Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme

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Summary

Background Innovative approaches are required for leprosy control to reduce cases and curb transmission of *Mycobacterium leprae*. Early case detection, contact screening, and chemoprophylaxis are the most promising tools. We aimed to generate evidence on the feasibility of integrating contact tracing and administration of single-dose rifampicin (SDR) into routine leprosy control activities.

Methods The leprosy post-exposure prophylaxis (LPEP) programme was an international, multicentre feasibility study implemented within the leprosy control programmes of Brazil, India, Indonesia, Myanmar, Nepal, Sri Lanka, and Tanzania. LPEP explored the feasibility of combining three key interventions: systematically tracing contacts of individuals newly diagnosed with leprosy; screening the traced contacts for leprosy; and administering SDR to eligible contacts. Outcomes were assessed in terms of number of contacts traced, screened, and SDR administration rates.

Findings Between Jan 1, 2015, and Aug 1, 2019, LPEP enrolled 9170 index patients and listed 179 769 contacts, of whom 174 782 (97·2%) were successfully traced and screened. Of those screened, 22 854 (13·1%) were excluded from SDR mainly because of health reasons and age. Among those excluded, 810 were confirmed as new patients (46 per 10 000 contacts screened). Among the eligible screened contacts, 1182 (0·7%) refused prophylactic treatment with SDR. Overall, SDR was administered to 151 928 (86·9%) screened contacts. No serious adverse events were reported.

Interpretation Post-exposure prophylaxis with SDR is safe; can be integrated into different leprosy control programmes with minimal additional efforts once contact tracing has been established; and is generally well accepted by index patients, their contacts, and health-care workers. The programme has also invigorated local leprosy control through the availability of a prophylactic intervention; therefore, we recommend rolling out SDR in all settings where contact tracing and screening have been established.

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Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The clinical manifestations are largely confined to the skin, peripheral nervous system, eyes, and upper respiratory tract. *M leprae* predominantly affects peripheral nerves and immunologically mediated reactions can cause nerve damage in the face, arms, and legs, often resulting in disability, which in turn can lead to stigma and social exclusion. Over the past decade, the annual number of new leprosy cases reported to WHO has plateaued at slightly more than 200 000 patients, from nearly 150 countries.[1] Leprosy is a neglected disease with poor awareness among both the public and medical practitioners. Innovation is needed to enhance the effectiveness of leprosy control by improving early case detection and reducing the risk of infection and disease among those most at risk.[2] The ultimate goal is to reduce morbidity and to interrupt transmission of *M leprae* between humans.[3] Consequently, WHO's Global Leprosy Strategy 2016–20 identified early case detection and targeted case finding among high-risk groups as key strategic operational components.[4] Although both early case detection and targeted case finding can make an impact, additional interventions are needed to interrupt transmission. No leprosy-specific immunoprophylactic intervention is available. Although BCG vaccination confers some level of protection,[5] no vaccine on the market specifically targets *M leprae*.[6] The most effective approach to reducing the risk of developing leprosy among individuals exposed to *M leprae* over extended periods is chemoprophylaxis, usually given to close contacts of individuals who have been diagnosed with leprosy within the past 3 months.[7–9]

The idea of chemoprophylaxis in leprosy is not new. In the 1960s and 1970s, trials were done in India and Uganda with dapsone administered as chemoprophylaxis,[10–14] subsequently followed by trials with acedapsone in India.[15,16] A meta-analysis indicated an

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Research in context

Evidence before this study

The evidence for this international feasibility programme was summarised by WHO as part of their guideline development process for leprosy, published in 2018. These evidence-based recommendations used guideline development methods based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE includes an assessment of quality of evidence (high, moderate, low, or very low), consideration of the overall balance of benefits to harms (at individual and population levels), patient or health worker values and preferences, resource use, effects on equity, cost–effectiveness, and consideration of feasibility and effectiveness across various settings, including resource-limited settings and those in which access to laboratory infrastructure and specialised tests is poor. The quality of evidence for post-exposure prophylaxis with single-dose rifampicin (SDR) in leprosy was considered moderate. The most authoritative study was a large single-centre, double-blind, cluster-randomised, placebo-controlled trial to establish the preventive efficacy of SDR as post-exposure chemoprophylaxis in leprosy. In this trial, SDR given to contacts of individuals with newly diagnosed leprosy resulted in an overall reduction in incidence of leprosy of 57%, and reduced the incidence of leprosy among the contacts to the level of the general population in the area within 2 years. The WHO Guidelines for the Diagnosis, Treatment and Prevention of leprosy suggested that to prevent leprosy in healthy close contacts of patients with leprosy, SDR should be administered if the contacts were aged 2 years or older, both leprosy and tuberculosis have been ruled out, and in the absence of other contraindications.

Added value of this study

This large-scale feasibility study in seven leprosy-endemic countries provides evidence that post-exposure prophylaxis with SDR is safe; can be integrated into different leprosy control programmes with minimal additional efforts once contact tracing has been established; and is generally well accepted by index patients, their contacts, and health-care workers. The programme has also been shown to invigorate local leprosy control through the availability of a prophylactic intervention.

Implications of all the available evidence

Implementation of post-exposure prophylaxis with SDR should be integrated in all leprosy-endemic countries as part of their routine leprosy control programme. In fact, India, Indonesia, and Nepal have already started this integration at a local scale, and are planning national roll-out as resources permit. Further research should focus on the optimal number of contacts to be included, which probably depends on the local epidemiological situation (eg, endemicity level and ratio of multibacillary to paucibacillary patients), household size, and health system characteristics. Also, alternative and possibly more effective prophylactic regimens should be investigated. Finally, the development of suitable field-friendly diagnostic tests for subclinical infection can help establish those contacts who would benefit most from post-exposure prophylaxis.

overall reduction in the risk of developing leprosy among contacts of up to 50%.[17] In 1988, a chemoprophylaxis study with single-dose rifampicin (SDR) was implemented in the Southern Marquesas Islands; this trial was not controlled. After 10 years, findings suggested an effectiveness of SDR of 35–40%.[18–20] Due to the high leprosy incidence in the Pacific islands, chemoprophylaxis programmes were also done in the Federated States of Micronesia, Kiribati, and Marshall Islands in the mid-1990s.[21] Rifampicin–ofloxacin–minocycline was given to adults (aged ≥15 years) and rifampicin only to children younger than 15 years.[22] By 1999, a substantial reduction in case detection rates was observed, but the latest figures from 2016 indicate that this reduction was not sustained.[1] In 2000, a chemoprophylaxis intervention study with rifampicin was started on five Indonesian islands where leprosy is highly endemic.[23,24] Two types of intervention strategies were compared with a control group. The blanket (complete population) group included three islands on which prophylaxis was given to all eligible individuals. The contact group included an island on which prophylaxis was given to all eligible contacts of all known and newly diagnosed individuals with leprosy. The control group was the population of an island to which no chemoprophylaxis was offered. This study showed that population-based chemoprophylaxis was associated with a reduced leprosy incidence in the first 3 years after implementation. The answer to the need for a more rigorous trial to establish the preventive efficacy of SDR as post-exposure chemoprophylaxis was the COLEP study in Bangladesh, a single-centre, double-blind, cluster randomised, placebo-controlled trial. SDR given to contacts of individuals with newly diagnosed leprosy resulted in an overall reduction in incidence of leprosy of 57%.[7] The efficacy of SDR depended on contact level. Some subgroups appeared to respond well to SDR, such as people who were not blood relatives and neighbours of neighbours and (other) social contacts, with protection up to around 70%. One particular subgroup, however, namely blood relatives (ie, parents, children, and siblings) responded less effectively to SDR (24% protection). The BCG vaccination status of the contact was also important.[25] If the contact had received the BCG vaccination as part of a childhood vaccination programme (as established by the presence of a BCG scar), the protective effect of SDR was 80%. The SDR treatment group reached the background level of the general population at 2 years, while the placebo group reached this level at 4 years. At 4 years and 6 years of follow-up, there were no longer differences between treatment and placebo groups.[26,27]

In 2018, based on the available evidence, WHO included a recommendation to implement chemoprophylaxis with SDR for adult and child (aged 2 years and older) contacts of patients with leprosy, after excluding leprosy and tuberculosis disease, and in the absence of other contraindications in their Guidelines for the Diagnosis, Treatment and Prevention of Leprosy.[28] Yet evidence on the feasibility of integrating contact tracing with SDR administration into routine leprosy control activities was required by the WHO Global Leprosy Programme and national health authorities to assess the benefits, costs, and risks of such interventions.[4] Feasibility data collected from the field would position programme managers to more easily take informed decisions on the introduction of contact tracing combined with SDR administration as a new routine into their national strategic plans for leprosy control.[29] To generate such evidence and explore the potential of the intervention under various epidemiological, cultural, and health system conditions, the comprehensive leprosy post-exposure prophylaxis (LPEP) programme was established in 2014, with implementation starting in 2015 in most sites.[30]

Here, we provide the main results of the LPEP feasibility study in seven countries participating in the programme. We aimed to generate evidence on the feasibility of integrating contact tracing and SDR administration into routine leprosy control activities.

Methods

Study design and participants

The LPEP programme was an international, multicentre feasibility study implemented within the leprosy control programmes of Brazil, India, Indonesia, Myanmar, Nepal, Sri Lanka, and Tanzania. LPEP explored the feasibility and impact of combining three key interventions: (1) to systematically trace the contacts of individuals newly diagnosed with leprosy; (2) to screen the traced contacts for signs of the disease; and (3) to administer SDR as post-exposure prophylaxis to eligible contacts. The activities were implemented through the established structures of national leprosy control programmes. The aim of this study was to generate evidence and explore the feasibility of the intervention package to improve leprosy case finding among contacts of index patients and thus enhance early case detection and reduce the risk of developing leprosy among contacts.[30] The intervention package was based on available evidence, most notably the benefits of contact tracing[31,32] and the results of the efficacy of SDR in the COLEP trial.[7,33] It combined these technical solutions with locally adapted strategies to deploy them under varying programme conditions and sociocultural contexts. The LPEP programme was not designed to establish efficacy of SDR and the study duration (approximately 3 years) was too short to establish epidemiological effect. Nevertheless, we have explored the potential effect of SDR in the LPEP areas through mathematical modelling and will report on this separately in future.

The basic protocol of the LPEP intervention was similar in all participating countries. The intervention was piloted in administrative units of the health system purposively selected based on the following criteria: a sufficiently high new case detection rate to achieve the calculated sample size; accessibility; and basic leprosy control infrastructure. The main characteristics of the selected districts have been described previously for six countries.[30] In Brazil, four study sites were included, namely one in Pernambuco with a mean of 319 new patients over the 5 years before the study, one in Tocantins (n=847), and two in Mato Grosso (n=214 and n=136). Individuals with leprosy diagnosed within a defined period before the start of the field work and throughout a 3-year implementation interval were invited by local health-care staff or by trained volunteers to participate in the study. In the absence of relevant routine leprosy programme regulations, written or oral informed consent from index patients was required to disclose their disease status to their contacts who were then traced and screened for signs and symptoms of leprosy disease. Contacts without any evidence of leprosy were assessed for their eligibility to receive SDR. Those identified with signs of active leprosy were evaluated according to the routine leprosy control programme procedures and, if the diagnosis was confirmed, received multidrug therapy (MDT). No incentives were paid to patients, contacts, health-care staff, or volunteers, but field workers were entitled to reimbursement of costs associated with contact tracing. Country-specific LPEP protocol adaptations refer to the retrospective contact tracing period (typically 1–2 years), the contact definition (household, neighbours, social), and the minimal age for SDR eligibility (2 years *vs* 6 years). In Sri Lanka and Tanzania, only household contacts were targeted. In Myanmar, only household and neighbour contacts were targeted, with neighbours defined as inhabitants of houses in the immediate vicinity. In all other countries, household, neighbour, and social contacts were targeted. Social contacts could include other relevant contacts, such as classmates.

Also, the approach for screening differed between countries, with Indonesia applying a self-screening protocol whereby contacts received simple pictorial and text aids to detect leprosy and then self-identified if they or their family members had detected possible signs of leprosy disease on their bodies. Those who showed possible signs of leprosy were then screened by health-care workers to confirm or exclude the presence of leprosy.[34] Subsequently, contact screening procedures and SDR-PEP administration followed the same inclusion and exclusion criteria. An important difference is that a higher number of contacts could be included. In other countries, nurses, midwives, community health-care workers, or volunteers were responsible for the screening effort. In Brazil, in accordance with routine

leprosy control programme procedures, BCG vaccination was offered as prophylaxis to contacts who had not previously received BCG as established by the absence of two BCG scars. Additionally, in accordance with local routine practices, contact tracing and screening were done anonymously, without disclosure of the index patient. Therefore, no informed consent was taken from the index patients in Brazil, but consent was still required from contacts before SDR administration.

Urine discolouration is a common side-effect of rifampicin and this factor was mentioned actively when seeking informed consent from participants. Reported urine colour changes were not considered as adverse events requiring follow-up. Leprosy control programmes were encouraged to report and investigate other adverse events potentially related to SDR, both through the provision of a LPEP-specific reporting form and through regular reminders during monitoring visits.

In all participating countries in which chemoprophylaxis had not yet been included in the list of standard interventions for leprosy control, clearance for the study was obtained from the competent ethical review committees.

Procedures

The strategic document underlying the LPEP protocol was developed by NLR and Novartis Foundation in close collaboration with other international partners and in consultation with national leprosy control programme representatives.[30] Based on the strategic document, country LPEP protocols were defined by the leprosy control programmes of the participating countries, in close collaboration with their designated International Federation of Anti-Leprosy Association partners.[34] Cambodia also participated in the LPEP programme, but followed a modified protocol and timelines owing to distinct health system and epidemiological conditions.[35,36] Consequently, the results pertaining to Cambodia will be published separately.

The national leprosy control programmes with their established partners including non-governmental organisations and volunteers implemented the study field work. Two academic partners determined the minimal sample size needed to show the effect of the intervention, developed the data recording and reporting system, did quality assurance missions throughout the implementation period in close coordination with International Federation of Anti-Leprosy Association partners and leprosy control programme managers, and supported data analysis and results dissemination. Quality assurance focused on protocol adherence, completeness of contact tracing and quality of contact screening, and integrity of the data collection and reporting. A steering committee representing independent academic advisers, leprosy experts, and observers from the WHO Global Leprosy Programme in addition to key LPEP programme stakeholders provided strategic guidance.

The data recording and reporting system was adapted to local conditions to minimise duplication with the routine leprosy programme documentation, align reporting channels, and accommodate preferred data entry locations. The data collection documenting the activities focused on the individual characteristics of the index patients and their contacts, and the reasons for exclusion at every stage of the process to provide data for the coverage achievable in different settings. Other variables of interest included the number of new patients with leprosy identified in the frame of the field work. Data were regularly shared with the academic partners and analysed at least once a year. Interim and final results were shared with all partners as part of the annual LPEP meetings and final dissemination workshops in the participating countries.

As part of the programme design process, the risk of introducing rifampicin resistance in *Mycobacterium tuberculosis* by providing SDR was formally assessed. The conclusion of the literature study and expert consultation focusing on this topic was that the risk of inducing resistance is negligible.[37] Key experts participating in the consultation were not otherwise linked to the LPEP programme. As a precaution and as suggested in the expert consultation, screening for signs of active tuberculosis was implemented so SDR was only given to contacts without suggestive symptoms, and patients suspected to have tuberculosis were referred for full evaluation and appropriate treatment. Extending the argumentation on risk of inducing resistance from *M tuberculosis* to *M leprae*, the expert group again concluded that it is highly improbable that the development of resistant mutants would be encouraged by SDR administration. Importantly, all potential SDR recipients were screened for signs of leprosy, and confirmed patients received standard MDT in line with national leprosy treatment protocols.

Integral parts of the LPEP programme were side studies to establish feasibility,[38] effect on perceptions of leprosy and acceptability of the intervention,[39,40] and health system and health economic parameters in different contexts.[34,41]

Role of the funding source

Novartis Foundation and International Federation of Anti-Leprosy Association partners provided technical input in the design phase of the LPEP programme and ensured overall programme coordination. Novartis Foundation funded most of the programme activities and ensured central coordination. The funder had no role in data interpretation or the decision to submit for publication. JHR and PS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Field work related to the LPEP programme started in a stepwise arrangement in six countries from Jan 1 to

	Brazil	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania	Total
Registered index patients	2669	1662	1197	540	2368	940	827	10 203
Multibacillary leprosy	1990 (74·6%)	481 (28·9%)	938 (78·4%)	392 (72·6%)	1275 (53·8%)	499 (53·1%)	668 (80·8%)	6243 (61·2%)
Grade 2 disability	138 (5·2%)	54 (3·2%)	45 (3·8%)	94 (17·4%)	43 (1·8%)	58 (6·2%)	30 (3·6%)	462 (4·5%)
Sex								
Female	1210 (45·3%)	893 (53·7%)	593 (49·5%)	231 (42·8%)	1007 (42·5%)	363 (38·6%)	374 (45·2%)	4671 (45·8%)
Male	1459 (54·7%)	769 (46·3%)	604 (50·5%)	309 (57·2%)	1361 (57·5%)	577 (61·4%)	453 (54·8%)	5532 (54·2%)
Children younger than 15 years	146 (5·5%)	362 (21·8%)	93 (7·8%)	22 (4·1%)	198 (8·4%)	86 (9·1%)	32 (3·9%)	939 (9·2%)
Not enrolled index patients	670 (25·1%)	19 (1·1%)	106 (8·9%)	26 (4·8%)	0	0	212 (25·6%)	1033 (10·1%)
Enrolled index patients	1999 (74·9%)	1643 (98·9%)	1091 (91·1%)	514 (95·2%)	2368 (100%)	940 (100%)	615 (74·4%)	9170 (89·9%)
Multibacillary leprosy	1526 (76·3%)	472 (28·7%)	853 (78·2%)	374 (72·8%)	1275 (53·8%)	499 (53·1%)	480 (78·0%)	5479 (59·7%)
Grade 2 disability	103 (5·2%)	53 (3·2%)	38 (3·5%)	90 (17·5%)	43 (1·8%)	58 (6·2%)	28 (4·6%)	413 (4·5%)
Sex								
Female	924 (46·2%)	887 (54·0%)	545 (50·0%)	222 (43·2%)	1007 (42·5%)	363 (38·6%)	299 (48·6%)	4247 (46·3%)
Male	1075 (53·8%)	756 (46·0%)	546 (50·0%)	292 (56·8%)	1361 (57·5%)	577 (61·4%)	316 (51·4%)	4923 (53·7%)
Children younger than 15 years	98 (4·9%)	360 (21·9%)	86 (7·9%)	20 (3·9%)	198 (8·4%)	86 (9·1%)	18 (2·9%)	866 (9·4%)

Data are n or n (%). Contact tracing was routinely implemented pre-leprosy post-exposure prophylaxis in Brazil, India, Indonesia, Myanmar, and Nepal (in Brazil and Myanmar only for household members). Contact tracing was not routinely implemented pre-leprosy post-exposure prophylaxis in Sri Lanka and Tanzania.

Table 1: **Patients with leprosy diagnosed in the leprosy post-exposure prophylaxis programme districts**

	Brazil	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania	Total
Total listed contacts*	24 219	43 305	40 517	9520	54 346	1968	5894	179 769
Listed contacts per enrolled index patient	12	26	37	19	23	2	10	20
Not screened	2444 (10·1%)	972 (2·2%)	350 (0·9%)	80 (0·8%)	494 (0·9)	560 (28·5%)	87 (1·5%)	4987 (2·8%)
Total screened	21 775	42 333	40 167	9440	53 852	1408	5807	174 782 (97·2%)
Reason for exclusion from single-dose rifampicin administration†								
Possible tuberculosis	0	1	39	21	29	2	3	..
Pregnancy	72	195	110	90	122	9	99	..
Other medical reason	1758	1624	563	399	1055	166	750	..
Other reason‡	1652§	10 078	0	38	1961	4	2	..
Suspected leprosy	NA	141	207	15	273	46	310	..
Refusal of single-dose rifampicin	1076	0	25	4	0	29	48	..
Received single-dose rifampicin of total screened	17 217 (79·1%)	30 295 (71·6%)	39 279 (97·8%)	8873 (94·0%)	50 412 (93·6%)	1161 (82·5%)	4691 (80·8%)	151 928 (86·9%)

Data are n or n (%). Percentages provided for relevant indicators. NA=not applicable. *In Sri Lanka and Tanzania, only household contacts were targeted. In Myanmar, only household and neighbour contacts were targeted. In all other countries, household, neighbour, and social contacts were targeted. †Multiple mentions possible. ‡Including recent alcohol consumption and old age perceived as risk factor for single-dose rifampicin administration by the field team. §Data not available to distinguish between exclusion due to other reasons or suspected leprosy.

Table 2: **Contacts of patients with leprosy enrolled and screened in the leprosy post-exposure prophylaxis programme districts by screening status and exclusion reason**

March 1, 2015, followed by Brazil in 2016. Within a 3-year period, index patients diagnosed since Jan 1, 2013 (India, Nepal), Jan 1, 2014 (Myanmar, Tanzania), or Jan 1, 2015 (Brazil, Indonesia, Sri Lanka) were approached for inclusion in the study. The number of new patients with leprosy registered in the project districts across the seven countries was 10 203, ranging from 540 (Myanmar) to 2669 (Brazil; table 1). The profiles of the country index patient cohorts differed markedly: the rate of multibacillary leprosy among the index patients varied between 28·9% (India) and 80·8% (Tanzania), the grade 2 disability rate was between 1·8% (Nepal) and 17·4% (Myanmar), and the proportion of girls and women was between 38·6% (Sri Lanka) and 53·7% (India). Finally, between 3·9% (Tanzania) and 21·8% (India) of the index patients were aged younger than 15 years (table 1).

Between Jan 1, 2015, and Aug 1, 2019, overall, 9170 (89·9%) of the 10 203 registered index patients were enrolled for participation in the study (table 1). In Sri Lanka, patients who were not enrolled were not registered, so these numbers are not available. Main reasons for not enrolling index patients were living outside of the LPEP district, absence of contacts according to the local contact definition, and unstated reasons. The profiles of registered and enrolled index patients in terms of proportion of multibacillary cases, grade 2 disability, sex, and children are similar. Approximately 1% of

	Brazil	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania	Total
Age, years								
<2 or <6*	135 (0·6%)	563 (1·3%)	347 (0·9%)	249 (2·6%)	512 (1·0%)	34 (2·4%)	726 (12·5%)	2566 (1·5%)
2–14 or 6–14*	4335 (20·2%)	13 231 (31·3%)	5986 (14·9%)	2162 (22·9%)	15 456 (28·7%)	404 (28·7%)	1481 (25·5%)	43 055 (24·7%)
15–24	3732 (17·4%)	9527 (22·5%)	5663 (14·1%)	1460 (15·5%)	10 861 (20·2%)	248 (17·6%)	1172 (20·2%)	32 663 (18·7%)
25–49	8608 (40·1%)	14 004 (33·1%)	16 406 (40·8%)	3420 (36·2%)	18 737 (34·8%)	480 (34·1%)	1714 (29·5%)	63 369 (36·3%)
≥50	4680 (21·8%)	5008 (11·8%)	11 765 (29·3%)	2149 (22·8%)	8286 (15·4%)	242 (17·2%)	714 (12·3%)	32 844 (18·8%)
Contact level†								
Household	4737 (21·8%)	9625 (22·7%)	3533 (8·8%)	2018 (21·4%)	13 516 (25·1%)	1408 (100%)	5807 (100%)	40 644 (100%)
Neighbour	12 571 (57·7%)	32 351 (76·4%)	36 521 (90·9%)	7422 (78·6%)	39 933 (74·2%)	..	..	..
Social†	4467 (20·5%)	357 (0·8%)	113 (0·3%)	..	403 (0·7%)	..	..	..

Data are n (%). *Sri Lanka and Tanzania set the lower age limit at 6 years, the other countries at 2 years. For Brazil, age information is missing for 285 contacts. †In Sri Lanka and Tanzania, only household contacts were targeted. In Myanmar, only household and neighbour contacts were targeted. In all other countries, household, neighbour, and social contacts were targeted. †Including classmates, co-workers, and residents in the same institution (eg, retirement home) as the index patient.

Table 3: **Contacts of patients with leprosy screened in the leprosy post-exposure prophylaxis programme districts by age and type of contact**

	Brazil	India	Indonesia	Myanmar	Nepal	Sri Lanka	Tanzania	Total
Total newly diagnosed*	308; NCDR 141	42; NCDR 10	98; NCDR 24	15; NCDR 16	244; NCDR 45	10; NCDR 71	93; NCDR 160	810
Younger than 15 years†	21 (6·8%); NCDR 47	15 (35·7%); NCDR 11	NA	1 (6·7%); NCDR 4	34 (13·9%); NCDR 21	2 (20·0%); NCDR 46	14 (15·1%); NCDR 63	..
Sex								
Male	139 (45·1%)	20 (47·6%)	NA	14 (93·3%)	130 (53·3%)	4 (40·0%)	53 (57·0%)	..
Female	169 (54·9%)	22 (52·4%)	NA	1 (6·7%)	114 (46·7%)	6 (60·0%)	40 (43·0%)	..
Type of Leprosy								
Paucibacillary	84 (27·3%)	37 (88·1%)	NA	8 (53·3%)	177 (72·5%)	NA	NA	..
Multibacillary	224 (72·7%)	5 (11·9%)	NA	7 (46·7%)	67 (27·5%)	NA	NA	..
Grade 2 disability	22 (7·1%)	0	NA	0	NA	NA	NA	..
Contact level‡								
Household	56; NCDR 118	11; NCDR 11	15; NCDR 42	6; NCDR 30	86; NCDR 64	10; NCDR 71	93; NCDR 160	277
Neighbour	193; NCDR 154	27; NCDR 8	80; NCDR 22	9; NCDR 12	155; NCDR 39	..	..	..
Social	59; NCDR 132	4; NCDR 112	3; NCDR 265	..	3; NCDR 74	..	..	..

Data are n (%); NCDR or n (%). NA=data not available due to difficulties in linking leprosy registers to contact tracing and screening registers. NCDR=new case detection rate per 10 000. *The denominators of the NCDRs are shown in table 2 under total screened. †The denominators of the NCDRs are the sum of the age groups younger than 2 years or 6 years and aged 2–14 years or 6–14 years shown in table 3. ‡In Sri Lanka and Tanzania, only household contacts were targeted. In Myanmar, only household and neighbour contacts were targeted. In all other countries, household, neighbour, and social contacts were targeted. The denominators of these rates are shown in table 2 under contact level.

Table 4: **Newly diagnosed patients with leprosy among contacts screened in the leprosy post-exposure prophylaxis programme districts**

the index patient cohort (data not shown) refused the disclosure of their condition to contacts and thus could not be enrolled.

179 769 contacts were registered for the 9170 index patients enrolled in the study (table 2). In Sri Lanka and Tanzania, where only household contacts were targeted, a mean of two contacts per index patient was listed for Sri Lanka and a mean of ten contacts per index patient was listed for Tanzania. In the other five countries, where neighbours (Myanmar) and social contacts (other countries) were also targeted, the mean number of contacts was 23 per index patient. The range in number of contacts per index patient was from 12 in Brazil to 37 in Indonesia. Among the listed contacts, 174 782 (97·2%) could be traced and screened. The remaining contacts (n=4987) were unavailable for screening. A stratification of the contacts by country, age group, and contact level (ie, household, neighbour, and social) is shown in table 3.

Among the 174 782 screened contacts, leprosy diagnosis was confirmed in 810 individuals (new case detection rate 46 per 10 000; table 4). The highest rates of individuals with newly diagnosed leprosy among screened contacts were observed in Tanzania (160 per 10 000) and Brazil (141 of 10 000), while the lowest rate was in India (10 per 10 000). All individuals with newly diagnosed leprosy were directly enrolled for MDT according to national leprosy treatment protocols. Of the 174 782 screened contacts, 22 854 (13·1%) were not eligible for SDR administration according to the exclusion criteria (table 2). Across the seven countries, 1182 contacts (0·7%; range 0%

in Myanmar, Nepal, and Tanzania to 4·9% in Brazil) refused the prophylactic treatment with SDR. Overall, SDR was administered to 151928 (86·9%) of the 174782 screened contacts (figure).

The data for characteristics of newly diagnosed patients with leprosy among the screened contacts regarding age, sex, type of leprosy, and grade 2 disability were not complete for four countries (Indonesia, Nepal, Sri Lanka, and Tanzania). Where available, these characteristics did not differ markedly from those of the index patient cohort in the same country including the high proportion of child patients in India and important differences in the proportion of multibacillary cases among the patient cohort. Table 4 also shows the new case detection rate per 10000 among the contact categories. In some countries (Indonesia, Myanmar, Nepal), a gradient is seen with a higher rate among household contacts than the neighbour contacts, while a reverse trend is seen in Brazil. A very high new case detection rate among social contacts was observed in India, Indonesia, and Nepal compared with household contacts and neighbours. However, the underlying numbers are very low.

Across the 3-year period in seven countries, three instances of adverse events following SDR were reported, namely one from Brazil in which a person developed an allergic reaction to rifampicin following SDR administration, and two from Nepal with skin reactions. After investigation, the adverse events in Nepal were considered to be due to existing underlying health conditions unrelated to SDR administration. No serious adverse events were reported.

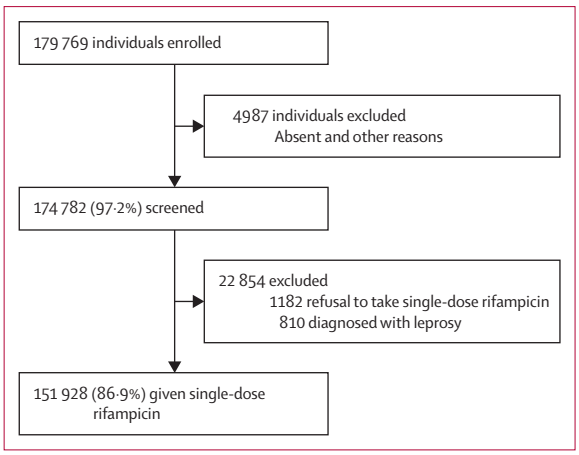

Figure: **Study profile**
Registration, screening, and single-dose rifampicin administration to contacts of individuals with leprosy recruited into the leprosy post-exposure prophylaxis programme.

Discussion

The LPEP programme was implemented in seven leprosy-endemic countries and showed that the approach of contact tracing followed by the provision of SDR is feasible as part of routine leprosy control programme activities. There was a high level of acceptance by patients and health-care staff of home-based or community-based contact screening and SDR administration across different sociocultural, epidemiological, and health system settings, with the notable exception of Sri Lanka where both health-care staff and patients preferred contact screening and SDR provision in health-care facilities rather than at home. Considerable efforts were necessary to implement contact tracing in settings where it had not previously been introduced into the routine control activities. This effort included the identification and training of field staff, formal supervision, and establishing the necessary documentation system, all integrated into existing leprosy control programme structures. Of crucial relevance was the management of logistics and documentation of contact tracing as well as training to boost and maintain the capacity of field workers to reliably detect suggestive signs of leprosy so that identified contacts could then be referred to trained medical personnel for confirmatory diagnosis. The documentation and training needs also highlight the requirement for quality control procedures to support the programme. By contrast, the administration of SDR was readily integrated into the field routines.

The main challenges with SDR management were that rifampicin was not registered for leprosy prevention by the regulatory authorities in all LPEP programme countries except Brazil, and that it was often restricted for use against tuberculosis and other clearly specified indications. Other issues included the need for liquid rifampicin formulations for young children aged 2–5 years in countries that had decided to also provide chemoprophylaxis to this age group. Also, for young children and contacts who were underweight, scales were required to establish bodyweight for calculating the correct rifampicin dose. Furthermore, the directly observed administration of SDR to contacts of individuals newly diagnosed with leprosy and individuals initially suspected of having leprosy but in whom confirmative diagnosis proved negative, posed a challenge in settings in which field workers do not routinely visit the homes of patients with leprosy. SDR should be given to contacts no earlier than 1 month after initiation of MDT of the individual newly diagnosed with leprosy to avoid immediate re-infection, as patients are assumed to become non-infectious within 4 weeks of treatment start. Contacts suspected of having leprosy and who after final evaluation are confirmed of not having leprosy should be given SDR as soon as possible after this confirmation. Both scenarios require a member of the contact tracing team to return to the household or that the contact presents to an assigned health centre.

Acceptance of SDR was generally good and there was a smooth integration of chemoprophylaxis into contact tracing procedures. Nevertheless, it remains crucial that the approach to identifying contacts is carefully tailored to the local context. In some populations, there is a marked reluctance of index patients to disclose their

disease status to neighbours and sometimes even to household members. In such situations, alternative approaches to contact tracing are needed, for which disclosure of the disease status of the index patient is not required. This alternative could be achieved by defining contact tracing perimeters around the index patient that cover more than just a few households, allowing the masking of the index patient's identity and guarding confidentiality. Community-wide screening, often termed blanket screening, has been explored as an option to achieve good coverage in highly endemic communities.[23,38]

Screening for signs of active tuberculosis took place as part of the LPEP intervention. In all but one country, individuals suspected to have tuberculosis were identified and referred for full evaluation and appropriate treatment. In some countries, the numbers might be less than expected based on known endemicity of tuberculosis in the country. This finding can be due to the quality of screening and the local epidemiology of tuberculosis.

There is a need to balance the target number of contacts per index patient with the benefits expected in terms of leprosy prevention and burden reduction. It is probable that the incremental benefit of adding ever more distant contacts at one point becomes negative as resource needs for contact tracing are likely to increase almost linearly with the number of households and contacts traced and screened. The optimal number of contacts probably also depends on the local epidemiological situation (eg, endemicity level and multibacillary to paucibacillary ratio), household size, and health system characteristics, and remains to be determined by country or region. Implementing SDR at a nationwide scale is challenging as systematic contact tracing and screening in leprosy is not widely or consistently done in many countries. Screening can best be managed locally, taking into account local culture, geography, and infrastructure, and preferably integrated with other contact tracing activities, such as for tuberculosis. But once contact tracing is in place, the provision of SDR only slightly increases the complexity of the programme. Chemoprophylaxis with SDR was shown to be cost-effective in Bangladesh[42] and India.[43] In India, it was shown that it is cost-effective in both the short (5 years) and long term (25 years), with benefits depending on the extent to which disability can be prevented.[43] Chemoprophylaxis is an important cornerstone of a leprosy elimination scenario and its cost-effectiveness should also be considered carefully from this perspective.[44]

For the evaluation of the LPEP programme, high-quality documentation of the field work was particularly important. National leprosy control programmes integrating contact tracing, screening, and SDR into their routine activities will also need to document these activities. We have proposed a set of minimal essential data for contact tracing, screening, and SDR administration to be recorded locally and reported to national and ultimately international agencies.[45]

The detection of previously undiagnosed patients with leprosy, including child cases among the screened contacts, indicates ongoing transmission and insufficient capacity of the routine programme for early detection. The public health benefits of improved early case detection are evident, such as the inclusion of population groups, who are often under-represented due to stigma or restricted health system access (eg, women and children), and the deployment of an intervention to reduce the risk of developing leprosy among contacts. However, the strategy will only have a long-term effect if it is embedded in a robust passive case detection system, possibly complemented by focused active case detection approaches, because index patients need to be identified before contact tracing can follow-up on the individuals at risk in their vicinity.

An important positive effect of the intervention was the reported qualitative invigoration of local leprosy control efforts. This positive effect on morale and efforts was seen in all settings irrespective of whether contact tracing and screening had already been integrated into the routine activities before the LPEP programme, and was reported by staff at different levels, from the periphery to the central leprosy control programme coordination. The increased motivation was associated mainly with the availability of a preventive intervention that is easy to administer as well as strengthened training and supervision. A challenge in several countries was the scarcity of health-care staff with a good command of leprosy-related knowledge, particularly the capacity to diagnose leprosy with confidence.

On the basis of the findings available to date from screening nearly 180 000 contacts and administering SDR to more than 150 000 of them across seven countries, we concluded that post-exposure prophylaxis with SDR is safe; can be integrated into the routines of different leprosy control programmes; and is generally well accepted by index patients, their contacts, and the health-care workforce. Chemoprophylaxis by definition provides temporary protection because it reduces the bacterial load with use of antimicrobial agents. It does not induce lasting immunological protection in the way that immunoprophylaxis with vaccines would. Contacts receiving SDR were routinely informed about this factor in the LPEP programme and advised to seek medical care any time in the future if signs and symptoms suspected of leprosy appeared. Although SDR is effective for most contacts, it is less effective for a small but important group of close contacts with an increased risk of leprosy (eg, blood-related household contacts and close contacts of patients with multibacillary leprosy). Research is ongoing into enhanced post-exposure prophylaxis regimens for these close contacts. Besides the protective effect of post-exposure prophylaxis, the intervention also invigorated local leprosy control through the introduction or strengthening of contact tracing, increased motivation associated with the availability of an effective and well accepted preventive

medication, and more frequent training and supervision. Together, these effects have translated into an improved leprosy control programme implementation, quality, and documentation. Since 2018, WHO has included post-exposure prophylaxis with SDR in their guidelines for leprosy control[28] and several countries (India, Indonesia, and Nepal) have already introduced or are preparing to introduce post-exposure prophylaxis with SDR in their national programmes and strategic plans, with roll-out planned as resources permit.

Contributors

All authors contributed to the planning, conducting of the study, analysis or interpretation of the data, reporting the work for the purpose of this publication, and have read and approved the final manuscript. JHR and PS wrote the paper.

Declaration of interests

Novartis Foundation and International Federation of Anti-Leprosy Association partners provided technical input in the design phase of the LPEP programme and ensured overall programme coordination. AC, ZG, and AA are staff of the Novartis Foundation; JHR, AT, TB-J, DJB, MB, HG, CK, LM, WHvB, BVP, and PS work as paid consultants for the programme described here; MAA, NLB, RB, TB, EI, DVK, PRM, BFN, BTP, BDP, RSi, NDS, ATM, TS, and MSDW act as national programme coordinators; and DB, PS, WCSS, RSt, JVB, and MV serve on the steering committee of the programme.

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