

Global Partnership for Zero Leprosy
Research Agenda Working Group
Subgroup on Post-Exposure Prophylaxis

Prepared by

Christa Kasang, German Leprosy and Tuberculosis Relief Association, Würzburg, Germany
Peter Steinmann, Swiss TPH, Basel, Switzerland and University of Basel, Basel, Switzerland

In consultation with

David Blaney, Centers for Disease Control and Prevention, United States
Raisa Caridad Rumbaut Castillo, Ministerio de Salud Pública, Cuba
Arielle Cavaliero, Novartis Foundation, Switzerland
Joydeepa Darlong, The Leprosy Mission Trust India
Duane Hinders, Netherlands Leprosy Relief
Ximena Illarramendi, Oswaldo Cruz Foundation (Fiocruz – Brazil)
Ibtissam Khoudri, Ministry of Health, Morocco
Laila de Laguiche, Brazilian Society of Leprology
Patrick Lammie, NTD Support Center, Task Force for Global Health, United States
José Alexandre Menezes da Silva, Netherlands Hanseniasis Relief – Brasil (NHR Brasil)
Roberta Olmo Pinheiro, Oswaldo Cruz Foundation (Fiocruz), Brazil
Nimer Ortuno-Gutierrez, Damien Foundation, Belgium
Cita Rosita Sigit Prakoeswa, Dr. Soetomo Teaching Hospital, Indonesia
Jan Hendrik Richardus, Erasmus MC, University Medical Center Rotterdam, The Netherlands
Anne Schoenmakers, Netherlands Leprosy Relief
Cairns Smith, University of Aberdeen, United Kingdom
Maria Solange Araújo Paiva Pinto, Netherlands Hanseniasis Relief – Brasil (NHR Brasil)

Introduction

Early case detection and prompt treatment with multi-drug therapy are the cornerstones of the World Health Organization (WHO) recommendations for leprosy control (1,2). The more than 200,000 new leprosy patients detected each year (3), of which 10% are children, indicate stable and ongoing transmission of *Mycobacterium leprae*. One of the main challenges to interrupting transmission is the disease's long incubation period: around 5 years until clinical and diagnostic symptoms appear (4). The risk of developing leprosy varies across contact groups (5). Household contacts have the highest risk, and neighbors of infected individuals have a risk more than four times higher than that of the general population. While no specific vaccine is currently available, work on the first leprosy-specific vaccine is advancing.

Transmission of *M. leprae* can best be interrupted by introducing new preventive interventions. Chemoprophylaxis in the form of single-dose rifampicin (SDR) given to close contacts of leprosy patients reduces their risk of developing leprosy by 60%; when combined with childhood Bacillus Calmette-

Guérin (BCG) vaccination, this risk is reduced by 80% (6). A large, double-blind randomized controlled trial in Bangladesh and a controlled trial in Indonesia have provided the bulk of evidence (7-9) indicating that SDR may also reduce transmission by killing *M. leprae* in exposed contacts. Before SDR is provided to contacts of leprosy patients, they must be screened for signs and symptoms of leprosy and other exclusion criteria through a clinical, non-invasive examination of the skin. Because of this component, which is identical to active case finding, the implementation of a chemoprophylaxis intervention contributes to early case detection. The possibility of inducing rifampicin resistance in *M. tuberculosis* has been examined by a group of experts who concluded that this risk is negligible—both on theoretical grounds and on evidence from the long-standing worldwide practice of giving monthly doses of rifampicin for the treatment of leprosy (10). Implementation research studies on how to best integrate contact screening and SDR distribution into routine leprosy control programmes are currently ongoing in several countries.

History of Leprosy Post-Exposure Prophylaxis

Systematic reviews with meta-analysis showed that several chemoprophylaxis projects had been conducted in the 1960s and 1970s using dapsonone once or twice weekly for 2–3 years or acedapsonone every 10 weeks for 7 months; since the 1990s, SDR has been used (7,8). All studies showed superiority of the intervention over placebo, with an overall reduction of the leprosy new case detection rate (NCDR) of 40%–60% in contacts.

The most important results concerning the efficacy of SDR in leprosy post-exposure prophylaxis (PEP) were generated by the COLEP trial in Bangladesh (11). This trial was a single-center, double-blind, cluster-randomised, placebo-controlled study that included 21,711 contacts of over 1,000 recently diagnosed leprosy patients. The overall risk reduction for contacts during the first 2 years after SDR administration was 57%; no further risk reduction was found beyond those 2 years. The highest protective efficacy was found in non-blood-related contacts, but the study was underpowered to evaluate the impact on particular contact groups. The calculated number of contacts needed to be treated to prevent a single case of leprosy was 265 after 2 years and 297 after 4 years (9). Childhood vaccination with BCG also had a protective effect of nearly 60%, and when combined with SDR an added benefit was observed resulting in a protective effect of 80% (12). Thus, there are strong indications that SDR in leprosy PEP (SDR-PEP) helps to decrease the incidence of leprosy (13).

Current and Recent Studies on Leprosy PEP

Indonesia (2014-2016):

A recent study in Indonesia has shown that in hyper-endemic foci SDR-PEP given to household contacts alone may not be effective (14). For high-incidence pockets ('hotspots') or populations ('hotpops'), a "blanket" or mass drug administration approach for SDR-PEP may be more appropriate (13). The feasibility of a population-wide administration of SDR was tested in a prospective follow-up study in a high endemic and isolated community in Indonesia. The feasibility could be proven, but the need for adequate planning and additional investments was highlighted (15). A follow-up of this study is needed to observe the long-term effect and determine the conditions to sustain it.

Leprosy Post-Exposure Prophylaxis (LPEP) (2015-2019):

The LPEP program is currently ongoing in India, Indonesia, Myanmar, Nepal, Sri Lanka, Tanzania, Brazil, and Cambodia. It is designed to evaluate effectiveness, impact, and feasibility of contact tracing and SDR-PEP for contacts of leprosy patients under routine program conditions (16-18). The core LPEP study explores the feasibility and impact of combining three key interventions: 1) systematically tracing the contacts of newly diagnosed leprosy patients; 2) screening the traced contacts for signs of the disease; and 3) administering SDR to eligible contacts (16). The activities are implemented through established structures of the national leprosy control programmes, with coordination and supervision support by international partners. Interim results based on data from 5,941 index patients (89.4% of registered index cases) and 110,512 contacts eligible to receive SDR (785 refused) show that the intervention is feasible in different settings and under varying circumstances. However, for implementation of SDR-PEP on a greater scale and in multiple socio-epidemiological conditions, more field-level evidence is needed about its feasibility and impact in settings with different levels of leprosy endemicity, particularly low-endemic populations.

PEOPLE Trial (2018-2022):

The PEOPLE trial will evaluate different modalities of PEP for leprosy prevention in Madagascar and the Comoros (19), with the goal of identifying optimal target populations for PEP. It is planned as a cluster randomized trial aiming to

- Test the safety and efficacy of a higher dose of rifampicin such as single-double dose (SDDR; 1200 mg rifampicin per adult compared to 600 mg rifampicin in the LPEP program)
- Identify which approach for selecting contacts eligible for PEP is most effective in reducing incident leprosy through four study arms:
 - Control (no PEP)
 - SDDR-PEP, only household contacts
 - SDDR-PEP, household contacts and anti-PGL1 positive village contacts
 - Blanket SDDR-PEP at village level

In all four study arms, annual door-to-door surveys will be conducted covering entire villages. All permanent residents will be offered leprosy screening. Risk ratios will be calculated for leprosy based on 1) physical distance from the nearest index household, 2) proportions of phylogenetically clustered patients, and 3) proportions of patients belonging to the social network of another patient. Additionally, costs per person treated with SDDR-PEP for each study arm will be calculated, and genotyping of bacilli on samples from all incident leprosy patients will be conducted.

PEP4LEP (2018-2022):

The PEP4LEP trial is an implementation trial in Mozambique, Ethiopia, and Tanzania. This cluster randomized study will compare PEP effectiveness in terms of the rate of leprosy patients detected and the delay in case detection through two SDR prophylaxis interventions: 1) a community “skin camp” and 2) a health-center based approach that treats household contacts only. Additionally, it will compare the feasibility of the two chemoprophylaxis interventions in terms of cost effectiveness and acceptability. Both interventions will use an integrated skin disease approach and rely on a validated skin disease diagnosis app ([the SkinApp](#)) to facilitate diagnosis. Other skin issues, such as common skin diseases, other neglected tropical diseases (NTDs) manifesting with skin lesions, and HIV/AIDS-related skin diseases, will also be diagnosed and treated. A capacity assessment will be used to evaluate the skills of health workers in using the common skin approach in practice.

Maltalep (2013-2019):

Maltalep is a cluster randomized controlled trial comparing immunization with BCG alone with BCG plus SDR in contacts of newly diagnosed leprosy patients. Contact groups of approximately 10 persons were established for each of the 1,500 leprosy patients enrolled in the trial, resulting in around 15,000 contacts in total. BCG was administered to the intervention group followed by SDR 2 months later. The control group received BCG only. Follow-up was at 1 year and 2 years after intake. The primary outcome is the occurrence of clinical leprosy within 2 years. Simultaneously with vaccination and SDR, blood samples for in vitro analyses have been obtained from 300 contacts participating in the trial to determine the effect of these chemo- and immune-prophylactic interventions on immune and genetic host parameters. Results of this trial will become available in 2019, after completion of 2 years follow-up for all participants.

PEP++ Project (2017-2022):

The PEP++ Project uses a cluster-randomized trial design to compare the efficacy of an enhanced chemoprophylaxis regimen (PEP++) with that of SDR PEP in close contacts who are seropositive for antibodies against the leprosy-specific ND-O-LID conjugate. PEP++ is a multi-dose regimen comprising moxifloxacin and rifampicin. The PEP++ intervention will complement a novel, cluster-based blanket implementation of SDR PEP. Clusters in the participating districts will be identified using geographic information system (GIS) technology. Both approaches will be supported by optimized leprosy case detection and treatment services, including health systems strengthening, contextualized community education on leprosy, stigma reduction interventions, and involvement of leprosy-affected persons in various roles in their communities.

Research Priorities and Key Questions

Basic Epidemiological Data Needs

A detailed understanding of disease distribution is essential for planning interventions like PEP.

Leprosy Prevalence and Surveillance

A number of countries, especially in Africa and the East Mediterranean region, are not reporting leprosy case numbers to WHO. Excluding European countries, only 32 countries, with a total population of 860 million people, reported new cases in 2016; 64 countries, with 530 million people, did not report at all (20). Additionally, in Brazil, India, and Africa high numbers of hidden cases were observed (21-23). Leprosy control programmes are often insufficient in these countries or not established at all. Being a focal disease, national statistics are also insufficient to identify priority areas for interventions. Activities like PEP should be integrated into local health services or combined with other disease control programmes to make them successful (13). Thus, prevalence studies and surveillance activities are increasingly needed—especially in areas where leprosy reporting is insufficient.

➤ *Key questions*

- Where are the leprosy endemic areas?
- How do we define endemic, and how many hidden cases do we have?

Mapping of Current and Retrospective Routine Surveillance Data

The [AIM Initiative](#) demonstrated that, based on routine (e.g. ministry of health) surveillance data of diagnosed leprosy patients, digital maps can be generated with village-level accuracy. These maps also

enable the overlay of geo-referenced health facility locations to show the availability of services related to the distribution of the diseases. Establishing a detailed understanding of disease distribution is essential for planning PEP intervention.

➤ *Key question*

- What is the geospatial distribution of leprosy patients in endemic countries?

Leprosy PEP Intervention

The most critical pending research questions for LPEP involve operational research on how to design and implement the intervention itself.

PEP Intervention Effectiveness

To make an intervention like PEP successful, effective and feasible active case-finding/contact-tracing approaches must be defined both for low- and high-endemic settings and for existing and novel approaches. PEP can be combined with different, active case-finding modes. Contact screening approaches that include households, neighbors, or social contacts could be done by actively visiting the houses or by asking the contacts to visit health care facilities. The screening could be done by volunteer health care workers or by experts on a case-by-case basis or during screening drives. PEP also could be given in a blanket approach, during “skin camps” or any other mass screening events. Many different interventions are and will be tested in the near future, and a periodically updated review of the evidence and coordination of studies is necessary to avoid duplication and identify optimal protocols for individual country/region or district settings.

➤ *Key question*

- Which type of PEP intervention fits best with which epidemiological setting?

PEP Effectiveness under Routine Conditions

Efficacy of PEP for contacts of leprosy patients has been proven in several studies under research conditions. As countries transition to implementing such interventions under routine program conditions, it is essential to monitor the effectiveness of this approach. Different routine conditions should be distinguished (integrated vs. vertical, and/or NTD integrated vs. TB integrated). Monitoring should also include good surveillance for adverse reactions.

➤ *Key question*

- How effective is PEP under routine conditions?

Detailed Cost Studies

To encourage ministries of health to introduce PEP as a routine approach in their countries, cost-benefit information is essential. Evaluations should consider the costs for active case finding and for PEP along with the individual, societal, financial, and other benefits. Cost evaluation should be considered part of a wider elimination investment, as the long-term perspective and elimination potential will be major drivers of cost-effectiveness.

➤ *Key questions*

- What are the costs of PEP?
- How cost effective are the different implementation approaches?

Quality of Leprosy Screening by Minimally Trained Staff

Active case finding and PEP interventions often rely on volunteer or paid community health workers (CHW) and other minimally trained staff. These individuals are expected to remain in their home village

or neighborhood, and usually work part-time. To assess their effectiveness, it is essential to study the diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) of their activities, to determine necessary training and re-training schedules, and to explore the problems and challenges they face in diagnosing leprosy.

➤ *Key questions*

- Is the quality of leprosy screening by CHW sufficient to justify their use in PEP activities?
- If so, under what conditions?

Surveillance for Rifampicin Resistance in Leprosy

Although the possibility of inducing rifampicin resistance in *M. leprae* and *M. tuberculosis* has been estimated to be very low, surveillance to compare resistances in SDR and non-SDR areas is needed. Particularly, samples and data from patients who develop leprosy or tuberculosis after the SDR administration should be collected.

➤ *Key question*

- Does implementation of PEP lead to development of rifampicin-resistant leprosy or tuberculosis?

Field-friendly Diagnostic Tests

The use of field-friendly, point-of-care (POC), rapid diagnostic test (RDTs) would facilitate the diagnosis of leprosy under field conditions, particularly by non-medical staff such as CHWs (see above). Issues surrounding the development, validation, and introduction of such tests were examined by the Subgroup on Diagnostics and are very relevant to the success of PEP activities.

➤ *Key question*

- What efforts are needed to ensure the development and validation of a field-friendly, rapid diagnostic test to support minimally trained staff in the diagnosis of leprosy?

Leprosy PEP Frequency and Drug Options

Efforts are needed to address several research questions on PEP medication.

Frequency of SDR in High Endemic Settings

The efficacy of SDR has been shown to persist over a 2-year period, with no additional benefit thereafter. The re-administration of SDR after this 2-year period could improve the effect, but the true benefit of re-treatment remains unclear.

➤ *Key questions*

- What is the additional benefit of SDR re-administration?
- Under which epidemiological conditions is re-administration of SDR justified?

Other Drugs for PEP

The potential of drugs like moxifloxacin and bedaquiline or drug combinations for PEP should be tested.

➤ *Key question*

- How effective are other (new) drugs for single and repeated PEP?

PEP for High-risk Contacts

The efficacy of SDR to reduce the risk of developing leprosy is lower among blood-related household contacts and other very close contacts compared to more distant contacts. Studies are ongoing to address this issue (e.g., PEP ++ and PEOPLE, see above), but other interventions should also be explored.

- Key question
 - How can the efficacy of PEP for blood-related household contacts and other high-risk contacts be increased?

Disturbance of Gut Microbiome through PEP

The use of antibiotics can disrupt the ecology of the human gut microbiome. It would be useful to study the short- and long-term consequences of single-dose antibiotic use on the human gut microbiome and its effect on diseases such as malnutrition, obesity, diabetes, and bacterial co-infections.

- Key question
 - What are the effects of SDR on the gut microbiome?

Combination of SDR and Vaccines

Immunization of newborns with BCG improves the protective effect of SDR. The effect of other vaccines, like newly developed TB vaccines, is unclear. The use of inactivated or recombinant vaccines would allow for possible co-administration with SDR PEP. Vaccine development issues were addressed by the Subgroup on Vaccines, but it is important to study their use in PEP activities.

- Key question
 - Which vaccines are useful in terms of immunoprophylaxis and could be combined with SDR?

Transmission

The impact of leprosy PEP interventions on transmission and thus toward zero leprosy can only be fully appreciated based on an improved understanding of *M. leprae* transmission. Increased knowledge on *M. leprae* transmission will also facilitate the design of targeted interventions to interrupt transmission that complement early case detection and PEP. The current state of knowledge on *M. leprae* transmission has been reviewed (24), and related research priorities formulated (25). An overview of tools and strategies to end *M. leprae* transmission, including through PEP, has also been published (26). Based on the above, four research areas have been identified by the Subgroup as priority concerns for understanding *M. leprae* transmission:

Human-to-human Transmission (Human Reservoir)

Areas of interest include 1) biomarkers for all clinical and subclinical cases of leprosy as well as biomarkers for asymptomatic carriers; 2) the role of colonization and route of entry of *M. leprae* into the human host; 3) roles of co-infections on the entry/exit of *M. leprae* from the human host; and 4) stages of pathogenicity of *M. leprae* to understand the migration (port of entry to the site of initial lesion to point of exit) of the bacterium inside the human host.

Non-human Reservoirs

Areas of interest include 1) distribution of *M. leprae* in armadillos in the Americas and corresponding zoonotic potential; 2) role of other animals in *M. leprae* transmission; 3) biological relationship between *M. leprae* and amoeba as well as arthropods; 4) presence of *M. leprae* in the environment in different

endemic settings; 5) genotyping to understand the role of *M. leprae* strains found in the environment and those found in the population; and 6) demonstrated viability of *M. leprae* in the environment.

Host-pathogen Interactions

Areas of interest include 1) relationships between *M. leprae* genetic characteristic and virulence, growth kinetics, drug resistance, tropisms for nerves, and the tendency to cause reactions; 2) the role of host genetic risk factors in susceptibility and resistance to *M. leprae* infection, clinical progression of leprosy, and reactions; 3) understanding how the immune response affects the various manifestations of leprosy including establishment of infection, progression of disease, nasal carriage, and reactions; and 4) understanding of the similarities/differences between *M. leprae* and *M. lepromatosis*.

Transmission Networks

Areas of interest include 1) collection of genome-sequenced *M. leprae* strains including isolates from various origins (e.g., worldwide, paucibacillary patients) complemented with detailed epidemiological data; and 2) genetic diversity of *M. leprae* from different sources (e.g., patients, nasal carriers, zoonotic and environmental sources) and various settings (e.g., high and low endemic regions) to understand the transmission ecology at the community level.

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