LEPRA STICHTING

STOP THE TRANSMISSION OF LEPROSY!

Blanket campaign participant in Janakpur, Nepal

STOP THE TRANSMISSION OF LEPROSY! PROJECT

Semester report, July - December 2024

THE LEPROSY MISSION

NATIONALE POSTCODE LOTERIJ

STOP THE TRANSMISSION OF LEPROSY!

Index

Acronyms/Abbreviations Used

PEP administration in Fatehpur, India

Acronyms/Abbreviations Used

ASHA	Accredited Social Health Activist (Community Health Workers in India)
BCT	Blanket Campaign Trial
BMRC	Bangladesh Medical Research Council
CEBC	Community Education and Behaviour Change
CLD	Central Leprosy Division (Ministry of Health, India)
FMDA	Focal mass drug administration
GCP	Good Clinical Practice
GIS	Geographic Information System
GPS	Global Positioning System
ICMR	Indian Council of Medical Research
ILEP	International Federation of Anti-Leprosy Associations
IRB	Institutional Review Board
ITM	Institute of Tropical Medicine (Antwerp, Belgium)
MO	Medical Officer
MoH	Ministry of Health
MoHFW	Ministry of Health and Family Welfare (India; Bangladesh)
NGO	Non-Governmental Organisation
NHRC	Nepal Health Research Council
NLR	International acronym for Leprastichting (Until No Leprosy Remains)
NLT	Nepal Leprosy Trust
NTD	Neglected Tropical Disease(s)
PEP++	New post-exposure chemoprophylaxis regimen used in project; also, an alternate name for the ***Stop the Transmission of Leprosy! Dream Fund project***
PI	Principal Investigator
QGIS	Quantum Geographic Information System
qPCR	Quantitative polymerase chain reaction
RA	Research Assistant
REDCap	Research Electronic Data Capture (data management platform)
RMP	Rifampicin
SDR-PEP	Single Dose Rifampicin used as leprosy Post-Exposure Prophylaxis
SOP	Standard Operating Procedure
SSC	Scientific Steering Committee
TLMI	The Leprosy Mission International
TLMI-B	The Leprosy Mission International Bangladesh Office
TLMN	The Leprosy Mission Nepal
TLMTI	The Leprosy Mission Trust India
WHO	World Health Organization

1. Summary

Following the successful conclusion of the PEP++ clinical trial intake in the first semester of 2024, most of the ***Stop the Transmission of Leprosy! Project*** countries shifted their attention to the blanket campaign trial in the second half of the year. These door-to-door campaigns took place in the three Asian countries – Bangladesh, India, and Nepal – with the intent to visit as many houses as possible in the high-risk areas defined through geospatial mapping of previously detected patients. This resulted in over **175,000 community members** in high-risk transmission areas who received preventive treatment and an additional **150 new cases of leprosy detected** in the past six months. These individuals would otherwise have continued to transmit leprosy bacteria in their communities. Between the PEP++ and blanket campaign trials, over **330,000** of the highest at-risk population of the six districts involved in the two trials have seen their risk of developing leprosy reduced. We expect this to lead to a massive reduction in transmission and serve as an example for how to achieve our common dream of eliminating leprosy in the world. We have now nearly finished the hard work of administering PEP to so many; now we eagerly await the final outcomes to share with the leprosy community.

Not only did the three country teams do an outstanding job of covering so many people – surpassing the total from the PEP++ clinical trial in only six months – but they did so in a spirit of joint learning and cooperation. At each step in the blanket trial, we discussed the best way to define the 'cluster areas' to be covered, using examples from the field in each country compared with initiatives undertaken by our partners at the Institute of Tropical Medicine (ITM) Antwerp in Belgium. This led to a series of adjustments in the buffer areas around each index case to accommodate the different population sizes and maintain operational viability. Even more impressive was the way each country made cultural adaptations to maintain the same objective – to preventively treat as many households as possible in the cluster areas – but with slightly different methods so as to ensure that community members would accept the approach.

Finally, the team in Bangladesh began an important side study with TLMI funding to determine the prevalence of leprosy infection among school-aged children in the study districts in partnership with the University of Leiden Medical Centre. They used serological testing to determine how many children from the ages of 5-10 have been infected with M. Leprae as a proxy indicator of wider community transmission. Over half of the 6,000-child sample size has been reached thus far. The data from this study will be used as a baseline in the future to help determine the impact of the combined trials on stopping leprosy transmission in endemic areas.

Participant in the serosurvey study in Nilphamari, Bangladesh

2. Progress towards planned milestones

The following is a summary of milestones by country compared with plans for the semester. Additional details are included in section 3:

Brazil:

Expected milestone	Target dates this semester	Progress end December 2024	Status
Complete the screening of the next 497 close contacts due for trial follow-up	December	The team surpassed the target as 515 close contacts were examined in the second semester of the year: 997 total to date (46%).	

India:

Expected milestone	Target dates this semester	Progress end December 2024	Status
Finish the data cleaning process for the PEP++ intake cohort	October	Nearly all contact records have been reviewed and adjusted; problems with GPS coordinates will be corrected during follow-up.	
Adjust the cluster areas according to the final agreed methodology and subsequent completion of the blanket campaign trial	December	The Indian team led a massive effort to treat over 90,000 community contacts in only six months.	
Define the location for qPCR/AMR testing to be conducted and submit amendment to ICMR for approval	Q4	A partnership agreement is in place with The Leprosy Mission Trust India to perform the testing and ethical clearance was obtained.	
Begin the PEP++ trial follow-up screening of close contacts	December	This phase was pushed back slightly to begin in January 2025 but will not impact the end date of the trial.	

Nepal:

Expected milestone	Target dates this semester	Progress end December 2024	Status
Correct and clean the PEP++ trial database	October	While there are still minor discrepancies in the database, we have made great progress in cleaning the records.	
Adjust the cluster areas and complete the blanket campaign trial	December	We had fruitful discussions to define the cluster areas and learn from each other; seven municipalities were completed (59,580 community contacts treated) with three left to finalise early in 2025.	
Begin the PEP++ trial follow-up in September following ethical approval of qPCR testing by NHRC	October	The follow-up started on time with 2,942 close contacts re-screened in the last months of the year; to date no new cases have been confirmed among study subjects.	
Sign partnership agreements with The Leprosy Mission Nepal and Nepal Leprosy Trust for their support during the PEP++ trial follow-up	October	The agreements have been signed with both local partners, paving the way for strong technical support during the follow-up phase.	

Bangladesh:

Expected milestone	Target dates this semester	Progress end December 2024	Status
Correct and clean the PEP++ trial database	September	The intake data from Bangladesh had relatively few errors and these have been adjusted.	
Conduct a child serosurvey study to show the baseline of community infection before the blanket campaign trial begins	July-August	This began in October in the two PEP++ districts; 3,000 children aged 5-10 in the study districts have been tested; the same number in other non-blanket and control area testing will continue in the first half of 2025.	
Start the blanket campaign trial following the receipt of necessary batches of rifampicin	September	This began in September and over 24,000 community contacts have been treated in 121 cluster areas.	
Determine the location for qPCR/AMR testing to be conducted and submit amendment to BMRC for approval	December	The TLMI-B team contacted officials at the icddr,b mycobacterium laboratory in Dhaka. Agreements have been made to conduct the testing there.	

International Office:

Expected milestone	Target dates this semester	Progress end December 2024	Status
Submit the blanket campaign trial article for publication following the adjustments made in each country	December	Great progress was made during the semester to define a common definition of cluster areas; work still needs to be done to write up the methodology in each country.	
Produce a consolidated data overview of the PEP++ trial cohort to prepare for final analysis in 2026 and for preliminary dissemination in international fora such as the International Leprosy Congress in Indonesia in 2025	December	A merged database is in place with a list of the few records that still need attention; further analysis will be undertaken before presentation to international stakeholders in 2025.	

completed as scheduled/on-track, partial progress towards completion, no progress

3. Programme Components

3.1 PEP++ field trial implementation

Brief background summary

The most essential programme indicators for the success of the PEP++ field trial are the number of close contacts listed, enrolled, included, and followed up. These are defined as follows:

- Close contacts *listed* are those household/family members, neighbours, or social contacts mentioned by the leprosy index case when approached by research staff.
- The ones *enrolled* are those who were listed by the former/current leprosy patient and subsequently located by the research teams and requested to participate. Any listed close contact who cannot be found is not 'enrolled' and therefore not part of the study.
- Close contacts *included* are those enrolled who give consent, are screened, present no exclusion criteria, and are thereafter medicated with PEP (SDR or PEP++, depending on the study arm). The trial was powered to include at least 162,000 such contacts.
- Those contacts who have been *followed up* are those who have been rescreened for signs and symptoms of leprosy two years after taking SDR-PEP or the final dose of PEP++ (which may be the first, second or third one depending on the individual). This is a crucial step as the primary study outcome is how many individuals in each trial arm develop leprosy despite taking the preventive treatment.

Updates

PEP++ Trial implementation data – end December 2024

Country	Index cases enrolled	Close contacts listed	Avg. CC/IC	Close contacts enrolled	Close contacts Included	SDR-PEP (Control contacts)	PEP++ (inter-vent contacts)	New cases detected	Doses PEP given	Contacts followed up	% contacts followed up
Bangladesh	2,428	58,403,0	24.1	54,065	52,686	26,233	26,470	90	101,730	0	
Brazil	810	3,286	4.1	2,814	2,148	1,031	1,117	15	3,925	997	46.4%
India	3,748	69,565	18.6	63,105	60,562	30,217	30,353	151	112,143	0	
Nepal	2,846	87,712	30.8	69,705	53,751	26,347	27,406	82	99,126	2,942	5.5%
Total	**9,832**	**218,966**	**22.3**	**189,689**	**169,147**	**83,828**	**85,346**	**338**	**316,924**	**3,939**	**2.3%**

- This semester, the PEP++ team worked to clean and analyse the intake database of the ***Stop the Transmission of Leprosy! Project***. Minor data entry errors were found and corrected, such that the overall data dashboard remains largely unchanged (above). The trial cohort has been closed at a little over 169,000 medicated close contacts of persons affected by leprosy, about 5% over the minimum total needed (162,000).
- Nepal began conducting the follow-up screenings of the close contacts in October, joining Brazil as the only other country in this phase. As seen in this table, Brazil has followed up nearly half of its contacts with Nepal at about 6% so far. This is discussed in more detail in section 3.3.

3.2 Blanket campaign trial/Mapping component

Brief background summary

In areas that are highly leprosy endemic, it is not sufficient to target only close contacts of persons affected by leprosy – as we have done in the PEP++ trial – to prevent community transmission. Such areas need to extend the coverage of active case finding coupled with preventive treatment as was part of the original ***Stop the Transmission of Leprosy! Project*** proposal.

Using geospatial methods, we have developed cluster maps showing concentrated cases in the project areas over the last seven years. We want to test the assumptions that in the identified clusters: a) additional transmission has occurred beyond those cases already detected, and b) that the general population is at greater risk of developing leprosy, thus requiring preventive treatment. We expect this will provide key evidence of the effectiveness of focal mass drug administration (FMDA) in leprosy based on mapping of endemic areas.

To do this, we designed a separate trial – the blanket campaign trial (BCT) – in randomised sub-districts of six of the nine ***Stop the Transmission of Leprosy! Project*** districts in India, Bangladesh, and Nepal. It uses a community coverage approach that targets as many people as possible in each cluster identified. This BCT, coupled with the effect of the PEP++ trial among close contacts, is expected to break the transmission of leprosy in these communities in coming years. It started in June 2024 – beginning in Nepal – and will run until the middle of 2025 – ending in Bangladesh. Due to contextual factors – high urbanisation or incomplete coverage – it was not possible to conduct this in the two municipalities of Brazil or in Sarlahi, the most recent district added in Nepal.

As a first step in the BCT, we were able to create a common definition of a cluster. Initially, we had used different criteria per country such that any 2 index cases across 500 metres would be a cluster in India; 3 IC in 300 metres in Nepal and 2 IC in 300 metres in Bangladesh. However, we saw that by using the Nepalese definition of 3 IC/300m, we were able to reduce the number of clusters in India and Bangladesh to make the intervention more operationally viable.

Example of a cluster (yellow) and cluster areas (orange circles) in India

However, this resulted in large clusters that could not be realistically covered by the study teams (the yellow area in the example). This led to several rounds of discussions with mapping and leprosy specialists. We agreed to use a specific radius, or buffer zone, around the index cases to guide the field operations – what we called 'cluster areas.' Due to differences in population and area, we arrived at the ideal cluster areas per country: 75m around each index case in India and 100m in Nepal and Bangladesh.

Blanket Campaign Trial implementation data – end December 2024

Country	Blanket contacts enrolled	Blanket contacts Included	New cases detected
Bangladesh	25,123	24,025	19
India	94,957	92,951	103
Nepal	66,631	59,580	28
Total	**186,711**	**176,556**	**150**

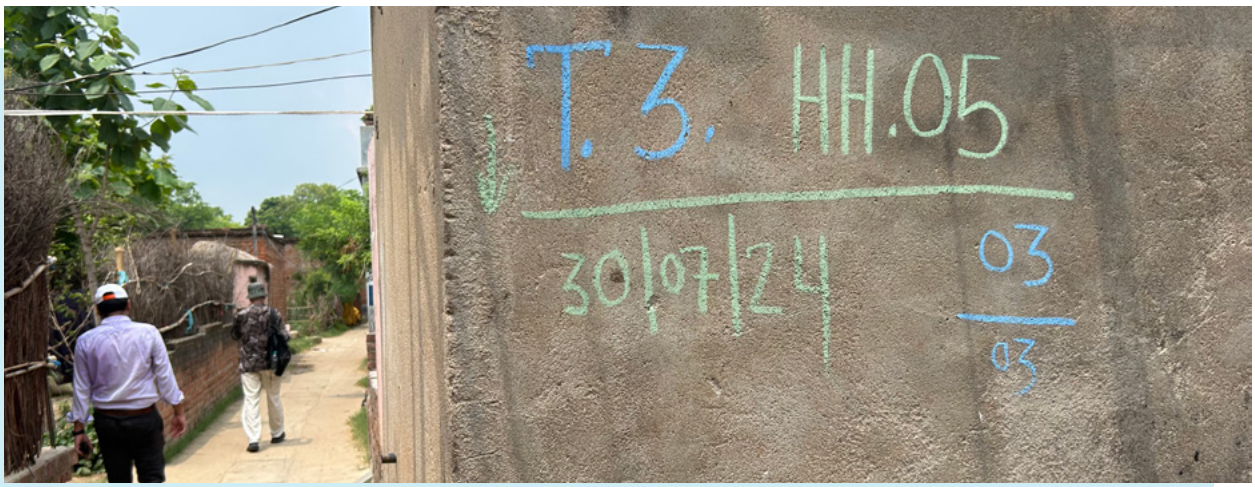
The results of the BCT have been very positive so far. We have already exceeded the initial estimation of between 150,000 and 175,000 community members treated with rifampicin in these highly endemic areas. The current total of **176,556** will increase even more as Bangladesh covers the final 45-50 clusters in the first months of 2025.

Nepal

- Since Nepal was the first country to start the full blanket campaign trial, we learned several lessons there that helped guide the other countries.
- The teams tried initially to cover all homes within a 300m radius of the index cases, which was three times the final definition of a 100m radius. These large cluster areas took far too long for the teams to cover. Following the adjustments, the researchers were able to cover almost all the municipalities in the BCT with only a few remaining for 2025.
- The team in Nepal also began the use of GPX Viewer, an application that allows the teams to clearly see their location within the cluster areas. This useful tool was subsequently used in the other countries and was essential to conduct the blanket campaigns. It will be part of the recommendation for scaling up this intervention in other areas in the future.

India

- India was the next country to start the BCT in July. Whereas there was only one team per cluster in Nepal, the Indian team took lessons learned from experiences with polio campaigns to send multiple teams into a single cluster area for a quicker and more intensive approach. This required the use of chalking (below) to guide the teams and avoid repetition. However, this was not deemed appropriate in the other two countries for cultural reasons.



Examples of the chalking method in India

- The administration of medication for blanket contacts was operationally more straightforward compared to the close contact administration in the PEP++ trial, as over 90,000 were treated in about six months. This had to do with the lower acceptability of the PEP++ regimen due to more adverse events. We will examine this further in a separate acceptability study.
- The team initially saw that using multiple apps at the same time – GPX Viewer, REDCap, and Google Maps – caused difficulties for the field researchers. However, over time, staff developed the expertise to handle them efficiently and comfortably.

Bangladesh

- The team in Bangladesh did not exactly follow the approach from either country when it began in September. It initially tried to use the door-to-door approach of the others but saw that it led to scepticism in the population and higher refusal rates. So, it went more to a 'community screening' approach where the contacts from several homes were invited to a single point that could be accessed by all. While screenings were done in private, the group administration of medication led to greater acceptance of the treatment being offered.

Although the approaches of the three countries differ slightly, the common definitions of clusters and cluster areas and the desire to cover all the homes in these areas unites them. It shows the importance of flexibility in the way the fieldwork is conducted, considering the acceptability of the approach and the other public health interventions common in each context.

3.3 PEP++ field trial implementation follow-up

Brief background summary

The main objective of the PEP++ trial is to provide evidence of the effectiveness of the enhanced regimen compared with SDR-PEP. The way we will measure this is by comparing the number of new leprosy cases detected in each arm of the study at two years after the last dose of treatment received by each close contact. This means that the research teams must find each individual who participated in the study and conduct a thorough examination for signs or symptoms of leprosy. Those who do have possible lesions must then be examined by a physician with extensive experience in diagnosing leprosy.

In order to demonstrate that there is no bias on the part of the study teams – i.e. to look harder for cases in the SDR-PEP/control area – we plan to run quantitative polymerase chain reaction (qPCR) testing of tissue samples of skin lesions (punch biopsies) of all new cases identified. This testing can often show the presence of M. leprae DNA in the lesions of the new cases detected among contacts as well as antimicrobial resistance (AMR) to rifampicin. The qPCR testing procedures are under development in all countries to be ready in time for the beginning of the follow-up phase.

Since Brazil was the first country to begin the trial back in October 2021, it was the first one to start the follow-up of close contacts in October 2023. Nepal followed up its first participants in October 2024. Finally, India will begin their follow-up phase in January 2025 and Bangladesh will start only in August-September 2025.

Brazil

Biopsy collection for qPCR study in the first diagnosed case of the PEP++ trial in Brazil

- This semester, the Brazilian research team followed up 515 close contacts from the clinical trial. It has now covered a total of 997 participants which represents 46% of its national total (2,148). To date, 66 contacts have been considered to be lost to follow-up after repeated efforts to locate them. This represents 6.2% of the number approached, but that is still significantly better than the 20% loss to follow-up that we calculated for the study. Given the difficult operational context in Brazil, this gives reason for optimism for the study as a whole.
- Among the total contacts re-screened to date, 37 of them had possible signs and symptoms of leprosy (3.7%). From this group, **the first new case of the trial, post-treatment, was detected in October**. She had to be approached several times before finally agreeing to see the referral dermatologist supporting the study. Once confirmed, she was also the first person in the study to have a biopsy taken from a lesion for qPCR/AMR testing. Due to the costs of the testing materials, it only makes sense to test several tissue samples at one time. It will remain cooled and stored until a later date.
- Another 14 contacts have been cleared by the referral dermatologist and five are possible cases that require monitoring and further testing. The remaining 17 still need to be examined, which often requires a concerted effort by the team to ensure that the contact attends the scheduled appointment.

Nepal

- The first 2,942 close contacts of the PEP++ trial were followed up in the last months of the year.
- Although none of those followed up have signs or symptoms of leprosy, the procedures for qPCR/AMR testing have been agreed by The Leprosy Mission Nepal (TLMN) and Nepal Leprosy Trust (NLT). Memoranda of understanding were established between NLR Nepal and each partner during this semester such that the system is in place to begin testing in 2025.

India

- The location of the qPCR testing was defined as the Stanley Browne laboratory run by The Leprosy Mission Trust India (TLMTI). This further solidifies the strong partnership between TLM and NLR in this study.
- An amendment to the original study protocol to include the additional testing was submitted by the Principal Investigator to the Ethics Committee of the Vardhman Mahavir Medical College/Safdarjung Hospital and approved.

Bangladesh

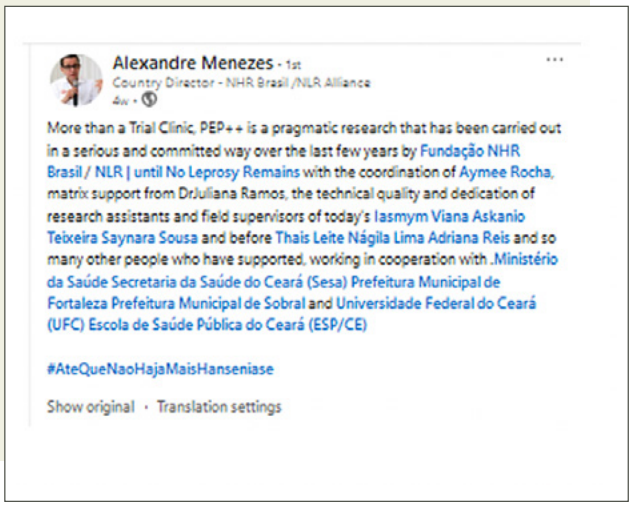
- In late October, the TLMI-B team visited icddr,b in Dhaka. It saw that this laboratory has the requisite capacity in terms of equipment and workforce for qPCR/antimicrobial resistance (AMR) testing needed.
- Although the follow-up phase will only begin in the second semester of 2025, an agreement has been reached between the partners to conduct the testing when it is necessary.

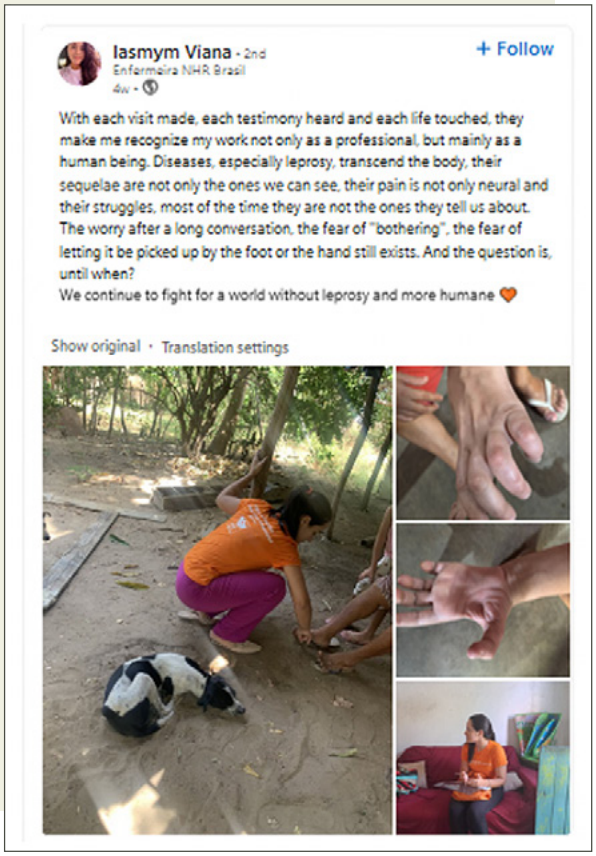
4. Communication

To communicate about the ***Stop the Transmission of Leprosy! Project*** in the last six months of 2024 NLR and TLMI posted often on social media, shared updates in newsletters and collected new photos from the project interventions.

LinkedIn-posts from NHR Brasil

The best posts are those made by staff who are directly involved and engaged with the project. The CEO of NLR's office in Brazil is very active on LinkedIn and regularly shares about the progress of the project and milestones achieved. The municipal supervisor of Sobral also posted on her work in the region and new cases detected.





NLR India's quarterly newsletter

NLR India shares a quarterly newsletter with their most important stakeholders. In the July-September newsletter of 2024, an article was dedicated to amplify the completion and success of the blanket campaign trial in districts of Fatehpur and Chandauli. In addition, the article refers to a data management committee meeting mentioning all the stakeholders that attended.

Health worker in Nepal providing PEP, screening and information of signs and symptoms in PEP++ area

Persons diagnosed with leprosy during screening of the blanket campaign trial around Janakpur, Nepal

Collecting photos and stories from participants in the project

In September and October 2024, a team dedicated multiple days to take photos of the interventions of the ***Stop the Transmission of Leprosy! Project*** in Nepal around Janakpur. A professional photographer from Nepal collected many great photos of research assistants and health workers distributing preventive treatment to close contacts and raising awareness of signs and symptoms within communities. In addition, we interviewed and portrayed a few people who were diagnosed with leprosy during the blanket campaign trial. These stories and images will be used for future communication purposes and highlight the progress of the project.

5. Finance and management

Although we do not yet have the final expenditures for 2024, we estimate that a total of approximately € 9.27 million or 99% of the original NPL project budget has been utilised. In addition, approximately € 400,000 was allocated by TLMI and NLR to cover the full costs of the blanket campaign trial. Another € 600,000 was budgeted by TLMI for its work in Bangladesh, taking the total study expenditures over € 10 million.

Additional resources of approximately € 1.25 million will be necessary to complete the final stages of the follow-up phase in Brazil, India, and Nepal in 2025-26. This shortfall was the result of a series of challenges to the study in the first years, such as:

- Delays in the ethical approval of the study protocol;
- Changes in the original PEP++ regimen;
- Impurities in the international supply of rifampicin;
- Political challenges; and
- The COVID-19 pandemic.

A supplementary funding request has been submitted to NPL to cover the key last steps of the study, for which we await final word in early 2025. With this, we can conclude the dream of demonstrating how a comprehensive approach can stop the transmission of leprosy in endemic areas.

Due to an unexpected financial setback at the end of 2024, NLR IO was forced to make difficult decisions, with impactful consequences for projects as well as the organisation. Although this resulted in a substantial reduction of NLR funded projects in the NLR Alliance, all steps were taken to ensure that the ***Stop the Transmission of Leprosy! Project*** can be successfully completed. NLR will work to maintain its impact in the countries with the highest leprosy burden, with an ongoing focus on scaling up the prevention of leprosy in interventions such as this one.

As mentioned, TLMI generously allocated funding from its Global Fellowship to cover the blanket campaign trial in Bangladesh this semester. It also made resources available for the child seroprevalence survey described in the report. We greatly appreciate the support of NPL, TLMI and all national partners in the final phases of this groundbreaking study.

6. Outlook next semester (January - June 2025)

Brazil:

- Complete the screening of the next 736 close contacts due for trial follow-up by the end of June.
- Continue qPCR/AMR testing for any confirmed new cases of leprosy among the PEP++ trial participants.

India:

- Retrain the medical officers of key Community Health Centres to refresh their diagnostic capacity for any contacts referred to them during the follow-up phase.
- Screen the first 7,598 close contacts eligible for follow-up screening by the end of June.
- Begin qPCR/AMR testing in partnership with The Leprosy Mission Trust India for any confirmed new cases of leprosy among the PEP++ trial participants.

Nepal:

- Complete the blanket campaign trial in the last three municipalities to be covered by the end of Q1.
- Conduct the follow-up screenings of 12,512 close contacts of the PEP++ trial by the end of June.
- Begin qPCR/AMR testing in partnership with The Leprosy Mission Nepal and Nepal Leprosy Trust for any confirmed new cases of leprosy among the PEP++ trial participants.

Bangladesh:

- Complete the child serosurvey study among children outside of the blanket campaign trial areas and the control district of Panchagarh.
- Finish the blanket campaign trial by May, covering the last 48 cluster areas.
- Conduct an acceptability study of the PEP++ regimen among close contacts, health professionals and administrators in the study districts (April-June).

International:

- Submit the blanket campaign trial article for publication detailing the methodological adjustments made in each country.
- Coordinate the submission of abstracts for the International Leprosy Congress to disseminate the full range of results achieved to date.