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Leprosy Post-Exposure Prophylaxis (LPEP) programme: 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 leprosy patients have shown a 50-60% reduction of the risk of developing leprosy over the following two 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, Tanzania; and complementary sites are foreseen in Brazil and Cambodia. From 2015-2017, contact persons of leprosy patients 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 committee in the countries. Results and lessons learned from the LPEP programme will be published in peer-reviewed journals and should provide important evidence and guidance for national and global policy makers to strengthen current leprosy elimination strategies.

Key words: leprosy, transmission, post-exposure prophylaxis, contact tracing, screening, rifampicin, prevention

Strengths and limitations of this study:

- Includes sites in 6 leprosy endemic countries in Asia and Africa and is complemented by sites in 2 additional countries in South America and Asia.
- Answers key questions of contact tracing and SDR PEP feasibility and impact across various health systems.
- Implementation and coordination by national programmes will help to facilitate PEP integration into national strategies and thus ensure sustainability.
- Expert guidance and close monitoring ensures quality data collection and analysis.
- Results may not be fully comparable to countries with fundamentally different health systems and low-endemic areas.
- Differing contact definitions limited the potential to pool results, and focus on household members may reduce the impact of SDR PEP.

INTRODUCTION

Over the past 30 years, the prevalence of leprosy has declined by 95%, from 5.2 million in 1985 to less than 200,000 in 2015.[1, 2] This remarkable reduction has often been cited as a major public health success. Indeed, in 2000, the World Health Organization's (WHO) goal to eliminate leprosy as a public health problem, defined as a prevalence of less than 1 leprosy patient per 10,000 population, was officially reached.[3] This resulted in a sharp decline in political 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 over subsequent years.[4-7] The reduction of the leprosy prevalence can be attributed to the widespread availability of free multidrug therapy (MDT), along with a shortening of the treatment duration from two to one year for multibacillary (MB) leprosy and to 6 months for paucibacillary (PB) leprosy, since the beginning of the nineties.[8] The reported annual number of new cases has plateaued at 200,000-250,000 globally in the last 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 remaining detection of patients with advanced disease is indicative of long diagnostic delays.[7] As a result, alternative control strategies are needed to interrupt transmission of *Mycobacterium leprae*, the causative agent of leprosy, and accelerate case detection.

The main risk factor for leprosy is prolonged close contact with an infectious patient, be it in the household or through social interaction.[9] And although early case detection and prompt treatment with MDT are the cornerstone of the current WHO recommendations,[10, 11] 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 two years following its administration.[12-15] Chemoprophylaxis has already been used in the sixties and seventies but with weekly dapsone for two to three years. That approach was 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 leprosy new case

detection rate (NCDR) of 40% in contacts (4,337 participants, RR 0.60, 95% CI 0.48–0.76),[16, 17, 20] while that of acedapsone was 51% (1,259 participants, RR 0.49, 95% CI 0.33–0.72).[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] Of the 2,786 inhabitants, 98.7% received preventive treatment; another 3,144 South Marquesans living elsewhere in French Polynesia were also given SDR. A follow-up survey ten years later suggested a 70% effectiveness of the 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 only 35-40%.[26] In the mid-1990s, chemoprophylaxis was introduced on different Pacific islands (Federated States of Micronesia, Kiribati, and the Republic of the Marshall Islands), where leprosy NCDR was still very high.[27] During two rounds of screening, with a one-year interval, 70% of the population was screened for leprosy and treated prophylactically. Healthy adults received a regimen of rifampicin, ofloxacin and minocycline (ROM), while children under 15 years received SDR.[28] By 1999, a substantial reduction in the NCDR was observed on the islands, but it was unclear whether transmission of *M. leprae* had been interrupted.[27] Recent data indicate that this has not been the case as neither Micronesia, nor the Marshall Islands reached the leprosy elimination target, while Kiribati failed to maintain it.[29] In 2000, a chemoprophylaxis study using rifampicin was initiated on five high-endemic Indonesian islands with a total of 3,965 inhabitants.[14] The population was screened before the intervention and subsequently once a year for three years; two doses of rifampicin were administered to asymptomatic inhabitants with a 3.5 months interval, 600 mg to adults and 300 mg to children between 6 and 14 years old. Two strategies were compared, a “blanket” approach where SDR was given to the entire population (on three islands) and a “contact” strategy where SDR was given only to eligible contacts of leprosy patients (on another island). No chemoprophylaxis was given to the control population (yet another island). The NCDR on the control island was 39/10,000. After three 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. In this study, mass administration of chemoprophylaxis was associated with a reduction in leprosy NCDR in the three years following its deployment, while prophylaxis for spatially defined contacts (household members and neighbours) did not influence leprosy NCDR in this highly endemic region.[14]

The COLEP trial in Bangladesh was a single-centre, double-blind, cluster-randomised, placebo-controlled study designed to determine the effectiveness of SDR for the prevention of leprosy 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 two years after SDR administration was 57% (95% CI: 33-72%). There was no further risk reduction after two years,[12] nor six years.[31] The overall number needed to treat (NNT) to prevent a single diagnosis of leprosy among contacts was 265 (95% CI: 176-537) after two years and 297 (95% CI: 170-206) after four years.[12] The protective effect of SDR was larger in non-blood related contacts, in contacts of index patients with PB leprosy, and in social contacts rather than household contacts or neighbours. In other words, the effect of SDR is highest in those contact groups with lowest *a priori* risk for leprosy.[12] Importantly, childhood vaccination with Bacillus Calmette-Guérin (BCG) also has a protective effect of nearly 60%, and previously immunised contacts appeared to benefit from an additive protective effect of SDR in this trial, resulting in an 80% risk reduction for developing leprosy.[32]

Considering all available evidence, it appears that chemoprophylaxis should target defined contact groups but under certain conditions, mass administration of prophylaxis may be warranted. High NCDRs, difficult geographical accessibility, insufficient availability of primary healthcare services, or a high level of stigma can all be reasons to prefer mass administration over targeted PEP.[13] The feasibility of reducing the risk of developing leprosy through preventive strategies was discussed in two international expert meetings hosted by the Novartis Foundation, including physicians, epidemiologists, and public health professionals in 2013 and 2014. The meetings concluded that contact tracing followed by PEP for asymptomatic contacts offers a degree of protection, across diverse settings, comparable to that reported in controlled trials.[1, 33] According to the meeting

participants, any solid programme embracing an approach to interrupt transmission would need to include: (i) early diagnosis and prompt treatment for all patients; (ii) tracing and post-exposure prophylaxis for contacts of newly diagnosed patients, and (iii) strict epidemiological surveillance and response systems to monitor progress.[1, 33]

To accelerate the translation of 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 and PEP under routine programme conditions, across a diversity of health systems, national leprosy programmes, and geographical characteristics, and to determine operational parameters needed at a local level.

OBJECTIVES

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

(i) Its impact on the new case detection rate, measured through strengthened surveillance and reporting systems

(ii) Its feasibility in diverse routine programme settings

Overall, the LPEP programme provides a comprehensive package, including support to organise systematic contact tracing and screening for early case detection, followed by referral for symptomatic contacts or PEP administration for asymptomatic contacts (**Figure 1**). In addition, the programme also promotes capacity building for front-line leprosy workers to strengthen screening and diagnosis services and for surveillance system managers to improve data collection and reporting.

METHODS AND ANALYSIS

Study coordination

The governance structure of the LPEP programme is shown in **Figure 2**: a steering committee composed of leprosy experts, policy makers, 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 and advises on strategic and operational matters. It also establishes the dissemination strategy and reviews programme publications. The Novartis Foundation manages 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 in-country ILEP partners. The Swiss Tropical and Public Health Institute (Swiss TPH) and the Erasmus University's Medical Centre (Erasmus MC) support the local programme protocol development, provide training and assist with the strengthening of surveillance systems operated by the national programmes in the pilot areas. 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. An international annual meeting facilitates progress and data reviews with exchange among the partners.

Study areas

Participation in the LPEP programme was open to countries meeting the following criteria: (i) sub-national administrative units (e.g. districts) with a high case detection rate, relatively easy access and a functioning leprosy control infrastructure, (ii) capacity for routine contact tracing and screening in the local leprosy programme, (iii) declared interest from the Ministry of Health, and (iv) 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 from 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 of 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)	Nyanung-U District	Myingyan District	Tharyar-waddy District	Jhapa District	Morang District	Parsa District	Kalutara District	Puttalam District	Kilombero District	Liwale District	Nanyumbu 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

G2D: grade 2 disability; MB: multibacillary; NA: not available; NCDR: New Case Detection Rate; *no data due to absence of leprosy services in this isolated village, but a visiting health worker from district level reported 30 suspected leprosy patients.

Study design

In agreement with its objectives of demonstrating feasibility and effectiveness of contact tracing, screening and PEP, 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 that are tailored to the realities of each country. Leprosy patients diagnosed less than two years prior to the start of the field work (retrospective index patients) and patients diagnosed during the programme period (two years prospective index patients) are eligible for inclusion. These index patients have to meet the following inclusion criteria: (i) confirmed leprosy diagnosis and being on MDT treatment for at least four weeks, (ii) residency in the LPEP pilot area, (iii) one or more contacts (as defined by the local definition of contacts), and (iv) willingness to provide informed consent. All contacts are screened for signs of leprosy. Exclusion criteria for SDR administration are: (i) refusal to give informed consent, (ii) age <2 or 6 years (country-specific age ranges are applied, see **Table 2**), (iii) pregnancy (PEP can be given after delivery), (iv) rifampicin use in the last two years (e.g. for tuberculosis (TB) or leprosy treatment, or preventively as a contact of another index patient), (v) history of liver or renal disorders (e.g. jaundice), (vi) leprosy disease, (vii) signs and/or symptoms of leprosy until negative diagnosis, (viii) 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 two weeks, night sweats, unexplained fever, weight loss), and (ix) known allergy to rifampicin.

Table 2 presents the study modalities in the different countries. Leprosy services are integrated into primary health care 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 (**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 done by different functions and persons in Sri Lanka, demanding particularly robust communication and information systems.

Table 2 Different LPEP modalities in the participating countries

Activities	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania
Routine contact tracing in the national programme	HH members and neighbours	HH members and neighbours	HH members	HH members 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	6	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

Abbreviations: CHV: community health volunteer; DTLC: District TB and Leprosy Coordinator; HH: Household; JLW: Junior Leprosy Worker; LI: Leprosy Inspector; LPEP: Leprosy Post-Exposure Prophylaxis; MOH: Medical Officer of Health; PHC: Primary health centre; PHS2: Public Health Supervisor 2; PMW: Para Medical Worker; VHW: voluntary health worker

In most study areas the LPEP programme targets specific contact groups. Because of the 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 administered to all asymptomatic individuals.

Sample size calculation

To establish a decreasing trend of 10-15% per year in the NCDR in each of the LPEP programme areas, with sufficient statistical power (p=0.05), LPEP will enrol between 175 (decrease of 15% in NCDR) and 400 (decrease of 10% in NCDR) new index patients per year. Given that the inter-country differences may not allow pooled analyses for several of the key outcome indicators, this sample size has to be reached within each country.

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 existing national leprosy control programmes, existing data collection and reporting systems were assessed in each country. 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 **Annex 1**. Socio-demographic 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 socio-demographic characteristics, relationship to the index patient, contact category (household, neighbour, social), BCG vaccination scar, outcome of the screening (signs of leprosy and TB), and SDR exclusion criteria. In addition, referrals and adverse events (AEs) following SDR PEP are documented (see ethics).

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 database based on the District Health Information System 2 (DHIS2) software is used. Data entry is done continuously, either at a central location in the country or at the LPEP programme sites; database copies are regularly shared with the technical and ILEP partners for verification and

analysis. Feasibility will be evaluated in terms of coverage (proportion of contacts that are 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.

On top of the routine surveillance 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 continue for at least one year beyond the two years of LPEP field work. During this period LPEP activities will be further integrated into the routine services of the national programmes.

ETHICS

An expert meeting, involving both tuberculosis and leprosy experts, focussed on the potential risk of promoting rifampicin resistance through the use of SDR in leprosy control. It concluded that current evidence suggests the risk of emerging rifampicin resistance in *M. tuberculosis* to be minimal, and that the benefits of reducing leprosy NCDR largely outweigh 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 committee in their country. The ethical committees involved were: (i) the Institutional Human Ethical Committee of the National Institute of Epidemiology in India (NIE/IHEC/201407-01); (ii) the Ethical Committee on Medical Research involving Human Subjects at the Department of Health of the Ministry of Health in Myanmar (13/2014/1087); (iii) the Ethical Review Board at the Nepal Health Research Council in Nepal (39/2015); (iv) the Ethics Review Committee of the Faculty of Medicine at the University of Kelaniya in Sri Lanka (P/134/08/2015); and (v) the Ethical Committee at the National Institute for Medical Research of the Ministry of Health and Social Welfare in Tanzania (approval date: 4 May 2015). 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 (i.e. flu-like syndrome and discoloration of urine) and details of how a leprosy expert can be contacted in case of AEs or other concerns. Adverse events are reported following national pharmacovigilance guidelines and using the LPEP AE Form, while referred for proper follow-up. The management of AEs is free of charge and according to the national treatment guidelines.

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 move towards leprosy elimination and sustainably reduce the number of new patients. The LPEP programme is designed to answer key questions regarding the implementation of chemoprophylaxis for leprosy control and to provide evidence on the feasibility and impact of contact tracing and PEP on new case detection rates across a range of different health systems and levels of leprosy endemicity.

The LPEP programme is accompanied by two ancillary studies, a first one focusing on the economic aspects of the intervention, and another one on the perception of leprosy and PEP by community members. Separate protocols are developed for these 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. As part of the study, the unit costs of the delivery of all relevant services will be captured and their overall costs related to outcomes (e.g. costs per averted

case). Indirect costs for the beneficiaries of leprosy control (e.g. out of pocket expenditures to access the free MDT) will be measured in routine leprosy services. The perception study will focus on knowledge and understanding of leprosy in communities where LPEP is implemented, and on attitudes and behaviour towards persons affected by leprosy, and their impact on programme activities.

In Brazil and Cambodia, similar approaches, complementing the evidence from the LPEP programme, are used. In Brazil, the government-funded "PEP-Hans" project explores the administration of chemo- and immunoprophylaxis with SDR and BCG, respectively, 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 identical and aligned with the LPEP programme, as are the main variables to evaluate efficiency and impact. Chemo- and immunoprophylaxis are not co-administered since there is a minimum waiting time of 24 hours for the administration of BCG after SDR, and one of 30 days for SDR after BCG. In Cambodia, the administration of SDR to household and neighbour contacts will be evaluated within the "Retrospective Active Case Finding" project started in 2011. Given the relatively low number of new leprosy patients diagnosed in this country, an alternative contact definition and tracing strategy is applied. Rather than tracing the contacts of each newly diagnosed leprosy patient individually, 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 (identified through high NCDR as primary criterion and the following sub-criteria: high proportion of child patients, high ratio of MB to PB patients and low proportion of female patients) 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), the Swiss TPH and the Novartis Foundation.

OUTLOOK

After two years of SDR administration to contacts of leprosy patients (covering contacts of new index patients diagnosed over a period of three to four years) the full impact and feasibility of the intervention will start to emerge. 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 amongst contacts of leprosy patients into routine action by providing solid data from a range of settings and conditions, and 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 learned from the LPEP programme will be done through publication in open access journals, as well as through reports and conference abstracts and presentations. The data will provide crucial guidance to Ministries of Health of all endemic countries that are interested in applying a similar approach to interrupt the transmission of leprosy. The results of the LPEP programme will also be of great value for global policy makers when deciding on resource allocation for leprosy elimination.

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Contributions of authors: LM, WvB, JHR, AC, BVP and AA designed the study. TBJ, PS, LM, WvB, JHR, AT, MB, AC, BVP, FM, and AA supported the development of country-specific protocols, and coordinate and monitor the study implementation. TBJ, PS, MB and JHR have drafted the manuscript. All authors have reviewed the draft manuscript, and have read and approved the final version. The LPEP study group ensures the scientific integrity of all aspects of the programme, and all LPEP study group members have received and approved the final version of the manuscript.

Competing interest: All co-authors are either staff of the Novartis Foundation or work as paid consultants for the programme described here.

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FIGURES

Figure 1 Conceptual framework of the impact of the LPEP programme on the transmission of *Mycobacterium leprae*

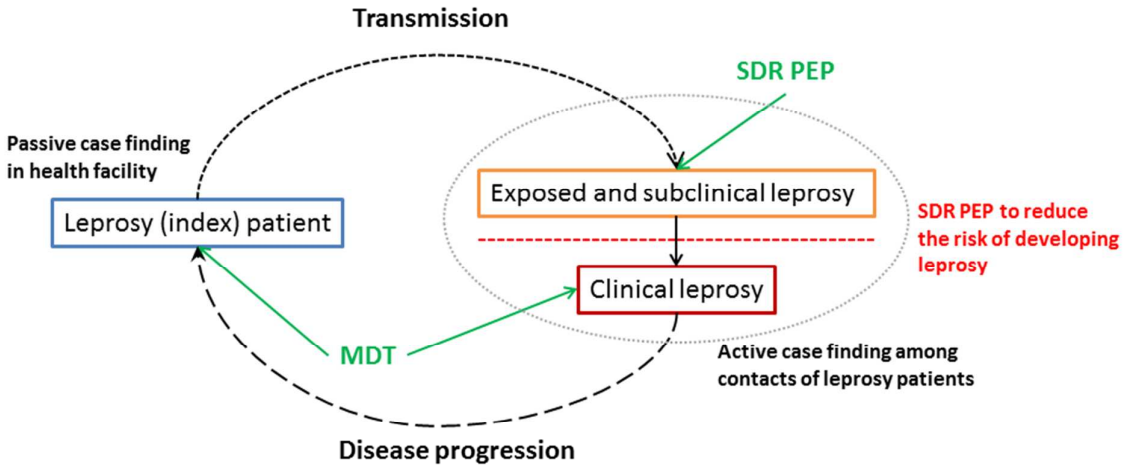

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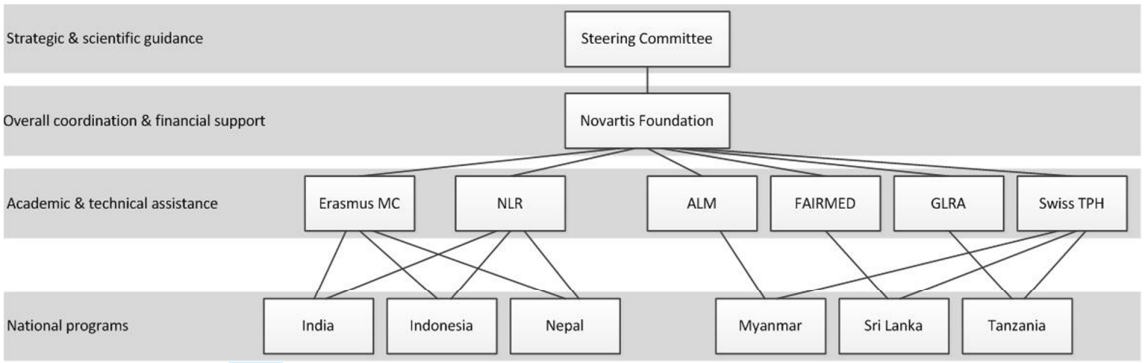
Figure 2 Governance structure of the LPEP programme



Abbreviations: ALM: American Leprosy Mission, Erasmus MC: Erasmus Medical Centre, GLRA: German Leprosy and Tuberculosis Relief Association, ILEP: International Federation of Anti-Leprosy Associations, NLR: Netherlands Leprosy Relief, Swiss TPH: Swiss Tropical and Public Health Institute

ANNEX

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

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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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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 leprosy patients have shown a 50-60% reduction of the risk of developing leprosy over the following two 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, Tanzania. Complementary sites are foreseen in Brazil and Cambodia. From 2015-2018, contact persons of leprosy patients 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 committee in the countries. Results and lessons learned from the LPEP programme will be published in peer-reviewed journals and should provide important evidence and guidance for national and global policy makers to strengthen current leprosy elimination strategies.

Key words: leprosy, transmission, post-exposure prophylaxis, contact tracing, screening, rifampicin, prevention

Strengths and limitations of this study:

- Includes sites in 6 leprosy endemic countries in Asia and Africa and is complemented by sites in 2 additional countries in South America and Asia.
- Answers key questions of contact tracing and SDR PEP feasibility and impact across various health systems.
- Implementation and coordination by national programmes will help to facilitate PEP integration into national strategies and thus ensure sustainability.
- Expert guidance and close monitoring ensures quality data collection and analysis.
- Results may not be fully relevant for countries with fundamentally different health systems and low-endemic areas.
- Differing contact definitions limit the potential to pool results, and a focus on household members in some LPEP countries may reduce the impact of SDR PEP.

INTRODUCTION

Over the past 30 years, the prevalence of diagnosed leprosy cases has declined by 95%, from 5.2 million in 1985 to less than 200,000 in 2015.[1, 2] This remarkable reduction has often been cited as a major public health success. Indeed, in 2000, the World Health Organization's (WHO) goal to eliminate leprosy as a public health problem, defined as a prevalence of less than 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 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 last 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 important 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 current WHO recommendations[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 two years following its administration.[12-15] Chemoprophylaxis has already been used in the sixties and seventies when weekly dapsone for two to three 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 ten 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 one-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 high-endemic Indonesian islands.[14] The population was screened before the intervention and subsequently once a year for three 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 leprosy patients. The NCDR on the control island was 39/10,000. After three 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 two years after SDR administration was 57%. There was no further risk reduction after two years[12] and thereafter.[31] The overall number needed to treat (NNT) to prevent a single diagnosis of leprosy among contacts was 265 after two years and 297 after four 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 PB 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 of prophylaxis may be warranted. High NCDRs, difficult geographical accessibility, insufficient availability of primary healthcare services, or a high level of stigma are reasons to prefer mass administration over 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:

(i) Impact on the new case detection rate, measured through strengthened surveillance and reporting systems

(ii) 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 (**Error! Reference source not found.**). In addition, the programme also promotes capacity building for

front-line leprosy workers to strengthen screening and diagnosis, and for surveillance system managers to improve data collection and reporting.

METHODS AND ANALYSIS

Study coordination

A steering committee of leprosy experts, policy makers, 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's Medical Centre (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 (Error! Reference source not found.). An annual meeting facilitates progress and review and exchange among the partners.

Study areas

Participation in the LPEP programme was open to countries meeting the following criteria: (i) sub-national administrative units (e.g. districts) with a high case detection rate, relatively easy access and a functioning leprosy control infrastructure, (ii) capacity for routine contact tracing and screening in the local leprosy programme, (iii) declared interest from the Ministry of Health, and (iv) 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)	Nyanung-U District	Myingyan District	Tharyar-waddy District	Jhapa District	Morang District	Parsa District	Kalutara District	Puttalam District	Kilombero District	Liwale District	Nanyumbu 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

G2D: grade 2 disability; MB: multibacillary; NA: not available; NCDR: New Case Detection Rate; *no data due to absence of leprosy services in this isolated village, but a visiting health worker from district level reported 30 suspected leprosy patients.

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. Leprosy patients diagnosed less than two years prior to the start of the field work (retrospective index patients) and patients diagnosed during the programme period (three years prospective index patients) are eligible for inclusion. These index patients have to meet the following inclusion criteria: (i) confirmed leprosy diagnosis and being on MDT treatment for at least four weeks, (ii) residency in the LPEP pilot area, (iii) one or more contacts (as defined by the local definition of contacts, see **Table 2**), and (iv) willingness to disclose their disease status. All traced contacts are screened for signs of leprosy. Exclusion criteria for SDR administration are: (i) refusal to give informed consent, (ii) age <2 or 6 years (country-specific age ranges are applied, see **Table 2**), (iii) pregnancy (PEP can be given after delivery), (iv) rifampicin use in the last two years (e.g. for tuberculosis (TB) or leprosy treatment, or preventively as a contact of another index patient), (v) history of liver or renal disorders (e.g. jaundice), (vi) leprosy disease, (vii) signs and/or symptoms of leprosy until negative diagnosis, (viii) 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 two weeks, night sweats, unexplained fever, weight loss), and (ix) known allergy to rifampicin.

Table 2 presents the study modalities in the different countries. Leprosy services are integrated into primary health care 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 (**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 done by different functions and persons in Sri Lanka, demanding particularly robust communication and information systems.

Table 2 Different LPEP modalities in the participating countries

Activities	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania
Routine contact tracing in the national programme	HH members and neighbours	HH members and neighbours	HH members	HH members 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	6	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

Abbreviations: CHV: community health volunteer; DTLC: District TB and Leprosy Coordinator; HH: Household; JLW: Junior Leprosy Worker; LI: Leprosy Inspector; LPEP: Leprosy Post-Exposure Prophylaxis; MOH: Medical Officer of Health; PHC: Primary health centre; PHS2: Public Health Supervisor 2; PMW: Para Medical Worker; VHW: voluntary health worker

In most study areas the LPEP programme targets specific contact groups. Because of the 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 administered to all asymptomatic individuals.

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 **Annex 1**. Socio-demographic 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 socio-demographic 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).

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 done continuously, either at national or district level; and database copies are regularly shared with the technical and ILEP partners for verification and analysis. 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 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 three years.

ETHICS

An expert meeting, involving both tuberculosis and leprosy experts, focussed on the potential risk of promoting rifampicin resistance through the use of SDR in leprosy control. It concluded that current evidence suggests the risk of emerging rifampicin resistance in *M. tuberculosis* is minimal, and that the benefits of reducing the leprosy NCDR largely outweigh 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 committee, namely: (i) the Institutional Human Ethical Committee of the National Institute of Epidemiology in India (NIE/IHEC/201407-01); (ii) the Ethical Committee on Medical Research involving Human Subjects at the Department of Health of the Ministry of Health in Myanmar (13/2014/1087); (iii) the Ethical Review Board at the Nepal Health Research Council in Nepal (39/2015); (iv) the Ethics Review Committee of the Faculty of Medicine at the University of Kelaniya in Sri Lanka (P/134/08/2015); and (v) the Ethical Committee at the National Institute for Medical Research of the Ministry of Health and Social Welfare in Tanzania (approval date: 4 May 2015). 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 (i.e. flu-like syndrome and discoloration of urine) and details of how a leprosy expert can be contacted in case of AEs or other concerns. Adverse events 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 leprosy elimination. 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 chemo- 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. Chemo- and immunoprophylaxis can not 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 number of new leprosy patients 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 three years of SDR administration to contacts of leprosy patients 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 amongst contacts of leprosy patients 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 learned from the LPEP programme will be done through publication in open access journals, as well as through reports and conference abstracts and presentations. The data will provide crucial guidance to Ministries of Health of all endemic countries that are interested in applying a similar approach to interrupt the transmission of leprosy. The results of the LPEP programme will also be of great value for global policy makers when deciding on resource allocation for leprosy elimination.

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Competing interest: All co-authors are either staff of the Novartis Foundation or work as paid consultants for the programme described here.

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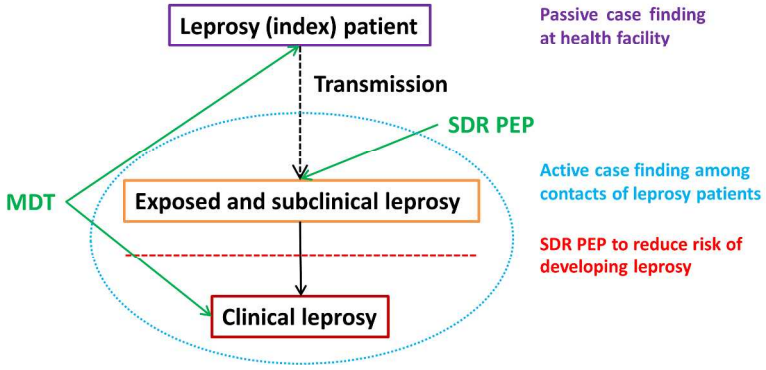

Figure 1 Conceptual framework of the impact of the LPEP programme on the transmission of Mycobacterium leprae
Figure 1
254x190mm (300 x 300 DPI)

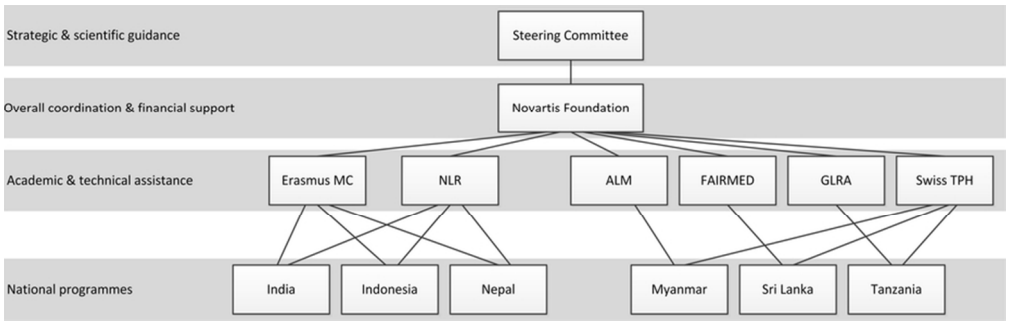

Figure 2 Governance structure of the LPEP Programme (Abbreviations: ALM: American Leprosy Mission, Erasmus MC: Erasmus Medical Centre, GLRA: German Leprosy and Tuberculosis Relief Association, ILEP: International Federation of Anti-Leprosy Associations, NLR: Netherlands Leprosy Relief, Swiss TPH: Swiss Tropical and Public Health Institute)
Figure 2
78x24mm (300 x 300 DPI)

ANNEX

Annex 1 Individual d**ata 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