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Preventing leprosy with retrospective active case finding combined with single-dose rifampicin for contacts in a low endemic setting: results of the Leprosy Post-Exposure Prophylaxis program in Cambodia

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ABSTRACT

Post-exposure prophylaxis (PEP) with single-dose rifampicin (SDR) reduces the risk of developing leprosy among contacts of leprosy patients. Most evidence for the feasibility of the intervention is from highly endemic settings while low-endemic areas present unique challenges including reduced awareness of the disease among the population and in the health system, and the only sporadic occurrence of cases which together make defining any type of routine process challenging.

We complemented the retrospective active case finding (RACF) approach with SDR administration to eligible contacts, and piloted the intervention across 31 operational districts in Cambodia. The aim was to demonstrate the feasibility of improving early case detection and administering SDR in a low endemic setting. The intervention focused on leprosy patients diagnosed since 2011 and was implemented between October 2016 – September 2019. The "drives" approach was employed to trace contacts: a trained team systematically contacted all eligible cases in a district, traced and screened contacts, and administered SDR.

A total of 555 index patients were traced by the drive team, and 10,410 contacts in their household and 5 immediate neighbor houses listed. Among these contacts, 72.0% could be screened while most others were absent on the screening day. A total of 33 new leprosy cases were diagnosed and 6189 contacts received SDR (82.6% of the screened contacts). Sixty-one contacts refused SDR administration.

We conclude that integrating PEP with SDR in RACF campaigns is feasible, and that this approach is appropriate in low resource and low endemic settings. Over time, evidence on whether or not the approach reduced leprosy transmission in Cambodia, may become clear.

1. Introduction

In 1998, Cambodia declared leprosy elimination at national level according to World Health Organization (WHO)-defined criteria (NLEP 2005). Over the next decade, the National Leprosy Elimination Program (NLEP) reported a drop in the number of new leprosy cases in Cambodia, from 2219 in 1995 (NLEP 2010), to 242 in 2008 (NLEP 2019). However, as from 2009, NLEP observed an increase in new child cases, indicating continuous transmission of *Mycobacterium leprae*, as well as an increase in grade II disability, reflecting a delay in leprosy diagnosis (NLEP 2019). In response, active case detection campaigns were re-started in 2011 with funding and staff support by international donors. Specifically, a retrospective active case finding protocol was developed whereby mobile teams traced leprosy patients diagnosed over several years and screened residents living in their vicinity for signs of leprosy disease (Fürst et al. 2017). These campaigns or "drives" resulted in a reversal of the case detection trend (Fürst et al. 2017). Drives were systematically conducted until all operational health districts (ODs) of the country had been covered at least once, thereby diagnosing a backlog of undetected leprosy patients and demonstrating the

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effectiveness of retrospective active case finding in low endemic settings with limited leprosy expertise in peripheral health services.

The Leprosy Post-Exposure Prophylaxis (LPEP) program explored the feasibility and impact of combining three key interventions: (i) systematic tracing of close contacts of newly diagnosed leprosy patients; (ii) screening the traced contacts for signs of the disease; and (iii) administering single-dose rifampicin (SDR) to eligible contacts under routine conditions (Barth-Jaeggi et al. 2016). The LPEP intervention package has been developed on available scientific and operational evidence. The three key pillars are (i) the risk of close contacts of untreated patients of developing leprosy themselves (Moet et al. 2004, Moet et al. 2006); (ii) the benefits from contact tracing (Blok et al. 2015, Smith and Aerts 2014); and (iii) the results of the COLEP randomized controlled trial on the efficacy of chemoprophylaxis with SDR (Moet et al. 2008). The core LPEP program included fieldwork in seven countries and was implemented in 2015 - 2019. The underlying protocol has been described in detail (Barth-Jaeggi et al. 2016, Steinmann et al. 2018). In brief, it combined technical solutions with locally adapted strategies to deploy them under varying programme conditions and socio-cultural contexts. The basic design of the LPEP intervention included the tracing of resident leprosy patients diagnosed within a defined period prior to the start of the fieldwork and throughout a 3-year implementation term. Consent was obtained from patients that their disease status could be disclosed to their contacts who were then traced and screened for signs and symptoms of leprosy no earlier than one month after multi-drug therapy (MDT) initiation of the index patient. In the absence of evidence of leprosy and other exclusion criteria including TB and pregnancy, an age and weight-dependent single dose of rifampicin was offered. Contacts with signs of active leprosy were evaluated as per routine leprosy control program procedures and, if the diagnosis was confirmed, received MDT treatment according to national treatment guidelines.

The objective of the complementary LPEP study in Cambodia, named "Retrospective Active Case Finding (cycle 2) with Leprosy Post-Exposure Prophylaxis" was to demonstrate feasibility and impact of retrospective contact tracing, leprosy screening and post-exposure prophylaxis (PEP) in the frame of "drives" as a strategy to improve early case detection and reduce leprosy risk in low endemic settings (Cavaliero et al. 2019). While the results of the overall LPEP program in the seven high endemic countries have recently been published (Blok et al. 2021, Richardus et al. 2021), this paper describes the results of the specific LPEP approach in Cambodia.

2. Methods

2.1. Study design, population and procedures

The study adopted the retrospective active case finding (RACF) approach in the form of "drives", as this was shown to be appropriate for contact tracing in low endemic settings (Fürst et al. 2017) and requires less local expertise and resources. This approach was combined with the general LPEP protocol (Barth-Jaeggi et al. 2016). In Cambodia, we focused on leprosy patients diagnosed since 2011, living in 31 high-priority ODs and identified from the national leprosy database which includes both data from the first cycle of the RACF drives (2011 - 2015) and routine passive case detection (Cavaliero et al. 2019).

The NLEP team included clinical and data management experts from central level. The team traced previously diagnosed patients who were living at their current address since three months or more. Operational District Supervisors (ODS), Health Center (HC) staff and Village Health Support Group (VHSG) members supported the leprosy expert team. After receiving informed consent from index patients and verifying the accuracy of their previous leprosy diagnosis, all contacts from the same household and from the five nearest neighbor households were invited to participate. Upon providing informed consent, these contacts were enrolled in the study and assigned a unique LPEP registration number. Contacts were screened on-site for signs of leprosy, including a comprehensive physical examination. Privacy was strictly respected and contacts were examined by a person of the same gender. A qualified NLEP clinician accompanying the "drive" team was responsible for establishing the clinical diagnosis of leprosy and newly detected patients were given MDT as per the current protocol of the NLEP. All new cases were included in the national leprosy database. Contacts screening negative for leprosy symptoms were offered PEP with SDR at the standard dose, unless they fulfilled one of the exclusion criteria (Barth-Jaeggi et al. 2016). The SDR administration to other contacts of such newly detected patients was postponed for one month after MDT initiation, to ensure the index patient would no longer be infectious.

The study covered all pre-identified 31 high-priority ODs in the period October 2016 – September 2019. Field activities were organized in "drives" covering one or several ODs per drive and typically lasting about 2 – 3 weeks. Local staff training in leprosy screening and diagnosis as well as data recording and reporting and community sensitization were integrated into the preparations for each drive. The implementation phase included contact tracing, screening and PEP administration to eligible contacts, with monitoring and quality control of field activities by a quality assurance officer. Forms were checked daily for completeness and consistency. Missing/inconsistent information was completed on the day after.

2.2. Data entry and analysis

Leprosy patients were recorded in the routine leprosy data collection system of the NLEP. For our study, additional information pertaining to consenting index cases was collected on separate forms. Since no national database existed for contact persons of leprosy patients, all information about contacts was collected on study forms. LPEP questionnaires were entered by the NLEP data management team into a dedicated database in Epidata 3.1. It contained all required information for index patients, without identifying information such as names and contact details. Appropriate checks and data entry restrictions were implemented at data entry.

Data analysis was descriptive and followed the approach, protocol, demographic stratification and indicators of the overall LPEP program (Richardus et al. 2021).

3. Results

Table 1 describes the characteristics of 154 leprosy patients diagnosed in Cambodia at baseline in 2016. The majority of those (69.5%)

Table 1
Leprosy epidemiology at baseline (2016) in Cambodia (Anonymous 2017).

Population	16,000,000
Number of new patients detected	154
New case detection rate (per 10,000)	0.1
New patients with MB leprosy (%)	107 (69.5)
New patients with grade 2 disability (%)	30 (19.5)
New female patients (%)	35 (22.7)
New child patients (<15 years old; %)	12 (7.8)

Table 2
Characteristics of index patients diagnosed since 2011, who were traced back and followed up in the frame of this study across 31 high-priority operational districts in Cambodia from 2016 – 2019.

Total patients diagnosed with leprosy in Cambodia since 2011	**555**
Passive case detection	263
Active case detection (RACF) Cycle 1 (2011-2015)	241
Active case detection (RACF) Cycle 2 (2016-2019)	51
New patients with multibacillary leprosy (%)	304 (54.8)
New patients with disability grade 2 (%)	66 (11.9)
New female patients (%)	246 (44.3)
Age Groups	
Under 2 years	0
Children (2-14 years; %)	33 (5.9)
Adolescents (15-24 years; %)	77 (13.9)
Adults (25-49 years; %)	247 (44.5)
Adults (>= 50 years; %)	198 (35.7)
Reason for Exclusion	
Refused disclosure	17
Refused disclosure to neighbors	2
Home not accessible	1

were classified as multibacillary (MB) leprosy, while 19.5% had grade 2 disability, and 7.8% were children under 15. This is consistent with the expected profile in low endemic settings where transmission is ongoing (Anonymous 2017). Only 22.7% of patients were female, suggesting underdiagnosis of this patient group.

Table 2, on the other hand, illustrates the characteristics of index patients diagnosed since 2011, who were traced back by the drive team across the 31 high-priority ODs. Of those 555 patients, 241 (43%) had been diagnosed during the previous RACF cycle and 263 through passive case detection. Another 51 patients were diagnosed since the start of this study in 2016. Among this cohort of index patients, 54.8% were classified as MB and 11.9% had grade 2 disability. Women and children under 15 years old represented 44.3% resp. 5.9% of the index patients. A total of 20 index patients (3.6%) could not be recruited into the study, either due to their refusal to disclose their leprosy diagnosis to family members

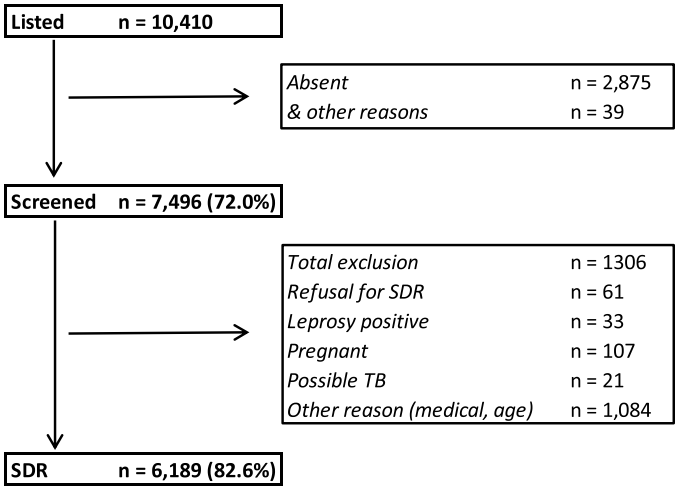

Fig. 1. Flow chart of contact persons of index patients with leprosy, who were recruited into the study across 31 operational districts in Cambodia from 2016 – 2019.

Table 3
Characteristics of index patients contacts, recruited into the study across 31 operational districts in Cambodia from 2016 – 2019.

Total contacts listed	10,410
Total contacts screened	7496
Age groups of screened contacts	
Under 6 years (%)	869 (11.6)
Children (6-14 years; %)	1530 (20.4)
Adolescents (15-24 years; %)	967 (12.9)
Adults (25-49 years; %)	2267 (30.2)
Adults (50+ years; %)	1863 (24.9)
Gender	
Male (%)	3183 (52.5)
Female (%)	4299 (57.4)
Unknown	14
Type of contact	
Household (%)	2093 (27.9)
Neighbor (%)	5403 (72.1)

Table 4
Characteristics of newly diagnosed leprosy patients in contact persons of index patients recruited into the study across 31 high-priority operational districts in Cambodia from 2016 – 2019.

Total newly diagnosed among contacts	33
Age groups	
Under 6 years	0
Children (6-14 years; %)	5 (15.2)
Adolescents (15-24 years; %)	5 (15.2)
Adults (25-49 years; %)	11 (33.3)
Adults (>= 50 years; %)	12 (36.3)
Gender	
Male (%)	19 (57.6)
Female (%)	14 (42.4)
Type of leprosy	
Paucibacillary (%)	17 (51.5)
Multibacillary (%)	16 (48.5)
Disability grade 2 (%)	2 (6.1)
Contact level	
Household (%)	23 (69.7)
Neighbor (%)	10 (30.3)

and neighbors ($n = 19$), or the inaccessibility of their home ($n = 1$).

Of 10,410 listed contacts, 72.0% ($n = 7496$) could be screened while 27.6% ($n = 2875$) were absent from home at the time of the drive team's visit. Only 0.4% ($n = 39$) of all contacts could not be screened for other reasons (Figure 1). Table 3 summarizes characteristics of screened contacts, of whom 27.9% lived in the same household as the index patient. Adolescents were somewhat underrepresented and the gender balance was skewed towards females.

Among the contacts, 33 new leprosy patients were diagnosed and only 61 contacts refused SDR (Figure 1). Other reasons for exclusion from SDR were pregnancy ($n = 107$), suspected untreated tuberculosis ($n = 21$), and unspecified medical or age-related reasons ($n = 1084$). After considering all exclusion criteria, 82.6% of the screened contacts received SDR at the appropriate dose.

The characteristics of the patients newly detected during the contact screening are described in Table 4. A majority of them ($n = 23$, 69.7%) were diagnosed among household contacts, 42.4% were female, and 15.2% were children under 15 years. In total 48.5% were classified as MB leprosy and 6.1% were diagnosed with grade 2 disability.

4. Discussion

The results of the LPEP program in Cambodia demonstrate the feasibility of integrating SDR administration into RACF campaigns or "drives". Very few (0.8%) of the screened contact persons declined PEP with SDR, which is comparable to the refusal rate we observed in LPEP overall (0.7%) (Richardus et al. 2021). The retrospective nature of the contact tracing and the high mobility of the Cambodian population were the main challenges to RACF implementation (Fürst et al. 2017), and resulted in missing around one third of the targeted index patients (data not shown) as they had moved or were absent at the time of the drive. As opposed to the approach in the overall LPEP program, the mobile and time-bound nature of the drives made it impossible to visit index patients and their contacts repeatedly in Cambodia. As only those index patients and contacts who were present on the day of the drive team visit could be screened, index patients were informed by local health staff a few days ahead of the visit and the exact time of the team arrival was communicated.

Previously undetected leprosy patients were diagnosed at a rate of 110 per 10,000 household contacts and 18 per 10,000 neighbor contacts. These rates are higher than those seen in most of the other countries implementing LPEP (11-160/10,000 resp. 8-154/10,000), and specifically the difference between new diagnoses in household and neighbor contacts is much larger than in the overall LPEP cohort (Richardus et al. 2021). The characteristics of the newly diagnosed leprosy patients suggest that the active nature of the case finding through RACF resulted in earlier diagnosis, with patients among contacts generally being younger at time of diagnosis and having a lower rate of grade 2 disability compared to patients detected through passive means. The high proportion of child patients suggests however active transmission in family clusters. We also observed a higher rate of paucibacillary leprosy compared to the passive case detection cohort, probably suggesting more reliable detection of subtle signs of leprosy.

RACF is a promising tool to strengthen community awareness, health worker skills and leprosy diagnosis among contacts in low endemic areas with insufficient health system capacity for contact tracing, screening and leprosy diagnosis (Fürst et al. 2017). However, to be effective the approach relies on systematic documentation of previous leprosy patients and ways to trace them back. When preparing a drive, information from the national leprosy database was cross-referenced with data in district leprosy registers. Since regular deviations between these data sources were found, the project triggered a strengthening of the leprosy data management and surveillance system of the NLEP: the national leprosy database was systematically updated, duplicate entries eliminated, and all locally available patient records included. Aware that active case finding by RACF for a relatively rare disease like leprosy is only effective when combined with a strong passive case detection system in the primary health care system, we advocated for the inclusion of leprosy into the national training curricula for frontline nurses and clinicians, as well as in their continuous medical education. In addition, the best results with such combined active and passive case finding efforts is achieved with efficient referral to the Provincial and Operational District Leprosy Supervisor for confirmation. Regular supervision by the NLEP at provincial and district level is also important.

Cambodia was the only low endemic country to participate in the LPEP program. A decline from 154 new leprosy diagnoses in 2016 (Anonymous 2017) to 127 in 2019 (Anonymous 2020) was observed over the project period. It is currently unclear which fraction of this decline can be directly attributed to the RACF and LPEP activities, but an effort to model the impact of the LPEP intervention on long-term trends in leprosy case detection rates suggested an important contribution (Blok et al. 2021). Indeed, that concrete impact in Cambodia can currently not be modelled as no repeat data is available for the study sites since each OD was covered only once by the RACF teams during the study period. Selecting the most efficient interventions to achieve interruption of leprosy transmission and ultimately eliminate leprosy, must be guided by scientific and operational evidence (Steinmann et al. 2020). Gradually, leprosy control programs worldwide will all operate in low endemic settings, which may lead to even steeper reductions in leprosy elimination budgets as attention may wane in political and public health circles. RACF offers such countries a systematic approach to identify hidden cases of leprosy, while PEP with SDR provides a proven tool to reduce the incidence of disease.

In line with WHO recommendations (WHO 2018) and based on the findings of the LPEP program in Cambodia and globally (Richardus et al. 2021), NLEP has now integrated the SDR-PEP approach into the NLEP National Strategic Plan 2018-2020 (NLEP 2019). With the help of the Partnership for Zero Leprosy (https://zeroleprosy.org/), NLEP is currently developing a comprehensive plan for *M. leprae* transmission interruption and leprosy elimination in Cambodia.

Author roles

Novartis Foundation provided technical input in the design phase of the LPEP programme and ensured overall programme coordination.

AC and AA are staff of the Novartis Foundation; SAS, JR and PS work as paid consultants for the programme described here; SL and VS are staff of the national leprosy programme.

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Conceptualization	x		x	x		x	x
Data curation		x			x		x
Formal analysis							x
Methodology	x	x		x	x	x	x
Project administration	x		x	x		x	
Original draft	x						x
Review/editing	x					x	x

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