# Guide to the Leprosy Post-Exposure Prophylaxis with Single-Dose Rifampicin Toolkit

## Introduction

In 2018, the World Health Organization (WHO) endorsed the concept of leprosy post-exposure prophylaxis (PEP), using a single dose of rifampicin (SDR) for contacts of leprosy patients, in their related guidelines [1]. This advocacy is based on the evidence generated over the past years. Bakker et al. demonstrated a reduction in leprosy incidence due rifampicin chemoprophylaxis on islands in Indonesia [2]. The effectiveness of SDR-PEP in contacts of newly diagnosed leprosy patients has been shown in the COLEP study in Bangladesh published in 2008. The study demonstrated that SDR-PEP reduces the risk of developing clinical leprosy among contacts of newly diagnosed patients by 57% [3]. This trial was followed by the three year Leprosy Post-Exposure Prophylaxis (LPEP) program which evaluated the feasibility and impact of SDR-PEP in eight countries (Brazil, Cambodia, India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania). LPEP provided the proof for operational feasibility in a variety of settings, with different leprosy epidemiology and health systems [4, 5].

This toolbox was created to facilitate the transition of the LPEP program into routine leprosy control activities in participating countries. Furthermore, additional leprosy endemic countries indicated interest to adopt the approach, and the aim of the toolbox is to assist the national leprosy control programs in the preparation and implementation of SDR-PEP in their specific context. This guide summarizes the extant evidence on leprosy PEP and introduces the instruments of the toolbox and modes of their handling and application. The experience of the LPEP program in the diverse settings was central to the development of the toolbox, but further evidence on leprosy PEP has been integrated, as appropriate. As additional findings become available, this toolbox may be updated to reflect the emerging evidence and increasing experience on best practice in leprosy post-exposure prophylaxis with single-dose rifampicin.

## Evidence on leprosy post-exposure prophylaxis

Leprosy control activities, as reflected in epidemiological statistics, have long been influenced by target-driven efforts; most notably to achieve elimination of leprosy as a public health problem (<1 new case/10,000 population and year) by the year 2000, expressed by WHO 1991. Another strong factor in the decrease in the global leprosy prevalence has been several reductions in duration of treatment, especially since 1981 when standard multi-drug therapy (MDT) was introduced. However, over the past decade the annual number of newly detected leprosy cases globally has stagnated at around 200,000 - 250,000, including children. This indicates that transmission remains on-going and new tools are needed to reach its interruption [6]. Today, neither an appropriate point-of-care test for asymptomatic leprosy nor a sufficiently effective immunoprophylaxis are available. On-going research in these areas provides hope that a rapid diagnostic test and/or a vaccine may become available in the coming years [7]. Meanwhile, tracing and screening of contacts of newly diagnosed leprosy patients by trained health personnel, and the provision of chemoprophylaxis to eligible contacts, is the most effective available tool to reach a reduction of the annual number of new clinical leprosy patients [7].

The COLEP study determined the efficacy of SDR chemoprophylaxis for the prevention of clinical leprosy among contacts of newly diagnosed leprosy patients, and identified characteristics of contact groups most at risk for infection and development of clinical leprosy [8, 9]. The randomized controlled trial demonstrated an overall reduction of 57% of the risk of developing leprosy among contacts after two years. This effect was maintained, but without additional difference between the placebo and SDR group beyond this time point. Chemoprophylaxis with SDR was most effective in protecting contacts that were at a moderately elevated risk of developing leprosy compared to the general population, such as neighbors and social contacts of the leprosy patient and contacts of patients with paucibacillary disease [3].

To ensure a safe application of SDR, especially in areas where tuberculosis (TB) is co-endemic, the risk of inducing rifampicin resistance in *Mycobacterium tuberculosis* was reviewed. The available evidence and experiences were discussed by a panel of tuberculosis and leprosy experts who concluded that the risk of promoting the development of rifampicin resistant TB by using SDR is negligible and is far outweighed by the beneficial effects of the intervention [10].

The LPEP program was designed to provide evidence on the feasibility and impact of chemoprophylaxis using SDR. The LPEP Study Group consists of the implementing partners (International Federation of Anti-Leprosy Associations (ILEP) members and national leprosy programs), the funder (the Novartis Foundation) and academic partners (Erasmus Medical Center and Swiss Tropical and Public Health Institute) [4]. The program was implemented in eight different leprosy endemic countries (Brazil, Cambodia, India, Indonesia, Myanmar, Nepal, Sri Lanka, and Tanzania) according to an overall study protocol that was readily adapted to the distinct health systems and aligned with national leprosy program activities. In Cambodia for example, contact tracing and chemoprophylaxis administration is done in drives. A fix team of experts is tracing the contacts of all newly detected leprosy patients of a defined administrative area (operational district) at once [11] (Cavaliero *et al* under review). In Indonesia a blanket approach was applied in a village (Lingat) on the highly endemic Selaru Island, where all asymptomatic and eligible inhabitants received SDR [4, 12]. The implementation of LPEP and the context-specific adaptations to the according health systems of India, Nepal and Indonesia was published by Tiwari *et al* [5]. A household expenditure study in the Indian LPEP setting explored the financial burden due to leprosy for outpatient services, aiming to link patients’ perception with the health system performance [13]. A detailed cost analysis of leprosy primary care in two settings in India can provide a basis for budgeting and financing of leprosy services and PEP [14].

Preliminary results from all LPEP countries (except Cambodia and Lingat village in Indonesia, which follow a slightly different protocol) showed that of over 6,600 enrolled leprosy patients, 120,000 contacts were listed, from which 99% could be successfully traced. Following application of exclusion criteria and screening, 90% were eligible and received SDR. Among those who were excluded from SDR, 406 new leprosy patients could be identified and referred for MDT treatment. Overall, only 0.3% contacts refused SDR. Based on these figures, together with the low refusal rates of leprosy patients (0.7%) to reveal their status to contacts and the high acceptance among the health workforce, it can be concluded that the operational feasibility of the integration of contact tracing and PEP with SDR into national leprosy control programs has been convincingly demonstrated across the different health systems. Furthermore, the LPEP program has invigorated local leprosy control through introduction or strengthening of contact tracing, and increased motivation of health staff trough training and supervision, and specifically also through the availability of a preventive tool that can be offered to the population at risk [15, 16]. This evidence led to the endorsement of the WHO Global Leprosy Programme (GLP) of leprosy PEP for endemic countries [1]. However, further studies are needed to add experiences from other settings on SDR-PEP and possibly using different approaches for contact tracing and screening, such as skin camps, pictorial aids to identify leprosy signs etc. Another area of active investigation is combining chemo- and immunoprophylaxis, as an analysis has shown that the additive protective effect of childhood BCG and SDR is 80% [17]. Different approaches may be combined in a long-term local elimination study, as for example in the MALTALEP trial currently ongoing in Bangladesh [18].

A minimal essential dataset has been proposed by the LPEP Study Group to keep the additional documentation needs as low as possible and to facilitate leprosy PEP associated record keeping into the leprosy control database of national programs [19]. While data regarding the leprosy patients mainly rely on the WHO GLP reporting requirements, which include age, gender, leprosy classification and disability grade; leprosy PEP additional variables assess (i) mode of detection, (ii) previous SDR (if known), (iii) presence of contacts, (iv) leprosy patient disclosure consent (if needed), and (v) a list of identified contacts. The suggested minimal information to be collected from contacts includes name, gender, age, refusal to screening, suspicion for leprosy and the exclusion criteria for SDR (low age (according to the country guidelines for SDR use), pregnancy, current treatment with rifampicin or during the last 2 years, liver or renal disease, refusal and others), and the SDR dose given [19]. Of note, not all of these variables need to be summarized and reported as some of them are operational in nature and collected to facilitate contact tracing rather than to be included in epidemiological analysis.

## Tools

### Information for policy makers and ministry-level staff (slide deck)

This power point slide deck has been created to inform higher-level staff and policy makers. The presentation covers the trends in leprosy epidemiology, diagnosis and control, and the need for additional activities in the light of elimination efforts. It presents contact tracing and chemoprophylaxis as two possible instruments to increase early case detection and reduce the risk among contacts to develop clinical leprosy. The principle of PEP using SDR is presented, as well as the first results of the LPEP program evaluating its feasibility and impact in 8 leprosy endemic countries and in diverse health system and socio-cultural settings around the world (Africa, Asia, and Latin America).

### Generic field guide (word file)

The field guide provides assistance in the implementation of SDR-PEP in new areas by serving as a quick reference for frontline staff. It provides a concise background on contact tracing and SDR-PEP, and an overview of the approach and summarizes the roles and responsibilities of the different key personnel. The key steps of index patient enrolment, tracing and screening of contacts, referral and suspicion for leprosy and TB, administration of SDR and data recording and reporting are presented.

### Field implementation training (slide deck)

This power point slide deck provides generic slides for the training of the health staff involved in leprosy PEP activities in the field. First, the selection criteria for the identification of the intervention areas are suggested. Then, the activity flow from the index patient identification and inclusion/exclusion, to contact tracing and inclusion/exclusion, SDR administration and side effects information/monitoring, and recording and reporting needs are described. The suggested minimal essential data to record index patients and contacts are presented [19]. Also, the reporting and SDR logistics (procurement, distribution and stock management) pathways are presented. Finally, the team composition, and the key tasks of each team member are described.

### Adaption of the study instruments

Prior to their use, the tools need adaption to the country specific conditions (i.e. local leprosy epidemiology, control, treatment and prevention of disability activities, as well as country-specific regulatory and supply chain aspects and the costs of leprosy PEP as applicable) to fully deploy their usefulness. On every tool, there is an instruction on how to adapt to the tool to fit the country’s needs. The specific sections of the documents that need adjustments are colored. Text colored in green are a selection of variables from the different settings of the LPEP program, the appropriate variable should be used and the others deleted. Sections where there is a need for input from the national program, such as numbers or correct wording, are colored in blue. Suggestions and comments are colored in purple and can be deleted if not appropriate for a given setting. Overall, pictures can be changed or deleted to reflect the country situations and formatting to fit corporate identity (logos etc.) is recommended.

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