socioeconomic parameters, however, they statistically significantly differed with regard to health seeking behaviour. As a behaviour, OPD visit frequency is higher, and a government facility is more preferred in DNH as compared to Umbergaon.

All the presented expenditure estimates are per visit. The mean consultation fee in DNH and Umbergaon was comparable (DNH: USD 1.2, Umbergaon: USD 1.6). The mean

Table 3. Direct and Indirect expenditure in INR by leprosy patients on outpatient care in DNH and Umbergaon.

	DNH					Umbergaon					p
	n reported	% N=0	*Pr N=0	Mean (USD)	95% CI	n reported	% N=0	*Pr N=0	Mean (USD)	95% CI	
*OPD direct expenditure per visit***											
Consultation	103	89	0.90	78 (1.2)	36-171	37	38	0.36	107 (1.6)	81-143	0.22
Medicines & supplies	103	91	0.89	478 (7.1)	167-1394	37	33	0.38	265 (4)	185-380	0.10
Total medical direct exp.	103	89	0.88	433 (6.5)	158-1200	37	33	0.35	365 (5.4)	252-528	0.60
Transport (non-medical direct)	103	0		54 (0.8)	45-66	37	0		94 (1.4)	53-166	0.005
*OPD indirect expenditure per visit (wage loss per illness episode)***											
Patient's wage loss (age>15)	77	0		264 (3.9)	211-330	25	0		306 (4.6)	156-601	0.53
School days lost (Age<16)	26	0		2	1-3	12	25		3	1-10	0.38
Patient's wage loss (assumed all adults)	103	0		346 (5.2)	285-420	37	0		489 (7.3)	277-864	0.07
Attendant's wage loss	103	32		183 (2.7)	151-223	37	19		246 (3.7)	139-436	0.13
Indirect exp.+ Transport (assumed all adult)	103	0		583 (8.7)	481-708	37	0		829 (12.4)	469-1464	0.07
Total (direct+ indirect) exp. (assumed all adults)	103	0		634 (9.5)	523-769	37	0		1075 (16)	609-1901	0.006

* Pr N=0: predicted probability of 0 expenditure

**Medical direct expenditure (exp.) estimates are derived by zero inflated negative binomial regression.
Non-medical direct, Indirect and Total exp. estimates are derived by negative binomial regression.
Investigations and food were reported negligible, therefore, not included in the table.

expenditure on medicines and supplies (USD 7) was 80% higher in DNH than Umbergaon (USD 4). Only 2 respondents reported investigation expenditure in Umbergaon and none in DNH. Only 1 respondent in Umbergaon and 2 respondents in DNH reported expenditure on food. The mean medical direct expenditure per visit (DNH: USD 6.5, Umbergaon: USD 5.4) was not statistically significantly different between the sites. In indirect expenditure, the mean wage loss for patients was the highest item (DNH: USD 5.2, Umbergaon: USD 7.3), followed by attendant wage loss (DNH: USD 2.7, Umbergaon: USD 3.7). Transportation expenditure (DNH: USD 0.8, Umbergaon: USD 1.4) differed significantly ($p \leq 0.01$) in the two groups.

The details on association of expenditures with patient's household characteristics are shown in Table 4. The proportion of patients with catastrophic expenditure in DNH was 88% less than in Umbergaon. If catastrophic expenditure occurred, then direct expenditure rose three-fold in DNH and two-fold in Umbergaon, (DNH: coef. 2.92, 95% CI: 1.86-3.98; Umbergaon: coef. 1.00, 95% CI: 0.23-1.77). In DNH, the direct expenditure decreased statistically significantly more than two-fold (coef. -2.49, 95% CI: -3.74 to -1.24) with the increase in age groups, whereas a decrease in indirect expenditure against age was not statistically significant (coef. -0.40, 95% CI: -0.92 to 0.12). Umbergaon's indirect expenditure decreased statistically significantly more than half (coef. -0.79, 95% CI: -1.49 to -0.09) among patients who visited both (government and private) facilities in comparison to those who visited only private facilities. For total expenditure, age and type of facility remained statistically significant factors, whereas catastrophic expenditure remained statistically significant only in DNH. Therefore these factors were considered for the next level of analysis, i.e. multivariate regression.

Table 5 presents the association when only statistically significant variables ($p < 0.05$) are modelled together with total expenditure (direct + indirect). When modelled separately for both sites, all the variables in Umbergaon turned statistically not-significant. Age however, remained a statistically significant factor ($p = 0.03$) in DNH. The overall model (Omnibus Test) was statistically significant in DNH ($p = 0.001$), but not in Umbergaon ($p = 0.06$). Furthermore, the same model was applied jointly for DNH and Umbergaon (n=140), which was overall highly significant ($p \leq 0.001$). The age ($p = 0.019$) and type of facility ($p = 0.002$) were statistically significant, but catastrophic expenditure became statistically not-significant. Catastrophic coefficients however, indicated that catastrophic expenditure groups (in both the areas) had risk of spending (total expenditure) almost twice, compared to non-catastrophic groups.

Table 4. Socioeconomic factors associated with expenditures by leprosy patients on outpatient services in DNH and Umbergaon (Bivariate analyses).

		DNH									Umbergaon								
		Direct			Indirect			Total			Direct			Indirect			Total		
		Coef.	95% CI	P	Coef.	95% CI	p	Coef.	95% CI	P	Coef.	95% CI	p	Coef.	95% CI	p	Coef.	95% CI	p
Age	<=18	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	19-35	-2.29	-3.66 -0.93	.001	-0.56	-1.00 -0.12	.01	-0.68	-1.12 -0.25	.002	0.01	-0.52 0.54	.97	-0.75	-1.52 0.02	.06	-0.87	-1.64 -0.10	.03
	>=36	-2.49	-3.74 -1.24	.000	-0.40	-0.92 0.12	.13	-0.52	-1.04 0.00	.048	-0.23	-0.90 0.45	.51	-0.53	-1.33 0.28	.20	-0.47	-1.27 0.33	.25
Sex	Male	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	Female	-0.43	-2.02 1.15	.59	-0.11	-0.50 0.29	.60	-0.14	-0.54 0.25	.48	-0.32	-0.80 0.14	.17	-0.26	-0.97 0.44	.47	-0.39	-1.09 0.32	.28
Occupation	Earning	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	Not Earning	2.09	0.13 4.05	.04	0.29	-0.14 0.71	.18	0.38	-0.04 0.81	.08	0.39	-0.09 0.89	.11	0.13	-0.60 0.85	.74	0.13	-0.59 0.86	.72
Income	<=5820	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	>5820	-0.28	-1.88 1.31	.73	0.20	-0.19 0.59	.31	0.17	-0.23 0.56	.41	0.32	-0.25 0.91	.27	0.33	-0.49 1.15	.43	0.31	-0.51 1.14	.46
Type leprosy	PB	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	MB	1.32	-0.66 3.32	.19	0.25	-0.47 0.97	.50	0.52	-0.20 1.24	.16	0.12	-0.47 0.72	.68	-0.27	-1.09 0.56	.53	-0.15	-0.97 0.68	.73
Distance to nearest facility	<=6 km	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	>6 km	-1.49	-3.25 0.27	.10	-0.15	-0.63 0.33	.53	-0.22	-0.70 0.27	.38	-.44	-0.89 0.01	.06	-0.43	-1.07 0.22	.19	-0.47	-1.12 0.17	.15
Type of facility visited	Private	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	Both	-3.11	-3.64 -2.58	.000	-1.09	-2.49 0.31	.13	-1.89	-3.29 -0.48	.01	0.02	-0.62 0.66	.95	-0.79	-1.49 -0.09	.03	-1.04	-1.74 -0.35	.00
	Government	-2.81	-3.49 -2.13	.000	-0.94	-2.64 0.76	.28	-1.62	-3.31 0.08	.06	-0.91	-2.01 0.18	.10	-0.51	-1.50 0.48	.31	-0.35	-1.34 0.64	.49

Table 4. (*continued*)

		DNH									Umbergaon								
		Direct			Indirect			Total			Direct			Indirect			Total		
		Coef.	95% CI	P	Coef.	95% CI	p	Coef.	95% CI	P	Coef.	95% CI	p	Coef.	95% CI	p	Coef.	95% CI	p
OPD visits frequency	1	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	2	-2.44	-3.54 -1.35	.000	0.09	-1.32 1.49	.90	0.05	-1.36 1.45	.95	0.01	-0.47 0.50	.95	-0.26	-2.26 1.74	.80	-0.13	-2.13 1.87	.90
	3	-2.67	-4.64 -0.70	.01	0.27	-0.19 0.73	0.25	0.21	-0.25 0.67	.38	-0.31	-1.55 0.91	.61	-0.02	-0.73 0.69	.96	0.11	-0.60 0.82	.77
HH size	<=5	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	>5	0.01	-1.57 1.59	.99	-0.29	-0.69 0.12	0.16	-0.30	-0.70 0.10	.14	0.11	-0.36 0.59	.63	-0.06	-0.73 0.60	.85	-0.12	-0.78 0.55	.73
Catastrophic exp.	No	1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)			1. (Ref)		
	Yes	2.92	1.86 3.98	.000	0.77	-0.05 1.60	0.07	1.21	0.39 2.03	.00	1.00	0.23 1.77	.01	1.25	-0.18 2.68	.09	1.29	-0.13 2.72	.08

Table 5. Socioeconomic factors associated with total expenditure by leprosy patients on outpatient services in DNH and Umbergaon (Multivariate analysis).

		Total expenditure											
		DNH (N=103)				Umbergaon (N=37)				DNH+ Umbergaon (N=140)			
		Coef.	Std Err.	95% CI	p	Coef.	Std Err.	95% CI	p	Coef.	Std Err.	95% CI	p
Age	<=18	1. (Ref)				1. (Ref)				1. (Ref)			
	19-35	-0.31	0.27	-0.83 0.21	.25	0.06	0.49	-0.89 1.01	.91	-0.21	0.23	-0.66 0.23	.35
	>=36	-0.53	0.23	-0.98 -0.08	.02	-0.20	0.49	-1.16 0.76	.69	-0.47	0.20	-0.86 -0.08	.02
Type of facility visited	Pvt.	1. (Ref)				1. (Ref)				1. (Ref)			
	Both	-0.67	1.02	-2.68 1.33	.51	-0.20	0.55	-1.28 0.88	.72	-0.24	0.42	-1.06 0.58	.56
	Gov.	-1.08	0.88	-2.80 0.64	.22	-0.80	0.44	-1.67 0.07	.07	-0.80	0.26	-1.30 -0.29	.00
Catastrophic exp.	No	1. (Ref)				1. (Ref)				1. (Ref)			
	Yes	0.58	0.51	-0.43 1.59	.26	0.97	0.77	-0.54 2.48	.21	0.73	0.39	-0.03 1.48	.06

DISCUSSION

Our study explored the leprosy patient's financial burden due to primary care outpatient services. Primary care is an important aspect of disease control under a public health program, therefore costs at this level are important for policy and planning. Moreover, a high out of pocket expenditure indicates public health systems inefficiency, and act as barrier to access services [46]. The results show that the sampled patients were mainly in their economically productive lifetime, indicating leprosy imposing a high economic burden. The leprosy patients of DNH went more frequently to the OPD, and preferred a government facility as compared to Umbergaon. Furthermore, the total expenditure (direct + indirect) was statistically significantly lower in DNH than Umbergaon. The age of the leprosy patients and type of health facilities were the major predictors of total expenditure. The higher the age, the higher the expenditure, and private health facilities were more expensive than government facilities, at both sites.

As a limitation, our study only considered direct and indirect costs, however skin anesthesia (a common phenomenon), neuropathic pain [1, 2], poor mental health [3] and stigma [4, 5] can be significant factors, which can elevate the total expenditure further. We could not focus on these parameters under patient characteristics, and recommend to explore this in detail in future. Next, the households belong to poor socioeconomic groups, which correlates with other studies [6-8], but we drew the sample from government records, which often caters mainly to poor. Also, adequate representation of patients who are diagnosed and treated completely in private facilities cannot be ascertained. The relatively small sample size is also a limitation of this study. The sample size turned out to be low (reduced power) because of high zero visits, meaning that patients often did not visit the outpatient clinics according to the official schedule. Moreover, to minimize recall bias, we only included the patients of the most recent one year, which was a small cohort. Many patients were not traceable due to migration. Furthermore, we computed catastrophic expenditure based on the income, rather than consumption pattern, which is a more rigorous method. The study is cross-sectional and there is no insight on how patients adapt over time. We recommend to repeat the survey after an appropriate time gap. Also, OPD expenditure is not as high as hospitalization, therefore often failed to be recalled. We do not reject the possibility of recall bias, but we further reduced this by averaging the expenditure from last three visits. Although we have quantified health seeking behaviour, this study does not identify the underlying reasons for these patterns, which would further necessitate qualitative studies.

So far, sound evidence is lacking on the private sector uptake of leprosy cases, therefore we compared the patient's selection of health facilities for primary leprosy care.

We observed that the government is mostly preferred over private health facilities (government 80.8% *vs.* private 1.7%) in an enhanced health system (DNH). In a non-enhanced health system (Umbergaon) however, private is equally preferred (private 15% *vs.* government 11.7%) . Moreover, in a non-enhanced health system (Umbergaon) patients have poor health seeking behaviour (zero OPD visits in last 6 months: Umbergaon 69% *vs.* DNH 14%). Contrary to the high number of subjects reporting zero visits, the predicted probability of zero direct medical expenditure (Umbergaon 0.35 *vs.* DNH 0.88) is lower in Umbergaon, and *vice versa* in DNH. It means that patients in Umbergaon avoid visiting any health facility, but if they visit then end up paying more than in DNH, therefore out of pocket direct medical expenditure acts as a potential barrier to access leprosy health care. The indirect expenditure is the largest cost impoverishing component for patients. Next, the indirect expenditure with transportation and total expenditure in an enhanced health system (DNH) is lower than non-enhanced health system (Umbergaon). Usually, a high variation is expected in indirect expenditure and transportation, because in many instances they are not paid out of pocket and are presumptive e.g. wage loss. This can lead to over or under reporting. For example, many people use their own vehicle or are supported by others, and often fail to report this. This in turn leads to unrealistic and non-comparable estimates, which are of low utility for policy purposes. Therefore, we used standard government labour market and transportation rates in both areas for comparable results, which are appropriate for the sampled socioeconomic groups. Our study identifies the linkage between socioeconomic factors and expenditure increase. The total expenditure peaked at the 19-35 age category, which correlates with the human capital approach, i.e. the productive age group is more weighted than early or old age [9, 10]. Next, private health facilities are significantly more expensive than government facilities, therefore one of the reasons for higher total expenditure in Umbergaon than DNH.

CONCLUSION

We conclude that the condition of public health systems has a direct relationship with the patient's expenditure, and the better the public health system, the lesser the expenditure from the leprosy patient's pocket. Next, the condition of public health system has a major effect on the patient's health seeking behaviour, i.e. selection of health facility and services uptake. If a health system is weak, then leprosy patients are forced to seek private health care, which is more expensive and imposes a significant financial burden on the leprosy affected population, proven to be catastrophic. If a public health system is enhanced, then patients prefer to avail government health facility services. We recommend to invest in health system strengthening to reduce the economic burden of leprosy.

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ANNEXURES

S1 Table. Model comparison for direct and indirect expenditure on leprosy outpatient care

S1.1. Model comparison of direct expenditures on leprosy outpatient care (supporting table 3 in the manuscript)

Dependent var.	Independent var.	Zero inflated var.	zip*		vuong**	
			chibar2	Pr>=chibar2	z	Pr>z
Consultation	Patient area	Type of facility and OPD frequency	1530.34	0.0000	7.86	0.0000
Medicines & supplies	Patient area	Type of facility and OPD frequency	1.1e+04	0.0000	5.32	0.0000
Direct medical expenditure	Patient area	Type of facility and OPD frequency	1.4e+04	0.0000	4.72	0.0000

*zero inflated negative binomial vs. zero inflated poisson
**zero inflated negative binomial vs. standard negative binomial

S1.2. Model comparison of transportation and indirect expenditures on leprosy outpatient care (supporting table 3 in the manuscript)

Dependent var.	Independent var.	Poisson		Negative binomial	
		Deviance	AIC	Deviance	AIC
Transportation	Patient area	24.748	4226.63	0.419	1444.5
Patient's wage loss (assumed all adults)	Patient area	209.224	29936.564	0.418	1946.839
Attendant's wage loss	Patient area	153.188	21885.321	3.234	1765.848
Indirect exp. (assumed all adult)	Patient area	195.994	28193.507	0.284	2093.485
Total (direct+ indirect) exp. (assumed all adults)	Patient area	318.302	45083.586	0.381	2129.936

S1.3. Model comparison of socioeconomic factors associated with direct medical expenditures on outpatient services in DNH and Umbergaon (supporting table 4 in the manuscript)

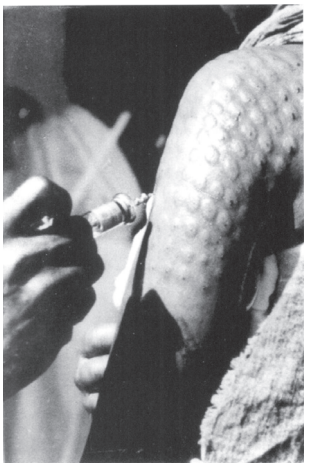
Dependent var.	Independent var.	zero inflated var.	Umbergaon						DNH					
			Overall model		zip*		vuong**		Overall model		zip*		vuong**	
			LR chi2	Prob > chi2	chibar2	Pr>=chibar2	z	Pr>z	LR chi2	Prob > chi2	chibar2	Pr>=chibar2	z	Pr>z
Direct medical expenditure per visit	Age	Type of facility and OPD frequency	0.46	0.7954	3603.55	0.0000	2.36	0.0092	11.50	0.0032	5249.57	0.0000	3.10	0.0010
	Sex	Type of facility and OPD frequency	1.83	0.1761	3418.71	0.0000	2.59	0.0048	0.29	0.5883	1.0e+04	0.0000	3.07	0.0011
	Occupation	Type of facility and OPD frequency	2.29	0.1306	3381.50	0.0000	2.19	0.0144	2.56	0.1096	9223.60	0.0000	3.31	0.0005
	Income	Type of facility	1.11	0.2929	3524.95	0.0000	2.55	0.0053	0.12	0.7275	1.0e+04	0.0000	2.7	0.0035
	Type leprosy	Type of facility and OPD frequency	0.17	0.6766	3637.75	0.0000	2.55	0.0054	2.08	0.1492	8379.49	0.0000	2.90	0.0019
	Distance to nearest facility	OPD frequency	3.32	0.0682	3251.21	0.0000	1.94	0.0259	1.89	0.1688	9168.17	0.0000	2.67	0.0038
	Type of facility	OPD frequency	3.42	0.1806	3328.78	0	1.88	0.3	19.79	0.0001	554.99	0.0000	2.39	0.0084
	OPD frequency	Type of facility	0.25	0.8827	3631.33	0.0000	2.66	0.0040	13.09	0.0014	4225.98	0.0000	2.49	0.0065
	HH size	Type of facility and OPD frequency	0.23	0.6315	3630.86	0.0000	2.41	0.0079	0.00	0.9854	1.0e+04	0.0000	3.13	0.0009
	Catastrophic expenditure	OPD frequency	7.52	0.0061	2521.74	0.0000	1.30	0.0968	19.35	0.0000	577.88	0.0000	2.48	0.0066

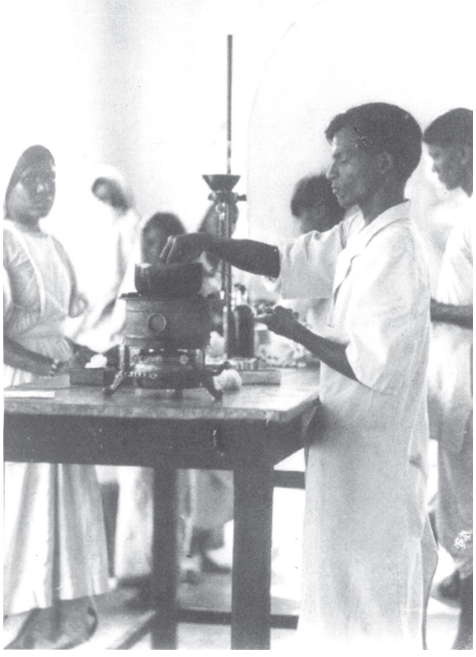
*zero inflated negative binomial vs. zero inflated poisson

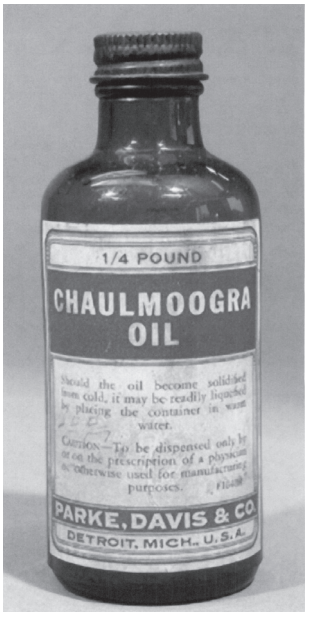
**zero inflated negative binomial vs. standard negative binomial

S1.4. Model comparison of socioeconomic factors associated with transport + indirect expenditures on outpatient services in DNH and Umbergaon (supporting table 4 in the manuscript)

Dependent var.	Independent var.	Umbergaon				DNH			
		Poisson		Negative binomial		Poisson		Negative binomial	
		Deviance	AIC	Deviance	AIC	Deviance	AIC	Deviance	AIC
Transport + Indirect expenditure per visit	Age	201.058	7153	0.215	573.3	130.664	13903.7	0.214	1517.6
	Sex	275.796	9967.9	0.305	574.7	165.884	17589.6	0.274	1521.9
	Occupation	286.690	10349.2	0.318	575.1	158.195	16813.1	0.260	1520.4
	Income	276.592	9995.7	0.304	574.7	161.788	17175.9	0.267	1521.1
	Type leprosy	280.907	10146.8	0.310	574.9	164.468	17446.6	0.272	1521.7
	Distance to nearest facility	250.367	9077.9	0.273	573.6	165.392	17540.0	0.273	1521.8
	Type of facility	184.304	6583.4	0.186	572.4	141.206	14958.0	0.245	1520.7
	OPD frequency	281.265	10438.6	0.328	577.2	165.898	17754.9	0.266	1522.8
	HH size	288.446	10410.6	0.320	575.3	155.765	16567.6	0.257	1520.2
	Catastrophic expenditure	146.385	5438.5	0.197	571.0	137.143	14686.7	0.235	1517.9







Description: Chaulmoogra (Hydnocarpus wightiana) seed oil was used in the treatment of leprosy in the nineteenth century before the era of sulfonamides and other antibiotics.

Source: Parascandola J (2003), Pharmacy in History.

6 Leprosy services in primary health care in India: a comparative economic cost analysis of two public-health settings

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ABSTRACT

Introduction

WHO has recommended to include post-exposure chemoprophylaxis with single-dose rifampicin in the nation leprosy control programmes. The objective was to estimate the cost of leprosy services at primary care level in two different public-health settings.

Methods

Ingredient-based costing was performed in a total of 8 Primary Health Centres (PHC) purposively selected in the Union Territory of Dadra and Nagar Haveli (DNH) and the Umbergaon block of Valsad district, Gujarat (India). All costs were bootstrapped, and to estimate the variation in total cost under uncertainty, a univariate sensitivity analysis was performed.

Results

The mean annual cost of providing leprosy services was USD 29,072 in the DNH PHC (95% CI: 22,125-36,020) and USD 11,082 in Umbergaon (95% CI: 8,334- 13,830). The single largest cost component was human resources: 79% in DNH and 83% in Umbergaon. The unit cost for screening the contact of a leprosy patient was USD 1 in DNH (95% CI: 0.8-1.2) and USD 0.3 in Umbergaon (95% CI: 0.2- 0.4). In DNH, the unit cost of delivering single-dose of rifampicin (SDR) as chemoprophylaxis for contacts was USD 2.9 (95% CI: 2.5- 3.7).

Conclusions

The setting with an enhanced public-health financing system invests more in leprosy services than that with more limited financial resources. When accounted for output (leprosy visits), the enhanced public-health system is hardly more expensive than the non-enhances public-health system. The unit cost of contact screening is not high, favouring its sustainability in the programme.

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. While the first outward sign is usually discolored painless skin patches, a delay in diagnosis can lead to complications including physical disability [1].

Many challenges are associated with leprosy infection. First, the transmission mechanism is unclear [2], and the incubation period with active transmission is long [3]. Second, those affected are vulnerable to co-infections and mental health problems [4, 5]. Third, the stigma caused by leprosy is more severe compared to other stigma-causing diseases such as epilepsy and tuberculosis [6]; stigma not only isolates socially, but also restricts employment opportunities [7, 8]. Fourth, disability is reported mainly in the productive age group, and discontinues labor market participation, sometimes lifelong [9]. Finally, the afflicted population is mainly poor [4, 10], and the cost of treatment imposes a high burden on households [11].

Sixty percent of the 210,758 new leprosy cases diagnosed worldwide in 2015 were diagnosed in India [12]. New case detection has remained almost stagnant in the past 9 years, indicating uninterrupted transmission [12, 13]. Although the Indian National Leprosy Eradication Programme (NLEP) showed an annual new case detection rate (ANCDR) of 9.71 per 100,000 and a prevalence rate of 0.66 per 10,000 population in 2015-16 [13], national average rates are not representative of leprosy-affected pockets. In 80 districts (12% of all districts in India), the ANCDR per 100,000 population was over 20 new cases, and 22 districts (3% of all districts) reported a rate higher than 50 new cases [13]. After the declaration of prevalence based elimination in 2005, Indian programme was criticized for being passive, and missing new cases [14, 15]. Therefore in 2016, the NLEP started a door-to-door Leprosy Case Detection Campaign (LCDC), covering 149 districts across 19 states [16, 17]. Since inception, LCDC claimed to detect more than 34,000 new cases under NLEP (source: Central Leprosy Division, India), but figure still lies below the number of estimated hidden cases [14, 15].

As leprosy recently gained a significant political commitment from the government of India, it is now back on the agenda of the Ministry of Health and Family Welfare [18]. The 2017 parliamentary budget speech also included a commitment to eradicate leprosy by 2018 [19] (a target that seems unrealistic given the present epidemiological level) [15]. However, as the NLEP is in the process of testing feasible strategies for interrupting transmission of *M. leprae*, economic analysis, particularly costing estimates, are important to guide the decisions that aim to improve financial efficiency [20].

As costing estimates at primary-care level in leprosy are also very limited [21], our study aimed to estimate the cost of leprosy services at primary care level in two different public-health settings. Because health care in India is organized at the provincial level, individual public-health settings differ in factors such as funding, staffing and infrastructure, which are linked directly to the cost of services, and indirectly to service coverage. To gain an overview of the possible variation in costs, we therefore examined two different public-health settings. The purpose of this study is to mainly provide cost estimates which can aid financial planning of a scale up. In future, these cost estimates will also be useful in assessing the cost-effectiveness of leprosy control activities, including post-exposure prophylaxis with single-dose of rifampicin (SDR).

METHODS

Study sites

The data were collected in the Union Territory of Dadra and Nagar Haveli (DNH) and the adjacent Umbergaon block of Valsad district, Gujarat, each a tribal area with a similar demographic and socioeconomic structure (Table 1). A block is a district sub-division administrative unit. As each area is rated as highly endemic for leprosy, its leprosy epidemiology is also comparable [13]. But the public-health systems are nonetheless different, because DNH operates directly under the federal government, and receives a higher central budgetary assistance per-capita for overall and health funding alike [22, 23]. Relative to Umbergaon, DNH's public-health system is enhanced in terms of its available infrastructure (Table 1), human resources (See online additional file Table 1), and service-delivery coverage (See online additional file Table 2) [24]. Due to these factors, leprosy patient's out of pocket expenditure on primary care in DNH is lower [25].

In both areas, leprosy services are integrated into the local public-health care delivery system. Other than routine leprosy programme activities, annual LCDC campaign has also been performed since 2016 in DNH and Umbergaon. From March 2015, LPEP programme is ongoing in DNH, but not in Umbergaon. The DNH was selected for LPEP due to the highest new case detection rate (NCDR), child case rate and prevalence rate in the year 2014-15 [26]. Moreover, DNH had a better infrastructure and human resources in place to experiment a pilot project. The LPEP programme—whose details are available in the published protocol [13]—is intended to assess the feasibility and impact of contact tracing and administration of single-dose rifampicin (SDR) to asymptomatic contacts of leprosy cases [13]. The contact was defined as someone who has had prolonged or regular contact with an index case. The efficacy of SDR was already established [27], and found to have a protective effect of 57% [28]. The operational alignment of LPEP

Table 1. Comparison of Dadra and Nagar Haveli and Umbergaon with regard to demography, epidemiology, socioeconomic factors, and public-health facilities

Indicators	DNH	Umbergaon
Demographic & Socioeconomic indicators (Census 2011)		
Number of households (HH)	76,121	54,814
Population	343,709	261,204
Rural population	53.2%	68.7%
Females (per 1000 males)	774	933
Literacy	76.2%	69.5%
Schedule tribes#	51.9%	51.3%
Total working population	45.7%	40.4%
Epidemiology (2015-16)		
Leprosy-screened population	388,613	371,731
New cases detected	425	287
NCDR* (per 100,000 per year)	109.3	77.2
New child cases (age < 14 years)	23.2%	16.0%
New female cases	57.8%	61.6%
Prevalence/Registered patient rate (per 10,000 per year)	6.7	3.8
Grade II disability in new cases	3.3%	2.4%
PB/MB** ratio	2.7	3.1
Public-health Infrastructure (2015-16)		
Area (sq. km)	491	343
Primary health centers (PHC)	15	10
Sub-centers	50	64
Average population screened for leprosy by health center	25,907	37,173

MB, multibacillary; NCDR, new case detection rate; PB, paucibacillary; Source: Tiwari et al. 2017 [30]. #The Scheduled Castes (SCs) and Scheduled Tribes (STs) are officially designated groups of historically disadvantaged indigenous people in India.

and NLEP is described elsewhere [29]. By including leprosy patients' neighbors and social contacts, the LPEP has intensified contact tracing, improved screening sensitivity, and broadened the coverage of contact examination.

Cost data collection and analysis

When designing the study we referred to the "WHO Guide to Cost-Effectiveness Analysis" and "Drummond's check-list for assessing economic evaluations" [30, 31], taking the perspective of the Health System. The first step was to identify financial sources that contribute to leprosy service delivery: the local public-health system, the NLEP, and LPEP (donor funds for DNH only). The data related to sampled PHCs were spread at three levels: district (which included only NLEP and LPEP expenditures), PHCs and sub-centre (Figure 1). The sub-centres, which are the most peripheral health units, managed by paramedical staff, and cater mainly for preventive care, with some curative services for

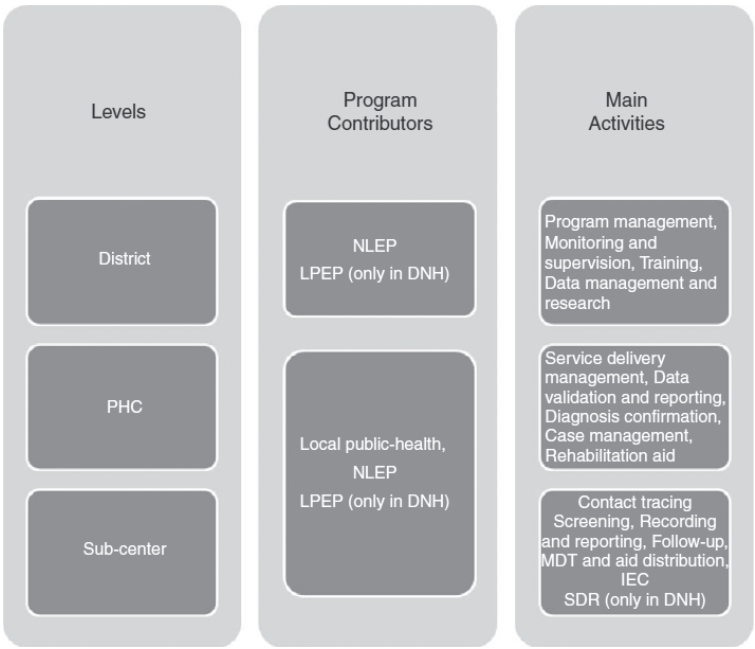

Figure 1. Data collection levels and corresponding leprosy control activities in DNH and Umbergaon

minor ailments [20]. We did not collect data on leprosy costs at international, national or state levels as we only focused on the primary care level.

The cost data were collected from June to October 2016, for 8 PHCs (4 PHCs at each study site), purposively selected on the basis of the leprosy prevalence of 2014-15, i.e., a mix of low, medium and high leprosy endemicity (See online additional file Table 3). The bottom-up ingredient-based approach was applied to costing [32]. Costs were categorized as follows: 1.) capital costs, including building, equipment and other consumables, that had lasted for a period of more than one year; and 2.) recurrent costs, i.e., staff salaries, reimbursements for leprosy schemes, monitoring, repeated training, drugs, consumables, and overheads such as water and electricity bills, that had been incurred in the previous year (June 2015 to May 2016). After facility assessment (to list all assets), records were crosschecked to determine the quantity of assets consumed with their purchasing price. For the assets, prices data were not available, we used data from other state government's pricing lists, or open market rates. To record total working durations and the proportion of time allocated to leprosy services, staff were interviewed on the basis of a semi-structured questionnaire. This proportion time allocated to leprosy was multiplied with the corresponding remuneration to derive HR cost. The annual cost of buildings was estimated by multiplying the government rental rates by the roof covered surface area of the facilities. Equipment was annualized

based on their useful life at a discount rate of 3% [30]. Shared-costs other than HR were apportioned on the bases of leprosy prevalence, i.e., the number of patients on the treatment register (See online additional file Table 3).

To review treatment progress, leprosy patients should ideally be examined every month [33]. During analysis, patients on monthly multidrug therapy (MDT)—the standard leprosy treatment—were aggregated to an annual proxy of leprosy visits, which, as a proportion of annual general outpatient department (OPD) visits, served as leprosy-proportion allocation (See online additional file Table 4) [31]. The term proxy is used because visits can be paid either by patients or by health staff; usually, patients visit PHCs irregularly and receive monthly services such as Multi-Drug therapy (MDT) and a general check-up (treatment-progress review) at their doorstep by field staff [25]. Patients tend to visit health facilities only for more severe medical conditions. It was also the case that PHCs had data only on general OPD visits, which were not classified into leprosy-related visits.

We surveyed one sub-centre in each sampled PHC in DNH and Umbergaon, and considered it as a standard example (See online additional file Table 5). The cost of a standard example was multiplied by the number of sub-centres under the respective PHCs. The sub-centres received medicines and consumables from their respective PHCs, which are covered under PHC costing, therefore excluded in the standard example to avoid double counting.

Using India GDP deflators, all prices were converted to the 2015 (base-year) price. The annual costs were collected for the complete 2015-16 financial year. US dollars (USD) were converted at an exchange rate of INR 67 [34]. Unit costs were derived by dividing the cost by the corresponding service output.

To overcome the small sample size, all costs were bootstrapped with 999 iterations to estimate robust point estimates and confidence intervals. We performed univariate sensitivity analysis with a first scenario of a 25% fluctuation in all cost components (upper and lower side of base estimate). In the second scenario, human resources and drug costs were fluctuated by 80% on lower side and 100% on upper side, and the rest of the components remained as in the first scenario (25% fluctuated on either side). In the third scenario, total programmatic (Local public-health, NLEP and LPEP) contributions fluctuated 25% on either side. The fluctuation percentages were referred from other published literature, specific to primary health care setting in India [20].

The database was created in Microsoft Excel, cost analysis was conducted in SPSS 21, and the sensitivity analysis was conducted using SensIt (TreePlan) in Microsoft Excel.

RESULTS

Profiling PHCs

A total of 8 PHCs were sampled (4 at each site), covering the leprosy-related cost from district to sub-center levels. The DNH had 6 sub-centers and Umbergaon had 9 sub-centers attached per sampled PHC. In DNH, a health centre was staffed by a mean of 47 people; in Umbergaon, the mean was 26. Mean leprosy-related staff (i.e., completely or partially engaged) was 31 in DNH and 23 in Umbergaon, including Accredited Social Health Activists (ASHAs), who are involved actively in NLEP.

The Umbergaon had to cater a higher mean catchment population (40,298) than DNH (27,237) with less staff. Conversely, mean general outpatient visits were higher in DNH (31,318) than in Umbergaon (22,021). The mean number of leprosy visits served by DNH (480) was twice as high as that served in Umbergaon (218). In 2015-16, 53% more new cases were detected in DNH than in Umbergaon. On average, 29,042 contacts of leprosy patients were registered at a PHC in DNH (including those registered in the LPEP programme); in Umbergaon, 38,475 contacts were registered. These covered contacts were close to the total catchment population, as they had been registered largely during the LCDC, which had had a high coverage (Table 2). The mean number of contacts registered per PHC under LPEP was 2,500, and 114 Index cases.

Table 2. Profile of sampled Primary Health Centres in Dadra Nagar Haveli and Umbergaon in 2015-16

S. no.	Characteristics (2015-16)	DNH (n=4)		Umbergaon (n=4)	
		Mean	Range	Mean	Range
2A	Catchment population	27,237	20,644-30,800	40,298	33,500-47,665
2B	Human resources*	47	36-69	26	14-45
2C	Leprosy human resources**	31	20-57	23	17-43
2D	General outpatient visits[8]	31,318	24,400-45,670	22,021	17,280-28,300
2E	Leprosy visits^	480	80-800	218	95-376
2F	New cases detected	55	5-88	36	14-67
2G	Contacts registered under NLEP	26,542	20,644-30,800	38,475	32,561-44,032
2H	Contacts registered under LPEP	2,500	200-4166		NA

The mean refers to an average value per PHC. NA, not applicable.

*Human resources (medical and non-medical staff, and active volunteers) deployed at or below PHC level. This does not include NLEP and LPEP staff.

**Human resources (medical and non-medical staff, and active volunteers) engaged in leprosy services (exclusive or shared). This does not include NLEP and LPEP staff at district level.

[8]The general outpatient visits are the number of visits, not persons.

^Leprosy visits calculated on the basis of leprosy prevalence.

Annual costs

The mean annual cost of providing leprosy services was USD 29,072 (95% CI: 22,125-36,020) in DNH and USD 11,082 (95% CI: 8,334- 13,830) in Umbergaon. HR costs were the single largest component (79% in DNH and 83% in Umbergaon). The cost of drugs (including MDT and SDR) was 10% in DNH and 11% in Umbergaon, and were followed by overhead costs of 8% in DNH and of 4% in Umbergaon.

Table 3 breaks down the annual mean cost of leprosy services under various components. Unlike the proportional cost distributions, the cost estimates differed between the two areas. In Umbergaon, HR costs was 60% lower than in DNH, drug costs were 61% lower, and overhead costs were 80% lower. In DNH, drug costs also included the rifampicin (SDR) used in the LPEP programme.

The cost of MDT was dependent on treatment duration according to the type of leprosy (PB or MB). The number of MB cases was higher in DNH than in Umbergaon (Table 1). Of all components, expenditure on consumables was the smallest, and can be considered as a part of expenditure on drugs or curative care. As capital costs, buildings and equipment together were also relatively low: 2.7% in DNH and 2.6% in Umbergaon (Table 3).

Table 4 shows the annual mean cost of leprosy programme components, at district and sub-centre level. The local public-health system's cost was 51% in DNH and 67% in Umbergaon, which was highest, compared to NLEP and LPEP (as other cost contributors). The NLEP expenditure was 31% in DNH and 33% in Umbergaon, while LPEP accounted for an additional 18% in DNH . The local public-health system cost in Umbergaon was 50% less than DNH; the difference being statistically significant. The NLEP cost in Umbergaon was 59% less than in DNH (Table 4).

Unit cost

The unit cost was derived as a ratio of mean total annual cost (Table 3 or 4) and service output (Table 2) in that year (Table S4). Separately, the LPEP unit cost was derived from the LPEP programme cost only. The unit cost for screening a leprosy patient's contact was USD 1 (95% CI: 0.8–1.2) in DNH (3G/(2G+2H)) and USD 0.3 (95% CI: 0.2- 0.4) in Umbergaon (3G/2G). The number of contacts registered and screened in Umbergaon was 32% higher than in DNH (Table 2). The cost per new case detected and managed was USD 531 (95% CI: 486.7- 575.3) in DNH and USD 312 (95% CI: 292.4- 331.9) in Umbergaon (3G/2F). The unit cost per leprosy visit was USD 60.5 (95% CI: 59.5- 61.6) in DNH and USD 50.9 (95% CI: 50.0- 51.8) in Umbergaon (3G/2E). Under LPEP, the cost per person screened in DNH was USD 2.1 (4C/2H). Out of the total number of contacts screened (10,000) under LPEP, 7,314 contacts received SDR (n=4 PHC DNH) at a unit cost of USD 2.9 (95% CI: 2.5- 3.7).

Table 3. Annual cost of delivering leprosy services in DNH and Umbergaon at primary health centres

S. no.	Annual Cost*	Mean INR (USD)	DNH (n=4)				Mean INR (USD)	Umbergaon (n=4)				*p***
			%	95% CI Lower (USD)	Upper (USD)	Mean INR per leprosy visit (USD)		%	95% CI Lower (USD)	Upper (USD)	Mean INR per leprosy visit (USD)	
3A	Human Resources	1,527,464 (22,798)	78.4	1,215,340 (18,139)	1,839,587 (27,457)	3181 (47.5)	612,748 (9,145)	80.3	450,778 (6,728)	744,181 (11,107)	2814 (42.0)	**0.017**
3B	Equipment	20,528 (306)	1.1	12,768 (191)	28,288 (422)	43 (0.6)	6,405 (96)	1.1	3,062 (46)	9,748 (145)	29 (0.4)	0.089
3C	Drugs	202,834 (3,027)	10.4	111,883 (1,670)	280,991 (4,194)	422 (6.3)	78,950 (1,178)	11.9	53,361 (796)	109,833 (1,639)	363 (5.4)	0.103
3D	Consumables	5,167 (77)	0.3	3,371 (50)	7,107 (106)	11 (0.2)	2,463 (37)	0.5	938 (14)	4,872 (73)	11 (0.2)	0.223
3E	Building	31,827 (475)	1.6	18,867 (282)	44,834 (669)	66 (1.0)	9,720 (145)	1.5	6,076 (91)	13,718 (205)	45 (0.7)	0.101
3F	Overheads	160,021 (2,388)	8.2	99,357 (1,483)	220,684 (3,294)	333 (5.0)	32,200 (481)	5.3	16,257 (243)	49,127 (733)	148 (2.2)	0.052
3G	Total	1,947,841 (29,072)	100	1,482,373 (22,125)	2,413,311 (36,020)	4056 (60.5)	742,490 (11,082)	100	558,392 (8,334)	926,587 (13,830)	3410 (50.9)	0.027

The mean refers to an average value per PHC.

*Comprisingg NLEP and LPEP costs in DNH, and only NLEP cost in Umbergaon.

**ANOVA of Mean INR (USD).

Table 4. Cost of leprosy program components in leprosy service delivery in DNH and Umbergaon

S. no.	Annual Cost	DNH (n=4) Mean INR (USD)	%	95%CI Lower (USD)	95%CI Upper (USD)	Mean INR per leprosy visit (USD)	Umbergaon (n=4) Mean INR (USD)	%	95%CI Lower (USD)	95%CI Upper (USD)	Mean INR per leprosy visit (USD)	*p**
4A	Local public-health	987,417 (14,738)	51	785,463 (11,723)	1,216,480 (18,156)	2056 (30.7)	494,719 (7,384)	67	380,520 (5,679)	557,880 (8,327)	2272 (33.9)	**0.004**
4B	NLEP	608,817 (9,087)	31	75,535 (1,127)	971,646 (14,502)	1268 (18.9)	247,771 (3,698)	33	102,480 (1,530)	441,798 (6,594)	1138 (17.0)	0.133
4C	LPEP	351,608 (5,248)	18	32,060 (479)	566,808 (8,460)	732 (10.9)				NA		NA
4D	Total	1,947,841 (29,072)	100	1,482,373 (22125)	2,413,311 (36,020)	4056 (60.5)	742,490 (11,082)	100	558,392 (8,334)	926,587 (13,830)	3410 (50.9)	**0.027**

Costs included IEC, training and other benefits; Leprosy visits are derived from prevalence. The 'mean' refers to an average value per PHC. LPEP, Leprosy Post-exposure Prophylaxis (LPEP) program. NA, not applicable; NLEP, National Leprosy Eradication Program.
*ANOVA of Mean INR (USD).

Sensitivity analysis

The univariate sensitivity analysis was performed to estimate the difference between the expected value and the observed value of total annual cost, based on the uncertainty of a specific cost component. The scenarios were 1) 25% fluctuation in all cost components, 2), human resource and drug costs fluctuated by 80% on lower side and 100% on upper side, 3) total programmatic contributions fluctuated 25% on either side. The total annual cost of the leprosy programme was most sensitive to HR; in DNH this was 97.2% for scenario 1 and 98.2% for scenario 2, against 98.1% for scenario 1 and 98.3% for scenario 2 in Umbergaon. In scenario 1, a fluctuation of 25% in HR cost resulted into 19.2% and 20.6% fluctuation in the total cost of DNH and Umbergaon, respectively. In scenario 2, a reduction of 80% in HR cost resulted into 62.7% and 66% reduction in the total cost of DNH and Umbergaon. Further, a 100% increase in HR cost resulted in 78.4% and 82.5% increase in the total cost of DNH and Umbergaon.

Drugs were the next most influential component for total cost (DNH: 1.7% for scenario 1 & 2; Umbergaon: 1.6% for scenario 1 & 2). There was little variation in the percentage between the two scenarios for HR and drugs in both areas, meaning that the total cost had a low threshold level with respect to HR and the change in the cost of drugs. Changing the cost of building, equipment, and consumables had a negligible impact on the total cost. In scenario 3, the total cost was most sensitive to the local public-health system cost (66.4% in DNH and 79.9% in Umbergaon), followed by NLEP (25.2% in DNH and 20.1% in Umbergaon). A fluctuation of 25% in the local public-health system and NLEP cost resulted into fluctuation of 12.7% and 7.8% in the total cost of DNH, respectively, and 16.7% and 8.3% in Umbergaon. The LPEP total cost for DNH had a swing of 8.4% with respect to the induced variation (See online additional file Figure 1 and 2). Changing the LPEP cost by 25% resulted into a fluctuation of 4.5% in the total cost.

DISCUSSION

By quantifying expenditures, this study provides a detailed cost analysis of leprosy primary care in two different public-health settings in India. The results informs about the allocative efficiency which is important for policy planning, aiming at the improvement of the leprosy control programme. As leprosy is a chronic disease whose treatment duration ranges from 6-12 months, primary care is an important aspect of disease management. Primary health centres are the nodal points for public-health care and for managing programmes at the grass-roots level.

Indian leprosy services are now largely integrated into the general public-health system [1]. Previously, the country's National Leprosy Eradication Programme (NLEP) was fully vertical, providing separate human resources and infrastructure to leprosy services, which later merged into the general health care. Nonetheless, NLEP still provides limited vertical support, especially to highly endemic areas, mainly for the following: non-capital expenditure on diagnostics; disability (rehabilitation, reconstructive surgeries and prosthetics); Information Education and Communications (IEC); additional human resources; and research. It is also the case that a network of non-governmental organizations (NGOs) supports various activities in line with the NLEP, including the implementation of pilot projects. The three main financial contributors in leprosy elimination are therefore the local public-health system, NLEP and NGOs. At district level, these financial contributors have their programme management teams support local public-health system (PHCs and Sub-centres) to provide leprosy services.

Although the two neighbouring study areas are comparable with regard to demographic and socioeconomic factors, DNH had better resources and detected more leprosy cases than Umbergaon. The number of new cases depends not only on endemicity levels, but also on active case-finding inputs, which are resource intensive. DNH is more active in case finding because it has an additional research project, LPEP, which facilitates active case detection and contact examination. However, LCDC also contributes to new case detection (in both areas), but the contact examination is more thorough in LPEP because it requires ineligible individuals to be excluded from taking single does rifampicin. Furthermore, the leprosy case-detection campaigns (LCDC) are implemented in a periodic and rapid (campaign) mode, reaching almost the full population within a short period (1-2 months per campaign), whereas LPEP is a continuous three-year project. As a result, LCDC covers a higher number of contacts than LPEP.

The mean annual cost of providing leprosy services was USD 29,072 in DNH and USD 11,082 in Umbergaon. The higher PHC cost in DNH was due mainly to the additional cost of LPEP and to a higher proportion allocation (See online additional file Table 4). The higher HR cost in DNH was mainly due to the higher time spent on leprosy (reported) by staff, and also higher remuneration scale. However, when accounted for output (leprosy visit), the percentage difference between the costs of DNH and Umbergaon fell dramatically. The percentage difference in the total mean costs was 90%, whereas mean costs per leprosy visit were only 17% different between DNH and Umbergaon (Table 3). This means that the higher cost in DNH was related more productivity. Next, the total cost of the NLEP was low in Umbergaon because it is a block whose resources are shared with rest of the Valsad district. The percentage difference in the mean NLEP costs was 84%, whereas NLEP costs per leprosy visit were only 10.6% different between DNH and

Umbergaon. Interestingly, the local public-health cost per leprosy visit was cheaper by USD 3.2 in DNH than Umbergaon. As exclusive public contribution, the aggregated unit cost (per visit) of Local public-health and NLEP was still USD 1.2 cheaper in DNH than Umbergaon. Certainly in the short run, LPEP masked the savings in DNH, but as an investment in prevention, it can still be cost-effective in the long run (See online additional file Table 6). Moreover, DNH investment in active case finding leads to early detection, and prevention of new cases. In future, this will also save cost (opportunity) of other governmen programmes such as poverty eradication, malnutrition, and disability support. Additionally, out of pocket expenditure in leprosy by households will also be saved in the long run. Our study only focused on the health system cost, but we recommend exploring opportunity costs, as there are not many data available, and required to measure the economic burden of leprosy. In both DNH (79%) and Umbergaon (83%), HR was the highest cost element. These high HR costs are in line with similar studies [2]. Capital cost, in contrast, turned out to be one of the lowest cost elements: 2.7% in DNH and 2.6% in Umbergaon. This high HR cost is due to the fact that national programme at primary care level is a field-driven public-health programme that provides services close to the community. The implementation of such programmes needs higher investment in HR rather than in fixed infrastructure (See online additional file Table 7). Patients also prefer to visit health facilities only for essential curative care such as acute co-morbidity or leprosy reactions, and remain non-regular for routine health check-ups. The afflicted population is mainly poor, and indirect costs such as wage loss and transportation are a disincentive for them to pay health-centre visits [3]. The same study informed that the out-of-pocket expenditure due to leprosy was lower in DNH than Umbergaon [3]. If aligned with our study results, then we can infer that an enhanced health system is comparatively costly, particularly due to the investment in prevention, but it also reduces the out-of-pocket expenditure burden on the households.

At micro level, we also observed that the low endemic PHCs are not necessarily relatively cheap, mainly due to fixed costs such as building and equipment and partially due to monthly recurrent salary cost.

The local public-health system is the backbone of leprosy service delivery. The cost of local public-health system was the highest (51% in DNH and 67% in Umbergaon), followed by NLEP and LPEP. Next, the unit costs can be used to estimate the budget by applying it to the desired level of coverage, but they are not the indicator for efficiency, therefore should not be interpreted as cost-effectiveness of programmes. Moreover, all unit costs are derivatives of the same overall programme cost and coverage (process indicators). A more realistic approach to determining financial efficiency would be to compare costs with impact indicators using an appropriate time horizon

[4]. Usually, when an infectious disease programme approaches elimination, it becomes more resource intensive, but, if it possible to eliminate or eradicate the disease, is still considered worthwhile [5].

The discussed results can provide basis to budget and financing. Due to the increased political commitment, the funds allocation for PEP should be not a problem, but, a possible financial issue can be the timely fund flow. More budget for HR means new recruitment which is a lengthy process due to governmental regulations. This can lead to under spending in the initial years, and adversely affecting the prospective budgets for PEP. More HR also means more training, therefore the general training budgets should also be revised accordingly. In general, there is a shortage of cost evidence on leprosy elimination for policy and planning [6]. To the best of our knowledge, this is the first comprehensive costing study to take a public-health-system perspective on leprosy primary care in India. Two of only 3 studies to present some costing results were based on hospitalization, and not on primary care. The third study, which focused on leprosy case-detection methods in Nigeria [7], was relevant, but, unlike our study, also included hospital costs. Another cost-effectiveness study from Bangladesh presented MDT treatment programme costs, with and without post-exposure prophylaxis (SDR) [8]. Although—in line with our own results—both the Nigerian and Bangladeshi studies reported HR cost as the largest component, the actual costs were not comparable due to the differences in epidemiology, unit of analysis and scope of the study. Another difference is that our study focused on primary care, whereas the other two were designed to evaluate specific activities of leprosy control. An another costing study on the PHCs (all diseases) of north-Indian states, also mentioned HR cost as the single largest component [2].

A limitation of our method is that our purposive selection of PHCs to assure representation of low and high performing PHCs may lead to a selection bias thus may not be representative of the actual distribution of low, medium and high performing PHC in the areas. This in turn may lead to a deviation in cost estimates if extrapolated to full district/ Union Territory or province. The cost difference between the two public-health settings indicates further cost variation within India as a whole. The random sampling would either not be a suitable approach due to very small number of PHCs in the selected areas. The effect of small sample size of PHCs was minimized by the bootstrapping method. As another limitation, HR time allocation was based on self-reporting rather than on observation, which would have been a better approach. Next, the NLEP and LPEP cost data were only available for full district level. To break-down the NLEP and LPEP costs for sampled PHCs, we used the unit cost per new cases on the assumption that new case detection solely depends on active case-finding efforts and pumped

resources. In reality, new case detection also depends on epidemiology, socioeconomic and environmental factors. However, as the two areas were close with regard to epidemiologic and socioeconomic characteristics, we believe that this risk was minimal in our study. The environmental factors were also fairly similar: the two areas adjoin, are both very small, and have no great geographical differences. As strength, we used an appropriate costing methodology and our collection of primary data for a complete year to minimize any seasonal variations.

CONCLUSION

We conclude that, due to differences in public-health system financing and structure, the annual leprosy cost at primary care level varies between areas of even comparable epidemiology. Our study shows that the setting with an enhanced public-health financing system invests more in leprosy services and prevention than that with more limited financial resources. The enhanced public-health system overall appears costly, but when accounted for productivity, it no more remains expensive. Additionally, it also facilitates reduction in out-of-pocket expenditure among households. Therefore, we recommend to invest in the health system for prevention and increased access services, which will promote early detection and transmission interruption. According to public-health norms in India, more resources are still needed to cover the population at risk, these costs should also be seen as an input that will strengthen the overall health system. Both systems invested mainly in human resources. In both the areas, the investment in human resources translates into active outreach programmes, particularly contact screening. The high investment in HR is essential to follow the global WHO leprosy guidelines sincerely [39].

We found that post-exposure prophylaxis as addition to the control programme is resource intensive. However, once post-exposure prophylaxis has been implemented in a routine setting, the costs are expected to fall. The WHO has recently recommended to use SDR for leprosy prevention, which will trigger scale-up of post-exposure prophylaxis [9]. Our results can immediately guide the fiscal planning during scale-up in India, and SDR role-out in other countries after considering the local economies. The relatively low unit cost of contact screening favors its sustainability in the programme, however, this does not mean that contact tracing should be avoided even if costly. In general, leprosy work is facing financial constraint since the global declaration of leprosy elimination. These results are promising for advocacy and fundraising, especially in support of SDR. The unit costs are of much interest for funding agencies to reimburse on case bases, and to plan a flexible investment with a measurable value of return.

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ONLINE LINKS TO THE ADDITIONAL FILES

tmi13182-sup-0003-TableS1-S7.docx
tmi13182-sup-0001-FigS1.docx
tmi13182-sup-0002-FigS2.docx

Description: Mahatma Gandhi nursing Parchure Shastri, the great Sanskrit scholar who suffered from leprosy.
Source: NLEP India report

7 Leprosy Post-Exposure Prophylaxis in the Indian Health System: A Cost-Effectiveness Analysis

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PLoS Negl Trop Dis (2020) 14: e0008521.

ABSTRACT

Introduction

India has the highest burden of leprosy in the world. Following a recent WHO guideline, the Indian National Leprosy Programme is introducing post-exposure prophylaxis with single-dose rifampicin (SDR-PEP) in all high-endemic districts of the country. The aim of this study is to estimate the long-term cost-effectiveness of SDR-PEP in different leprosy disability burden situations.

Methods

We used a stochastic individual-based model (SIMCOLEP) to simulate the leprosy new case detection rate trend and the impact of implementing contact screening and SDR-PEP from 2016 to 2040 (25 years) in the Union Territory of Dadra Nagar Haveli (DNH) in India. Effects of the intervention were expressed as disability adjusted life years (DALY) averted under three assumption of disability prevention: 1) all grade 1 disability (G1D) cases prevented; 2) G1D cases prevented in PB cases only; 3) no disability prevented. Costs were US$ 2.9 per contact. Costs and effects were discounted at 3%.

Results

The incremental cost per DALY averted by SDR-PEP was US$ 210, US$ 447, and US$ 5,673 in the 25th year under assumption 1, 2, and 3, respectively. If prevention of G1D was assumed, the probability of cost-effectiveness was 1.0 at the threshold of US$ 2,000, which is equivalent to the GDP per capita of India. The probability of cost-effectiveness was 0.6, if no disability prevention was assumed. The cost per new leprosy case averted was US$ 2,873.

Conclusions

Contact listing, screening and the provision of SDR-PEP is a cost-effective strategy in leprosy control in both the short (5 years) and long term (25 years). The cost-effectiveness depends on the extent to which disability can be prevented. As the intervention becomes increasingly cost-effective in the long term, we recommend a long-term commitment for its implementation.

INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae* affecting mainly the skin and peripheral nerves, and may lead to life-long disability when untreated. Three disability grades are recognized: grade 0 (no disability); grade I disability (G1D); and grade II disability (G2D), the latter being more severe including visible deformities. Globally, 208,619 new cases were detected in 2018 [1]. Due to a long incubation period [2], an infected person may remain asymptomatic and undetected for a long time and can transmit the bacteria to others. The introduction of multidrug therapy (MDT) in the 1980s substantially decreased prevalence of the disease, but the new case detection rate (incidence) remained almost stagnant [3]. Therefore, the goal of leprosy elimination and past investments into this goal are at risk [4].

In India, 18.7% districts are still reporting more than one new case per 10,000 population. The National Leprosy Eradication Programme (NLEP) aims to eliminate leprosy in these high-endemic districts [5]. There are, however, important challenges to interrupt transmission of *M. leprae*. The current leprosy burden is underestimated and needs correction by accounting for hidden cases [6, 7]. Active case finding needs to be intensified for early detection and treatment. The available prevention methods, such as post-exposure prophylaxis through single-dose rifampicin (SDR-PEP) needs a scale-up to demonstrate its impact. This is challenging [8], as countries need information for the introduction of new interventions such as on the cost-effectiveness, duration of implementation, expected outcomes, and uncertainties.

SDR-PEP was field-tested in the Union Territory of Dadra and Nagar Haveli (DNH) between 2015 and 2018 as part of the Leprosy Post-Exposure Prophylaxis (LPEP) program [9]. The LPEP program was designed to assess the feasibility and impact of contact tracing and SDR-PEP to asymptomatic contacts of leprosy cases [10]. The necessary complementary activities to the routine leprosy programme were contact listing, screening, and follow-up. Additionally, LPEP also increased the awareness of leprosy in the community [9]. In DNH a total of 30,295 contacts received SDR-PEP between 2015 and 2018. The distribution of SDR-PEP is currently ongoing, but now as a routine activity under NLEP.

The LPEP program systematically captured relevant data that can guide the scale-up of the intervention [9, 11]. The actual impact of SDR-PEP however, is difficult to observe in a three-year programme, because of the existing backlog of leprosy cases. Therefore, we use mathematical modelling to estimate the long term impact of SDR-PEP on the NCDR. The aim of this study is to estimate the long-term cost-effectiveness of SDR-PEP in different leprosy disability burden situations. The results can assist governmental

and non-government organisations in planning their investment for leprosy control and ultimately contribute to a global investment case for leprosy elimination [12].

METHODS

Ethics statement

The study was conducted under the Leprosy Post Exposure Prophylaxis (LPEP) program, approved in India by the Institutional Human Ethics Committees of the National Institute of Epidemiology (NIE/IHEC201407-01).

Study setting

DNH is highly endemic for leprosy with the highest annual new case detection rate (ANCDR) in India in 2017 [13, 14]. Until recently DNH also had a high number of child cases, which is considered an indication of active transmission of *M. leprae* [13]. More than half of the DNH population is tribal (Census 2011), living mostly in rural areas with limited resources. Despite the highest ANCDR in DNH, the G2D rate is low (0.37% of all new cases) compared to other endemic parts of India [14]. In DNH, the uptake of leprosy services and public health expenditure is better than the neighbouring areas [15, 16]. The supplemental S1 Table provide detailed information on demography, socioeconomics and epidemiology of DNH.

Model description

We used the stochastic individual-based model SIMCOLEP to predict trends of the new cases per 100,000. The model simulates life-histories of individuals and the spread of *M. leprae* in the population in DNH. Transmission can occur when an infectious individual has contact with a susceptible individual. Two transmission processes are modelled separately: transmission in the general population and within-household. The latter reflects the increased risk of transmission among close contacts. The natural history of leprosy was modelled following the same methodology as described in Fischer *et al*. 2010 and Blok *et al*. 2015 [17, 18]. In the model, infected individuals can develop either paucibacillary (PB) or multibacillary (MB) leprosy following the observed MB / PB ratio (i.e. 26/74). In the model, PB leprosy cases are assumed to self-heal with a rate of 20% per year, while MB leprosy remains chronic until detection and treatment (S2 Table). Leprosy control includes passive case detection and treatment with multidrug therapy (MDT), and additional active case finding activities such as contact tracing and survey. In the model, the quality of the control programme is reflected by detection delays, and active case finding activities are specified using annual coverage rates.

The model was fitted to the leprosy trends in DNH. The model was quantified with demographic data from the census (S3 Table). The model was then fitted to the household size distribution in DNH (Figure S1). The transmission risk (i.e. contact rate) and the passive case detection delays mimic historic NCDR trends (S2 Table). Data were used from NLEP for the period 1995-2015. The model was first calibrated to data points until 2012, then validated for the years 2013-2015 (Figure S2). After validation, the model was calibrated using the complete dataset. This was regarded as the situation of continuation of the routine national programme prior to the introduction of the LPEP program. Projections of the NCDR trend were based on 1,000 runs.

Modelled scenarios

We compared two scenarios: A) the SDR-PEP intervention; and B) the continuation of the routine programme. The SDR-PEP intervention represents the LPEP program in addition to the ongoing NLEP in DNH. The necessary complementary activities to the routine leprosy programme were contact tracing, screening, and follow-up. SDR-PEP was provided to contacts without leprosy or other contra-indications. A contact detected with leprosy during screening was referred for MDT treatment. Contacts were listed retro- and prospectively. Retrospective tracing includes contacts from leprosy patients diagnosed up to 2 years prior to the intervention programme in 2015. Additionally, the programme also increased the awareness of leprosy in the community [9]. On average, 26 contacts were screened per index patient. Based on results from the COLEP trial, we assumed that the effectiveness of SDR-PEP was higher among neighbours and social contacts (70%) than household contacts (50%) [19].

Predictions of the number of new MB and PB leprosy cases were made from 2015 until 2040 for the SDR-PEP intervention and the routine programme scenario (Figure S3). Using age proportions of leprosy patients in DNH of the last 6 years (2013-2018), the modelled new MB and PB leprosy cases were apportioned into five age groups: 0-4, 5-14, 15-44, 45-59, and 60+ years. We also predicted the annual number of contacts that received SDR until 2040 (Figure S4).

Disability-adjusted life years

Health effects were measured as disability adjusted life years (DALYs). Leprosy disability weights were obtained from the global burden of disease study (GBD 2017), which were 0.011 for G1D and 0.067 for G2D [20]. We assumed that disability is irreversible and that leprosy does not cause any mortality; therefore, the DALY is equal to years lived with disability (YLD). The DALYs were calculated as follows:

$$DALY(t) = \sum_{a=1}^{n_a} (IG1D(a,t) \cdot DG1D \cdot (a)) + (IG2D(a,t) \cdot DG2D \cdot L(a))$$

With:

n_a= number of age groups (0-4, 5-14, 15-44, 45-59, 60+ years);

I_{G1D} $(a,t)/I_{G1D}(a,t)$= Number of cases with G1D / G2D per 100,000 in age group a at time t;

D_{G1D}/D_{G2D} = Disability weights for G1D/G2D;

$L(a)$ = Life Expectancy of age group a. Data obtained from SRS Based Life Table 2011-15, Census of India

The annual number of new cases with G1D and G2D in the SDR-PEP intervention and routine scenario were estimated using the modelled new MB and PB leprosy cases per year. Since no data were available on the proportion of new cases with G1D and G2D among PB and MB leprosy cases, we made the following assumptions to calculate the number of cases with G1D and G2D:

1. 3.6% of total leprosy cases have G2D (following the reported statistics on leprosy in India [14]; all G2D cases emerge from MB leprosy cases.
2. All remaining MB leprosy cases have G1D.
3. 50% of the total PB leprosy cases have G1D.
4. All remaining PB leprosy cases have no disability.

As the SDR-PEP intervention scenario includes active contact tracing and screening, it is highly likely that the time until diagnosis would be reduced, which would prevent (progression to) disability. To account for this in the SDR-PEP intervention, we calculated DALYs under three assumptions of disability prevention (Table 1):

1. Prevention of all G1D cases.
2. Prevention of G1D in PB cases only.
3. No additional prevention (i.e. same as routine scenario).

Table 1. Assumptions to estimate disease burden in the routine and SDR-PEP intervention scenario.

Assumptions	Routine	SDR-PEP intervention		
		Assumption 1: All G1D cases prevented	Assumption 2: G1D cases prevented in PB cases only	Assumption 3: No disability prevented
1. 3.6% of total leprosy cases have G2D (emerged from MB leprosy cases)	Included	Included	Included	Included
2. All remaining MB leprosy cases have G1D	Included	Prevented by intervention	Included	Included
3. 50% of PB leprosy cases have G1D	Included	Prevented by intervention	Prevented by intervention	Included
4. All remaining PB leprosy cases have no disability	Included	Included	Included	Included

Note: The shaded cells indicate whether the assumption was included in the analysis or not

Costs

Costs of the intervention included the cost of contact listing, tracing, screening, and drug, and were calculated from the perspective of the health system. The composite cost for SDR-PEP intervention was estimated to be US$ 2.9 (95% CI: 2.5- 3.7) per contact [16]. The cost per contact was sampled 1,000 times and multiplied with the modelled number of contacts that received SDR-PEP to calculate the total costs of the intervention in DNH per year.

Cost-effectiveness analysis

Cost-effectiveness of the SDR-PEP intervention was assessed using incremental cost-effectiveness ratios (ICERs):

$$ICER = \frac{Cost_{SDR-PEP} - Cost_{Routine}}{DALY_{SDR-PEP} - DALY_{Routine}}$$

DALYs and costs were cumulative and both discounted at 3%. The time horizon was 25 years, i.e. 2016 to 2040, and cost-effectiveness was assessed at five-year intervals. We applied a willingness to pay (WTP) threshold equal to one and three times the GDP per capita of India 2017 as, i.e., $2,000 and $6,000, respectively, following the suggestion of the WHO [21]. If results were cost-effective at $2,000, we did not present the results using a threshold of $6,000. Using cost-effectiveness acceptability curves (CEAC), we assessed the probability of the SDR-PEP intervention to be cost-effective against a range of willingness-to-pay thresholds. This depicts the uncertainty associated with the results. [21, 22]. Additionally, we also calculated the incremental cost per new leprosy case averted by SDR-PEP. We used the BCEA package in the software R 3.6.1 for the analysis [23].

RESULTS

Figure 1 shows the trend in annual cost of SDR-PEP implementation for the next 25 years (Figure 1A) and model predicted new cases detection rate per 100,000 persons (Figure 1B). As the number of SDR-PEP for contacts depends on the number of new cases, both graphs showed a declining trend. In the first year, the cost was on average $16,000, but subsequently dropped to around $600 in the last five years due to the decreasing numbers of new leprosy patients. On average, the cost decreased by 11 % annually over 25 years. The percentage decrease was highest in the 2nd year (74.1%) and least in the 23rd year (4.9%).

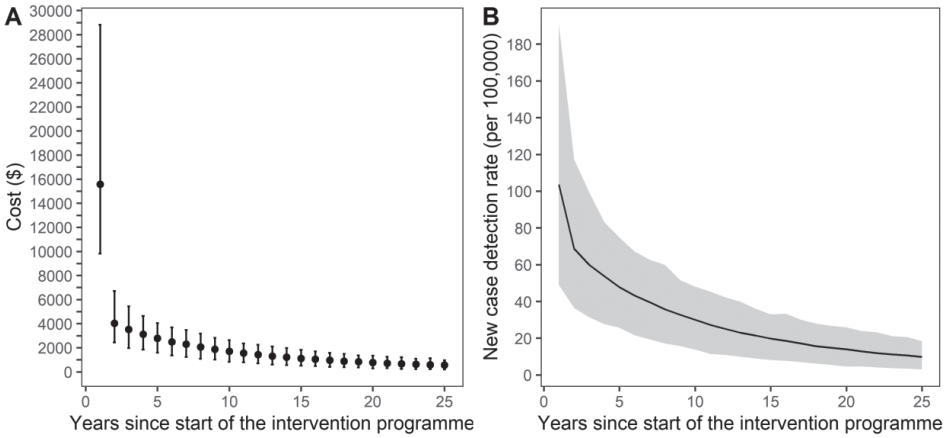

Figure 1. SDR-PEP intervention (A) estimated cost and (B) predicted new cases detection rate per 100,000 persons. (A) *Points represent the mean cost in US$ per year and the error bars represent the 95% uncertainty interval based on 1,000 simulation runs. (B) The black line represents the mean new case detection rate and shaded region represents the 95% uncertainty interval based on 1,000 simulation runs.*

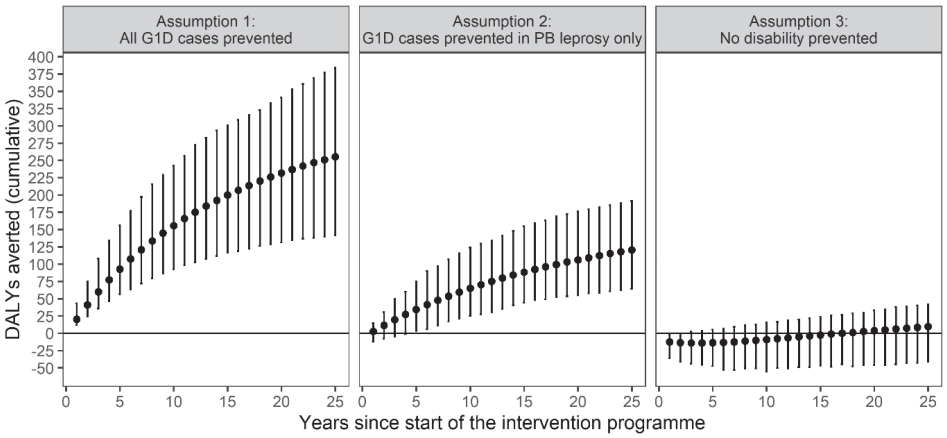

Figure 2. Estimated cumulative DALYs averted as a result of the SDR-PEP intervention under three assumptions of disability prevention. Points represent the mean cumulative DALYs averted per year. The error bars represent the 95% uncertainty interval based on 1,000 simulation runs.

Figure 2 shows the trend in averted DALYs as a result of the SDR-PEP intervention under three assumptions of disability prevention. Over a period of 25 years, the number of averted DALYs were 250, 65 and 10 when assuming prevention of all G1D cases, prevention of G1D case in PB leprosy cases and no prevention of disability, respectively.

Figure 3A presents the incremental cost and effect in the 25th year of the intervention. The incremental cost to avert one DALY was US$210, US$447 and US$5,673 if

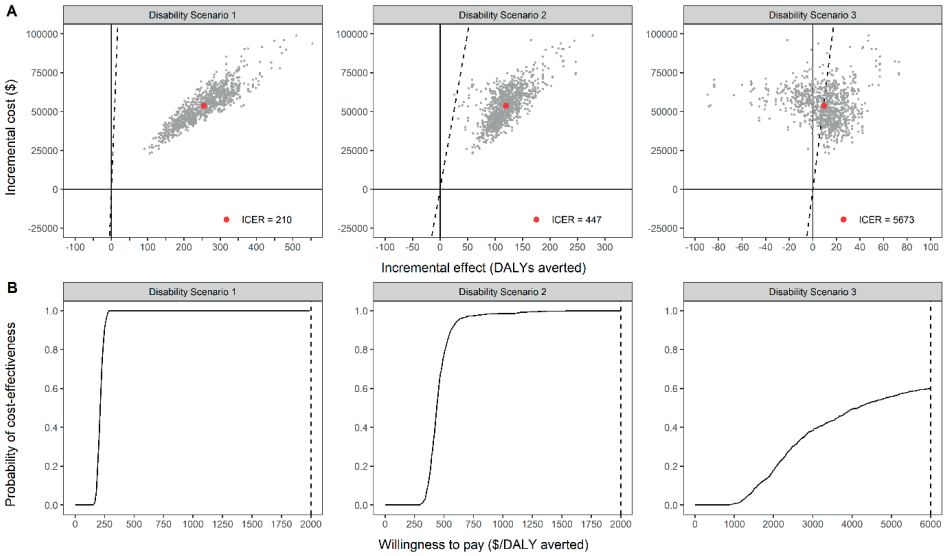

Figure 3. Cost-effectiveness plane and acceptability curve of assumption 1-3 at 25th year. *(A) Red dot represents the incremental cost-effectiveness ratio, and dotted line represents the threshold. (B) Blackline represent the cost-effectiveness acceptability curve.*

we assumed prevention of all G1D cases, prevention of G1D case in PB leprosy cases and no prevention of disability, respectively. The probability of cost-effectiveness at a willingness to pay threshold of US$2,000 was 100% in the two scenarios with assumed prevention of disability (Figure 3B). In the scenario without prevention of disability, there is 60% chance that the intervention is cost-effective given a willingness-to-pay threshold of US$ 6,000. The cost per new leprosy case averted was US$ 2,873.

Table 2 provides results at five-year time intervals. In the assumption 1 and 2, the incremental cost to avert a DALY remained under the WTP threshold of US$ 2,000 in all the intervals. There was a high probability (CEAC 0.94-1.00) that the result remains cost-effective under uncertainty. In both assumptions, the SDR-PEP intervention becomes more cost-effective with increasing time horizon. In assumption 3, which was conservative in assuming the reduction in disability as a result of the intervention porgramme, the incremental cost-effectiveness ratio crossed US$ 2000 but remained below WTP threshold of US$ 6000. The probability of the intervention to be cost-effective was 0.6 at the 25th year.

In a sensitivity analysis, we explored what the proportion of G1D prevented should be in order for the intervention to be cost-effective with a 90% probability. The break point is at 40% of G1D prevented in PB cases.

Table 2. SDR-PEP incremental cost-effectiveness ratio and probability of cost-effectiveness at five year intervals.

Time horizon in years		Assumption 1: All G1D cases prevented*	Assumption 2: G1D cases prevented in PB cases only*	Assumption 3: No disability prevented**
	ICER (US$/DALY averted)	210	447	5,673
25	Probability of cost-effectiveness	1.00	1.00	0.60
	ICER (US$/DALY averted)	218	476	
20	Probability of cost-effectiveness	1.00	1.00	
	ICER (US$/DALY averted)	230	521	
15	Probability of cost-effectiveness	1.00	0.99	
	ICER (US$/DALY averted)	253	607	
10	Probability of cost-effectiveness	1.00	0.98	
	ICER (US$/DALY averted)	312	843	
5	Probability of cost-effectiveness	1.00	0.94	Dominated

* Willingness to pay threshold: $2000
** Willingness to pay threshold: $6000
ICER: Incremental cost-effectiveness ratio

DISCUSSION

The aim of this study was to estimate the cost-effectiveness of SDR-PEP in different leprosy disability burden situations. The SDR-PEP intervention was very cost-effective when we assumed that G1D cases could be completely or partially prevented. In those cases, the cost-effectiveness was attained within the first 5 years, which indicates that SDR-PEP can be quick in returning the investment. Even when no prevention of disability was assumed, the ICER remained below the willingness-to-pay threshold, but only in the long term.

The annual cost of SDR-PEP implementation was highest at the start of the intervention and decreased sharply over time. The SDR-PEP intervention will not be resource-intensive for a long time and the cost may come down to an affordable level for the general health care system within 7-10 years of implementation (Figure 1A). The 'cost per new leprosy case averted' was high, but this measure cannot be considered similar to cost-effectiveness, because WHO guidelines on cost-effectiveness analysis allow conclusions only on 'DALYs averted' and not on 'cases prevented' [21]. However, the cost per case is useful for programme planning and case base reimbursement.

Our results highlight that the assumptions regarding prevention of disability due to SDR-PEP implementation have a large impact on the cost-effectiveness of the intervention. From literature, we know that active case finding with robust screening reduces

detection delay of leprosy, thus preventing disabilities [11]. Additionally, prevention projects increase awareness in communities, which increase self-reporting and further reduce detection delay and disability [24]. The quality of screening is also better when accompanied with the distribution of a drug (SDR-PEP), because of the strict need to establish contra-indications and avoid adverse events [9, 25]. To be conservative, we only included assumptions on preventing G1D in the analysis. Prevention of all G1D can be regarded as optimistic, while prevention of some (e.g. 50%) G1D is a more realistic assumption. We did not assume any prevention of G2D (i.e. 3.6% of total cases remained G2D). It is, however, reasonable to assume that this proportion might go down too, especially in the long term. This would result in a higher number of DALYs averted, especially in areas reporting a high proportion of G2D such as Chhattisgarh (4.3%) and Andhra Pradesh (4.8%) [14]. Even when we assumed no prevention of disability, the ICER was below the WTP threshold of $6,000, which was cost-effective, but with a low probability of cost-effectiveness under uncertainty. However, the gap to achieve a high level of probability was not large.

Besides epidemiology, methodological factors can also influence cost-effectiveness. The first factor is the selection of a threshold. According to the WHO CHOICE guidelines, an ICER below GDP per capita is very cost-effective and below the three times of GDP per capita it is cost-effective [21]. Despite being commonly used, this rule is also criticized [26, 27]. Especially in low and middle income country settings, the suggested WTP threshold might be too optimistic. However, even if we would have assumed a WTP threshold that is equal to 50% of the GDP (i.e. US$ 1,000), the SDR-PEP intervention remains cost-effective if prevention of disability is taken into account. Formally the recommendation is to use the value of a statistical life (VSL). Because VSL accounts for productivity and consumption, it is higher than the GDP per capita [28, 29]. Further, some studies used GDP per capita at purchasing power parity (PPP), which is also higher than the GDP per capita constant [30].

The second factor is the disability weights (i.e. G1D = 0.011 and G2D = 0.067). In fact, these weights are not specific for leprosy and are generally considered to be too low [20]. As a result, the number of DALYs averted in this study is underestimated. It is important that leprosy disability weights should be updated and account more realistically for mental health problems, discomfort and reduced mobility due to leprosy [4, 31]. Nevertheless, our estimates are in-line with GBD 2017 because we used the same disability weights.

To our knowledge, this is the first leprosy specific publication that presents the results of an cost-effectiveness analysis in DALYs averted. Existing leprosy cost-effectiveness stud-

ies measured effects in terms of cases or consequences prevented [32-34]. The COLEP study looked at the cost-effectiveness of SDR-PEP in Bangladesh. This study reported an ICER of $158 per leprosy case prevented, ICER $214 in neighbours of neighbours and social contacts, ICER $497 in next-door neighbours, and ICER $856 among household contacts.

There are limitations to this study. First, our analysis has a health system and not a societal perspective. The patient's opportunity cost to avail the SDR-PEP was not considered in the analysis. Second, the cost-saving by preventing cases and disabilities were not considered in the analysis. Third, data on the G1D proportion out of total disabilities was not available at any level. We could therefore not model this figure, but needed to assume the value. Finally, our results are only applicable to the Indian setting where contact tracing is formally part of the national programme, but its implementation level may vary in different states. The results are not necessarily applicable to other countries as the leprosy epidemiology and cost may vary considerably. We therefore recommend similar studies in the other endemic countries for global generalizability.

CONCLUSION

We conclude that contact listing, screening and the provision of SDR-PEP is a cost-effective strategy in leprosy control in both the short (5 years) and long term (25 years). The cost-effectiveness of the SDR-PEP intervention depends on the extent to which disability can be prevented. As the intervention becomes increasingly cost-effective in the long term, we recommend a long-term commitment for the implementation of this intervention.

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ANNEXURES

S1 Table. Pre and post LPEP comparison of Dadra and Nagar Haveli (DNH) on demography, socio-economics and epidemiology.

DN Indicators	2011	
Demographic and socio-economic indicators		
Population	343,709	
Population growth (1991-2011)	57.4 %	
Females (per 1000 males)	774	
Scheduled tribes†	51.9%	
	Pre-LPEP (2014-15)	**Post LPEP (2018-19)**
Epidemiology		
Population*	409,015	424,394
New leprosy cases detected	318	75
NCDR (per 100 000 per year)	77.7	59.9
Grade II disability in new cases	2% (4.89 per million)	Not available
New child cases (age <14 years)	66 (20.7%)	16 (Not available %)
New female cases	57.5%	Not available
Prevalence/Registered patient rate (per 10,000 per year)	5.0	3.55
Multibacillary (MB) leprosy	35.8%	Not available

Sources: Census 2011 and NLEP reports
NCDR: new case detection rate
† The Scheduled Castes (SCs) and Scheduled Tribes (STs) are officially designated groups of historically disadvantaged indigenous people in India.

S2 Table. Epidemiologic data and parameters to quantify the model

Data	Years	Source
Epidemiologic data		
New case detection rate	1995-2015	NLEP India [1]
MB / PB ratio of new cases	1995-2015	NLEP India [1]
BCG coverage	1980-2011	WHO [2]
Parameters	**Value**	**Source**
Natural history of infection		
Proportion susceptible	20%	Assumption
MB / PB ratio	26 / 76	NLEP India [1]
PB subclinical duration mean	4.2 years; SD =1.9 (gamma distributed)	Fischer et al. 2010 & Fine 1982 [3, 4]
PB self-healing rate	20% per year	Fischer et al. 2010 & Sirumban et al. 1988 [3, 5]
MB subclinical duration mean	11.1 years; SD = 5.0 (gamma distributed)	Fischer et al. 2010 & Fine 1982 [3, 4]
Treatment		
MDT use	1990 onwards	

S2 Table (*continued*)

Data	Years	Source
MDT relapse rate	0.01 per year To MB: 90% To PB: 10%	
Transmission		
Infectivity function		Meima et al. 2004 [6]
PB	0	
Asymptomatic MB	Linear from 0 to 1	
Symptomatic MB	1	
Transmission rate		
General population	(3, 7)[a]	Calibrated [a]
Within households	0.98	Fischer et al. 2010 [3]
Control		
Passive case detection delays		
Years of improved detection delay	1995, 1998, 1999, 2001, 2011, 2012	Based on data from NLEP India [1]
Detection delay function: $DD(t) = \left(\frac{max - min}{1 + e^{b \cdot (t - mid)}}\right) + min$		
Min	2	Calibrated [a]
Max	(20, 40)[a]	
Mid	(0.05, 2)[a]	
b (slope)	(0, 9)[a]	
Survey		
Year	2002	Based on data from NLEP India [1] Calibrated [a]
Coverage	(0.05, 0.2)	
BCG protection	60%	Schuring et al. 2009 [7]

[a] Calibrated to match modelled leprosy new case detection rate trend to data. We randomly drew parameter values from uniform distributions within these intervals. The model was run with these parameter values, which were accepted if the fit was good. The goodness of fit was assessed using a log-likelihood assuming a Poisson distribution. We repeated this until we had 1,000 parameter combinations that produced a good fit. Uncertainty intervals, which reflect uncertainty in the parameter values, were calculated by discarding the 2.5% highest and lowest values.

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S3 Table. Demographic data and parameters to quantify the model

Demographic data		
Data	**Years**	**Source**
Population growth	1901–2011	Census India [8][8][8][8][8][8][8][8][8][8][297][297][298][298][41][1]
Fraction married	1991, 2001, 2011	Census India [9]
Survival rates	1995, 1999, 2003, 2007, 2011	Census India [10]
Fertility rates	1990, 1993, 1996, 1999, 2006, 2011	Census India [10]
Age distribution	2011	Census India [9]
Distribution of household size	2011	Census India [9]
Household movement parameters		
Parameter	**Value**	**Source**
Fraction random movement	0.71	Calibrated [a]
Fraction creates own household	0	Assumption
Household size to move to	Start =0, End = 4, Max =3 (Triangular distributed)	Calibrated [a]
Fraction of married couple creating own household	0.25	Fischer et al. 2010 [3]
Time until splitting of a married household from parental household	Mean = 12 (Exponentially distributed)	Fischer et al. 2010 [3]
Fraction single widow(er)s moving back to children	1.0	Fischer et al. 2010 [3]

[a] Calibrated to match modelled household size distribution to data

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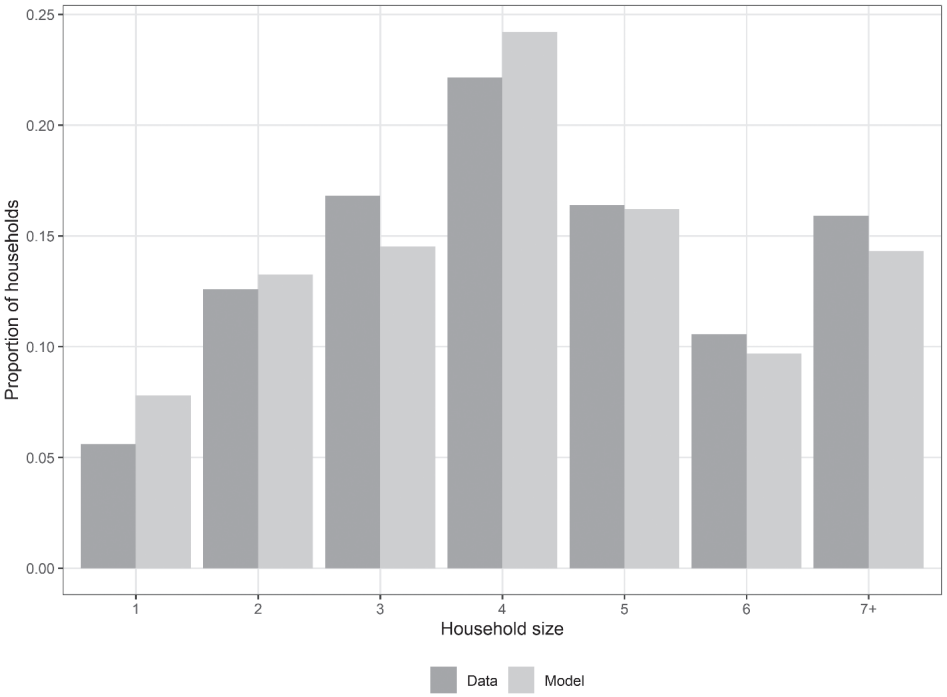
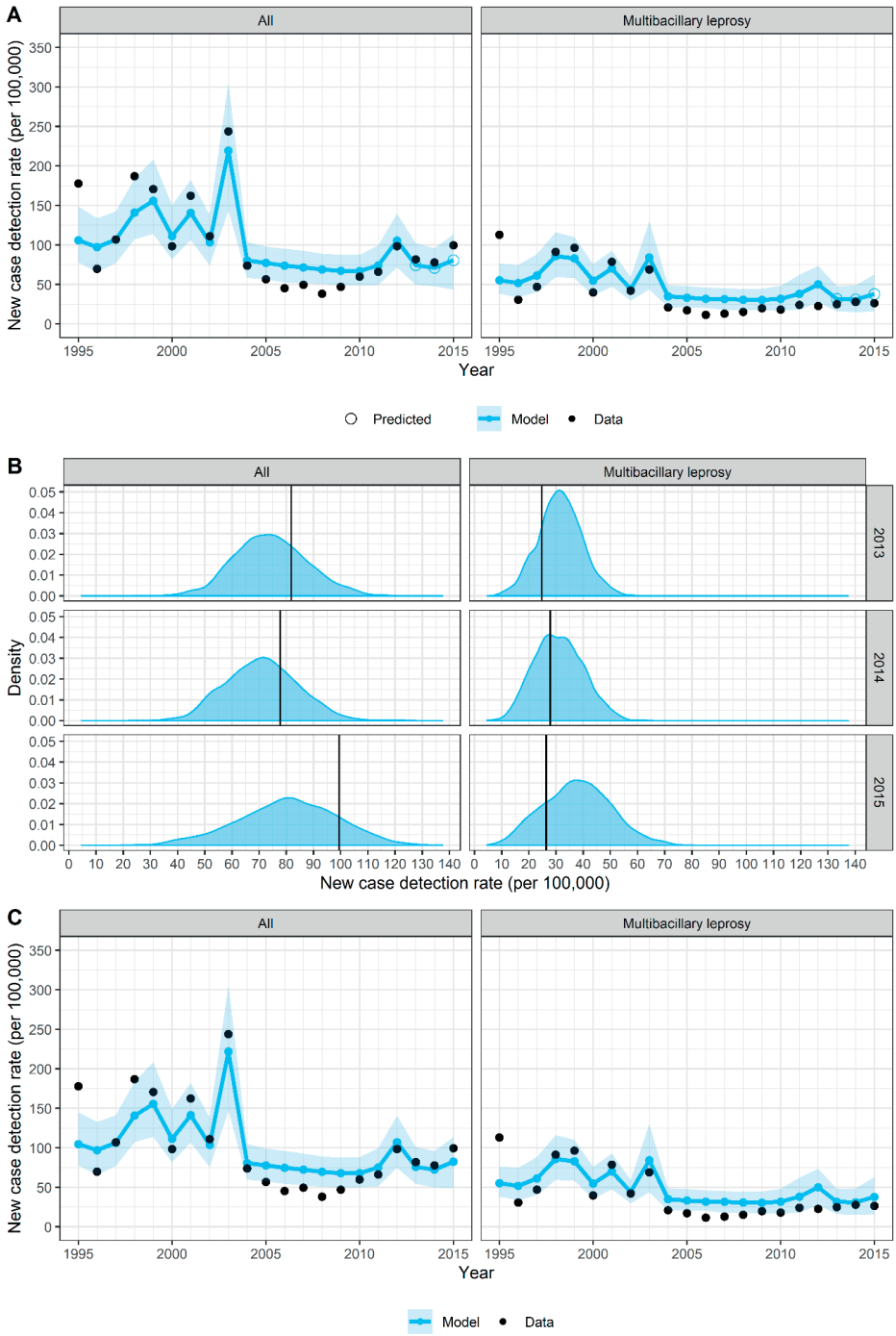
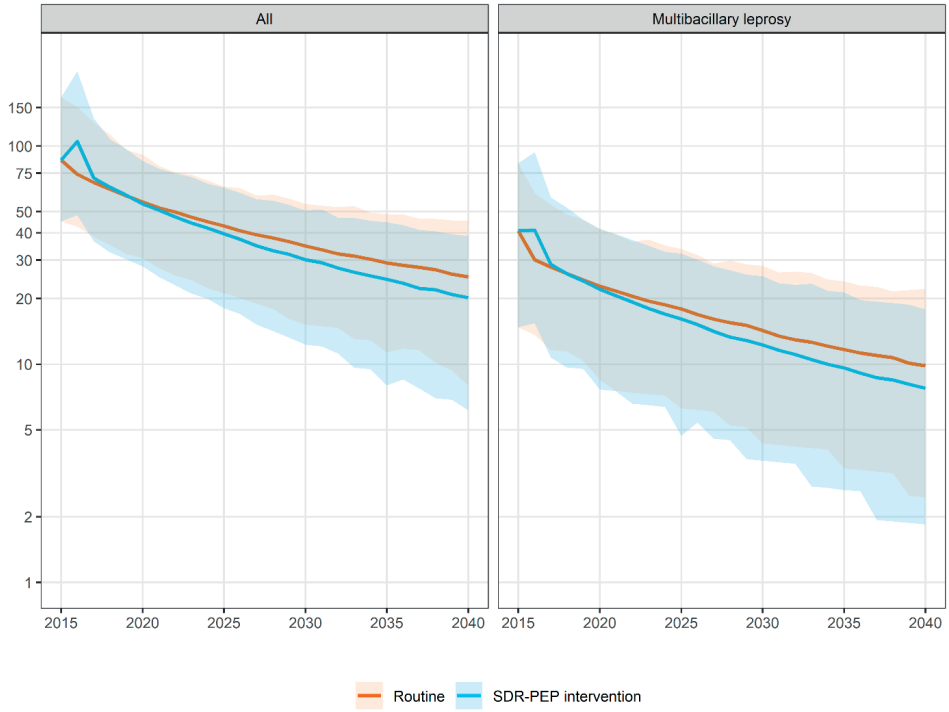


S1 Figure. The observed and modelled household size distribution.
The observed distribution is household size distribution of Dadra Nagar Haveli in India in 2011. Data were obtained from Census India (2011). The simulated distribution was obtained by fitting the model to this data. There is no significant difference between data and modeled distribution: India ($p = 0.96$, x^2- test).

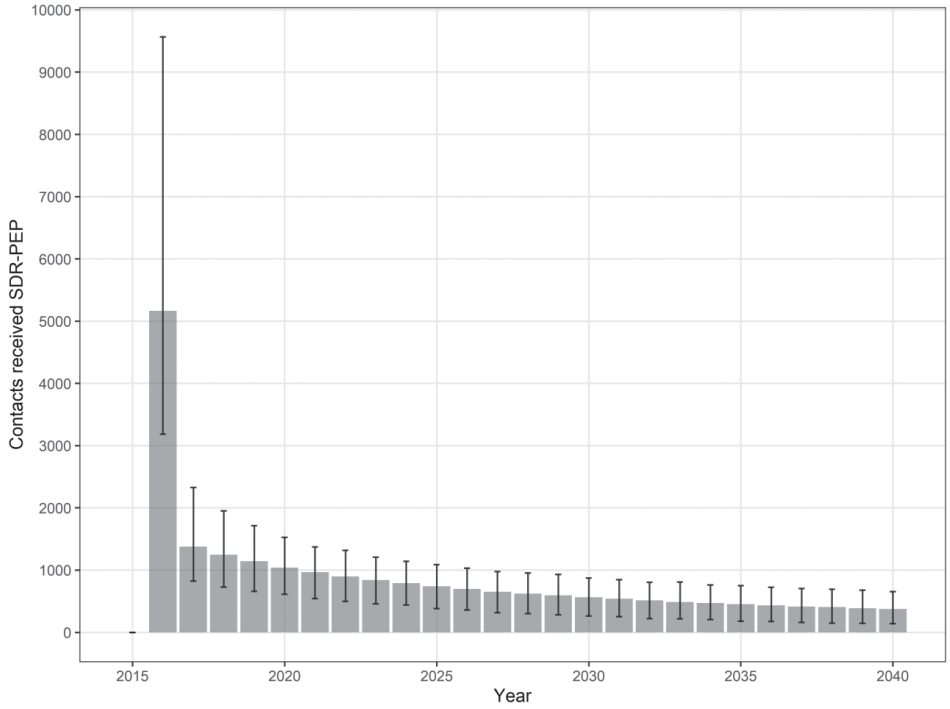


S2 Figure. Model calibration and validation of leprosy epidemiology in Dadra Nagar & Haveli India

(A) Comparison of predicted trends with the observed numbers of all new cases and new multibacillary leprosy cases. The model was fitted to the observed cases from 1995 to 2012. Short-term predictions (2013-2015) were evaluated to validate the model. Results are the average of 1000 runs. The shaded area is the 95% uncertainty interval, representing the uncertainty in parameter estimates.
(B) Distribution of predicted numbers of new cases of leprosy in 2013-2015. The observed value for each year is indicated by a vertical black line. The observed data falls within the distribution for each year.
(C) Comparison of predicted trends with the observed numbers of all new cases and new multibacillary leprosy cases. After evaluation, the model was fitted to the complete dataset (1995-2015), which will be used to make predictions beyond 2015. Results are the average of 1000 runs. The shaded area is the 95% uncertainty interval, representing the uncertainty in parameter estimates.



S3 Figure. Predicted impact of SDR-PEP intervention in Dadra Nagar & Haveli India
Predicted trends of a continuation of the routine programme and the SDR-PEP intervention. Results are the average of 1000 runs. The shaded area is the 95% uncertainty interval, representing the uncertainty in parameter estimates.



S4 Figure. Contacts received SDR-PEP

Model outcomes are represented by means (bars) and 95% uncertainty intervals (error bars). Predictions were made for the years 2015 to 2040.

LEPROSY IN INDIA.

A REPORT

BY

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1877.

Description: A report on leprosy submitted in 1877. Picture credit: Wellcome Collection, London

8 General discussion

In this thesis, we studied the health economic aspects of leprosy prevention through leprosy post-exposure prophylaxis with single-dose rifampicin in India. The thesis trajectory required defining the framework, set the baseline, explain the intervention, estimate the costs and determine the cost-effectiveness. This section contains a discussion of the research questions mentioned in the introduction section, strengths and limitations of the results, and recommendations for policy, practice and future research.

MAIN FINDINGS

Research Question 1

How do investment case concepts apply to leprosy elimination?

Answer

Based on an existing generic framework for a disease eradication investment case, we developed a 11-topic framework for leprosy elimination.

We selected the 'guide to prepare an eradication investment case' to develop an 11-topic framework for leprosy elimination [1]. The guide contains sections and subsections that describe the aspects necessary for an investment case. However, not all sub-sections of the guide were relevant to leprosy elimination or needed adjustment. After adjusting and finalising the framework, we identified the existing knowledge and information gaps for completing the investment case for leprosy. We synthesised available information through a systematic literature review under these topics and discussed the findings. Below, we highlight the main topics of the framework and discuss the overall scope of an investment case for leprosy elimination.

With regard to disease burden, the three decades long case detection trend (Figure 1) demonstrates the changes over time that can feed into the investment case. But the number of cases is a poor indicator for comparison across diseases which is desired for setting priorities and resource allocation. The other method to measure the burden is QALYs or DALYs. But before using DALYs widely in leprosy, the disability weights for grade I and II disabilities need revision to realistically reflect the suffering. Currently, the disability weights are low due to methodological challenges such as non-availability of data on sequelae, including grade I disability. In literature, the burden of leprosy is presented as either the number of new cases, registered prevalence rate, and proportion of grade-2 disability among new cases [2]. From the case trend, we observed that the global leprosy programme was not active enough in the recent past. In the last decade, the decline in the number of new cases was marginal in South-East Asia, which

indicates that the transmission is ongoing and that additional measures are required for further reduction [3]. By 2015, WHO pledged to reduce grade-2 disability by 35%, but the target was missed due to passiveness [4]. Now, WHO proposes to seriously follow its previous recommendation of contact tracing, but now combined with SDR [5]. These targets and evolving guidelines are important information for planning a realistic investment case for leprosy elimination.

Among elimination tools, SDR is most advanced due to a successful feasibility trial (LPEP) and its scientific documentation [6-11]. This information is ready to be part of the investment case. However, for comparison, similar information is also desired from other tools such as vaccines and rapid diagnostic tests. Vaccines still need to prove their feasibility, and rapid diagnostic test needs to be more accurate (sensitive and specific). The biological feasibility of eradication is doubtful because *M. leprae* and *M. lepromatosis* also have reservoirs in the environment and animals, and not only in humans. However, elimination of the disease is certainly achievable as seen before in Europe, therefore the investment case is focused on the elimination. Furthermore, genome sequencing studies can bring more clarity on the topic, which should also be proposed in the investment case. On the programmatic front, it is clear that vertical service delivery is not feasible and sustainable when elimination is close. Rather, integration of the national leprosy programmes with other programmes is a better strategy. The integration of a leprosy programme into the general health care is widely reported and these lessons can feed into the investment case. However, integration alone is not sufficient, but continuous awareness and training is also crucial to sustain and improve the services. The future requirement is to integrate leprosy services with other NTDs programmes and bring them all under a poverty alleviation agenda.

The investment case still needs more information than what is currently available and presented in the above paragraph. The current leprosy burden is an underestimation because many new cases and grade-2 disability cases are hidden, especially in India [12]. Further, leprosy consequences such as stigma, discrimination, and poor mental health are not seen as a burden, but are certainly important to calculate the economic burden of leprosy [13]. As a prominent finding of this thesis, health economic evidence on leprosy is limited and currently not sufficient to build an investment case; especially cost-effectiveness studies are very few. Cost-effectiveness studies are required under topics such as socioeconomic burden of leprosy, financing leprosy elimination, health systems and its capacity. The information on feasibility of new tools is also desired to interpret cost-effectiveness results. Certainly, leprosy elimination is in demand, and partnership is the way to meet that demand. An investment case document can help in advocacy, fund sharing and planning between stakeholders.

To fill the information gaps, we conducted health economic studies, which are included in this thesis. In chapter 3, we selected SDR as the new tool and explored its operational alignment with the health system. This has provided more information on how to roll-out SDR and in which circumstances we can expect effectiveness. SDR is feasible to implement in most endemic countries along with their national programmes. It is, however, less effective in countries where a contact tracing system is not in place. Further in chapter 4, we focused on the economic burden of leprosy on society by estimating the household expenditure on leprosy. This was high, and as a result, the health-seeking behaviour of patients was poor. If we invest in prevention, this economic burden can be lessened substantially. In chapter 5, we focused on the economic burden of leprosy on the health systems. We found that the prevention of leprosy by SDR is financially feasible if implemented as an additional activity under ongoing contact tracing. In chapter 6, we estimated the cost-effectiveness of SDR in different disability burden situations, and showed that it can realistically be scaled-up in India.

We only conducted studies in India, which is not sufficient to complete an investment case at the global level, but we demonstrated how to systematically collect the information. We conclude that the investment case for leprosy elimination is an important and relevant concept. We already have much information to complete the investment case, including the results of this thesis. More health economic information on the new tools of prevention is desired from other endemic countries. For completion of the global investment case with SDR, we require similar cost-effectiveness estimates from Indonesia and Brazil, which together with India constitute 80% of the global caseload. The information should be collected in a planned and collaborative manner as described in chapter 3. We recommend completing the global investment case for leprosy elimination with SDR in other leprosy endemic countries to contribute to the WHO guidelines for 2021-2025.

Research Question 2

Can post-exposure prophylaxis with SDR be implemented into a national leprosy control programme?

Answer

SDR is feasible to implement along with the national leprosy control programmes in endemic countries without many structural and human resource changes.

The implementation feasibility of SDR was demonstrated by the LPEP program in seven countries within their respective national leprosy control programmes. The LPEP program explored the feasibility and impact of combining three key interventions, i.e.,

contact tracing, contact screening, and administration of SDR. The activities were implemented through established structures of the national leprosy programmes. The aim was to explore the feasibility of the intervention package to improve early case detection, prevent leprosy and integrate with the national leprosy programmes.

The LPEP program was implemented in countries that were different with regard to the level of endemicity, national programme activity, and health system capacity. The programme ran for several years (2015-18) without any country dropout, which is in itself evidence of feasibility. However, due to health system differences, one fixed approach was not suitable to implement the programme. Therefore, countries were consulted to define their functional parameters and targets. However, it was ensured that these changes and adjustments were documented to interpret the results correctly. Another indication of feasibility is the high coverage of the LPEP program, which enrolled 9,186 index patients and listed 179,769 contacts, of which 174,782 (97.2%) were traced and screened. Further, SDR as an intervention was well accepted by the community, contacts and health staff as only 0.7% (n=1,182) contacts refused the SDR, which was otherwise administered to 86.9% (n= 151,928) of the screened contacts. LPEP also demonstrated that high coverage is feasible without compromising on the quality of screening. Out of those screened, only 13.1% (n=22,854) were excluded from SDR for various reasons. LPEP also increased the case detection by finding 1,300 persons suspected for leprosy, and confirming 810 (62.3%) of them as new leprosy patients. The countries that had some level of contact tracing in place had better coverage than those without any previous contact tracing. Next, rifampicin was yet again proven to be a safe drug as no adverse events were reported from any country. The challenge was to cover neighbour and social contacts, because the availability of health staff was limited, the area to cover was large, and contacts were often absent during the house visits. This resulted in extra workload for the health staff, but their high level of motivation led to success [9].

SDR distribution is still ongoing in 4 out of 6 LPEP countries after completion of the LPEP program. The WHO recommendation in the recent leprosy guidelines played an important role to adopt it as a policy in countries [5]. Another factor for SDR sustainability was a planned exit policy of the LPEP program. In the last year of LPEP and a year after completion, countries received some funds and technical support to carry on the SDR work independently. Two examples of technical support are delivery of an SDR tool kit and minimal data set recommendation for recording and reporting [7, 10]. We conclude that SDR is feasible and safe to implement in different epidemic and programmatic situations. Sustainability is high when the local public health staff own the intervention.

Research Question 3

What is the cost-effectiveness of SDR?

Answer

SDR is cost-effective when assuming that disability could be prevented, i.e., US$ 443 per DALY averted over 25 years.

The result of our cost-effectiveness analysis for SDR in India was below the GDP per capita (2017) of India, and therefore SDR can be said to be very cost-effective. The cost-effectiveness was mainly due to the intensified supporting activities such as contact screening and awareness, which translated into high coverage. These results apply to areas where some form of contact tracing is already part of the routine programme. The SDR cost (USD 2.9; 95% CI: 2.5–3.7) used in the analysis pertains to only SDR activities such as contact listing, screening and administering the rifampicin. A fresh introduction of contact tracing with SDR will surely be expensive as existing contact tracing reduces the cost of training and infrastructure. Furthermore, motivation and skills of health staff are better if they are already familiar with contact tracing, leading to better effectiveness.

The presented cost-effectiveness results are based on the health system perspective. If the patient's perspective is also added, SDR will certainly yield more benefit. Precisely, if we prevent a leprosy case then we also prevent US$ 9.5-12.4 per health care visit by the patient, resulting in cost savings. During the treatment, there are at least 12 visits for a MB patient and 6 visits for a PB patient. The majority of the patient's expenditure is contributed by the indirect expenditure such as wage loss, which is often hidden, but a factor for delay in detection. The affected person avoids the diagnosis due to wage loss, spreads infection, and increases the chance of disability. In addition, we recommend that high endemic areas with high disability rates should be prioritised first to secure larger impact. In summary, each case prevented will contribute manifold in reduction of the economic burden due to leprosy. We conclude that SDR is a cost-effective strategy and its scale-up is recommended in India, prioritizing high endemic areas first.

STRENGTHS AND LIMITATIONS

A wide range of methodologies were applied in this thesis. We conducted a systematic literature review (**chapter 2**), a mixed method study with qualitative research (**chapter 4**), two costing studies (**chapter 5 and 6**) and a cost-effectiveness analysis with simulation modelling (**chapter 7**).

The systematic literature provided detailed information on the topic of investment case and comprehensively arranged the available evidence. The review followed a strict criterion-based search and selection, which ensured the validity of results. Generally, literature review results dilute quickly due to inflow of new information from new publications, therefore the results of our review from 2016 would need an update. In 2019, a report on the proceedings of an expert consultation on the leprosy elimination investment case was published [14] and summarized developments, providing updated information.

The mixed method study provided a comprehensive overview of the baseline situation before the intervention. Particularly, the qualitative analysis provided critical explanations about the quantitative data. However, as a limitation, qualitative results are difficult to generalize to another country or population, therefore, caution is warranted when extrapolating results. However, the qualitative information will provide a base to design future studies. Finally, we used a widely accepted and simple WHO framework on health systems, which provided consistency for data collection and analysis in the multicentre nature of the mixed method study.

The costing studies were part of following-up the recommendation of chapter 2 and covered the health systems and societal perspective. The health system cost was addressed by estimating the public expenditure, whereas the societal aspect was addressed by estimating the expenditure by the patients. This provided a complete overview of the economic burden of leprosy. We used deterministic and stochastic methodology to generalize the costing results. Generally, cost data are skewed, requiring a suitable distribution to build a deterministic model. We accounted for such situations by performing a detailed diagnostic and model fitting exercise. We used different sampling methods suitable for health systems (purposive) and societal (random) costing because the unit of analysis was different. However, random sampling is the gold standard, but due to a large number of health facilities and financial constraints, it was not feasible for health system costing. The cost alone does not inform on the long-term efficiency or decision to scale-up, therefore we performed cost-effectiveness analysis by utilizing the SDR costing results.

For the cost-effectiveness analysis, a long term perspective was needed because interventions that include contact tracing and screening will initially increase the number of new cases due to the existing backlog of cases [15]. Also, effects of leprosy interventions are known to only be visible after years due to the long incubation time [16]. We therefore applied modelling to analyse the long term impact of SDR. Mathematical modeling is the only tool for predicting future leprosy trends and the potential im-

pact of interventions [17]. However, results are only valid on the assumption that the deployment of the intervention remains unchanged over the forecasted period. Also the modelling was limited because of lack of data about disability, which is a problem in general. Cost-effectiveness studies for leprosy would improve generally, if more detailed data would be collected on different types of disability. The costing results are also time-bound and the decision is dependent on the applied willingness-to-pay threshold. We provided detailed information in our study on factors or assumptions that can influence the results, also with regard to the setting. The costing results are difficult to apply to other economic regions, therefore more such evidence is needed in a reasonable time frame to complete the global investment case for leprosy elimination.

RECOMMENDATIONS FOR POLICY AND PRACTICE

From the above discussion, we summarize the following recommendations for leprosy control policy and practice:

1. We recommend completing a global investment case for leprosy elimination with SDR in other leprosy endemic countries to contribute to the WHO guidelines for 2021-2025. For this purpose a roadmap can be developed including (at least) the following steps:
    - Estimate health system cost of SDR for other endemic countries, particularly Indonesia and Brazil
    - Estimate patient's expenditure on leprosy care and opportunity cost to receive SDR
    - Estimate the fund required globally to cover contacts - family and neighbours - of leprosy patients in different programmatic situations
    - Estimate the cost-effectiveness of SDR globally with revised disability weights for leprosy
2. We showed SDR to be a cost-effective strategy in India and for that reason recommend its scale-up in that country.
3. SDR is a cost-effective intervention with a return of investment after 5 years and onwards. For a larger benefit, we recommend long term implementation of SDR.
4. The best results of SDR can be expected in moderate to high disability burden areas, as there will more chance for SDR to prevent disabilities. We recommend to prioritize these areas for implementation of SDR-PEP.
5. The leprosy burden estimates need revision by accounting for hidden cases. We recommend active case surveys as part of routine leprosy control programmes in endemic countries with standardized monitoring and reporting.

6. The leprosy programme performance was better and the patient expenditure was low under the enhanced health system of DNH in India. We recommend that in India the state leprosy programmes that are part of the general health care system should be enhanced as well to reduce the economic burden of leprosy patients.

RECOMMENDATIONS FOR FUTURE RESEARCH

The studies in this thesis are among the first to contribute to the development of an investment case for leprosy elimination. It is important that research in leprosy continues to focus on leprosy elimination and its economic aspects. Factors that have an indirect effect on policy and planning should also be considered for future research. Based on studies in this thesis, we formulate the following set of recommendations for further research:

1. Future studies should include cost and cost-effectiveness analysis of SDR and other preventive interventions to feed into the global leprosy elimination investment case.
2. Better health system capacity leads to better implementation of SDR, which also determines its cost-effectiveness. We therefore recommend the collection of information on the health system together with costing studies to interpret the effects of preventive interventions such as SDR accurately.
3. Health system studies should focus on the financial sustainability of integration of leprosy health services with other co-existing NTDs.
4. We found that human resource is an important factor from the point of view of health financing and operational research. Health systems research should also focus on enhancing human resource (HR) capacity.
5. We recommend economic studies in areas with no leprosy contact tracing to enable cost-effective implementation of contact tracing in their health system and prepare for the implementation of SDR.
6. We recommend to systematically study the lessons learnt from the experience of other infectious diseases that have been eliminated or at the verge of elimination in order to apply these where possible to the leprosy elimination investment case.

CONCLUSION

An investment case is applicable to plan and advocate the investment in leprosy elimination, but is as yet far from complete. Completion of a leprosy elimination investment case is the collective responsibility of all stakeholders working in the field of leprosy, and their data collection and research for an investment case needs to be coordinated and aligned. Sustainability of an intervention is high when the local public health staff own the intervention. Other than the level of leprosy endemicity, the health system capacity for contact tracing is important for the cost-effectiveness of implementing SDR-PEP in a leprosy control programme. In this thesis we conclude that post-exposure prophylaxis with SDR is feasible, safe, cost-effective, and compatible with most national leprosy programmes, including that of India, the focus country of this thesis.

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Description: Reconstructive surgery of the hand of a leprosy patient. The surgery is required in severe deformity causing physical and activity limitation. Photograph: George Butler
Source: The guardian

SUMMARY

Leprosy is an infectious disease caused by the bacteria *Mycobacterium leprae*. The affected population mainly belongs to the lower socioeconomic strata of society. Detection and treatment delay are common, because many people affected by leprosy live in remote areas with limited access to health care. According to the World Health Organization (WHO), leprosy is officially eliminated worldwide, defined as less than 1 patient per 10,000 people, but this does not mean that leprosy transmission is no more existing. Every year, over 200,000 new patients are detected in the world and their households enter into the hardships of job loss, stigma, discrimination and poor mental health. At a national level, this reflects a high economic burden, which is not inevitable because leprosy is preventable.

The main factor determining the risk and course of leprosy is decreased host immunity, which is determined genetically, but also affected by poor nutrition and hygiene. Leprosy has a long incubation time and sub-clinical phase during which transmission of *M. leprae* can take place. Once a person shows symptoms, the disease can be diagnosed clinically and treated with multidrug therapy (MDT), but the prognosis with regard to the occurrence of nerve damage and resulting disability and social stigma is dependent on the type of leprosy and timely diagnosis. There is not yet a field-friendly diagnostic test available to establish sub-clinical infection. BCG vaccine against Tuberculosis provides some protection against leprosy, but post-exposure immunoprophylaxis with vaccines is still under development. Post-exposure chemoprophylaxis with a single-dose of rifampicin (SDR) is shown to be effective to prevent leprosy in contacts of leprosy patients.

The Leprosy Post-Exposure Prophylaxis program (LPEP) was a multi-centre study to investigate the feasibility of SDR implementation in national leprosy control programmes. Feasibility also included the economic aspects of applying SDR in routine conditions. The main objective of this thesis is to study the health economic aspects of leprosy prevention. This includes a 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?

After a general introduction in **Chapter 1,** we introduce in **Chapter 2** the investment case as a concept. The aim was to review systematically the literature regarding the elimination of leprosy, and to assess this information on its applicability for defining a Leprosy Elimination Investment Case (LEIC) based on Eradication Investment Case guidelines. We conducted a literature search on leprosy elimination and its public health aspects. A total of 1007 articles were considered and 112 were included in the final selection. The LEIC framework was adapted from an existing "Guide to Preparing an Eradication Investment Case". The LEIC framework provided 11 topics under which information was synthesized from the literature. The fields were categorised under sections: 1) Proposed investment; 2) Rationale for investing; 3) Issues to consider when moving from control to eradication; 4) Management and governance. Scanty quantitative data are available for developing a LEIC, particularly regarding disease burden, and new interventions that could contribute to elimination are not yet applied routinely. We concluded that for monitoring global elimination, it is necessary to measure disease burden comprehensively, and contact centred preventive interventions should be part of a global elimination strategy. The biological and technical feasibility of elimination is not certain and advanced microbiological and operational research is necessary to understand transmission better. The current WHO road map for leprosy elimination is too vague and needs further structuring through a thoroughly prepared LEIC.

Chapter 3 is a protocol explaining the objective, definitions and operating procedures of the LPEP program. LPEP evaluated feasibility, effectiveness and impact of PEP with SDR in pilot areas situated in several leprosy endemic countries: India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania. Complementary sites are located in Brazil and Cambodia. From 2015 to 2018, contact persons of patients with leprosy were traced, screened for symptoms and assessed for eligibility to receive SDR. The intervention is implemented by the national leprosy programmes, tailored to local conditions and capacities, and relying on available human and material resources. It is coordinated on the ground with the help of the in-country partners of the International Federation of Anti-Leprosy Associations (ILEP). A robust data collection and reporting system is established in the pilot areas with regular monitoring and quality control, contributing to the strengthening of the national surveillance systems to become more action-oriented.

In **Chapter 4** we aimed to compare national leprosy control programs and adapted LPEP strategies in India, Nepal and Indonesia with the purpose to establish a baseline of the health system's situation and document the subsequent adjustment of LPEP. This will provide the context for interpreting the LPEP results in future. The data collection methods were direct observation, in-depth interviews and desk review. The study was divided into two phases, i.e. review of national leprosy programs and description

of the LPEP program. The comparative analysis was performed using the WHO health system frameworks (2007). We found that in all countries leprosy services including contact tracing is integrated into the health systems. LPEP is fully integrated into the established national leprosy programs, with SDR and increased documentation, which need major additions to standard procedures. SDR administration was widely perceived as well manageable, but the additional LPEP data collection was reported to increase workload in the first year. The findings of our study led to the recommendation that human resource (HR) capacity should be enhanced for better implementation and sustainability of SDR intervention. The national leprosy programs are diverse in terms of organizational hierarchy, human resource quantity and capacity. We concluded that SDR is compatible with different health systems and can integrate without major structural and personal changes, but provisions are necessary for the additional monitoring requirements.

In **Chapter 5** we aimed to estimate the expenditure in primary care (outpatient) by leprosy households in two different public health settings. To this end we performed a cross-sectional study, comparing the Union Territory of Dadra and Nagar Haveli with the Umbergaon block of Valsad, Gujrat, India. A household (HH) survey was conducted between May and October, 2016. We calculated direct and indirect expenditure. The sampled households were comparable on socioeconomic indicators. The mean direct expenditure was US$ 6.5 (95% CI: 2.4 - 17.9) in Dadra and Nagar Haveli and US$ 5.4 (95% CI: 3.8 - 7.9) per visit in Umbergaon. The mean indirect expenditure was US$ 8.7 (95% CI: 7.2 - 10.6) in Dadra and Nagar Haveli and US$ 12.4 (95% CI: 7.0 - 21.9) in Umbergaon. The age of the leprosy patients and type of health facilities were the major predictors of total expenditure on leprosy primary care. The higher the age, the higher the expenditure at both sites. The private facilities are more expensive than the government facilities at both sites. If the public health system is enhanced, government facilities are the first preference for patients. We concluded that an enhanced public health system reduces the patient's expenditure and improves the health seeking behaviour, and recommend investing in health system strengthening to reduce the economic burden of leprosy.

In **Chapter 6** we aimed to estimate the cost of leprosy services at primary care level in two different public-health settings. We performed Ingredient-based costing in eight primary health centres (PHCs) purposively selected in the Union Territory of Dadra and Nagar Haveli (DNH) and the Umbergaon block of Valsad district, Gujarat, India. All costs were bootstrapped, and to estimate the variation in total cost under uncertainty, a univariate sensitivity analysis was performed. We found that the mean annual cost of providing leprosy services was USD 29,072 in the DNH PHC (95% CI: 22,125 - 36,020) and

US$ 11,082 in Umbergaon (95% CI: 8,334 - 13,830). The single largest cost component was human resources: 79% in DNH and 83% in Umbergaon. The unit cost for screening the contact of a leprosy patient was US$ 1 in DNH (95% CI: 0.8 - 1.2) and US$ 0.3 in Umbergaon (95% CI: 0.2 - 0.4). In DNH, the unit cost of delivering SDR as chemoprophylaxis for contacts was US$ 2.9 (95% CI: 2.5 - 3.7). We concluded that leprosy programme performance was better under the enhanced health system of DNH which also justifies the higher investment than Umbergaon. The unit cost of contact screening is not high, favouring its sustainability in the programme.

In **Chapter 7** we aimed to estimate the cost-effectiveness of SDR-PEP in the Union Territory of Dadra Nagar Haveli (DNH) in India. We used a stochastic individual-based model (SIMCOLEP) to simulate the leprosy new case detection rate trend and the impact of implementing contact screening and SDR-PEP from 2016 to 2040 (25 years) in DNH. Effects of the intervention were expressed as disability adjusted life years (DALY) averted under three assumption of disability prevention: 1) all grade 1 disability (G1D) cases prevented; 2) G1D cases prevented in PB cases only; and 3) no disability prevented. Mean costs were US$ 2.9 per contact. Costs and effects were discounted at 3%. We found that the incremental cost per DALY averted by SDR-PEP was US$ 210, US$ 447, and US$ 5,673 in the 25th year under disability prevention assumption 1, 2, and 3, respectively. If prevention of G1D was assumed, the probability of the intervention being cost-effective was 100% at a willingness-to-pay threshold of US$ 2,000, which is equivalent to the GDP per capita of India. The probability of cost-effectiveness was 60%, if no disability prevention was assumed. The cost per new leprosy case averted was US$ 2,873. We concluded that contact screening in combination with SDR-PEP is a cost-effective strategy and its scale-up is recommended in India, prioritizing high endemic areas first.

Finally, **in Chapter 8**, we discuss answers to the research questions and provide recommendations for policy and practice, and for future research.

Recommendations for policy and practice

1. We recommend completing a global investment case for leprosy elimination with SDR in other leprosy endemic countries to contribute to the WHO guidelines for 2021-2025. For this purpose a roadmap can be developed including (at least) the following steps:
    - Estimate health system cost of SDR for other endemic countries, particularly Indonesia and Brazil
    - Estimate patient's expenditure on leprosy care and opportunity cost to receive SDR

- Estimate the fund required globally to cover contacts - family and neighbours - of leprosy patients in different programmatic situations
- Estimate the cost-effectiveness of SDR globally with revised disability weights for leprosy

2. We showed SDR to be a cost-effective strategy in India and for that reason recommend its scale-up in that country.
3. SDR is a cost-effective intervention with a return of investment after 5 years and onwards. For a larger benefit, we recommend long term implementation of SDR.
4. The best results of SDR can be expected in moderate to high disability burden areas, as there will more chance for SDR to prevent disabilities. We recommend to prioritize these areas for implementation of SDR-PEP.
5. The leprosy burden estimates need revision by accounting for hidden cases. We recommend active case surveys as part of routine leprosy control programmes in endemic countries with standardized monitoring and reporting.
6. The leprosy programme performance was better and the patient expenditure was low under the enhanced health system of DNH in India. We recommend that in India the state leprosy programmes that are part of the general health care system should be enhanced as well to reduce the economic burden of leprosy patients.

Recommendations for future research

The studies in this thesis are among the first to contribute to the development of an investment case for leprosy elimination. It is important that research in leprosy continues to focus on leprosy elimination and its economic aspects. Factors that have an indirect effect on policy and planning should also be considered for future research. Based on studies in this thesis, we formulate the following set of recommendations for further research:

1. Future studies should include cost and cost-effectiveness analysis of SDR and other preventive interventions to feed into the global leprosy elimination investment case.
2. Better health system capacity leads to better implementation of SDR, which also determines its cost-effectiveness. We therefore recommend the collection of information on the health system together with costing studies to interpret the effects of preventive interventions such as SDR accurately.
3. Health system studies should focus on the financial sustainability of integration of leprosy health services with other co-existing NTDs.
4. We found that human resource is an important factor from the point of view of health financing and operational research. Health systems research should also focus on enhancing human resource (HR) capacity.

5. We recommend economic studies in areas with no leprosy contact tracing to enable cost-effective implementation of contact tracing in their health system and prepare for the implementation of SDR.
6. We recommend to systematically study the lessons learnt from the experience of other infectious diseases that have been eliminated or at the verge of elimination in order to apply these where possible to the leprosy elimination investment case.

The **conclusions** of this thesis are that an investment case is applicable to plan and advocate the investment in leprosy elimination, but is far from complete. Completion of a leprosy elimination investment case is the collective responsibility of all stake-holders working in the field of leprosy, and their data collection and research for an investment case needs to be coordinated and aligned. Sustainability of an intervention is high when the local public health staff own the intervention. Other than the level of leprosy endemicity, the health system capacity for contact tracing is important for cost-effectiveness of a leprosy control programme. Finally, post-exposure prophylaxis with SDR is feasible, cost-effective, and compatible with most national leprosy programmes, including that of India, the focus country of this thesis.

SAMENVATTING

Lepra is een infectieziekte die wordt veroorzaakt door de bacterie *Mycobacterium leprae*. Deze ziekte treft voornamelijk mensen uit de lagere sociaaleconomische klasse van de bevolking. De opsporing en behandeling van lepra is vaak traag, omdat patiënten vaak in afgelegen gebieden wonen met beperkte toegang tot de gezondheidszorg. Volgens de Wereldgezondheidsorganisatie (WHO) is lepra wereldwijd officieel geëlimineerd (gedefinieerd als minder dan 1 geregistreerde patiënt per 10.000 mensen). Dit betekent echter niet dat de transmissie van de leprabacterie is gestopt. Elk jaar worden wereldwijd meer dan 200.000 nieuwe patiënten gedetecteerd. Dit brengt ook sociaaleconomische consequenties met zich mee, zoals baanverlies, stigma en discriminatie, wat weer leidt tot een verslechtering van de psychische gezondheid. De gevolgen raken het hele huishouden. Lepra veroorzaakt een hoge economische last, die te vermijden is.

Een belangrijke risicofactor voor het ontwikkelen van lepra is een verminderde immuniteit, die genetisch bepaald is. Slechte voeding en hygiëne kunnen echter de immuniteit verder verslechteren. Lepra wordt gekenmerkt door een lange incubatietijd, waarin transmissie van *M. leprae* kan plaatsvinden. Patiënten met symptomen kunnen worden gediagnosticeerd en vervolgens worden behandeld met multidrug therapie (MDT). De mate van zenuwbeschadiging, fysieke beperkingen en sociaal stigma is afhankelijk van het type lepra en tijdige diagnose. Er is nog geen veldvriendelijke diagnostische test beschikbaar om een subklinische infectie vast te stellen. Het BCG-vaccin dat wordt gebruikt voor tuberculose biedt ook enige bescherming tegen lepra, maar een lepra-specifiek vaccin is nog in ontwikkeling. Chemoprofylaxe met een enkelvoudige dosis rifampicine (SDR) blijkt effectief te zijn om lepra te voorkomen onder contacten van leprapatiënten.

Het “Leprosy Post-Exposure Prophylaxis” (LPEP) programma was een multicenter studie met als doel om de haalbaarheid van SDR-implementatie in nationale leprabestrijdingsprogramma’s te onderzoeken. Onder haalbaarheid behoren ook de economische aspecten van het toepassen van SDR in bestaande programma’s. Het hoofddoel van dit proefschrift is het bestuderen van de gezondheidseconomische aspecten van lepra-preventie. Dit omvat een kosteneffectiviteitsanalyse van profylaxe-na-blootstelling (PEP) met SDR. Het doel is om bij te dragen aan een wereldwijde investeringscasus voor de eliminatie van lepra. Onze studie richt zich op India, het land met de meeste leprapatiënten ter wereld. De specifieke onderzoeksvragen zijn:

1. Hoe zijn de concepten van een investeringscasus voor eliminatie van toepassing op de eliminatie van lepra?

2. Kan profylaxe na blootstelling met SDR worden geïmplementeerd in een nationaal leprabestrijdingsprogramma?
3. Wat is de kosteneffectiviteit van SDR?

Na de algemene inleiding in **hoofdstuk 1** bespreken we in **hoofdstuk 2** de concepten van een investeringscasus voor eliminatie. Het doel was om een systematische review van de literatuur met betrekking tot de eliminatie van lepra uit te voeren en de uitkomsten te beoordelen op de toepasbaarheid voor het definiëren van een Lepra Eliminatie InvesteringsCasus (LEIC). De zoekstrategie omvatte de eliminatie van lepra inclusief de aspecten van de volksgezondheid. In totaal werden 1007 relevante artikelen gevonden waarvan 112 uiteindelijk zijn geselecteerd. De structuur van de LEIC is gebaseerd op de "Eradication Investment Case Guidelines". De LEIC bestaat uit 11 onderwerpen, die zijn onderverdeeld in vier secties: 1) Investeringsvoorstel; 2) Rationale voor investeren; 3) Mogelijke obstakels bij de overgang van het controleren naar eliminatie van lepra; en 4) Management en bestuur. Uit de resultaten blijkt dat er weinig kwantitatieve onderzoeken beschikbaar zijn om een LEIC van informatie te voorzien. Met name onderzoek naar de volledige ziektelast van lepra ontbreekt. Ook blijken nieuwe interventies die zouden kunnen bijdragen aan eliminatie van lepra nog niet routinematig te worden toegepast. We concludeerden dat voor het monitoren van de eliminatie van lepra het noodzakelijk is om de ziektelast te meten en dat preventieve interventies voor contacten van patiënten deel moeten uitmaken van een wereldwijde eliminatiestrategie. Daarnaast bestaat er onzekerheid met betrekking tot de biologische en technische haalbaarheid van eliminatie. Operationeel onderzoek is daarom nodig om transmissie beter te begrijpen. De huidige WHO-routekaart voor de eliminatie van lepra is te vaag en moet verder worden gestructureerd door middel van een grondig voorbereide LEIC.

In **Hoofdstuk 3** wordt het protocol van het LPEP-programma uiteengezet. Het doel van het LPEP-programma is om de haalbaarheid, effectiviteit en impact van PEP met SDR te onderzoeken in verschillende lepra-endemische landen: India, Indonesië, Myanmar, Nepal, Sri Lanka, Tanzania, Brazilië en Cambodja. Tussen 2015 en 2018 werden contacten van leprapatiënten opgespoord, gescreend op klachten en beoordeeld op geschiktheid om SDR te ontvangen. De interventie werd uitgevoerd door de nationale leprabestrijdingsprogramma's, afgestemd op de lokale omstandigheden, capaciteiten, en de beschikbare personele en materiële middelen. Het LPEP-programma werd gecoördineerd met de hulp van de lokale partners van de International Federation of Anti-Leprosy Associations (ILEP). In de studiegebieden werd tevens een robuust systeem voor dataverzameling en rapportage opgezet met regelmatige monitoring en kwaliteitscontrole. Dit zal uiteindelijk bijdragen aan de versterking van de nationale monitoring om gerichter acties te kunnen ondernemen.

In **Hoofdstuk 4** hebben we de nationale leprabestrijdingsprogramma's in India, Nepal en Indonesië bestudeerd. Op basis van de situatie van het nationale gezondheidssysteem is het LPEP-programma verder aangepast. De interpretatie van de LPEP-resultaten is afhankelijk van de situatie van het gezondheidssysteem voor aanvang van het LPEP-programma. De methoden voor dataverzameling waren directe observatie, diepte-interviews en desk review. De studie was verdeeld in twee fasen; de beoordeling van nationale leprabestrijdingsprogramma's, en de beschrijving van het LPEP-programma. Om de programma's te kunnen analyseren en met elkaar te vergelijken, hebben we gebruikgemaakt van de *WHO health system frameworks* (2007). We vonden dat de lepra-activiteiten, waaronder contactopsporing, in alle landen zijn geïntegreerd in het nationale gezondheidssysteem. Daarom is LPEP volledig geïntegreerd in de gevestigde nationale leprabestrijdingsprogramma's. SDR en de vereiste dataverzameling voor monitoring zijn de belangrijkste aanvullingen op de standaardprocedures. De toediening van SDR werd beoordeeld als goed haalbaar, maar de aanvullende LPEP-dataverzameling zou de werklast in het eerste jaar verhogen. De bevindingen van ons onderzoek leidden tot de aanbeveling om de capaciteit van het personeel (HR) te vergroten om een betere implementatie en duurzaamheid van SDR-interventie te waarborgen. De nationale leprabestrijdingsprogramma's zijn divers in termen van organisatiehiërarchie, kwantiteit van personeel en capaciteit. We concludeerden dat SDR geïmplementeerd kan worden in verschillende gezondheidssystemen en kan integreren zonder grote structurele en personele veranderingen. Er zijn echter wel extra voorzieningen nodig voor de aanvullende monitoringvereisten.

In **Hoofdstuk 5** hebben we een schatting gemaakt van de uitgaven van huishoudens met leprapatiënten in de eerste lijn (polikliniek) in twee gebieden in India. Daarvoor hebben we een cross-sectionele studie uitgevoerd, waarbij de Union Territory of Dadra and Nagar Haveli (DNH) werd vergeleken met het Umbergaon blok van Valsad, Gujrat, India. Tussen mei en oktober 2016 werd een huishoudenonderzoek (HH) uitgevoerd in de twee gebieden. De huishoudens uit de steekproef waren vergelijkbaar op sociaaleconomische indicatoren. Voor beide gebieden hebben we de directe en indirecte uitgaven berekend. De gemiddelde directe uitgaven was US$ 6,5 (95% CI: 2,4 - 17,9) per bezoek aan de kliniek in DNH en US$ 5,4 dollar (95% CI: 3,8 - 7,9) in Umbergaon. De gemiddelde indirecte uitgaven waren US$ 8,7 (95% CI: 7,2 - 10,6) per bezoek in DNH en US$ 12,4 (95% CI: 7,0 - 21,9) in Umbergaon. De leeftijd van de leprapatiënten en het type gezondheidsvoorzieningen waren de belangrijkste determinanten van de totale uitgaven voor lepra-eerstelijnszorg. Hoe hoger de leeftijd, hoe hoger de uitgaven in beide locaties. De particuliere voorzieningen zijn in beide locaties duurder dan de overheidsvoorzieningen. Overheidsvoorzieningen zullen alleen de voorkeur hebben van patiënten als deze worden verbeterd. We concludeerden dat een verbeterd publieke

gezondheidssysteem de uitgaven van de patiënt kan verminderen en bezoeken aan klinieken kan bevorderen. We raden aan om te investeren in verbetering van het gezondheidssysteem om de economische last van lepra te verminderen.

In **Hoofdstuk 6** hebben we de kosten van lepra-diensten in de eerstelijnszorg geschat in twee gebieden. We hebben *ingredient-based costing* toegepast op acht primaire gezondheidscentra (PHC's) in DNH en het Umbergaon-blok in het Valsad-district, Gujarat, India. Bootstrapping en een univariate sensitiviteitsanalyse zijn uitgevoerd om de variatie in totale kosten onder onzekerheid te schatten. De gemiddelde jaarlijkse kosten van het verlenen van lepradiensten was US$ 29.072 in de DNH PHC (95% CI: 22.125–36.020) en US$ 11.082 in Umbergaon (95% CI: 8.334 – 13.830). De grootste kostencomponent was het personeel: 79% in DNH en 83% in Umbergaon. De kosten voor het screenen van contacten van een leprapatiënt waren US$ 1 (95% CI: 0,8 - 1,2) per contact in DNH en US$ 0,3 in Umbergaon (95% CI: 0,2 - 0,4). De kosten voor het toedienen van SDR waren US$ 2,9 (95% CI: 2,5 - 3,7) per contact. We concludeerden dat de het leprabestrijdingsprogramma beter was in DNH dan Umbergaon. Een verbeterd programma rechtvaardigt ook de hogere investering. De kosten van het opsporen en screenen van contacten zijn niet hoog, wat de duurzaamheid van het programma kan waarborgen.

In **Hoofdstuk 7** wordt de kosteneffectiviteit van SDR-PEP in DNH in India geschat. We gebruikten de *individual-based* model SIMCOLEP om de trend van nieuwe lepragevallen en de impact van het implementeren van contactscreening en SDR-PEP tussen 2016 tot 2040 (25 jaar) te simuleren. De effecten van de interventie werden uitgedrukt in disability-adjusted-life-years (DALY) onder drie aannames van de preventie van fysieke beperkingen van lepra: 1) alle gevallen van fysiek beperkingen graad 1 (G1D) worden voorkomen; 2) G1D-gevallen worden alleen voorkomen in PB lepragevallen; en 3) geen preventie van fysieke beperkingen. De gemiddelde kosten waren US$ 2,9 per contact. Kosten en effecten werden verdisconteerd tegen 3%. We vonden dat de incrementele kosten om 1 DALY te voorkomen (door SDR-PEP) US$ 210, US$ 447 en US$ 5.673 in het 25^{e} jaar bedroegen onder aanname 1, 2 en 3 van de preventie van fysieke beperkingen, respectievelijk. Als we aannemen dat G1D zou worden voorkomen, was de kans dat de interventie kosteneffectief is 100% bij een *willingness-to-pay* drempel van US$ 2.000, wat overeenkomt met het BBP per hoofd van de bevolking van India. De kans op kosteneffectiviteit was 60% als niet werd uitgegaan van preventie van fysieke beperkingen. De kosten per 1 voorkomen nieuw lepravaal waren US$ 2.873. Contactscreening in combinatie met SDR-PEP is een kosteneffectieve strategie. We adviseren om de interventie op te schalen in India, waarbij eerst prioriteit wordt gegeven aan hoog-endemische gebieden.

Ten slotte bespreken we in **hoofdstuk 8** de antwoorden op de onderzoeksvragen en geven we aanbevelingen voor beleid en praktijk, en toekomstig onderzoek.

Aanbevelingen voor beleid en praktijk

1. We adviseren om een investeringscasus voor de eliminatie van lepra aan te vullen met SDR studies uit andere lepra-endemische landen. De investeringscasus kan bijdragen aan de aanscherping van de WHO-richtlijnen voor 2021-2025. We stellen een investeringscasus stappenplan voor met de (minimaal) de volgende stappen:
   - Het schatten van de kosten van SDR voor het gezondheidssysteem van andere endemische landen, met name Indonesië en Brazilië.
   - Het schatten van de uitgaven van de patiënt voor leprazorg en alternatieve kosten om SDR te ontvangen.
   - Het schatten van de benodigde financiële middelen om contacten - familie en buren - van leprapatiënten in verschillende programmatische situaties op te sporen en te screenen.
   - Het schatten van de kosteneffectiviteit van SDR wereldwijd met herziene gewichten van de fysieke beperkingen van lepra.
2. SDR is een kosteneffectieve strategie in India en daarom bevelen we de opschaling in dat land aan.
3. Het investeringsrendement van de SDR interventie groeit na 5 jaar. Daarom adviseren we de implementatie van SDR voor een lange termijn.
4. De beste resultaten van SDR kunnen worden verwacht in gebieden met matige tot hoge aantallen fysieke lepra beperkingen, aangezien er meer ruimte is om fysiek beperkingen te voorkomen. We raden aan om prioriteit te geven aan deze gebieden voor de implementatie van SDR-PEP.
5. De schattingen van de ziektelast ten gevolge van lepra moeten worden herzien door rekening te houden met verborgen gevallen. We adviseren actieve opsporing van leprapatiënten als onderdeel van bestaande leprabestrijdingsprogramma's in endemische landen met gestandaardiseerde monitoring en rapportage.
6. De prestaties van het leprabestrijdingsprogramma waren beter en de uitgaven van patiënten waren lager onder het verbeterde gezondheidssysteem van DNH in India. We adviseren om de leprabestrijdingsprogramma’s in staten in India die volledig vertrouwen op het gezondheidszorgsysteem van de overheid te versterken, om zo de economische last van leprapatiënten te verminderen.

Aanbevelingen voor toekomstig onderzoek

De studies in dit proefschrift behoren tot de eersten die bijdragen aan de ontwikkeling van een investeringscasus voor de eliminatie van lepra. Het is belangrijk dat onderzoek naar lepra zich blijft concentreren op de eliminatie van lepra en de economische

aspecten ervan. Bij toekomstig onderzoek moet ook rekening worden gehouden met factoren die een indirect effect hebben op beleid en planning. Op basis van studies in dit proefschrift formuleren we de volgende reeks aanbevelingen voor verder onderzoek:

1. Toekomstige studies moeten een kosten- en kosteneffectiviteitsanalyse van SDR en andere preventieve interventies bevatten om in te spelen op de wereldwijde investeringscasus voor de eliminatie van lepra.
2. Een betere capaciteit van het gezondheidssysteem leidt tot een betere implementatie van SDR, wat ook de kosteneffectiviteit ervan bepaalt. We raden daarom aan om informatie over het gezondheidssysteem te verzamelen, samen met kostenstudies om de effecten van preventieve interventies zoals SDR nauwkeurig te interpreteren.
3. Onderzoek naar gezondheidssystemen moet gericht zijn op de financiële duurzaamheid van de integratie van lepra-gezondheidsdiensten met andere *neglected tropical diseases* (NTD's).
4. We vonden dat *human resources* (HR) een belangrijke factor is voor zowel de financiële uitgaven als de operationalisering van de SDR-interventie. Onderzoek naar gezondheidssystemen moet ook gericht zijn op het vergroten van de capaciteit van HR.
5. We bevelen economische studies aan in gebieden waar nog geen contactopsporing wordt uitgevoerd. Dit om de kosten en effecten van implementatie van contactopsporing in kaart te brengen ter voorbereiding van de implementatie van SDR.
6. We raden aan om systematisch de lessen en ervaringen uit andere infectieziekten, die zijn geëlimineerd of op het punt staan te worden geëlimineerd, te bestuderen, en om deze waar mogelijk toe te passen op de investeringscasus voor de eliminatie van lepra.

De **conclusies** van dit proefschrift zijn dat een investeringscasus nuttig is voor het plannen en bepleiten van de eliminatie van lepra, maar op dit moment nog niet compleet is. De voltooiing van een investeringscasus voor de eliminatie van lepra is een collectieve verantwoordelijkheid van alle belanghebbenden die werkzaam zijn op het gebied van lepra. De dataverzameling en onderzoek voor een investeringscasus moeten door alle belanghebbenden worden gecoördineerd en afgestemd. De duurzaamheid van een interventie kan het best worden gewaarborgd wanneer de lokale belanghebbenden het eigenaarschap van de interventie bezitten. Afgezien van het niveau van de endemiciteit van lepra, is de capaciteit van het gezondheidssysteem voor het opsporen van contacten belangrijk voor de kosteneffectiviteit van een leprabestrijdingsprogramma. Ten slotte is profylaxe (na blootstelling) met SDR haalbaar, kosteneffectief en compatibel met de meeste nationale leprabestrijdingsprogramma's, waaronder die van India, het focusland van dit proefschrift.

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I may not recall all who supported me directly and indirectly in this journey. But, I want to thank them all because the manifestation of the current moment was not possible if any of them were missing. ‘Thank you’ is a very short word to communicate my gratitude, however, it is the only word I have. I also thank wise souls who brought simplicity in the vision by saying that there is no achievement in life other than life itself, and the biggest miracle is to see life flourishing surrounded by death.

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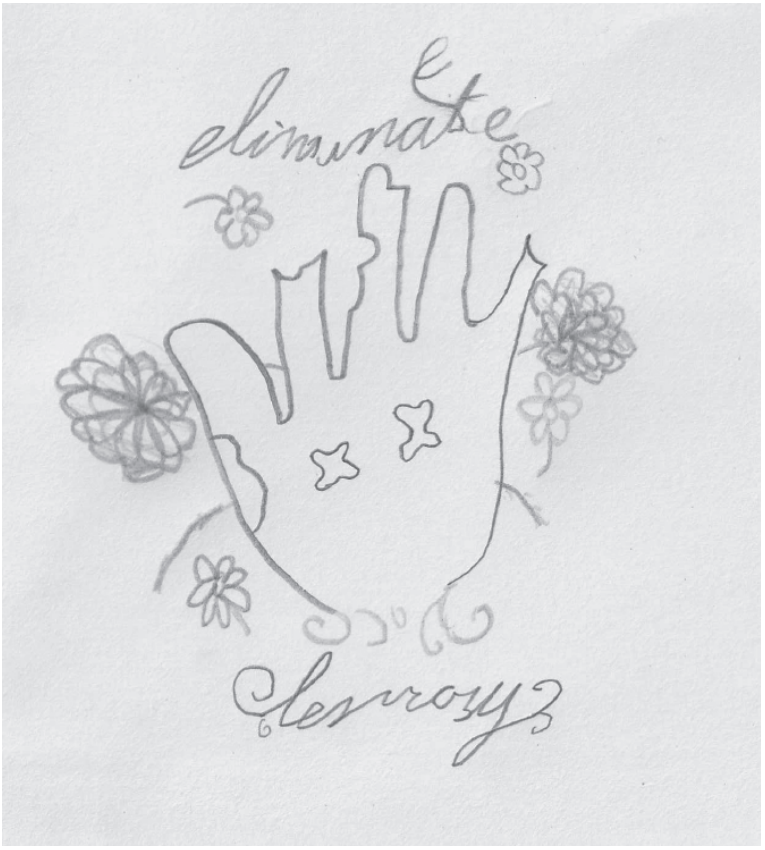
Finally, I want to thank all the leprosy patients and their families who are beating the odds with their smiles and attitude.



Picture credit: Kaustubh Tiwari

CURRICULUM VITAE

Anuj Tiwari was born in the town Alwar located in the Rajasthan province of India on the 8th November, 1982. After secondary education, he completed his Bachelors in Ayurveda, Medicine and Surgery in 2008. Later, he developed an interest in the public health and completed a post-graduation diploma in health economics, financing and policy from the Indian Institute of Public Health, New Delhi. He continued education with a two-year Master programme in economics from Sam Higginbottom University of Agriculture, Technology and Sciences in Prayagraj and graduated in 2012. During this period, he researched on Public-Private Partnership (PPP) models in the healthcare system of India. Subsequently, he provided technical support to TB and HIV/AIDS national programmes under the Ministry of Health and Family Welfare, India. His work was on monitoring and evaluation. In 2015, he started his PhD studies in the Department of Public Health at Erasmus MC, University Medical Center Rotterdam, on leprosy post-exposure prophylaxis under the supervision of Professor Jan Hendrik Richardus. He worked on the Leprosy Post-Exposure Prophylaxis (LPEP) program, which was carried out in cooperation with Novartis Foundation in Basel, NLR in Amsterdam, and other governmental and non-governmental partners in many countries. His work involved intensive travelling for data collection, monitoring visits and annual meetings in the partner countries. During his PhD studies, he also completed a MSc Health Sciences (Public Health) at the Netherlands Institute of Health Sciences (NIHES) at Erasmus MC.

LIST OF PUBLICATIONS

1. **Tiwari A**, Blok DJ, Arif M, Richardus JH (2020). Leprosy Post-Exposure Prophylaxis in the Indian Health System: A Cost-Effectiveness Analysis. PLoS Negl Trop Dis 14(8): e0008521.

2. Carvalho AG, Luz JGG, Dias JVL, **Tiwari A**, Steinmann P, Ignotti E (2020). Hyperendemicity, heterogeneity and spatial overlap of leprosy and cutaneous leishmaniasis in the southern Amazon region of Brazil. Geospatial Health (in press).

3. **Tiwari A**, Blok DJ, Suryawanshi P, Raikwar A, Arif M, Richardus JH (2019). Leprosy services in primary health care in India: comparative economic cost analysis of two public-health settings. Trop Med Int Health; 24(2): 155-165.

4. van 't Noordende AT, Hinders DC, **Tiwari A**, Richardus JH, van Brakel WH (2019). A leprosy elimination investment case: proceedings of an expert consultation. Lepr Rev; 90: 124–127.

5. Barth-Jaeggi T, Cavaliero A, Aerts A, Anand S, Sarady A, Banstola NL, Baskota R, Blaney D, Bonenberger M, Van Brakel W, Cross H, Das V, Budiawan T, Fernando N, Gani Z, Greter H, Ignotti E, Kamara D, Kasang C, Komm B, Kumar A, Lay S, Mieras L, Mirza F, Mutayoba B, Njako B, Pakasi T, Richardus JH, Saunderson P, Smith CS, Staheli R, Suriyarachchi N, Shwe T, **Tiwari A**, Supun M, Wijesinghe D, van Berkel J, Plaetse BV, Virmond M, Peter S (2019). Leprosy post-exposure prophylaxis with single-dose rifampicin: Toolkit for implementation. Lepr Rev; 90: 356- 363.

6. **Tiwari A**, Suryawanshi P, Raikwar A, Arif M, Richardus JH. (2018). Household expenditure on leprosy outpatient services in the Indian health system: A comparative study. PLoS Negl Trop Dis; 12(1): e0006181.

7. **Tiwari A**, Dandel S, Djupuri R, et al. (2018). Population-wide administration of single dose rifampicin for leprosy prevention in isolated communities: a three year follow-up feasibility study in Indonesia. BMC Infect Dis; 18(1): 324.

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PhD PORTFOLIO

PhD training	Year	Workload or ECTS
Research skills		
MSc, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2020	70.2
Core curriculum		
Study Design (CC01)	2016	4.3
Biostatistical Methods I: Basic Principles (CC02)	2018	5.7
Biostatistical Methods II: Classical Regression Models (EP03)	2019	4.3
English Language (SC01)	2016	1.4
Introduction to Medical Writing (SC02)	2017	2.0
M Research (M-RES)	2017	32.6
Public Health		
Principles of Research in Medicine and Epidemiology (ESP01)	2016	0.7
Methods of Public Health Research (ESP11)	2016	0.7
Introduction to Public Health (ESP41)	2016	0.7
Methods of Health Services Research (ESP42)	2016	0.7
Primary and Secondary Prevention Research (ESP45)	2016	0.7
Social Epidemiology (ESP61)	2016	0.7
Site Visit to the Municipal Health Service Rotterdam (PU03)	2017	0.3
Integration Module (PU04)	2017	0.3
International Comparison of Health Care Systems (HS03A)	2018	1.4
Public Health Research: Analysis of Population Health (HS02A)	2019	1.9
Public Health Research: Analysis of Determinants (HS02B)	2018	1.9
Public Health Research: Intervention Development and Evaluation (HS02C)	2019	1.9
Other elective courses		
Health Economics (ESP25)	2017	0.7
The Practice of Epidemiologic Analysis (ESP65)	2017	0.7
Logistic Regression (ESP66)	2017	1.4
Fundamentals of Medical Decision Making (ESP70)	2017	0.7
Joint Models for Longitudinal and Survival Data (ESP72)	2017	0.7
Principles of Epidemiologic Data-analysis (EWP25)	2016	0.7
Planning and Evaluation of Screening (HS05)	2017	1.4
Courses for the Quantitative Researcher (SC17)	2017	1.4
Erasmus MC PhD course Scientific integrity	2019	0.3
Conference presentations		
Poster presentation at 9th European Congress on Tropical Medicine and International Health, Basel Switzerland	2015	1
Oral presentation at 19th International Leprosy Congress, Beijing, China	2016	1

PhD training	Year	Workload or ECTS
ePosters at 4th Global Symposium on Health Systems Research, Vancover, Canada	2016	1
Poster presentation at 10th European Congress on Tropical Medicine and International Health, Antwerp, Belgium	2017	1
Oral presentation at 20th International Leprosy Congress, Manila, Philippines	2019	1

Other scientific activities

Review of scientific articles for PLOS Neglected Tropical Diseases, Welcome open research, African Health Sciences, Annals of Clinical Microbiology and Antimicrobials and BMC Health Service Research.

Other organizational activities

Contribution to the preparation of the departmental activity report 2018-19.
Participation in the organization of the Erasmus MC PhD day 2019.
Contribution to the design of social intranet platform Agora, Erasmus MC.
Contribution to the planning and organizing activities for Diversity and Inclusion (D&I) group, Erasmus MC.

LPEP programme field visits in India, Nepal and Indonesia.

Photo 1: A leprosy health worker collecting data from leprosy affected household in Dadra Nagar Haveli, India (2016). Photo by AT

Photo 2: Monitoring field visit to a health centre in Dadra Nagar Haveli, India (2016). In the picture (left to right): Former Deputy Director-General (Leprosy), LPEP research assistant, Former country director NLR India, State Leprosy Officer (DNH). Photo credit: Liesbeth Mieras.

Photo 3: Leprosy health workers conducting house visits with the monitoring team in Dadra Nagar Haveli (2017). Photo credit: Liesbeth Mieras

Photo 4: A young Indian boy with feet deformity admitted in Anandban hospital, Kathmandu, Nepal (2019). He had to discontinue formal education due to deformity in feet, but did not abandon his dream to be successful in life. Photo by AT with consent

Photo 5: Leprosy health worker explaining the sign and symptoms of leprosy in a community meeting in Jhapa district, Nepal (2018). Photo by AT

Photo 6: A lady practising self-care with a smile and confidence in one of the catchment villages of Lalgarh hospital in Nepal (2018). Photo by AT with consent

Photo 7: A leprosy health worker reading the LPEP consent form to a family in Morang district, Nepal (2016). Photo by AT with consent

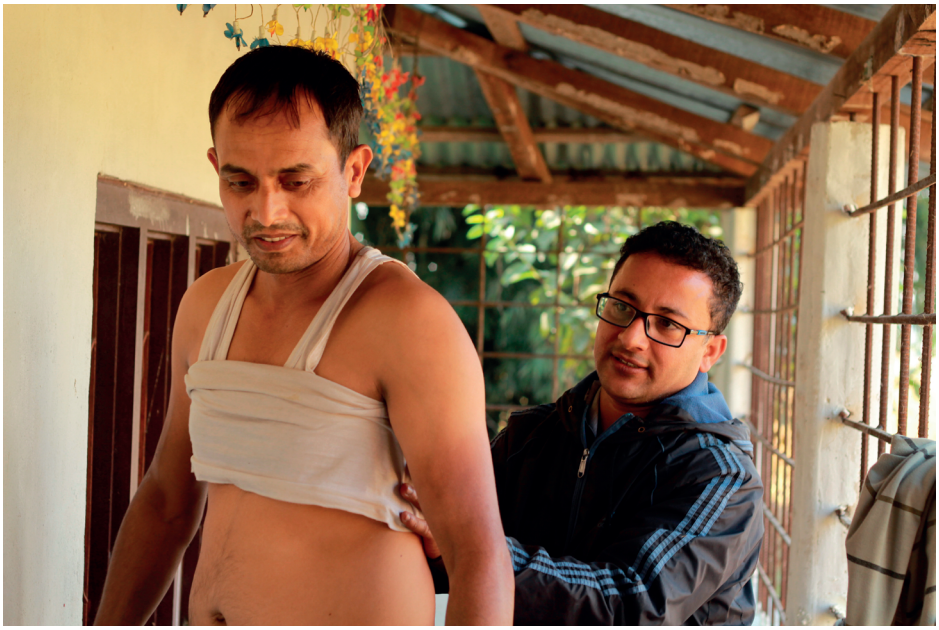

Photo 8: A leprosy health worker conducting a physical examination to suspect leprosy in a contact of a leprosy patient in Jhapa district, Nepal (2018). Photo by AT with consent

Photo 9: A contact of a leprosy patient drinking water after consuming the single-dose rifampicin capsule for leprosy prevention in Jhapa district, Nepal (2018). Photo by AT

Photo 10: Member of the monitoring team interacting with the village children over their studies in the catchment area of the Lalgarh leprosy hospital, Nepal (2018). Photo by AT

Photo 11: Picture of a community meeting conducted by a leprosy health worker in Sumenep district, Madura Island, Indonesia (2016). Photo by AT

Photo 12: A small ferry boat in the backwaters of Sumenep district (2017). Photo by AT

Photo 13: A visit to Guluk-Guluk health centre (Puskemas) in Sumenep district, Madura island, Indonesia (2015) which was implementing LPEP in its area. Photo by AT

Photo 14: It is not unusual to encounter roadside local restaurants which may be a dream holiday destination for some people. Location: somewhere in Sumenep districts, Madura Island, Indonesia (2017). Photo by AT

Photo 15: Selfie time after the community meeting. Photo by AT

Photo 16: When caught sleeping during the field visit. The typical answer was "I was meditating"
Photo credit: Liesbeth Mieras