Investment case concepts in leprosy elimination: A systematic review

Anuj Tiwari
Jan Hendrik Richardus

Leprosy Review (2016) 87: 1-21.

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.

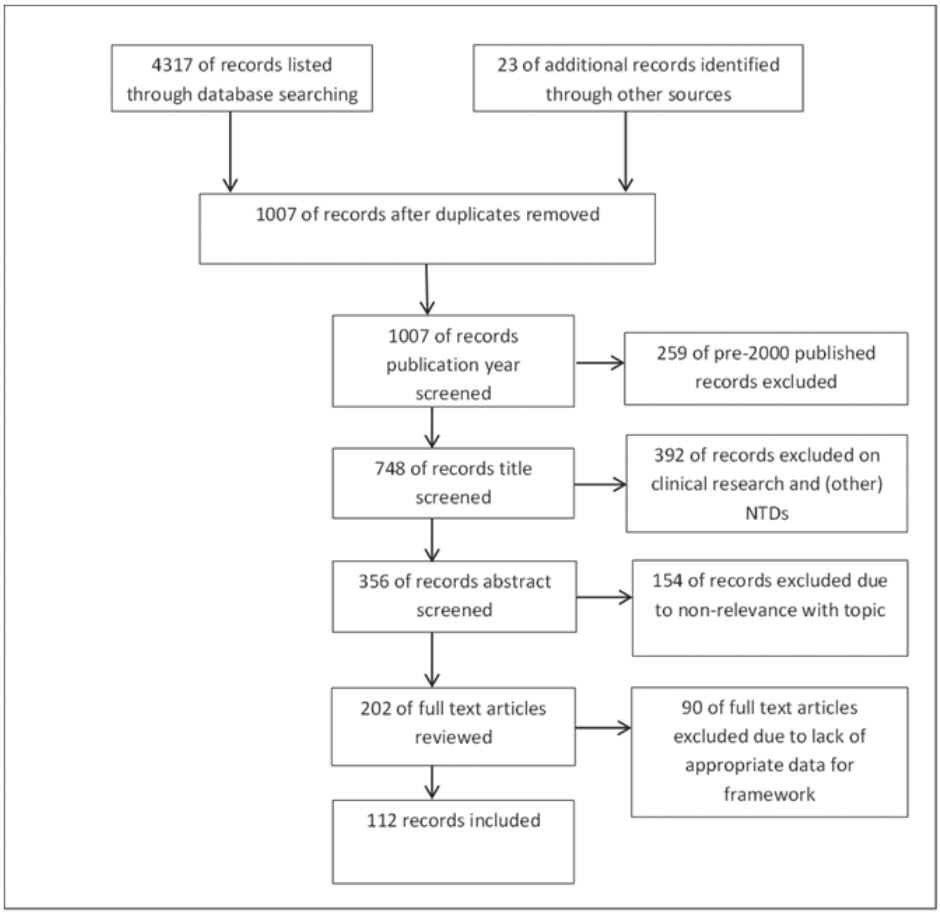

Figure 1: Flow chart of the literature review

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.

REFERENCES

1. Global leprosy update, 2014: need for early case detection. Wkly Epidemiol Rec. 2015;90: 461-474.
2. Smith CS, Noordeen SK, Richardus JH, Sansarricq H, Cole ST, Soares RC, et al. A strategy to halt leprosy transmission. Lancet Infect Dis. 2014;14: 96-98.
3. Kerr-Pontes LR, Montenegro AC, Barreto ML, Werneck GL, Feldmeier H. Inequality and leprosy in Northeast Brazil: an ecological study. Int J Epidemiol. 2004;33: 262-269.
4. Lockwood DN, Shetty V, Penna GO. Hazards of setting targets to eliminate disease: lessons from the leprosy elimination campaign. BMJ. 2014;348: g1136.
5. World Health Org. Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: A Roadmap for Implementation. http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf?ua=1 2012; [cited Accessed 25 September 2015].
6. Thompson KM, Rabinovich R, Conteh L, Emerson CI, Hall BF, Singer PA, et al. Group Report: Developing an Eradication Investment Case. Strungmann Forum Rep. 2011: 133-148.
7. Alberts CJ, Smith WC, Meima A, Wang L, Richardus JH. Potential effect of the World Health Organization's 2011-2015 global leprosy strategy on the prevalence of grade 2 disability: a trend analysis. Bull World Health Organ. 2011;89: 487-495.
8. Thompson KM, Tebbens RJD. Development of Investment Cases for Globally-Coordinated Management of Infectious Diseases. J Vaccines Vaccin. 2012;3: 164.
9. Walker D, Lupp J. Guide for preparing an eradication investment case. http://eic-guidelines.org/ 2011; [cited Accessed 14 August 2015].
10. Richardus JH, Habbema JDF. The impact of leprosy control on the transmission of M. leprae: is elimination being attained? Lepr Rev. 2007;78: 330-337.
11. Lockwood DNJ. Leprosy elimination - a virtual phenomenon or a reality? BMJ. 2002;324: 1516-1518.
12. Basel P, Pahan D, Moet FJ, Oskam L, Richardus JH. Leprosy incidence: six years follow-up of a population cohort in Bangladesh. Lepr Rev. 2014;85: 158-169.
13. Durrheim DN, Speare R. Global leprosy elimination: time to change more than the elimination target date J Epidemiol Community Health. 2003;57: 316-317.
14. Fine PEM. Leprosy: what is being "eliminated"? Bulletin of the World Health Organization. 2007;85: 2-2.
15. Penna MLF, Penna GO. Trend of case detection and leprosy elimination in Brazil. Trop Med Int Health. 2007;12: 647-650.
16. Lockwood DNJ, Suneetha S. Leprosy: too complex a disease for a simple elimination paradigm. Bulletin of the World Health Organization. 2005;83: 230-235.
17. Kumar A, Girdhar BK. Is increasing MB ratio a positive indicator of declining leprosy? J Commun Dis. 2006;38: 24-31.
18. Rinaldi A. The global campaign to eliminate leprosy. PLoS Med. 2005;2: e341.
19. Rodrigues LC, Lockwood D. Leprosy now: epidemiology, progress, challenges, and research gaps. Lancet Infect Dis. 2011;11: 464-470.
20. Global leprosy update, 2013; reducing disease burden. Wkly Epidemiol Rec. 2014;89: 389-400.
21. Saunderson PR. Leprosy elimination: not as straightforward as it seemed. Public Health Rep. 2008;12: 213-216.

22. Smith WC, van Brakel W, Gillis T, Saunderson P, Richardus JH. The Missing Millions: A Threat to the Elimination of Leprosy. PLoS Negl Trop Dis. 2015;9: e0003658.
23. World Health Org. The Enhanced Global Strategy for Further Reducing the Disease Burden Due to Leprosy (Plan period: 2011 – 2015): Operational Guidelines (Updated). http://www.searo.who.int/entity/leprosy/documents/SEA_GLP_2009_3/en/ 2009; [cited Accessed 9 October 2015].
24. Pannikar V. Enhanced global strategy for further reducing the disease burden due to leprosy: 2011-2015. Lepr Rev. 2009;80: 353-354.
25. Blanc LJ. Summary of leprosy chemoprophylaxis programs in the Western Pacific Region. Int J Lepr Other Mycobact Dis. 1999;67: S30-31.
26. Banerjee S, Sarkar K, Gupta S, Mahapatra PS, Gupta S, Guha S. Multiplex PCR technique could be an alternative approach for early detection of leprosy among close contacts-a pilot study from India. BMC Infect Dis. 2010;10: 252.
27. Goulart IM, Goulart LR. Leprosy: diagnostic and control challenges for a worldwide disease. Arch Dermatol Res. 2008;300: 269-290.
28. Richardus JH, Meima A, van Marrewijk CJ, Croft RP, Smith TC. Close contacts with leprosy in newly diagnosed leprosy patients in a high and low endemic area: comparison between Bangladesh and Thailand. Int J Lepr Other Mycobact Dis. 2005;73: 249-257.
29. Lockwood DNJ, Krishnamurthy P, Pannikar V, Penna GO. Reply to the role of contact tracing and prevention strategies in the interruption of leprosy transmission. Lepr Rev. 2015;86: 124-125.
30. Duthie MS, Saunderson P, Reed SG. The potential for vaccination in leprosy elimination: new tools for targeted interventions. Mem Inst Oswaldo Cruz. 2012;107: 109-106.
31. Reveiz L, Buendía JA, Téllez D. Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis. Rev Panam Salud Publica. 2009;26: 341-349.
32. Moet FJ, Oskam L, Faber R, Pahan D, Richardus JH. A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: design, methodology and recruitment findings of COLEP. Lepr Rev. 2004;75: 376-388.
33. Idema WJ, Majer IM, Pahan D, Oskam L, Polinder S, Richardus JH. Cost-effectiveness of a chemoprophylactic intervention with single dose rifampicin in contacts of new leprosy patients. PLoS Negl Trop Dis. 2010;4: e874.
34. Bakker MI, Hatta M, Kwenang A, Van Benthem BH. Prevention of leprosy using rifampicin as chemoprophylaxis. Am J Trop Med Hyg. 2005;72: 443-448.
35. Douglas JT, Cellona RV, Fajardo Jr TT, Abalos RM. Prospective study of serological conversion as a risk factor for development of leprosy among household contacts. Clin Diagn Lab Immunol. 2004;11: 897-900.
36. Gillis T. Is there a role for a vaccine in leprosy control? Lepr Rev. 2007;78: 338-342.
37. Oskam L, Slim E, Buhrer-Sekula S. Serology: recent developments, strengths, limitations and prospects: a state of the art overview. Lepr Rev. 2003;74: 196-205.
38. Moura RS, Calado KL, Oliveira ML, Buhrer-Sekula S. Leprosy serology using PGL-I: a systematic review. Rev Soc Bras Med Trop. 2008;41: 11-18.
39. Spencer JS, Duthie MS, Geluk A, Balagon MF, Kim HJ. Identification of serological biomarkers of infection, disease progression and treatment efficacy for leprosy. Mem Inst Oswaldo Cruz. 2012;107: 79-89.
40. Dockrell HM, Geluk A, Brennan P, Saunderson PR. Report on the sixth meeting of the IDEAL (Initiative for Diagnostic and Epidemiological Assays for Leprosy) consortium held in Beijing, China on 23-25 August 2010. Lepr Rev. 2011;82: 80-85.

41. Geluk A, Bobosha K, van der Ploeg-van Schip JJ, Spencer JS. New biomarkers with relevance to leprosy diagnosis applicable in areas hyperendemic for leprosy. J Immunol. 2012;188: 4782-4791.
42. Geluk A. Biomarkers for Leprosy: would you prefer T (cells)? Lepr Rev. 2013;84: 1-10.
43. Fischer EAJ, Vlas SJD, Habbema JDF, H. RJ. The long term effect of current and new interventions on the new case detection of leprosy: a modeling study. PLoS Negl Trop Dis. 2011;5: e1330.
44. van Brakel W, Cross H, Declercq E, Deepak S. Review of leprosy research evidence (2002-2009) and implications for current policy and practice. Lepr Rev. 2010;81: 228-275.
45. Singh GP. Psychosocial aspects of Hansen's disease (leprosy). Indian Dermatol Online J. 2012;3: 166-170.
46. Daumerie D. World Health Org. Elimination of leprosy as a public health problem—current status and challenges ahead, Scientific Working Group Report on leprosy. http://www.who.int/lep/resources/SWG04.pdf 2003; 57–72. [cited Accessed 13 October 2015].
47. Prasad PVS, Kaviarasan PK. Leprosy therapy, past and present: Can we hope to eliminate it? Indian J Dermatol. 2010;55: 316-324.
48. Joshi PL, Thorat DM, Manglani PR. Need and strategy for sentinel surveillance for drug resistance in leprosy in India. Indian J Lepr. 2009;81: 113-118.
49. Paula Vaz Cardoso L, Dias RF, Freitas AA, Hungria EM. Development of a quantitative rapid diagnostic test for multibacillary leprosy using smart phone technology. BMC Infect Dis. 2013;23: 497.
50. Bakker MI, Scheelbeek PF, Beers SMV. The use of GIS in leprosy control. Lepr Rev. 2009;80: 327–331.
51. Jim R, Johnson E, Pavlin BI. Role of GIS technology during leprosy elimination efforts in Pohnpei. Pac Health Dialog. 2010;16: 109-114.
52. De Souza Dias MC, Dias GH, Nobre ML. The use of Geographical Information System (GIS) to improve active leprosy case finding campaigns in the municipality of Mossoró, Rio Grande do Norte State, Brazil. Lepr Rev. 2007;78: 261-269.
53. Smith WCS. Chemoprophylaxis in the prevention of leprosy. BMJ. 2008;336: 730–731.
54. Samy AA. 'Leprosy elimination'--need for sample survey. Lepr Rev. 2007;78: 167-169.
55. Kumar B. World Leprosy Day 2015: Renewing commitment for a leprosy free world! Indian J Med Res. 2015;141: 1-4.
56. Lockwood DNJ. Commentary: leprosy and poverty. Int J Epidemiol. 2004;33: 269-270.
57. Veen NHV, McNamee P, Richardus JH, Smith WC. Cost-effectiveness of interventions to prevent disability in leprosy: a systematic review PLoS One. 2009;4: e4548.
58. Palit A, Inamadar AC. Histoid leprosy as reservoir of the disease; a challenge to leprosy elimination. Lepr Rev. 2007;78: 47-49.
59. Bratschi MW, Steinmann P, Wickenden A, Gillis TP. Current knowledge on Mycobacterium leprae transmission: a systematic literature review. Lepr Rev. 2015;86: 142-155.
60. Cardona-Castro N, Beltrán JC, Ortiz-Bernal A, Vissa V. Detection of Mycobacterium leprae DNA in nine-banded armadillos (Dasypus novemcinctus) from the Andean region of Colombia. Lepr Rev. 2009;80: 424-431.
61. Tadesse Argaw A, Shannon EJ, Assefa A, Mikru FS, Mariam BK. A geospatial risk assessment model for leprosy in Ethiopia based on environmental thermal-hydrological regime analysis. Geospat Health. 2006;1: 105-113.
62. Nsagha DS, Bamgboye EA, Assob JC, Njunda AL. Elimination of leprosy as a public health problem by 2000 AD: an epidemiological perspective. Pan Afr Med J. 2011;9: 4.

63. Sandle T. Global Strategies for Elimination of Leprosy: A Review of Current Progress. J Anc Dis Prev Rem. 2013;1: e112.
64. Smith C, Richardus JH. Leprosy strategy is about control, not eradication. Lancet Infect Dis. 2008;371: 969-970.
65. Awofeso N. The place of leprosy in the control-elimination-eradication spectrum. Bull World Health Organ. 2005;83: 558.
66. Nicholls PG BZ, van Brakel W, Das-Pattanaya RK, K. Risk factors for participation restriction in leprosy and development of a screening tool to identify individuals at risk. Lepr Rev. 2005;76: 305-315.
67. Meima A, van Veen NH, Richardus JH. Future prevalence of WHO grade 2 impairment in relation to incidence trends in leprosy: an exploration. Trop Med Int Health. 2008;13: 241-246.
68. Engers H MC. Leprosy. Nat Rev Microbiol. 2003;1: 94-95.
69. Mathers CD, Ezzati M, Lopez AD. Measuring the Burden of Neglected Tropical Diseases: The Global Burden of Disease Framework. PLoS Negl Trop Dis. 2007;1: e114.
70. Richardus JH. Leprosy remains an important public health challenge in India. Indian J Med Res. 2013;137: 878-879.
71. Hogeweg M, Keunen JEE. Prevention of blindness in leprosy and the role of the Vision 2020 Programme. Eye (Lond). 2005;19: 1099-1105.
72. Rao PSS, Darlong F, Timothy M, Kumar S. Disability adjusted working life years (DAWLYs) of leprosy affected persons in India. Indian J Med Res. 2013;137: 907-910.
73. Feenstra P. " Elimination" of Leprosy and the Need to Sustain Leprosy Services, Expectations, Predictions, and Reality. Int J Lepr Other Mycobact Dis. 2003;71: 248-256.
74. Nery JS, Pereira SM, Rasella D, l. Effect of the Brazilian Conditional Cash Transfer and Primary Health Care Programs on the New Case Detection Rate of Leprosy. PLoS Negl Trop Dis. 2014;8: e3357.
75. Bennett BH, Parker DL, Robson M. Leprosy: Steps Along the Journey of Eradication. Public Health Reports. 2008;123: 198-205.
76. Roosta N, Black DS, Rea TH. A comparison of stigma among patients with leprosy in rural Tanzania and urban United States: a role for public health in dermatology. Int J Dermatol. 2013;52: 432-440.
77. Try L. Asia Pacific Disability Rehabilitation Journal Gendered experiences: marriage and the stigma of leprosy. http://english.aifo.it/disability/apdrj/apdrj206/gender-lep.pdf 2006; [cited Accessed 15 August 2015].
78. Burki T. Old problems still mar fight against ancient disease. Lancet. 2009;373: 287-288.
79. Raju MS, Rao PSS. 3 Medical and social concerns of leprosy cured after integration in India. Indian J Lepr. 2011;83: 145-155.
80. Erinfolami AR, Adeyemi JD. A case control study of psychiatric morbidities among subjects with leprosy in Lagos, Nigeria. Int J Psychiatry Med. 2009;39: 89-99.
81. Tsutsumi A, Izutsu T, Islam AM, Maksuda AN. The quality of life, mental health, and perceived stigma of leprosy patients in Bangladesh. Soc Sci Med. 2007;64: 2443-2453.
82. Penna ML, de Oliveira ML, Penna GO. The epidemiological behaviour of leprosy in Brazil. Lepr Rev. 2009;80: 332-344.
83. Sachdeva S, Sood AK. Leprosy elimination monitoring (LEM) in India: A novel exercise of monitoring, learning, and capacity building. Indian J Community Med. 2014;39: 59-62.

84. World Health Org. Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected tropical diseases. http://apps.who.int/iris/bitstream/10665/152781/1/9789241564861_eng.pdf?ua=1 2015; [cited Accessed 9 October 2015].

85. Chandler DJ, Hansen KS, Mahato B, Darlong J. Household costs of leprosy reactions (ENL) in rural India. PLoS Negl Trop Dis. 2015;9: e0003431.

86. Withington SG, Joha S, Baird D, Brink M, Brink J. Assessing socio-economic factors in relation to stigmatization, impairment status, and selection for socio-economic rehabilitation: A 1 year cohort of new leprosy cases in north Bangladesh. Lepr Rev. 2003;74: 120-132.

87. Arole S, Premkumar R, Arole R, Maury M, Saunderson P. Social stigma: a comparative qualitative study of integrated and vertical care approaches to leprosy. Lepr Rev. 2002;73: 186-196.

88. Shen J, Zhou M, Xu X, Ray A. A big challenge in case finding at low endemic situation: analysis on 1462 new leprosy patients detected in China in 2007. Lepr Rev. 2010;81: 176-183.

89. Shetty VP. Challenges facing the control of leprosy in the Indian context. Ann Acad Med Singapore. 2010;39: 1-3.

90. Atun R, Jongh Td, Secci F, Ohiri K, Adeyi A. A systematic review of the evidence on integration of targeted health interventions into health systems. Health Policy Plan. 2010;25: 1-14.

91. Rao PS. A Study on Non-adherence to MDT among Leprosy Patients. Indian J Lepr. 2008;80: 149-154.

92. Pandey A, Patel R, Uddin MJ. Leprosy control activities in India: integration into general health system. Lepr Rev. 2006;77: 210-218.

93. Rachmani E, Hsu CY, Kurniadi A. How health information system could help the leprosy control program in Indonesia? ICICI-BME. 2013.

94. Barkakaty BN. How can the private practitioners support leprosy elimination in India. J Indian Med Assoc. 2006;104: 673-674.

95. Deepak S. Answering the rehabilitation needs of leprosy-affected persons in integrated setting through primary health care services and community-based rehabilitation. Indian J Lepr. 2003;75: 127-142.

96. World Health Org. WHO Expert Committee on Leprosy-Eighth report. http://www.searo.who.int/entity/global_leprosy_programme/publications/8th_expert_comm_2012.pdf 2012; [cited Accessed 14 January 2016].

97. Renita L, Pulimood SA, Eapen EP, Muliyil J, John KR. Health care utilisation in Indian leprosy patients in the era of elimination. Lepr Rev. 2010;81: 299-305.

98. Nsagha DS, Bamgboye EA, Oyediran AB. Operational barriers to the implementation of multidrug therapy and leprosy elimination in Cameroon. Indian J Dermatol Venereol Leprol. 2009;75: 469-475

99. Scollard DM. Chemotherapy of leprosy has changed (almost) everything. Lepr Rev. 2012;83: 245-246.

100. Scollard DM. Leprosy research declines, but most of the basic questions remain unanswered. Int J Lepr Other Mycobact Dis. 2005;73: 25-27.

101. Harris K. Pride and prejudice-identity and stigma in leprosy work. Lepr Rev. 2011;82: 135-146

102. Mensah-Awere D BM, Steinmann P, Fairley JK, Gillis TP. Symposium Report: Developing Strategies to Block the Transmission of Leprosy. Lepr Rev. 2015;86: 156-164.

103. Richardus JH, Oskam L. Protecting people against leprosy: Chemoprophylaxis and immunoprophylaxis. Clin Dermatol. 2015;33: 19-25.

104. Atre SR, Rangan SG, Shetty VP, Gaikwad N, Mistry NF. Perceptions, health seeking behaviour and access to diagnosis and treatment initiation among previously undetected leprosy cases in rural Maharashtra, India. Lepr Rev. 2011;82: 222-234

105. Chalise SC. Leprosy disease in Nepal: knowledge and non-compliance of patients. J Nepal Med Assoc. 2005;44: 39-43

106. Yadav N, Kar S, Madke B, Dashatwar D. Leprosy elimination: A myth busted. . J Neurosci Rural Pract. 2014;5: S28-32.

107. Smith WC. Sustaining anti-leprosy activities requires radical changes. Lepr Rev. 2010;81: 281-283

108. Dhillon GP. Public private partnership for elimination of leprosy. J Indian Med Assoc. 2004;102: 670.

109. Peters RM, Dadun, Lusli M, Miranda-Galarza B. The meaning of leprosy and everyday experiences: an exploration in Cirebon, Indonesia. J Trop Med. 2013;2013: 507034.

110. Rao PS. Referral system: a vital link in the sustainability of leprosy services Lepr Rev. 2010;81: 292-298.

111. Ganapati R, Pai VV, Rao R. Dermatologist's role in leprosy elimination/post-elimination. Lepr Rev. 2007;78: 17-21.

112. Penna ML, Temporão JG, Grossi MA, x. Leprosy control: knowledge shall not be neglected. J Epidemiol Community Health. 2011;65: 473-474.