Post-exposure prophylaxis in leprosy (PEOPLE): a cluster randomised trial

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Summary

Background Post-exposure prophylaxis (PEP) using single-dose rifampicin reduces progression from infection with *Mycobacterium leprae* to leprosy disease. We compared effectiveness of different administration modalities, using a higher (20 mg/kg) dose of rifampicin—single double-dose rifampicin (SDDR)-PEP.

Methods We did a cluster randomised study in 16 villages in Madagascar and 48 villages in Comoros. Villages were randomly assigned to four study arms and inhabitants were screened once a year for leprosy, for 4 consecutive years. All permanent residents (no age restriction) were eligible to participate and all identified patients with leprosy were treated with multidrug therapy (SDDR-PEP was provided to asymptomatic contacts aged ≥2 years). Arm 1 was the comparator arm, in which no PEP was provided. In arm 2, SDDR-PEP was provided to household contacts of patients with leprosy, whereas arm 3 extended SDDR-PEP to anyone living within 100 m. In arm 4, SDDR-PEP was offered to household contacts and to anyone living within 100 m and testing positive to anti-phenolic glycolipid-I. The main outcome was the incidence rate ratio (IRR) of leprosy between the comparator arm and each of the intervention arms. We also assessed the individual protective effect of SDDR-PEP and explored spatial associations. This trial is registered with ClinicalTrials.gov, NCT03662022, and is completed.

Findings Between Jan 11, 2019, and Jan 16, 2023, we enrolled 109 436 individuals, of whom 95 762 had evaluable follow-up data. Our primary analysis showed a non-significant reduction in leprosy incidence in arm 2 (IRR 0·95), arm 3 (IRR 0·80), and arm 4 (IRR 0·58). After controlling for baseline prevalence, the reduction in arm 3 became stronger and significant (IRR 0·56, p=0·0030). At an individual level SDDR-PEP was also protective with an IRR of 0·55 (p=0·0050). Risk of leprosy was two to four times higher for those living within 75 m of an index patient at baseline.

Interpretation SDDR-PEP appears to protect against leprosy but less than anticipated. Strong spatial associations were observed within 75 m of index patients. Targeted door-to-door screening around index patients complemented by a blanket SDDR-PEP approach will probably have a substantial effect on transmission.

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For the French translation of the abstract see **Online** for appendix 1

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Introduction

In 2018 WHO issued a conditional recommendation to offer post-exposure prophylaxis (PEP) for leprosy with single-dose rifampicin (SDR) to close contacts of patients with leprosy.[1] This recommendation was based on a significant reduction in the risk of leprosy after SDR found in the COLEP trial in Bangladesh (incidence rate ratio [IRR] 0·43, 95% CI 0·28–0·67).[2,3] SDR-PEP therefore represents a promising tool to mitigate the impact of this ancient and persistent disease, aiming in the first place to prevent individual suffering but ultimately to eliminate transmission of *Mycobacterium leprae*.[3,4]

An earlier study in high-endemicity settings in Indonesia did not show any protective effect when administering two doses of rifampicin, with three months in between doses, to household and social contacts of patients with leprosy; however, providing PEP to an entire island population resulted in a four-fold reduction in leprosy incidence.[5] Comparable results with the COLEP trial, were obtained in a more recent study in a low endemicity setting in China, which showed a moderate protective effect of SDR-PEP provided to close contacts of patients with leprosy (IRR 0·59, 95% CI 0·22–1·57) but a stronger effect of rifapentine (IRR 0·16, 95% CI 0·03–0·87).[6]

In the Post ExpOsure Prophylaxis for LEprosy (PEOPLE) study, we aimed to identify the optimal approach to roll-out PEP in a population-based cluster randomised trial in Comoros and Madagascar. The study countries are among the 23 nations considered as high-burden countries for leprosy by WHO.[7] Comoros is an

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Research in context

Evidence before this study

This study was conceptualised in close consultation with various partners within the International Federation of Anti-Leprosy Associations (ILEP). We also searched PubMed for all studies published in English from database inception to May 31, 2018, in which results on rifampicin-based post-exposure prophylaxis (PEP) for leprosy were reported, using combinations of the following keywords: "leprosy" AND "prevention OR prophylaxis" AND "rifampicin OR rifampin". The main studies identified were the study by Bakker and colleagues in Indonesia and the COLEP trial in Bangladesh. From the study in Indonesia, conducted on isolated islands with extremely high leprosy endemicity, we knew that rifampicin as PEP provided only to close contacts of patients with leprosy had not been very effective, whereas blanket coverage of an entire island had resulted in a four-fold reduction in incidence. From the COLEP trial we knew that in an area of moderate endemicity, single-dose rifampicin provided as PEP to close contacts of patients with leprosy resulted in a 50–60% reduction in leprosy risk over a 2-year period. After that period the risk went back to that of the surrounding community but there was no rebound effect. In an update of the PubMed search (using the same database on Jan 24, 2024) a new study, published in 2023, came forward. In this study, conducted in a low-incidence setting in China, a non-significant protective effect was found for single-dose rifampicin (41% reduction, p=0·24) but a strong and significant effect was shown for rifapentine (84% reduction, p=0·02).

Added value of this study

This study was the largest study to date on effectiveness of PEP for leprosy. We were able to directly compare the effect of different modalities of PEP administration in an environment of high endemicity. In an elaborate data collection system every household in the participating villages was mapped and all individuals were recorded and followed up. This allowed us to assess not only the effect of PEP at a community level (the main research question) but also the individual protective effect of PEP and the spatial associations between patients with leprosy. We also used a dose of rifampicin that was twice the regular dose, anticipating an increased effectiveness.

Implications of all the available evidence

We confirmed that rifampicin PEP reduces the risk of leprosy, both individually and at a community level, although the reduction in risk observed was not as strong as in the COLEP study. We also showed that even in highly endemic villages, leprosy is geographically clustered around index patients, beyond the level of the household. Screening of contacts should therefore not be limited to household members and providing PEP in addition can further reduce leprosy risk, even in an environment of high endemicity. Stronger PEP regimens—eg, regimens based on a combination of drugs—need to be explored for greater efficacy.

island nation in the Indian Ocean, situated between Mozambique and the northern tip of Madagascar. Over the 5-year period preceding the study (2014–18) Comoros reported 1681 patients newly diagnosed with leprosy in a total population of approximately 800 000, equivalent to an annual incidence rate of 4·2 per 10 000.[8] The vast majority of these patients were from the island of Anjouan, where annual incidence rates of ten per 10 000 and above had been reported in earlier years.[9] Madagascar reported 7738 patients newly diagnosed with leprosy in the period of 2014–18, on a total population of approximately 26 million, equivalent to an annual incidence rate of 0·6 per 10 000.[8]

The primary objective of the PEOPLE trial was to compare the effectiveness at a population level of three different modalities of provision of PEP with a comparator arm in which no PEP was provided. The hypothesis we tested was that, given the high background incidence of leprosy in the study areas, as in the Indonesia trial, PEP would be most effective in a blanket approach—ie, covering an entire geographic zone such as a neighborhood, village, or island.[5] In addition, in all three intervention arms we used a higher than usual dose of rifampicin. This choice was made based on studies in tuberculosis treatment by Boeree and colleagues[10] that showed a non-linear increase in exposure of higher doses of rifampicin without major safety concerns, and by Diacon and colleagues[11] that showed a near-linear increase in early bactericidal activity when using 20 mg/kg instead of 10 mg/kg; we thus opted for double the regular dose of rifampicin—ie, 20 mg/kg.[10,11] We hereafter refer to this regimen as single double-dose rifampicin (SDDR)-PEP.

As secondary analyses, we evaluated the protective effect of PEP at individual level by measuring the risk of leprosy for individuals who received PEP compared to individuals that did not receive PEP irrespective of study arms. We also explored spatial associations via assessing the risk of developing leprosy as a function of distance to nearest index patient at baseline. Furthermore, we investigated whether there was an additional protective effect from BCG vaccination given at birth.

Methods

Study design

The PEOPLE study is a population-based cluster randomised trial that took place in 64 leprosy-endemic villages in Comoros and Madagascar between Jan 11, 2019, and Jan 16, 2023. The country selection was motivated by the high burden of leprosy and well established national tuberculosis and leprosy programmes (NTLPs). In Comoros, the highly endemic islands of Anjouan and Mohéli were included, with annual case notification rates

of up to ten per 10 000 population.[9] In Madagascar, the southern part of the Miandrivazo district, located in the Menabe area in the central-west part of the country, was selected based on assumed high incidence, athough no accurate recent data were available. In consultation with the NTLPs we selected 48 villages in Comoros (32 on Anjouan and 16 on Mohéli) and 16 in Madagascar, considering expected incidence and accessibility.

In each of the three study islands, Madagascar, Anjouan, and Mohéli, villages were randomised to four trial arms, in each of which door-to-door screening for leprosy was done once a year and PEP was distributed according to study-arm-specific criteria. In arm 1, the comparator arm, no PEP was provided. In arm 2 all eligible household contacts were offered PEP. In arm 3, the blanket arm, anyone living within 100 m of an index patient was eligible, and eligibility was extended to the entire village population if over 50% of participants lived within this perimeter. In arm 4 villages, a serological test, anti-phenolic glycolipid-I (anti-PGL-I), was performed and PEP was provided to all household contacts as well as to all anti-PGL-I-positive participants residing within a 100 m perimeter, extended to anti-PGL-I positives in the entire village if more than 75% of participants lived within this 100 m radius. Field teams therefore revisited participating households for PEP distribution upon completion of screening activities in each village.

The design chosen allowed us to measure the effect of PEP on leprosy incidence at a study-arm level as well as at an individual level, bridging the gap between the COLEP trial and the Indonesia trial.[2,5] The blanket approach has since been recommended by WHO in hyperendemic settings to avoid potential stigma related to disclosure of a leprosy diagnosis.[1]

The trial was registered on ClinicalTrials.gov (NCT03662022) before recruitment started, and the protocol has been published.[12] Ethics approval was obtained from the relevant committees in Madagascar, Comoros, and Belgium (Comité d'Éthique de la Recherche Biomédicale in Madagascar, Comité National d'Éthique pour les Sciences de la Vie et de la Santé in Comoros, and Institutional Review Board of the Institute of Tropical Medicine, Ethics Committee of the University of Antwerp Hospital, Antwerp, in Belgium).

Participants

Anyone permanently residing within the study villages was eligible for inclusion and was offered annual screening for leprosy, and SDDR-PEP based on study-arm-specific eligibility criteria. Screening was offered also to non-permanent residents and to those who had not agreed to PEP. We obtained written informed consent or parent or guardian approval for participants younger than 18 years, as well as assent for minors aged 12 years or older. Newly identified patients with leprosy were invited for a substudy exploring molecular markers of drug resistance and phylogenetic clustering of leprosy, with additional informed consent.

Individual eligibility criteria were based on WHO recommendations for SDR-PEP—ie, healthy contacts aged 2 years and older, excluding possible patients with leprosy or tuberculosis, or both, in the absence of other contraindications.[1] Eligibility was reassessed during follow-up screening rounds and SDDR-PEP repeated if required. To avoid any theoretical risk of inducing rifampicin resistance, having received rifampicin in the preceding 2-year period was an additional exclusion criterion for SDDR-PEP.[13]

Randomisation and masking

By island (Madagascar, Anjouan, and Mohéli), villages were randomised to four study arms. In Comoros, randomisation was based on reported pretrial incidence over the period of 2014–18. In Madagascar, in the absence of reliable baseline data, randomisation was based on leprosy prevalence during the first screening round in 2019. Villages, listed per island in order of decreasing incidence (Comoros) or prevalence (Madagascar), were regrouped into consecutive blocks of four. Within each block they were randomised to each of the four trial arms, based on random numbers.

In Comoros SDDR-PEP distribution started immediately after the first screening in each village, whereas in Madagascar randomisation was done at the end of the first study year and therefore SDDR-PEP distribution only started in the second year. Thus, in Comoros we had approximately 3 years of follow-up, versus 2 years in Madagascar.

Masking was not possible due to study design but potential bias was assessed through comparison of *M leprae*-specific repetitive element (RLEP) quantitative PCR (qPCR) results of biopsies from the edge of lesions obtained from consenting incident patients with leprosy across the four study arms, as described in the procedures. Although we recognise that patients on the paucibacillary side of the spectrum are less likely to test qPCR positive, we would expect to find similar proportions of qPCR-confirmed cases across the four study arms.

Procedures

In the 64 participating villages, NTLP teams and community health workers conducted one screening per year over a 4-year period in which participants were recruited. In each household visited, all household members were registered. All consenting participants present underwent screening for leprosy, tuberculosis, and presence of a BCG-scar. Screening involved clinical examination for skin lesions and thickening of peripheral nerves, inquiry about a persistent chronic cough for over 2 weeks (suspect tuberculosis), and assessment of history of previous leprosy diagnosis or treatment. Chronic cough reports prompted sputum sampling, with subsequent follow-up per NTLP guidelines.

On site, experienced NTLP staff diagnosed leprosy based on clinical symptoms, classifying it as paucibacillary (one to five lesions) or multibacillary (more than five lesions) leprosy per WHO criteria. Any newly identified patients with leprosy were offered free multi-drug therapy according to NTLP guidelines. Skin biopsies from the edge of lesions, excluding facial lesions, were collected for a substudy among consenting patients.[14] The DNA extracted from these biopsies underwent *M leprae* testing using RLEP qPCR as described by Braet and colleagues.[15]

In arm 4 villages, a minimally invasive fingerstick blood sample (20 µL) was collected from participants, directly added to assay-buffer (980 µL), and transported at ambient temperature to NTLP laboratories where samples were quantitatively assessed for IgM antibodies against *M leprae* specific PGL-I, using upconverting reporter particle technology in a low-cost lateral flow-based assay format.[16]

Patients with newly detected leprosy or already under treatment during the initial screening round in 2019 were categorised as prevalent cases. Patients with disease detected after the first screening round were classified as incident cases if already under follow-up at time of diagnosis or as other cases if disease had been detected after the first screening but patients had not been enrolled before diagnosis. These other patients included participants who had relocated to the study village after having developed signs of leprosy, as well as residents not enrolled earlier due to reasons such as absence or refusal. Of note, such patients categorised as other cases were not under follow-up at time of diagnosis and therefore also would not have received SDDR-PEP. They were therefore excluded from the analyses.

We aimed to have the SDDR-PEP distributed within 1 month following the completion of the annual screening round in each village, based on the cases detected during these screening rounds and, for arm 4, based also on anti-PGL-I test results. In the first year, the index patients for study-arm-specific criteria were prevalent cases detected in the initial screening round. In the subsequent years, index patients were new cases detected after the previous screening round, until and including the current round. In Madagascar the intervention (SDDR-PEP) only started during the second screening round. In the study's fourth and final year, only screening occurred, without PEP distribution.

Outcomes

The primary outcome was the effectiveness of SDDR-PEP in reducing leprosy incidence at a population level by computing the incidence rate ratios (IRRs) between the comparator arm and each of the intervention arms using an intention-to-treat analysis. We also did a per-protocol analysis.

Additionally, the study assessed the individual-level protective effect of SDDR-PEP, adjusting for confounding factors such as distance to the nearest index patient at baseline, age, and sex. We also explored the effect of BCG vaccination at birth based on presence or absence of a BCG scar. In a subgroup analysis we explored the individual protective effect of SDDR-PEP among household contacts.

We calculated the number needed to be exposed per leprosy case averted overall and separately for household contacts.

As a proxy for quality of diagnostic procedures in the field we assessed proportions of qPCR positives among incident patients with leprosy recruited into the substudy.

Adverse events were collected passively, participants were encouraged to report any possible adverse events while the study teams were in the village or via reporting to community health workers during the whole study period. There were no systematic revisits to follow up on adverse events.

Statistical analysis

The study aimed to show a reduction in incidence across the three intervention arms compared with the comparator arm over a 3-year follow-up period. The sample size was determined using the Hayes and Bennet methodology for pair-matched randomised controlled trials, assuming an annual incidence rate of 1·5 per 1000 derived from 2013–17 data from Comoros.[17] Recognising the multiple (three) comparisons made, a conservative significance level of 0·017 was chosen. Using Comoros data, we calculated a coefficient of variation between clusters (κ) of 0·29. To achieve a power of 80% with an average cluster size of 2400, 13 clusters per study arm would be required (31 200 participants in each arm; 124 800 in total). To be on the safe side we opted for 16 clusters per arm, with a total estimated population of 144 000.

For the intention-to-treat analysis a mixed effects Poisson model was fitted, incorporating random effects for village, nested in randomisation block, nested in island. Incident leprosy cases served as an outcome variable, with total follow-up time per trial arm as offset. In the comparator arm, individual follow-up began on the date of the first screening; in Madagascar this was first screening after the 2019 round. For participants in the intervention arms, follow-up time started on the median date of the first SDDR-PEP distribution in their village. As end dates we used date of final examination or date of diagnosis for incident cases. Villages in the intervention arms where no PEP was ever distributed were excluded from this analysis. As a sensitivity analysis we included village-level leprosy prevalence at baseline as a fixed effect, instead of village as a random effect.

In the per-protocol analysis, we excluded participants eligible for SDDR-PEP in one of the distribution rounds who did not receive SDDR-PEP at that time, as well as participants who received SDDR-PEP in any of the rounds but were not eligible at that time.

For the individual-level analysis, follow-up time was calculated based on individual starting dates and end dates, irrespective of study arm. For non-PEP recipients, the starting date was the date of the first examination, excluding the first screening round in Madagascar. For PEP recipients the starting date was defined as the date of the last examination before receiving their first dose of SDDR-PEP. As end dates we used date of final examination or date of diagnosis for incident cases. We fitted a Poisson model with village nested in randomisation block, nested in island as random effect and follow-up time as offset. As explanatory

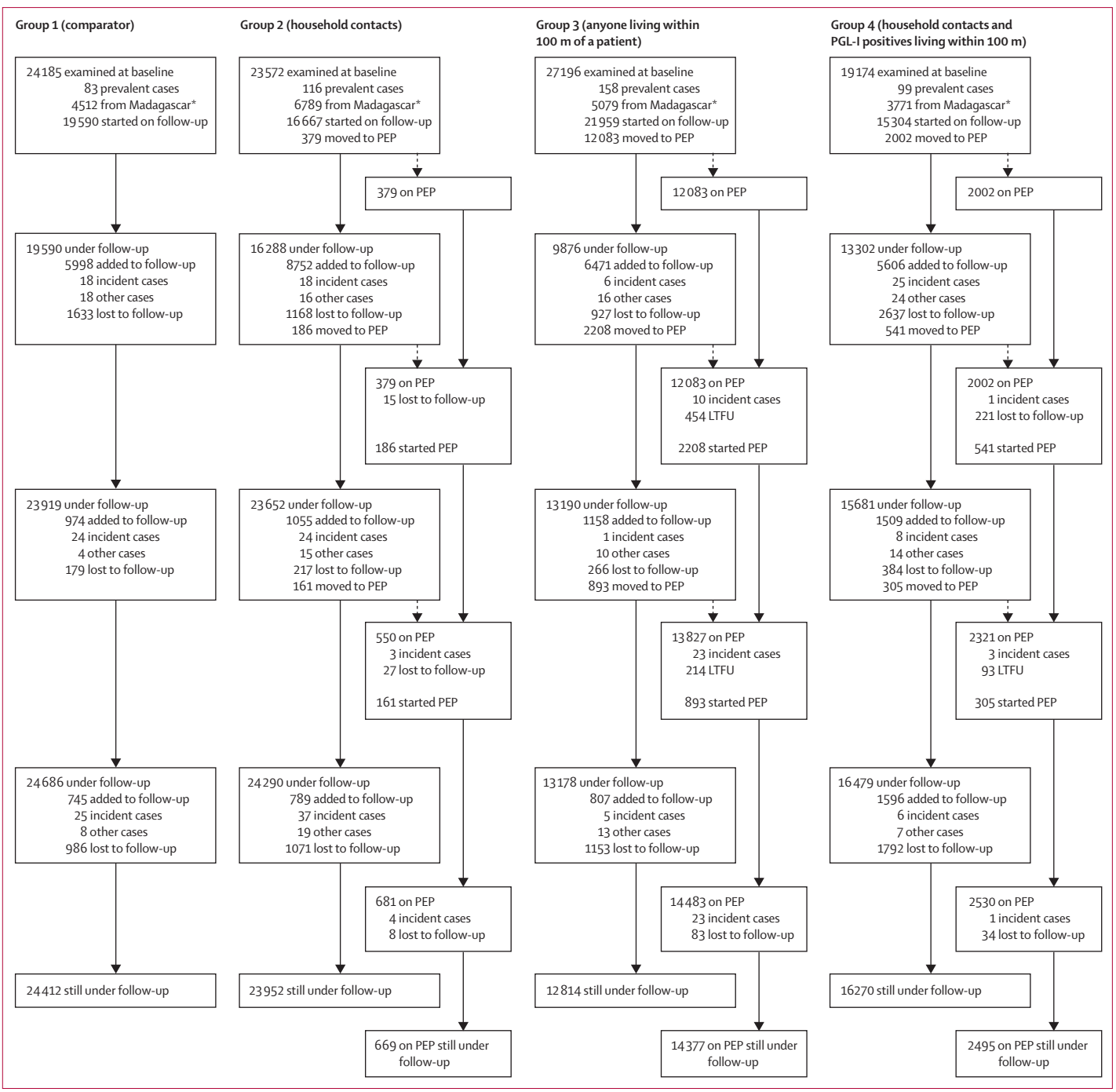

Figure: **Trial profile**
64 villages were randomly assigned to four study arms, participants were then enrolled for screening and follow-up. Over the study period (2019–22) 109 436 individuals were enrolled. *In Madagascar follow-up started only in year 2.

variables we explored age group (0–4, 5–14, 15–24, and ≥25 years), sex, presence of BCG scar, and distance to nearest index patient at baseline. For the distance variable participants were regrouped into six distance categories based on distance to nearest prevalent case at baseline (household contacts, neighbours at <25 m, neighbourhood contacts at 25 m to <50 m, at 50 m to <75 m, at 75 m to <100 m, and at 100 m or beyond).[18] For this purpose multiple nuclear families sharing the same house or the same courtyard (same GPS coordinates) were classified as household contacts. A sensitivity analysis assessed using the date of first SDDR-PEP intake as a starting point of follow-up time for SDDR-PEP recipients.

We compared proportions of multibacillary and paucibacillary leprosy among incident leprosy cases with and without previous SDDR-PEP.[19]

Based on the individual effectiveness of SDDR-PEP we calculated the number needed to be exposed per leprosy case averted according to the methodology described by Bender and Blettner, for the overall population and separately for household contacts.[20]

Additionally, to assess the quality of clinical leprosy diagnosis and explore potential biases, we computed the percentage of qPCR confirmed by trial arm among incident cases with available results.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 11, 2019, and Jan 16, 2023, we recorded a study population of 110 666 individuals. Of those 109 436 were examined at least once and 95 762 had at least one follow-up, were not yet diagnosed with leprosy at the time of recruitment, and could therefore be evaluated (figure).

	Anjouan	Mohéli	Madagascar	Total
Sex				
Female	32 262 (51·0%)	12 520 (50·0%)	10 835 (51·3%)	55 617 (50·8%)
Male	31 015 (49·0%)	12 508 (50·0%)	10 294 (48·7%)	53 817 (49·2%)
Age group, years				
0–4	11 031 (17·4%)	4136 (16·5%)	3338 (15·8%)	18 505 (16·9%)
5–14	18 945 (29·9%)	7454 (29·8%)	5935 (28·1%)	32 334 (29·6%)
15–24	12 437 (19·7%)	4812 (19·2%)	4465 (21·1%)	21 714 (19·8%)
≥25	20 860 (33·0%)	8624 (34·5%)	7389 (35·0%)	36 863 (33·7%)
BCG vaccine scar				
Present	37 228 (61·1%)	16 018 (66·7%)	14 013 (67·8%)	67 259 (63·7%)
Absent	23 752 (39·0%)	7992 (33·3%)	6661 (32·2%)	38 405 (36·4%)
Leprosy patients diagnosed				
Prevalent	348	38	70	456
Incident	243	20	2	265
Other	153	3	8	164

Sex data were available for 109 434 participants, age data for 109 426 participants, and BCG vaccine scar data for 105 664 participants.

Table 1: **Overview of the study population by site**

Prevalence rates in 2019 as the start of the study ranged from 65·0 per 10 000 on Anjouan in Comoros to 34·6 per 10 000 in Madagascar and 18·7 per 10 000 on Mohéli in Comoros. The average annual incidence rate was 10·9 per 10 000 with variability between the sites. Most incident cases were identified on Anjouan (n=243), corresponding to an average annual incidence of 16·7 per 10 000. On Mohéli there were 20 patients with incident disease, equivalent to an average annual incidence of 3·2 per 10 000. In Madagascar there were only two patients with incident disease, equivalent to an average annual incidence of 0·57 per 10 000 (table 1).

Leprosy prevalence at baseline was highest in arm 3 (58·1 per 10 000) and lowest in arm 1 (34·3 per 10 000). Proportions of multibacillary leprosy among prevalent cases at baseline were similar in arms 1, 2, and 3 (30·5, 34·8, and 32·9%, respectively) and somewhat lower in arm 4 (24·5%). Out of 265 patients diagnosed with incident leprosy, 67 occurred in arm 1, 86 in arm 2, 68 in arm 3, and 44 in arm 4 (table 2).

We observed a strong association between distance to the nearest person with leprosy at baseline and the probability of being diagnosed with leprosy during follow-up. Whereas among household members of patients with prevalent leprosy at baseline 1·10% developed leprosy over the duration of follow-up, for those living at more than 100 m the cumulative risk was ten times lower (0·11%; table 3). Prevalent and other leprosy cases were excluded, as well as records of participants without follow-up or with missing geographic coordinates.

SDDR-PEP was distributed at least once to 18 784 participants, of those 17 379 (93%) had at least one follow-up and could be evaluated. Among them, 68 individuals developed incident leprosy (0·39%) versus 197 out of 78 383 (0·25%) among non-PEP recipients.

Logically, SDDR-PEP provision was strongly associated with distance from nearest index patient at baseline, with 70% of all household contacts receiving SDDR-PEP (none in arm 1, 437 [88%] of 497 in arm 2, 658 [92%] of 717 in arm 3, and 315 [77%] of 411 in arm 4). In arm 3, 11 707 (87%) of 13 397 participants residing within 100 m of a patient with prevalent leprosy at baseline received SDDR-PEP versus 2047 (24%) of 8398 in arm 4. SDDR-PEP uptake among those eligible was 84% in arm 2, 91% in arm 3, and 85% in arm 4. Overall 13 896 (51%) of 27 272 in arm 3 were eligible, versus 1881 (10%) of 19 334 in arm 4.

The primary outcome of the PEOPLE trial was the incidence rate ratio between arm 1 and each of the intervention arms, based on a random effects model with island, randomisation group, and village as random effects. From this analysis we excluded two villages in arm 4 in which no cases were found and hence no SDDR-PEP was ever distributed. There was little or no reduction

	Arm 1 (comparator)	Arm 2 (household contacts)	Arm 3 (blanket coverage)	Arm 4 (household contacts plus anti-PGL-I positives)
Total enrolled	27390	27379	30553	24114
Prevalent cases (paucibacillary, multibacillary)*	83 (57, 25)	116 (75, 40)	158 (106, 52)	99 (74, 24)
Prevalence rate per 10000	34·3	49·2	58·1	51·6
Incident cases (paucibacillary, multibacillary)	67 (40, 27)	86 (44, 42)	68 (49, 19)	44 (31, 13)
Annual incidence rate per 10000	10·4	14·2	9·8	9·2

Anti-PGL-I=anti-phenolic glycolipid-I. ITT=intention to treat. *WHO classification unknown for three prevalent cases.

Table 2: **Prevalence and incidence of leprosy cases by study arm**

of leprosy incidence in arm 2 (IRR 0·95, p=0·88), some reduction in arm 3 (IRR 0·80, p=0·52), and more reduction in arm 4 (IRR 0·58, p=0·19). However, none of these reductions were significant (table 4). The per-protocol analysis was based on a total population of 86715 and showed comparable results. None of the associations observed were significant. In a sensitivity analysis we controlled for background prevalence at baseline at village level. This had an impact on arm 3, which had the highest baseline prevalence. For this arm controlling for baseline prevalence resulted in an IRR of 0·56 (p=0·0030).

In our secondary analysis at an individual level we found a modest but significant protective effect of SDDR-PEP. After controlling for confounding by distance to nearest prevalent case at baseline, age, and sex, SDDR-PEP reduced leprosy risk by 45% (IRR 0·55, 95% CI 0·36–0·83). As a sensitivity analysis we tested the effect of starting follow-up time on the date of PEP for SDDR-PEP recipients, rather than on the date of last pre-PEP examination. This led to a slight decrease in the estimate of effectiveness of SDDR-PEP (IRR 0·62, 95% CI 0·41–0·95). We also tested the effect of SDDR-PEP controlled for age, sex, and BCG scar status for household members only. In this subgroup analysis the protective effect of SDDR-PEP was stronger (IRR 0·35, 95% CI 0·15–0·82).

Despite being much more likely to have received SDDR-PEP, and the stronger protective effect observed, household members of people with prevalent disease at baseline were still at more than four times' higher risk compared with those living at 100 m or beyond from a patient with leprosy. The effect of exposure to a neighbourhood contact remained significant up to 75 m, with an approximately two-fold increase in risk (table 5).

Men tended to be more at risk than women (IRR 1·74, 95% CI 1·35–2·23) and children younger than 5 years were significantly less likely to be diagnosed with leprosy during follow-up (IRR 0·39, 95% CI 0·23–0·66) when compared with participants aged 25 years or older. BCG at birth (ie, presence of a BCG scar) reduced risk by 38% (IRR 0·62, 95% CI 0·48–0·79; table 5). We did not find an indication for an interaction between SDDR-PEP and BCG (p=0·99).

	Population enrolled	Incident cases (%)
Distance category		
Same household	2004	22 (1·10%)
Neighbour <25 m	8945	59 (0·66%)
Neighbourhood contact 25 m to <50 m	13274	58 (0·44%)
Neighbourhood contact 50 m to <75 m	10719	51 (0·48%)
Neighbourhood contact 75 m to <100 m	8188	16 (0·20%)
Neighbourhood contact ≥100 m	52569	59 (0·11%)
Total	95699	265 (0·28%)

Table 3: **Proportion of incident leprosy cases in function of distance to nearest prevalent case at baseline (excluding participants with no follow-up)**

The proportion of patients with multibacillary disease among the 68 participants who developed leprosy despite having received SDDR-PEP was 31% (21 of 68), which was lower than the proportion of multibacillary among incident patients without SDDR-PEP, which was 41% (80 of 197).

Results of qPCR were available for 178 (67%) of 265 patients with incident disease; of those, 154 (87%) tested positive with RLEP qPCR. The highest proportion of cases confirmed by the presence of *M leprae* DNA in lesions was in arm 1 (45 [96%] of 47); the lowest in arm 3 (38 [73%] of 52). In arm 2, 49 (91%) of 54 patients were qPCR positive, versus 22 (88%) of 25 in arm 4.

The number needed to be exposed to prevent one case of leprosy was calculated for the entire population and separately for household members. For the study population as a whole this was 870, for household members it was 82.

Discussion

In this population-based intervention trial, the largest to date assessing the effectiveness of PEP for leprosy, over 2–3 years of follow-up, a very high leprosy incidence was recorded with 265 patients diagnosed after the first screening round, equivalent to an average annual incidence of 10·9 per 10000.

Effectiveness of the intervention varied between the three study arms assessed. In the household-contacts-only arm (arm 2), almost no difference was observed

	ITT (n=96 650)	Per protocol (n=86 715)	ITT adjusted for baseline prevalence (n=96 650)
Arm 1 (comparator)	1 (ref)	1 (ref)	1 (ref)
Arm 2 (household contacts)	0·95 (0·40–2·23)	0·89 (0·37–2·17)	0·80 (0·50–1·29)
Arm 3 (blanket)	0·80 (0·34–1·87)	0·62 (0·23–1·63)	0·56 (0·35–0·89)
Arm 4 (household contacts and anti-PGL-I positives)	0·58 (0·22–1·56)	0·60 (0·22–1·68)	0·62 (0·37–1·05)

Anti-PGL-I=anti-phenolic glycolipid-I. ITT=intention to treat.

Table 4: **Incidence rate ratios with 98·3% CIs of intervention arms**

	Incidence rate ratio (95% CI)
PEP provided	0·55 (0·36–0·83)
Age group, years	
0–4	0·39 (0·23–0·66)
5–14	1·14 (0·85–1·54)
15–24	1·46 (1·05–2·02)
≥25	1 (ref)
Male sex	1·74 (1·35–2·23)
Distance category	
Same household	4·34 (2·39–7·87)
Neighbour <25 m	2·10 (1·33–3·31)
Neighbourhood contact 25 m to <50 m	1·71 (1·10–2·65)
Neighbourhood contact 50 m to <75 m	2·29 (1·49–3·53)
Neighbourhood contact 75 m to <100 m	1·11 (0·61–2·00)
Neighbourhood contact ≥100 m	1 (ref)
BCG vaccine scar	0·62 (0·48–0·79)

PEP=post-exposure prophylaxis.

Table 5: **Factors associated with leprosy risk at an individual level**

when compared with the comparator arm (arm 1). The blanket arm (arm 3) showed a non-significant 20% reduction in incidence. In the intervention arm, in which SDDR-PEP was provided to household contacts and serologically positive neighbourhood contacts (arm 4), a non-significant 42% reduction in leprosy incidence was observed. Baseline prevalence varied between the study arms, mainly because available pre-trial incidence data used for randomisation in Comoros did not match with actually observed prevalence at the start of the intervention. Proportions of multibacillary disease among prevalent cases at baseline were comparable between the arms. When controlling for the imbalance in baseline prevalence, the effect of the intervention became stronger and significant in arm 3 (IRR 0·56, 98·3% CI 0·35–0·89) but still not significant in arm 4 (IRR 0·62, 98·3% CI 0·37–1·05).

The protective effect of the intervention was lower than expected, in particular in the blanket arm in which we observed a 44% reduction, compared with the 74% reduction observed in the trial by Bakker and colleagues in their blanket arm; the effect we found was less even with a higher dose of rifampicin.[5] A major difference with this earlier trial is that it covered an entire island population, whereas in arm 3 of the PEOPLE trial only 51% of the population were eligible for PEP. Although within this group coverage was very high (91%), the overall proportion of the population covered by PEP was much lower, and in addition the PEOPLE trial was not conducted in the closed environment of an entire island—greater interaction is to be expected between the populations of villages belonging to other study arms and populations of non-study villages.

The 45% protective effect at an individual level observed in the PEOPLE trial was slightly lower than the COLEP trial's reported protection of 57%; however, it was within its 95% CI range of 33–72% and significant.[2] Comoros in particular is an environment of extremely high transmission of *M leprae* and, as Moet and colleagues hypothesise, this might be associated with a higher bacillary load and therefore probably requires a stronger prophylactic regimen.[2,9] In addition, the annual screening rounds needed to ascertain incident cases, and treating all identified patients with leprosy, will in itself already have a major effect on transmission that could have obscured part of the impact of SDDR-PEP.

BCG vaccination was associated with a significant 38% reduction in leprosy risk, but the protective effect might be influenced by genetic factors related to a robust vaccine response.[21,22] Consistent with the COLEP trial findings, there was no indication of an interaction between BCG vaccine and PEP.[2] The protective effect of BCG appears comparable to that of SDDR-PEP; however, while SDDR-PEP will only protect until the next exposure, protection provided by BCG vaccination is assumed to be long lasting.[23]

This study addressed the concerns that SDDR-PEP might primarily prevent non-infectious paucibacillary cases and be less effective in household contacts, its prime target group.[19] In this study, the proportion of multibacillary disease among patients after SDDR-PEP (31%) was lower than that in those not exposed to PEP (41%). In addition, the effectiveness of SDDR-PEP among household contacts was not lower than in other groups. The subgroup analysis for household contacts showed a higher effectiveness, IRR 0·35 (95% CI 0·15–0·82), contradicting earlier findings from the COLEP trial.[24] Taking into account the high effectiveness of PEP in household contacts combined with the high incidence of leprosy in this group, the number needed to be exposed to SDDR-PEP to prevent one case of leprosy was low at 82. For the overall population this number was much higher at 870.

A large population-based trial on prevention of leprosy such as the PEOPLE trial can only be carried out in an environment with a high incidence of leprosy, which is very different from the settings in which most other clinical trials are implemented. The fact that population

figures in Comoros appeared to be over-estimates caused us not to reach the intended sample size of 144 000. In addition, out of the 109 436 participants enrolled, only 95 762 (87·5%) had at least one follow-up and thus could be evaluated. Yet confounding by differences in exposure to index cases at baseline appeared to have a had a larger impact than inadequacies in sample size. We assume that loss to follow-up was not associated with incident leprosy.

We did not conduct active follow-up for adverse events. Probably there were no serious adverse events since none were reported. In the LPEP study, which was a feasibility study on PEP in which 151 928 contacts of patients with leprosy spread out across seven countries received SDR-PEP, only three adverse events were reported, none of which was considered serious.[25]

Leprosy is a clinical diagnosis, there is no gold standard diagnostic test available. However, the diagnostic procedures within the PEOPLE trial showed a high level of reliability, as 87% of clinically diagnosed patients with available RLEP qPCR results were microbiologically confirmed. Probably this is the highest possible proportion of qPCR-confirmed cases to be expected as patients on the tuberculoid side of the spectrum are prone to be qPCR-negative. Importantly, there was also no indication of bias among the patients diagnosed in the different study arms. The proportion of RLEP qPCR-confirmed cases was highest in arm 1 (96%) and lowest in arm 3 (73%). This makes it highly unlikely that there was overdiagnosis in the comparator arm or underdiagnosis in the intervention arms.

Efficacy of rifampicin-based PEP varies between settings and is probably lower in high incidence environments such as Comoros. Yet a significant protective effect at an individual level was observed. A key lesson learned from the PEOPLE trial is that it is worthwhile conducting well targeted, active case-finding around index patients, as we found a much higher risk in household contacts and near neighbours. If in addition to targeted screening SDDR-PEP is provided, leprosy risk could be reduced by another 40–50%. A stronger PEP regimen would be desirable and for this reason we have started a second trial in Comoros in which we will compare the effect of SDR-PEP at standard dose to that of a combination PEP regimen made up of rifampicin and bedaquiline.[26]

Contributors

EH and BCdJ: conceptualisation, formal analysis, funding acquisition, methodology, supervision, validation, and writing original draft. YA and AR: conceptualisation, methodology, project administration, supervision, and writing, review, and editing of the Article. SR, SMB, and BC: conceptualisation, methodology, and writing, review, and editing of the Article. AB, AM, ZS, MA, SG, NA, SHG, MR, KPG, MR-A, HH, PSup, PSuf, TR, and PC: investigation, methodology, and writing, review, and editing of the Article. RS: data curation, formal analysis, validation, project administration, and writing, review, and editing of the Article. CH: data curation, validation, project administration, and writing, review, and editing of the Article. AT: formal analysis, validation, and writing, review, and editing of the Article. NO-G: conceptualisation, funding acquisition, methodology, and writing, review, and editing of the Article. AG: conceptualisation, funding acquisition, and writing, review, and editing of the Article. EC: conceptualisation and writing, review, and editing of the Article. AT and EH accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2 p 79). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

See **Online** for appendix 2

Declaration of interests

We declare no competing interests.

Data sharing

The data supporting the findings of this study are retained at the Institute of Tropical Medicine (ITM), Antwerp, and will not be made openly accessible due to ethical and privacy concerns. Data can however me made available after approval of a motivated and written request to the ITM at ITMresearchdataaccess@itg.be.

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References

1 WHO. Guidelines for the diagnosis, treatment and prevention of leprosy. 2018. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017.
2 Moet FJ, Pahan D, Oskam L, Richardus JH, Group CS. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ* 2008; **336:** 761–64.
3 Moraes MO, Düppre NC. Leprosy post-exposure prophylaxis: innovation and precision public health. *Lancet Glob Health* 2021; **9:** e8–9.
4 Tió-Coma M, Avanzi C, Verhard EM, et al. Genomic characterization of *Mycobacterium leprae* to explore transmission patterns identifies new subtype in Bangladesh. *Front Microbiol* 2020; **11:** 1220.
5 Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *Am J Trop Med Hyg* 2005; **72:** 443–48.
6 Wang L, Wang H, Yan L, et al. Single-dose rifapentine in household contacts of patients with leprosy. *N Engl J Med* 2023; **388:** 1843–52.
7 WHO. Leprosy—number of new leprosy cases 2021. https://apps.who.int/gho/data/node.main.A1639?lang=en (accessed Jan 24, 2024).
8 WHO. ANNEX 4 TB burden estimates, notifications and treatment outcomes for individual countries and territories, WHO regions and the world. Global Tuberculosis Report 2018. Geneva: World Health Organization; 2018.
9 Hasker E, Baco A, Assoumani Y, et al. Leprosy on Anjouan (Comoros): persistent hyper-endemicity despite decades of solid control efforts. *Lepr Rev* 2017; **88:** 334–42.
10 Boeree MJ, Diacon AH, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015; **191:** 1058–65.
11 Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrob Agents Chemother* 2007; **51:** 2994–96.

12 Ortuno-Gutierrez N, Younoussa A, Randrianantoandro A, et al. Protocol, rationale and design of PEOPLE (Post ExpOsure Prophylaxis for LEprosy in the Comoros and Madagascar): a cluster randomized trial on effectiveness of different modalities of implementation of post-exposure prophylaxis of leprosy contacts. *BMC Infect Dis* 2019; **19:** 1033.

13 Mieras L, Anthony R, van Brakel W, et al. Negligible risk of inducing resistance in Mycobacterium tuberculosis with single-dose rifampicin as post-exposure prophylaxis for leprosy. *Infect Dis Poverty* 2016; **5:** 46.

14 Braet SM, van Hooij A, Hasker E, et al. Minimally invasive sampling to identify leprosy patients with a high bacterial burden in the Union of the Comoros. *PLoS Negl Trop Dis* 2021; **15:** e0009924.

15 Braet SM, Jouet A, Aubry A, et al. Investigating drug resistance of Mycobacterium leprae in the Comoros: an observational deep-sequencing study. *Lancet Microbe* 2022; **3:** e693–700.

16 Corstjens PLAM, van Hooij A, Tjon Kon Fat EM, et al. Fingerstick test quantifying humoral and cellular biomarkers indicative for *M leprae* infection. *Clin Biochem* 2019; **66:** 76–82.

17 Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999; **28:** 319–26.

18 Ortuño-Gutiérrez N, Mzembaba A, Ramboarina S, et al. Exploring clustering of leprosy in the Comoros and Madagascar: a geospatial analysis. *Int J Infect Dis* 2021; **108:** 96–101.

19 Lockwood DNJ, Krishnamurthy P, Kumar B, Penna G. Single-dose rifampicin chemoprophylaxis protects those who need it least and is not a cost-effective intervention. *PLoS Negl Trop Dis* 2018; **12:** e0006403.

20 Bender R, Blettner M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies. *J Clin Epidemiol* 2002; **55:** 525–30.

21 Richardus R, van Hooij A, van den Eeden SJF, et al. BCG and adverse events in the context of leprosy. *Front Immunol* 2018; **9:** 629.

22 van Hooij A, van den Eeden SJF, Khatun M, et al. BCG-induced immunity profiles in household contacts of leprosy patients differentiate between protection and disease. *Vaccine* 2021; **39:** 7230–37.

23 Duthie MS, Balagon MF. Combination chemoprophylaxis and immunoprophylaxis in reducing the incidence of leprosy. *Risk Manag Healthc Policy* 2016; **9:** 43–53.

24 Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. *J Infect Dis* 2006; **193:** 346–53.

25 Richardus JH, Tiwari A, Barth-Jaeggi T, et al. Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme. *Lancet Glob Health* 2021; **9:** e81–90.

26 Younoussa A, Samidine SN, Bergeman AT, et al. Protocol, rationale and design of BE-PEOPLE (Bedaquiline enhanced exposure prophylaxis for LEprosy in the Comoros): a cluster randomized trial on effectiveness of rifampicin and bedaquiline as post-exposure prophylaxis of leprosy contacts. *BMC Infect Dis* 2023; **23:** 310.