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Interrupting transmission of *Mycobacterium leprae*: synthesis of new evidence and research recommendations

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Summary On May 23–25, 2024, a multidisciplinary expert group met in Bergen, Norway, the site of the first description of *Mycobacterium leprae* (*M. leprae*) in 1873, to discuss advancements and remaining knowledge gaps in the transmission of *M. leprae* at the Global Partnership for Zero Leprosy Zero Transmission Symposium. Research and operational approaches to interruption of transmission were identified; the research approaches from the symposium are described here.
Updates since a previous symposium at the National School of Tropical Medicine, Baylor College of Medicine in Houston (USA), in 2014 from these fields of research are presented here: epidemiology; microbiological diagnosis; immunodiagnostics;

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genotyping; geospatial mapping; leprosy elimination monitoring and transmission under low-endemic circumstances; leprosy post-exposure prophylaxis (PEP); modelling relevant to interruption of transmission of *M. leprae*; OneHealth; environmental transmission of *M. leprae*; social determinants; control programmes relevant to interruption of transmission of *M. leprae*; and organizations of persons affected. Progress and outstanding gaps since 2014 are identified, and recommendations for relevant research in these areas to achieve interruption of transmission are presented. These include research into human reservoirs, including platforms for field-friendly diagnostics; routes of entry/exit of *M. leprae*; the roles of animals or vectors in transmission; the role of social determinants in transmission; host-pathogen interactions; transmission networks; and enhanced epidemiological data.
Fulfilment of these research recommendations and further understanding of which settings require intensified control efforts, will help to advance the aim of achieving complete interruption of transmission of *M. leprae* and the elimination of leprosy disease.

Keywords: Transmission, leprosy, *Mycobacterium leprae*

Background and context

Leprosy is a communicable disease.[1] The infectious agent causing leprosy, which was described for the first time by Gerhard Armauer Hansen in Bergen (Norway) in 1873, is an acid-fast bacterium (AFB) later given the name *Mycobacterium (M.) leprae*. A second species causing leprosy, *M. lepromatosis*, was described over 100 years later in 2008.

This report is based on a three-day symposium organised by Global Partnership for Zero Leprosy in May 2024, taking place in Bergen, the cradle of modern leprosy research. The first day was hosted by NLA Høgskolen in Pleiestiftelsen No. 1 ("The Caring Institution No. 1"), where researchers such as Daniel Danielssen and Armauer Hansen worked some 150 years ago. In the 1840s, Danielssen published the first modern clinical description of the disease.[2] About three decades later, his son-in-law, Armauer Hansen, discovered the leprosy bacillus. Based on the Norwegian leprosy registry, which started in 1856, Hansen also published the first epidemiological model of leprosy as a slightly contagious disease.[3,4] Later, Hansen took the initiative to formulate the first global policy advice on leprosy.[5] The last two days of the symposium were hosted by the University of Bergen (UiB) in their newly refurbished administrative building, Nygårdsgaten 5. The venues were chosen to symbolise the links between past and present, and the enduring efforts of ridding the world of leprosy.[1]

The WHO Global Leprosy Strategy 2021–2030 sets an ambitious goal to interrupt transmission of *M. leprae* by 2030. However, there are some major challenges to reaching this goal, including large numbers of new cases that are persistently identified in endemic areas, despite leprosy control efforts. Proper understanding of the precise mode and route of transmission of leprosy is yet to be achieved. While transmission assessment is based mostly on reported cases of leprosy, new tools have emerged, such as serological markers of infection and *M. leprae* genotyping in clinical samples. Moving away from the slow decline in incidence following the global elimination of leprosy as a public health problem, the current Global Leprosy Strategy (GLS) 2021–2030 focuses on interrupting leprosy transmission.[6]

In the sections of this report below, a multidisciplinary panel has provided brief updates on developments in their field of expertise, in particular new developments since a previous symposium that took place at the National School of Tropical Medicine, Baylor College of Medicine in Houston (USA), in 2014.

An analysis, carried out to compare the gaps in understanding of transmission and identified needs at the 2014 symposium with their current status, is also presented here along with corresponding research recommendations.

UPDATE ON EVIDENCE FROM THE FIELD OF EPIDEMIOLOGY RELEVANT TO INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*

Worldwide leprosy incidence is gradually decreasing in most endemic countries, although in the World Health Organization (WHO) AFRO (African) region there has been no real decline since 2010, and in the EMRO (Eastern Mediterranean) region there has even been an increase in recent years, mainly due to improved reporting from Somalia. Trends are driven by the SEARO (Southeast Asia) region, dominated by India, which shows a slow decrease.[7]

Bratschi *et al.* published a literature review in 2015 in which they concluded that there was solid evidence for human-to-human transmission to contacts of leprosy patients and also for zoonotic transmission from armadillos in the southern USA.[8,9] The main route of transmission is probably aerosols and droplets, although skin contact cannot be ruled out. There could be transmission from bacilli shed into the environment, although there is no direct evidence of this happening.[10] To date, there is no unequivocal evidence of the mechanisms by which *M. leprae* "travels" from one individual to another.[11]

More recently, leprosy has also been found in squirrels and chimpanzees.[12,13] Whereas the strains circulating among armadillos in the southern USA are identical to those currently circulating among humans, the bacilli found in squirrels in England, however, belong to strains that circulated there among humans in the Middle Ages.[14] Apparently, transmission has continued among squirrels but without transmission to humans.[15]

In 2021, a literature review by Hambridge *et al.* showed that in countries where few cases remain, there is no evidence of ongoing transmission; while most of the remaining cases are multibacillary (MB), there is no suggestion these cases give rise to secondary infection.[16]

Over the past 10 years, advancement in unravelling transmission pathways of *M. leprae* has been relatively slow, although new and improved methodologies are now available that will speed up progress in the years to come. These include spatial analyses, molecular techniques, and exploratory platforms for host biomarker identification. Spatial analyses have become much more straightforward with the wide availability of smartphones and tablets with GPS.[17] A study in Comoros showed clustering at the sub-village level, extending the increased risk to well beyond the household.[18] At higher levels also, major differences in endemicity are observed between regions within the same country.

Regarding molecular techniques, in Comoros, 68% of paucibacillary (PB) cases and 80% of MB cases sampled in recent years were quantitative (q)PCR positive.[19] Approximately half of the MB cases had sufficient DNA for sequencing, which allows for molecular epidemiology studies. Other new developments are RNA-based viability assays that can help to determine whether *M. leprae* DNA found in patients, nasal carriers, or in the environment is from viable bacilli. Several new methods are in the pipeline. Host biomarkers of infection, both humoral and cellular, are being further refined, allowing improvement of quantitative immunodiagnostic tests in field- and environment-friendly formats.[20,21] Further progress in unravelling as well as monitoring the effect of interventions on transmission is within reach.

DEVELOPMENTS IN MICROBIOLOGICAL DIAGNOSIS OF LEPROSY

While it has not been possible to cultivate *M. leprae* in vitro, multiplication in the mouse footpad or in the nine-banded armadillo (*Dasypus novemcinctus*) showed that the growth

is very slow. Its doubling time is estimated as 14 days, significantly longer than other mycobacteria such as *M. tuberculosis* (20 h) and other bacterial pathogens, e.g., 20 min for *E. coli*.

A critical characteristic of *M. leprae* is its optimal temperature of multiplication, preferring body zones at 33°/34 °C, which might explain why it is usually found in the skin and peripheral nerves, where sources of nutrients could also be found. As a result of advances in molecular biology, it has been known since 2001 that *M. leprae* has a small genome of 3.27 Mb, which is degenerated compared to *M. tuberculosis*, with many genes deleted or incomplete, evidence of its adaptation to host and parasitic life.[22]

Classic microbiological diagnostic tools include skin smear microscopy detecting AFB.[23] Although microscopy facilities are still active, many disappeared following the previous optimistic WHO strategy of the 1990s.[24] Today, molecular detection of *M. leprae* by PCR targeting the repeating element RLEP is mostly carried out in research labs because there are no commercial kits or ready-to-use cartridges, such as those developed for detection of SARS-CoV-2 or HIV viruses. Sensitivity of microbiological tools (microscopy and PCR) is high in patients with MB leprosy but lower in PB leprosy (in PB leprosy, microscopy is negative by definition) and pure neurological forms.

Previously, antimicrobial susceptibility testing was carried out using the mouse footpad experiment; over the last 10 years, this has rarely been carried out because of the constraints of animal facilities, the time taken to obtain results (up to 1 year), and technical requirements.[25] Antimicrobial resistance (AMR) is now detected using molecular techniques as described by the WHO guide.[26] The first global results on AMR in leprosy provided by the WHO surveillance network, published in 2018, report a global resistance (dapsone or rifampicin or fluoroquinolones) rate of 8% (154/1932).[27] The rifampicin-resistance rate (5.1% in retreated patients and 2% in new cases) is an important parameter because resistance hampers the efficacy of the standard multidrug therapy (MDT) combining dapsone, rifampicin, and clofazimine. In addition to the current list of mutations known to confer resistance and published in the WHO guide, a specific tool called HARP (Hansen's Disease Antimicrobial Resistance Profiles [https://harp-leprosy.org/]) was developed for modelling the mutations found by molecular detection that could impact antimicrobial resistance.[28] The latest tool, now commercially available, is the Deeplex Myc-Lep test.[29] This test is based on amplicon (PCR-generated) sequencing using next-generation sequencers, targeting the detection of mutations and single nucleotide polymorphisms (SNPs) in genes potentially involved in antimicrobial resistance, as well as providing genotyping results based on the analysis of 18 other markers. This gives information on the relationship between two or more strains of *M. leprae and* can help in tracing the transmission within a population.

Microbiological tools have different predictive values depending on prevalence. When used in a high-prevalence setting, such as endemic countries, the positive predictive value (PPV) will be high. In contrast, when the tools are used in a low-prevalence setting, the PPV will be low but the negative predictive value high.[30]

In conclusion, at present, microbiological tools for detection of *M. leprae* rely on AFB in skin smears and on positive RLEP PCR. Detection of AMR in *M. leprae* using molecular detection tools should be implemented in all countries, especially in areas where post-exposure prophylaxis (PEP) is implemented on a large scale. Currently, genotyping is mostly used as a research tool but has potential for identifying regions where transmission is ongoing that would benefit most from active case detection and prevention.

UPDATE ON IMMUNODIAGNOSTIC APPROACHES WITH RELEVANCE TO INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*[i]

Since the (clinical) manifestations after exposure to *M. leprae* strongly parallel host immunity against this mycobacterium, various outcomes, ranging from clearance, colonisation and infection to disease, represent possible post-exposure scenarios after such an encounter.[31] The inter-individual differences in coping with the presence of the mycobacterium become particularly apparent when disease occurs; host phenotypes vary between MB and PB, reflecting the unique immuno-pathological spectrum of leprosy.

Immunological sequelae determine the outcome after an encounter with *M. leprae*, which forms the basis of immunodiagnostic tests, i.e., using host immunity to detect infection and (early) disease even when the causative agent is no longer detectable or when its detection requires invasive sampling.[32] Blood-derived biomarkers based on the host immune response to *M. leprae* are thus ideally suited to aid in the diagnosis of infection and disease, especially since the detection of *M. leprae* is challenging in self-limiting and preclinical disease stages.

The classical paradigm of clinical leprosy is that disseminated/MB and self-limiting/PB disease are associated with Th2 and Th1 immunity, respectively.[33] However, advanced knowledge of the immunopathological spectrum of leprosy provides evidence that newly identified T-cell subsets (Th9, Th17, Th22, and regulatory T cells) also contribute considerably to the outcome of *M. leprae* infection.[34,35]

Cutting-edge technology for exploratory analysis of host proteins such as cytokines, chemokines, and growth factors (CCGF) produced by a plethora of cells involved in *M. leprae* immunity has been key to leprosy biomarker research in the past decade.[36–39] Proteomic and transcriptomic biomarker analysis in a unique 9-year follow-up study among >5,000 contacts of leprosy patients resulted in the identification of the following:

(1) a biomarker-signature accurately detecting patients across the leprosy spectrum, including overnight whole blood stimulation with *M. leprae* unique proteins, which provided increased specificity for leprosy.[32,37,39]
(2) the first transcriptional risk signature (RISK4LEP) predicting development of PB leprosy 4–61 months before diagnosis.

Furthermore, robust tests applying the unique up-converting reporter particle technology to a low lateral flow assay (UCP-LFA) format have been developed for operator-independent, quantitative detection of one or multiple biomarkers using capillary or venous blood.[20,21,37–40] Use cases for these immunodiagnostic tests besides (early) detection of leprosy include:

- Determination of the direct, immunological effect on *M. leprae* infection of PEP in an individual (e.g. INDIGO#2 trial: NCT06222372; BE-PEOPLE-trial: NCT05597280).
- Detection of *M. leprae* infection in armadillos and red squirrels.[41–44]
- Serosurveys in healthy young children to monitor the effect of interventions on transmission in a population.[45–47]

TRANSMISSION OF *M. LEPRAE*[ii]: KNOWLEDGE GAPS AND POTENTIAL SOLUTIONS FROM A GENOTYPING PERSPECTIVE

Transmission of *M. leprae* most likely takes place through the nasal secretions of an MB patient, with infectious droplets being inhaled by a contact. It cannot yet be excluded that

[i] Also applicable to *M. lepromatosis*.
[ii] Also applicable to *M. lepromatosis*.

M. leprae is spread by skin transmission or by aerosolization of live *M. leprae* from dust or on surfaces. *M. leprae* transmission is believed to be interrupted quickly by treatment, because mouse footpad inoculation shows rapidly declining viability within days.[48]

Several knowledge gaps prevent us from identifying who is most at risk of acquiring leprosy. It would be helpful to understand the proportion of genetically clustered leprosy bacilli; if clustering is high, this may favour door-to-door case finding with or without PEP around the patients diagnosed with leprosy in the area in the last 5 years.[49]

To measure the secondary case rate, population-based long follow-up periods and highly sensitive (high resolution) genotyping are required as well as better estimates of the mutation rate of *M. leprae* in order to date when transmission events took place.

Genotyping requires abundant bacterial DNA and is therefore more complete in MB patients, who are also the most infectious. The amount of bacterial DNA can be quantified by RLEP qPCR to predict the success of genotyping techniques. Different genotyping techniques have different limits of detection, with Deeplex MycLep-based target deep sequencing requiring less DNA than whole genome sequencing.

Phylodynamic analysis of whole genome sequences may help to estimate the total bacterial burden in a population, including the undiagnosed patients, and to date transmission events.

Together these techniques aim to address how much of the remaining cases of leprosy are due to relatively recent/ongoing transmission, which in a pre-elimination setting may guide the most appropriate approach to leprosy control. These techniques may also allow a comparison of the relative impact of different control strategies on leprosy incidence.

RECENT EVIDENCE FROM THE FIELD OF GEOSPATIAL MAPPING RELEVANT TO INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*: A LITERATURE REVIEW ON EXPERIENCES OF MAPPING LEPROSY CASES OVER A 10-YEAR PERIOD (JAN 2014–MAY 2024)

Geographic precision is one basic step towards precision public health i.e. targeted interventions for populations that need them most. Geographic precision also means that public health resources are used more efficiently.[50]

Using the electronic databases "Web of Science," "PubMed," "MEDLINE," and "SCIELO" with the keywords "leprosy," "spatial analysis," and "mapping," about 100 peer-reviewed published papers were identified, considering the period of 01/01/2014 to 20/05/2024. The number of publications increased from three in 2014 to 15 in 2020, with a decrease to nine papers in 2023, probably due to the COVID-19 pandemic. Approximately 77% of the studies were carried out in Brazil, mapping cases at different levels, from national and subnational, using aggregated data, to individual level.

The following lessons were learned during the last 10 years in this field:

(1) The spatial distribution of leprosy is heterogeneous. We can identify clusters, or hotspots, of cases, where the transmission risk seems much higher.[17]
(2) Case mapping can identify priority areas, but we cannot neglect regions with few or no registrations, the so-called "silent areas".[51]
(3) Spatial analysis helps to identify operational problems, such as lack of health services in specific territories, sometimes correlated with the absence of case detection and high seroprevalence of antibodies against *M. leprae*.[52]
(4) Leprosy spatial distribution seems to correlate with other neglected tropical diseases and poor socioeconomic conditions.[53–57]
(5) Spatial analysis increases the efficiency of active case-finding activities.[58]
(6) Case mapping helps plan intervention and research projects, such as PEP. [59–61]

(7) The definition of a cluster may vary according to the needs of its application. It is possible to use a contextualised spatial approach to determine the cluster size more precisely than a standard statistical approach.[62]

The challenges and future directions include:

(1) Increasing data quality to avoid bias and inaccuracy of predictions.
(2) Improving the interpretability of complex models.
(3) Guaranteeing ethical aspects, including data protection and privacy.
(4) Enhancing scalability to apply this technology to other endemic countries, particularly in Africa, where data are scarce.
(5) Developing alternative and creative methods to increase applicability across diverse contexts in order to map cases in all endemic countries/regions.
(6) Developing systems for real-time case mapping.
(7) Exploring the potential benefits of the association of geographic information systems (GIS) with artificial intelligence (GEO-AI), which combines GIS's spatial analysis capabilities with AI's predictive capabilities to create a powerful tool for public health.

MONITORING LEPROSY ELIMINATION AND THE RISK OF TRANSMISSION UNDER LOW-ENDEMIC CIRCUMSTANCES

Leprosy data trends are typically monitored at a national or even global level. This is important but masks a large heterogeneity between sub-national areas at every level. The WHO has developed new tools that help to monitor progress towards elimination at each level as desired. These are part of the technical guidance on interruption of transmission and elimination of leprosy.[63] A core component of this guidance is the Leprosy Elimination Framework (LEF) that visualises the trajectory of areas and countries through three phases of elimination and to the eventual non-endemic status. Milestones were defined that mark the transition from one phase to the next with associated indicators and targets.

The Leprosy Elimination Monitoring Tool (LEMT) was developed to promote a standard way to monitor progress towards interruption of transmission and elimination of leprosy disease in detail and at the sub-national level and a bottom-up process of building up evidence for interruption of transmission and elimination of leprosy disease.[64] The LEMT is based on the phases of elimination in the LEF and visually displays progress through the phases at a subnational and national level, using the traffic light-colouring scheme that corresponds to the LEF.

The LEMT was used to analyse sub-national level data from 13 countries (Botswana, Brazil (5 states: Amazonas, Ceará, Rio Grande do Sul, Para, Rondônia, and Rio Grande do Norte), Cambodia, Ghana, Guam, India, Maldives, Morocco, Nepal (Koshi and Sudhurpaschim province), Sri Lanka, St. Lucia, Thailand, and Vietnam). This included 258 Level 1 areas (provinces, states, etc.) and 3364 Level 2 areas (districts, municipalities, etc.). An LEMT v.8 or higher was used. Data ranges varied slightly per country. Most were available from 2000 or 2001 up to 2020–2022.

The results showed that of Level 1 areas, 23% were in Phase 1 (59), 38% were in Phase 2 (99), 25% were in Phase 3 (65), and 14% were non-endemic (35). For Level 2 areas, these figures were 24% Phase 1 (812), 21% Phase 2 (719), 8% Phase 3 (263), and 47% non-endemic (1570); i.e., more than 75% had already achieved the interruption of transmission milestone, and over half of the areas were in the post-elimination phase (Phase 3) or beyond in 2022.

The risk of re-emergence of leprosy was calculated, defined as "3 or more new autochthonous cases in 3 consecutive years detected in an area during Phase 3 or after becoming non-endemic." This occurred 6 times in 1824 L2 areas that were either in Phase 3 or were non-endemic (4 occurrences in Brazil and 2 in Nepal), giving a risk of 0.33%. Of these, 4 were temporary and 2 ran up to the final year for which data were available. This means that even the occurrence of unconfirmed re-emergence of leprosy is very rare once the milestone of interruption of transmission has been achieved.

The risk of missing continued transmission when the LEMT classified areas as being in Phase 2, Phase 3, or already non-endemic was modelled mathematically by Davis *et al.* at the University of Warwick.[65] They found that the combined criteria in the LEF appeared sensitive and specific for detecting interruption of transmission. There was a <0.5% risk of achieving all three phases before a final transmission event. When modelling a scenario with low-level ongoing transmission, there was a <1% risk of achieving all three phases across a 20-year period. They concluded that "*if implemented with a balanced and comprehensive understanding of what each one represents, the combined phases and milestones outlined in the WHO technical guidance are likely to effectively classify elimination of leprosy transmission*."

The minimal risk of re-emergence of leprosy in Phase 3 and beyond was also confirmed by a systematic literature review conducted by Hambridge *et al.*[16] Their key finding was that secondary cases are extremely rare in low-endemic settings. While there was a high proportion of MB cases and the presence of cases of suspected relapse, the number of new cases reported remained low. They concluded that, "*this evidence suggests that such cases do not represent a considerable source of M. leprae transmission in low endemic areas*." In addition, they found that an increase in foreign-born leprosy cases from high endemic areas did not contribute to a noticeable rise in local transmission. These findings support the results of the LEMT analyses that showed that, while sporadic child cases in Phase 2 and sporadic adult cases in Phase 3 were not uncommon, these did not lead to a re-emergence of leprosy in the area.

In summary, the phases of elimination and corresponding indicators and milestones performed well both in data analysis of a large number of sub-national areas in a range of leprosy-endemic countries and in mathematical modelling. The Leprosy Elimination Framework and LEMT can therefore be used with confidence in public health practice, provided good quality long-term data are available.

LEPROSY POST-EXPOSURE PROPHYLAXIS (PEP)

Leprosy PEP using a single dose of rifampicin (SDR) has been recommended by the WHO since 2018 in their Guidelines for the Diagnosis, Treatment and Prevention of Leprosy,[23] supported by the Technical Guidance for its implementation.[66]

Evidence leading to this recommendation has mainly come from the COLEP study in Bangladesh that demonstrated the effectiveness of an SDR-PEP in a double-blind, cluster-randomised, placebo-controlled trial;[67] and the LPEP Program that looked at the feasibility of implementing SDR-PEP as part of routine leprosy control programmes in eight countries.[68]

Prevention of leprosy is of important added value because the control strategy that has been in place for many years, namely early case finding and multi-drug treatment (MDT), has proven to be insufficient. Because it is believed to start long before diagnosis, transmission of *M. leprae* has continued in many areas in the world.

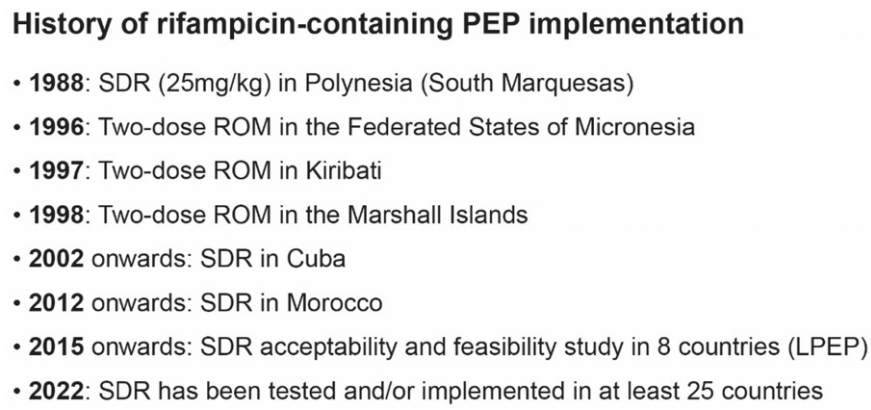

Figure 1. History of the use of rifampicin-based PEP.[69,70] PEP: post-exposure prophylaxis; ROM: rifampicin-ofloxacin-minocycline; SDR: single-dose rifampicin.

Indeed, rifampicin has already been used as part of isolated PEP implementation projects since 1988, particularly in small island states (Figure 1).

The efficacy of SDR-PEP has been shown in several trials i.e. a risk reduction of developing leprosy ranging between 52% and 74% when PEP is given to contacts of persons with leprosy (Table 1).

Experience with SDR-PEP implementation has taught us that the regimen is acceptable and has a good safety profile: the LPEP Program, an international feasibility study, showed that >99% of contacts agreed to contact screening and accepted SDR-PEP and that no serious adverse events were reported in >150,000 contacts.[68]

Furthermore, SDR-PEP invigorates leprosy control programmes: a positive effect on morale and efforts was seen in all settings, leading to strengthened training and supervision as well as increased motivation. The implementation of SDR-PEP not only reduces the risk of developing leprosy but also contributes to reducing transmission of *M. leprae* and strengthens the leprosy control programme as a whole.

We also learned from the LPEP Program that it is important to provide clear information when implementing SDR-PEP: it is not 100% effective but reduces the risk of developing leprosy by >50% among contacts. Approaches in which the identity of the index patient can be protected need to be further developed and tested; specific approaches have to be developed for SDR-PEP implementation to reduce the risk of developing leprosy in very high endemic areas.

Cost-effective SDR-PEP implementation approaches need to be developed, if possible integrated with other disease programmes, for example, those for skin neglected tropical diseases (NTDs). The results and experiences with SDR-PEP show us that there is scope to further improve and fine-tune the intervention, in particular making it context specific. There are several encouraging examples of SDR-PEP implementation as part of routine leprosy control from Sampang, a very high endemic district on Madura Island in Indonesia (Figure 2a), and from Morocco, a very low endemic setting (Figure 2b), both of which began in 2012. A clear downward trend in the number of new cases detected has been seen since 2012 in both settings.

Mathematical modelling with SIMCOLEP, conducted by Erasmus MC in collaboration with NLR, has shown that a global roll-out of SDR-PEP, given to contacts of leprosy patients,

Table 1. Summary of trial evidence on SDR-PEP

	India[71]		Thailand[72]		Indonesia[73]			Bangladesh (COLEP)[65]	
	Intervention 3,760	Control 3,877	Intervention 1,400	Control 1,349	"Blanket" 1,080	HH+N 1,632	Control 1,251	Intervention 9,951	Control 10,006
Follow up	4–5 years		5 years		3 years (last follow up 10 years)			2–6 years	
Intervention	1 × rifampicin		1 × rifampicin		2 × rifampicin, 3.5 month interval			1 × rifampicin	
Incidence rate*	2.3	8.7	10	21	31	99	110	14.6	33.5
Protective effect	74%		52%		75%	63%		57%	
NNT	1,566		186		127	116		265	

HH+N: Household contacts and neighbours; SDR-PEP: single-dose rifampicin post-exposure prophylaxis. *Cumulative rate per 10,000 person-years at risk.

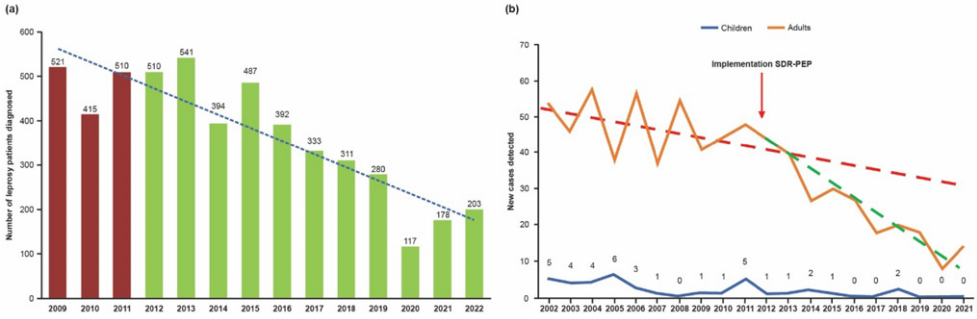

Figure 2. Impact of SDR-PEP in Indonesia and Morocco. (a) Impact of SDR-PEP in Sampang district, Java, Indonesia. (b) Leprosy elimination in Morocco: impact of SDR-PEP.[75] SDR-PEP: single-dose rifampicin post-exposure prophylaxis.

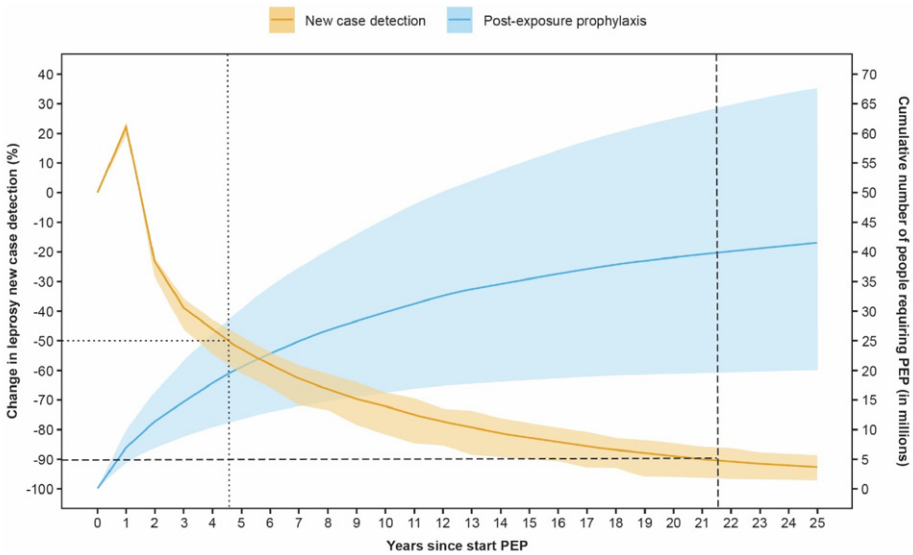

Figure 3. SIMCOLEP prediction of impact of SDR-PEP. PEP: post-exposure prophylaxis. Reproduced from Taal *et al.* 2021.[64]

can significantly reduce the incidence of leprosy over time. By providing SDR-PEP to 40 million close contacts over a period of around 20 years, a 90% reduction can be achieved in the number of new leprosy patients detected (Figure 3).[74]

The same model has also shown how the impact on the leprosy patient detection rate can be increased with a stronger PEP regimen, such as PEP++, an enhanced regimen combining rifampicin and clarithromycin, which is currently being tested and a wider coverage of contacts (Figure 4).[59]

The PEOPLE project has tested a double dose of rifampicin in Madagascar and the Comoros and demonstrated that the effectiveness was slightly lower than that shown in the COLEP trial, probably explained by the very high baseline prevalence in the Comoros.[30] Furthermore, distance to the household of the nearest index case was a strong predictor of the risk of leprosy,

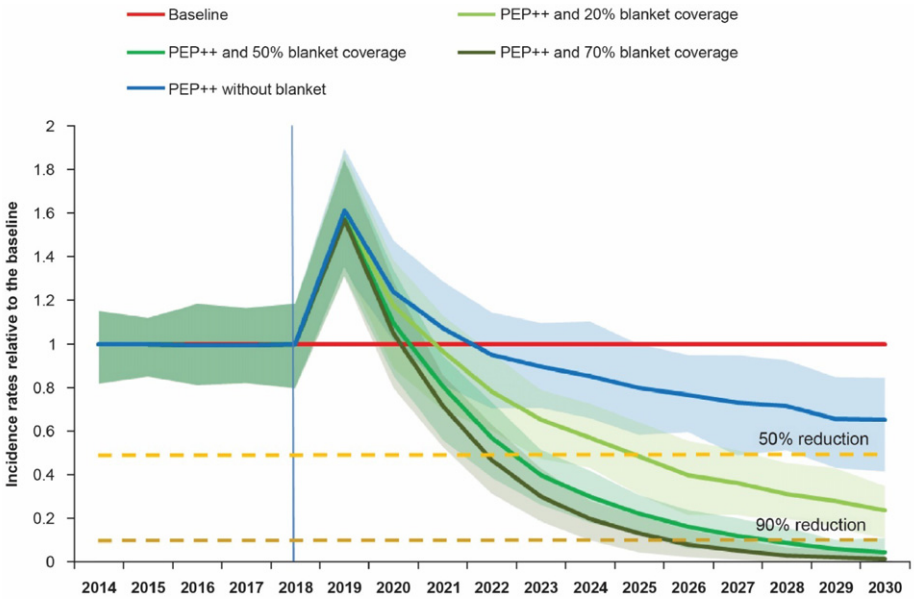

Figure 4. SIMCOLEP prediction of effect of stronger PEP regimens. PEP: post-exposure prophylaxis.

with a significantly increased risk up to 75 metres. The researchers recommend implementing PEP in combination with well-targeted active case finding and investigating a stronger PEP regimen.

Various approaches are being tested to look for the highest impact, cost-effectiveness, and context-appropriate approaches, including the standard contact approach, community skin health events, the "blanket" approach, retroactive case finding, and self-screening.[66,76] Stronger regimens are being tested, including rifampicin combined with clarithromycin (PEP++) in India, Brazil, Nepal, and Bangladesh and a combination of bedaquiline and rifampicin in the BE-PEOPLE study in Comoros. Bedaquiline has already proven to have a good safety profile; the efficacy trial has now started.[77,78] A recent study in China showed that rifapentine is more effective in household contacts than rifampicin, with a protective effect of 84%.[79]

Bedaquiline was developed as a tuberculosis (TB) drug, and its use for leprosy is currently being tested.[78] Another drug developed for TB is telacebec, which has been shown in a mouse study to be very potent against the leprosy bacteria and also against *M. ulcerans*, the causative pathogen of Buruli ulcer. The exquisite sensitivity of *M. leprae* for telacebec has raised the expectation that it may help shorten the treatment duration of leprosy and may also be used as strong preventive medication.[80] Preclinical studies and clinical trials are currently being prepared.

RECENT INSIGHTS FROM THE FIELD OF MODELLING RELEVANT TO INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*

In the past decade, leprosy modelling has focused on two primary aims: to forecast trends of new case detection and to evaluate various intervention strategies for accelerating the reduction of the number of new cases.

Generally, new case detection trends are declining in most subnational settings. The rate of decline is primarily determined by endemicity level and quality of the control programmes (i.e., long vs. short case detection delays). It is evident from forecasting trends that elimination of disease in many subnational settings is not feasible in the short run. Many other settings are about to reach (or have already reached) interruption of transmission, such as the Maldives. Therefore, the field of modelling has explored various intervention strategies, using existing tools and tools under development, to assess its population-level impact. These include (1) contact tracing and other active case-finding strategies with and without SDR-PEP,[54,81,82] (2) a diagnostic test for subclinical infection,[73,83] and (3) leprosy vaccines (LepVax) (manuscript in preparation).

Contact tracing and active case finding typically increase the number of new cases detected because of the backlog in cases. Modelling showed that, although the number of new cases increases on the surface, the number of undetected symptomatic cases decreases (hidden cases). Adding SDR-PEP could further prevent new cases and accelerate the reduction of new case detection.[54,81] However, the impact of contact screening with SDR-PEP depends on the endemicity level and quality of historic/current leprosy control and the number of contacts included. In high endemic settings, the greater the number of contacts included, the larger the reduction of the new case detection. A blanket approach is preferable in high-endemic island settings because it can reduce the number of cases significantly in the short run.[84] In very low endemic settings, targeting household contacts seems to be the best option.

Modelling analysis showed that a screening test to detect subclinical leprosy with a sensitivity of at least 50% (as well as treating positives) could substantially reduce the number of new cases. To effectively reduce new case detection rates (NCDR) in the short run, a population survey is preferable to household contact tracing in high endemic settings. Finally, a leprosy-specific vaccine (LepVax) could potentially have a significant impact on the incidence of leprosy; even with low efficacy and late introduction, a positive impact could be observed (manuscript in preparation).

ONE HEALTH AND LEPROSY

The concept of One Health (OH) emphasises the interconnectedness of human, animal, and environmental health. Highlighting the need for an OH approach ensures comprehensive strategies considering all potential transmission routes, including zoonotic and environmental sources.[85] Nine-banded armadillos (*Dasypus novemcinctus*), native to the Americas, are particularly susceptible to *M. leprae* infection.[86] They act as important reservoirs for sustaining *M. leprae* transmission in humans in the USA, with both hosts sharing the common SNP subtype 3I-2, highlighting a strong zoonotic connection in the spread of the bacterium.[8,87–89] In addition, nine-banded armadillos represent a useful model for leprosy, especially since the time point of experimental infection is known and susceptible as well as resistant animals occur.[44]

Epidemiological, molecular, and serological evidence of *M. leprae* infection and its involvement in human disease has been shown in a leprosy endemic state in Brazil since 2002, demonstrating the zoonotic potential of the disease in South America.[90–94] A meta-analysis in 2020 of ten Brazilian studies representing a total sample of 302 armadillos showed that approximately 1 in 10 armadillos in Brazil were infected with *M. leprae*.[95] Notably, three studies reported no cases of infected armadillos,[96–98] while one study found that all captured armadillos were infected.[99] The authors concluded that the observed variation may be attributed to the relatively small sample sizes and localised differences in infection rates.

Epidemiological analyses combining results from several case-control studies indicate a strong association between direct contact with wild armadillos and an increased risk of leprosy.[90,99–103] Direct contact with armadillos, including activities such as hunting, meat preparation, and uncooked consumption, increases the odds of developing leprosy approximately two times compared with those with no contact.[104,105]

The relationship between armadillo hunting and the spread of leprosy in Brazil is significant. Models analysing hunting activities highlighted human population density and the number of firearms as the most important explanatory variables. Specifically, the direct contribution of areas favourable for both armadillo hunting and the presence of leprosy in armadillos accounted for 16.3% of the risk of leprosy in humans.[106] The Population Attributable Fraction (PAF) for leprosy, calculated using case-control studies, estimates the proportion of cases that could be prevented if exposure to armadillos were eliminated, considering both the risk to exposed individuals and the prevalence of exposure in the population; in Brazil the PAF is 3.3% (1 in 30 cases) if 10% of people have direct contact, 1 in 10 cases if 33% have direct contact, and 1 in 7 cases if half the people in the community have direct contact.[85]

The OH approach involves multi-professional research collaboration focused on *M. leprae* DNA genotyping analysis from armadillos captured in Brazil. Key strategies include continuous monitoring of human and armadillo populations for *M. leprae* using diagnostic tools, public education to reduce transmission risks, and collaborative research to understand the ecology of *M. leprae* in armadillos and develop predictive models for the effectiveness of interventions, such as stoppage of armadillo direct contact (hunting and consumption) and controlling armadillo populations to mitigate leprosy transmission to humans.

ENVIRONMENTAL TRANSMISSION OF *M. LEPRAE*[iii]

Optimal understanding of all aspects of transmission through existing and emerging tools and strategies remains important.[107] Understanding environmental transmission of leprosy is one such strategy that needs special attention.

The Oxford dictionary defines environment as "the surroundings or conditions in which a person, animal, or plant lives or operates" or "the natural world, as a whole or in a particular geographical area, especially as affected by human activity." Scientific evidence of the presence of *M. leprae* in environmental elements such as water and soil indicates the possibility of environmental transmission.[108]

Ecology of water

Several studies conducted across India, Brazil, and Bangladesh reported the presence of *M. leprae* DNA in approximately 30–35% of soil and 19–55% of water samples collected from the houses of persons with leprosy and other surroundings. Approximately half of these soil and water samples demonstrated viable *M. leprae* bacilli.[108–111] While person-to-person transmission is considered to be the main route of transmission of *M. leprae*, a fresh re-examination of the historical, phylogeographic, sociocultural, and environmental factors linked to the spread of *M. leprae* among human populations is warranted.[112,113] The Leprosy Transmission Symposium that took place in 2014 identified some critical gaps in the evidence and understanding of environmental transmission.[114] Among these, the role of free-living amoeba in leprosy transmission was still to be substantiated. *M. leprae*, which is

[iii] Also applicable to *M. lepromatosis*.

an obligate intracellular organism, has the potential to spill over into environmental niches and survive endosymbiotically inside free-living amoebae. Free-living pathogenic amoebae potentially act as "external" reservoirs capable of ingesting and supporting the survival of *M. leprae* expelled by infectious persons in the environment, thus acting as macrophage-like niches. *M. leprae* remains viable for prolonged periods inside *Acanthamoeba castellani* and *A. polyphaga*.[115] However, it remains to be determined whether *M. leprae*-infected amoebae can transport bacilli through the nasal mucosa or through intact or abraded skin to produce clinical disease.[116–118]

While the environmental presence of *M. leprae* has been well demonstrated, the route of entry and exit of environmental *M. leprae* into and out of the human host remains to be understood. Robust evidence on this aspect is the critical gap in our understanding of *M. leprae* transmission.[114] Genetic diversity of *M. leprae* from different sources (patients, nasal carriers, zoonotic and environmental) and various settings (e.g., high and low endemic) needs to be investigated to study the transmission ecology at the community level. Detailed studies on environmental presence and genotyping have unfortunately been carried out in silos and now need to be linked to broader clinical and epidemiological data. There remains a need to develop molecular epidemiology tools customised to regions to allow for fine typing from primary samples and investigation of transmission links.

Generally, mycobacteria are ubiquitous microorganisms that live in natural waters, soils, and man-made water systems and play a role in nutrient cycling. *M. tuberculosis*, M. leprae, and *M. ulcerans* are thought to have evolved from these environmental pools to become major human pathogens. While *M. tuberculosis* and *M. leprae* developed niches as intracellular organisms, *M. ulcerans* has evolved as a water-thriving pathogen. Biofilm formation is one of the persistence mechanisms of *M. tuberculosis* and *M. ulcerans*. In a comparative study from Cameroon, abiotic and biotic environmental factors were significantly associated with the environmental multiplication of *M. ulcerans*.[119] Similar persistence mechanisms could potentially play a role in the case of *M. leprae* as well, which needs to be further investigated in the context of its environmental presence and potential transmission.

Considering the critical evidence gaps that have been identified in understanding the role of environmental factors in transmission in leprosy, there is an urgent need to investigate other non-human reservoir sources including animals, free living amoeba, aquatic animals, plants and biofilms.

Searching for common ecological patterns and transmission dynamics among the three closely phylogenetically related mycobacterial species (*M. tuberculosis*, non-tuberculous mycobacteria, *and M. ulcerans*) may assist in identifying hitherto unknown environmental sources of persistence of *M. leprae*. Identifying transmission networks through holistic longitudinal studies involving screening for environmental presence linked to new case detection, molecular epidemiology, and socio-cultural attributes could play a significant role in understanding the route of entry and exit as well as exact transmission pathways. Studies involving multiple countries with endemic and non-endemic settings with a common standardised protocol would be an ideal approach to understanding leprosy transmission and achieving the goal of zero transmission.

SOCIAL DETERMINANTS OF LEPROSY

The increasing focus on the social determinants of health in leprosy has generated a more comprehensive understanding of the disease. Studies such as those by Pescarini *et al.* have

identified key socioeconomic vulnerabilities at both individual and community levels, including advanced age, poor sanitation, and food insecurity, as significant risk factors for leprosy, emphasising the need for targeted control policies for vulnerable groups.[120] Additionally, research by Leano *et al.* and Matos *et al.* has highlighted the influence of social inequality on the incidence and distribution of leprosy, underscoring the importance of addressing inequities to achieve disease elimination.[121,122] Simionato de Assis *et al.* and Leano *et al.* identified poverty, lack of education, and limited access to healthcare as critical determinants in the persistence of leprosy.[121,123] Matos *et al.* demonstrated a strong correlation between leprosy distribution and socioeconomic indicators, with higher prevalence in areas with greater poverty and inequality.[122]

Poor housing conditions and lack of basic infrastructure are key determinants in leprosy transmission. Chastonay reviewed housing-related risk factors and concluded that overcrowding and poor water and sanitation quality increase transmission risk.[124] Parente *et al.* examined leprosy prevalence among Brazilian female prisoners, identifying associated factors such as incarceration history, skin colour, and cell overcrowding, finding a high prevalence among incarcerated women and highlighting their vulnerability and potential transmission within prison settings.[125]

Social stigma related to leprosy significantly impedes treatment seeking and social support for affected individuals. Additionally, economic hardship and limited access to adequate healthcare have been identified as major barriers to early diagnosis and effective management of leprosy.[123] Santacroce *et al.* and Stangl *et al.* pointed out that social stigma and discrimination against leprosy patients contribute to delays in seeking medical care and social isolation, perpetuating disease transmission.[126,127] Deps and Cruz argued that changing the terminology used for leprosy could reduce associated stigma and improve social acceptance.[128]

Migration and population mobility also play a significant role in the spread of leprosy, as they can introduce the disease to new areas and complicate the delivery of continuous healthcare services.[129] Additionally, gender disparities in healthcare access and the disproportionate impact of stigma on women can increase their vulnerability to leprosy.[130]

Women affected by leprosy face additional barriers stemming from gender inequalities in healthcare access and social support. Sarkar and Pradhan highlighted that women with leprosy suffer a dual burden of stigmatization and discrimination.[131] Shoemaker *et al.* and Gonçalves *et al.* documented the specific challenges faced by women in work roles and the impact of leprosy on their economic and social well-being.[130,132] Price reviewed literature on factors preventing early case detection for women affected by leprosy, highlighting societal stigma, women's dependence, self-stigmatizing attitudes, and gender insensitivity of leprosy services as barriers to timely diagnosis.[133] Understanding these factors can support efforts to encourage early reporting of symptoms among women.

Late detection of leprosy is also a problem mediated by socioeconomic characteristics associated with health-seeking behaviour. Furthermore, studies such as those by de Oliveira Serra *et al.* have identified knowledge gaps, economic barriers, and health system deficiencies contributing to delays in seeking medical care and treatment for leprosy, highlighting the need for targeted interventions.[134]

Education and community awareness have emerged as important strategies for addressing stigma and improving early detection and treatment of leprosy. Additionally, social inequalities, such as poverty and exclusion, have been identified as factors contributing to the disproportionate burden of leprosy in marginalised communities.

Leprosy and other neglected tropical diseases can have severe financial consequences for patients, with high direct costs contributing to impoverishment.[135] This underscores the importance of strategies such as conditional cash transfer programmes to improve health outcomes and alleviate the economic burden of the disease.[136]

The implementation of appropriate health policies and intervention strategies is fundamental to addressing the social determinants of leprosy. Ackley *et al.* emphasise the importance of health promotion interventions and effective communication to reduce the burden of leprosy.[137] Moreover, studies like that of Aya Pastrana *et al.* highlight the role of social marketing interventions in the prevention and control of neglected tropical diseases, including leprosy.[138]

Despite notable advancements in elucidating the role of social determinants in leprosy transmission, substantial gaps persist in our understanding. Future research endeavours should prioritise elucidating pathways linking social determinants to leprosy transmission. Additionally, operational pilot projects are warranted to ascertain the feasibility, effectiveness, and cost-effectiveness of interventions targeting social determinants, thus facilitating evidence-based decision-making in leprosy control efforts.

RECENT EVIDENCE FROM CONTROL PROGRAMMES RELEVANT TO INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*[iv]

The introduction of effective therapeutics against leprosy between the 1940s and 1980s changed the trajectory of leprosy control.[139–141] Coupled with early case finding, a remarkable drop in cases on treatment was observed by 2000, but annual new case reduction since 2005 was slower,[142] with approximately 200,000 cases reported annually until the COVID-19 years (March 2020–May 2023).[143] In Ghana, where case numbers have steadily declined with a stable, low child proportion of <3% recorded yearly for over a decade, the scaling up of leprosy prevention alongside integrated active case-detection in line with GLS 2021–2030 has produced useful insights.[144] Preparatory actions undertaken between 2019 and 2021 included re-orientation of coordinators, introduction of new tools, external review of the situation, and incorporation of leprosy chemoprophylaxis as part of the country's Zero-Leprosy Roadmap and Action Plan. Subsequently, a progressive implementation with 3 stages was chosen, with the first in 2021 and 2022 employing the retro-active case finding (RACF) approach for only household and neighbour contacts in the two most endemic regions. Then, there was an extension in 2022 and 2023 to four other regions, using both the RACF approach and quarterly campaigns for household, neighbour, and social contacts, followed by the current ongoing stage employing routine quarterly contact tracing/SDR-PEP drives since the latter part of 2023 in the same six regions.

Rifampicin was procured from the Global Drug Facility by partnering with the TB programme; paediatric extemporaneous formulations were prepared locally. Other key implementation activities included training of healthcare workers, engaging key stakeholders for buy-in, public sensitization and community mobilization, guideline adaptation for local context, screening and administering SDR to contacts, and monitoring and evaluation. At the same time, the programme has continued to work with the other skin-NTD programmes to carry out integrated population surveys and case searches in hard-to-reach areas and targeted skin camps, not limited to SDR-PEP regions.

[iv] Also applicable to *M. lepromatosis*.

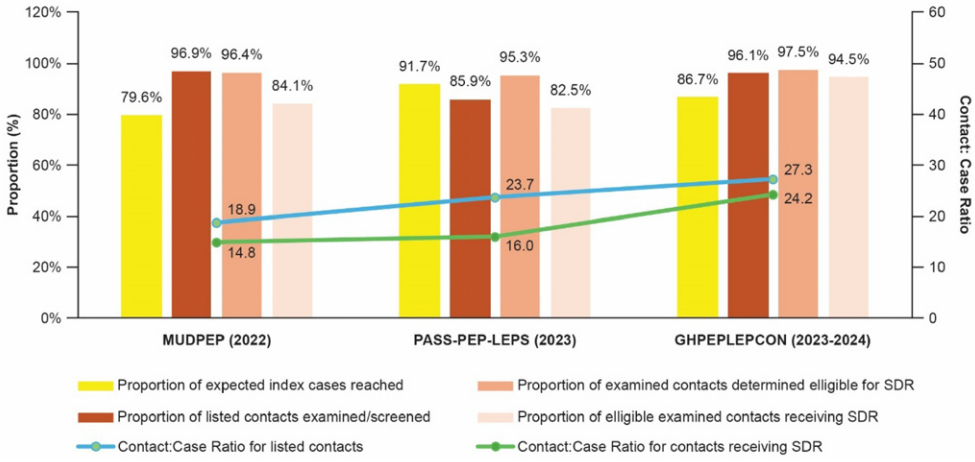

Figure 5. Leprosy contact and SDR-PEP administration cascade. SDR-PEP: single-dose rifampicin post-exposure prophylaxis; MUDPEP: Mop-Up Drive for Post-Exposure Prophylaxis; PASS-PEP-LEPS: Passive to Active Search Switch and Post-Exposure Prophylaxis for Leprosy and other Skin-NTDs; GHPEPLEPCON: Ghana Post-Exposure for Leprosy Contacts (Routine).

In stages 1, 2, and 3 of implementation, 79.6%, 91.7%, and 86.7% of expected index cases were reached with listed contact-to-case ratios (CCR) of 18.9, 23.7, and 27.3, respectively (Figure 5). For the proportion of listed contacts screened, 96.9%, 85.9%, and 96.1% were achieved across the 3 stages, respectively. Of these, 96.4%, 95.3%, and 97.5% of contacts were determined to be eligible, and 84.1%, 82.5%, and 94.5% of these were eventually dosed with SDR, giving final CCRs of 14.8, 16.0, and 24.2, respectively, for the 3 stages. The major causes of losses across the cascade were contacts not receiving SDR for operational reasons and contacts not examined or excluded for other reasons. In 2023, a 20.6% reduction in the number of new cases was observed in the six SDR-PEP regions compared with a 12.8% reduction in 10 non-SDR-PEP regions.

These findings add to evidence that SDR-PEP is effective and can be integrated into routine leprosy services,[68] but several enablers are required. Narrowing the gap between contact-listing CCR and SDR CCR requires optimizing coverage along the various components of the cascade. It is crucial to minimise the time between diagnosis and application of contact tracing/SDR-PEP, with quarterly drives appearing to be sufficiently effective. Other factors, as observed in non-SDR-PEP regions, may also be contributing to the decline in cases, making an argument for continued intense and targeted case finding, with contact tracing/SDR-PEP as an add-on. Using annually detected new case numbers to choose SDR-PEP start-up areas has also been observed not to directly correlate with Phase 1 areas based on the recently introduced LEMT Template.[64] These findings add to the call for strengthened data systems to follow up cases, better targeted interventions, and evaluation of the impact of the ongoing SDR-PEP roll-out.

ORGANISATIONS OF PERSONS AFFECTED CAN FACILITATE THE INTERRUPTION OF TRANSMISSION OF *M. LEPRAE*

Recently, there has been a steady growth and strengthening of organisations of persons affected by leprosy in nearly all endemic countries. These organisations are already present at nearly all

levels, from community to sub-national to national to regional and even global levels. They are also already working alongside health delivery programmes in the endemic communities. This emerging phenomenon of empowered organizations of persons affected can be a key element of a strong horizontal health programme. Specifically, these organisations working alongside or together with other partners can facilitate the interruption of transmission of *M. leprae* in three fundamental ways. Firstly, they offer an ideal way of achieving a strongly human rights-based approach in all programmes and activities aiming to interrupt transmission of *M. leprae*. This is best achieved when persons affected are enabled to participate directly. Their participation has been shown to help in reducing the critical barriers of discrimination and stigma. Involving people affected in programmes and activities also demonstrates accountability and transparency.

Secondly, organisations of persons affected can facilitate a more person-centred approach in programmes and activities. They can help national programmes and other partners to listen to the local people. The affected individuals can be deployed as local advocates to help to address local realities of complacency, learned helplessness, and lack of interest in their local communities. Their insights and expertise can help governments and other partners to tailor their strategies appropriately for every local situation as they understand the experiences and concerns of the local persons affected.

Third and finally, organisations of persons affected can facilitate the development of a more sustainable health and welfare system. This will require that partners develop models that have people affected at the core of their activities and programmes. This will have a domino effect as the models can be used for other NTD eradication initiatives as well as to support people with disabilities.

Generally, if organisations of persons affected are strengthened appropriately, they can contribute significantly to building sustainable models of health and welfare delivery systems that will create a team of persons affected with experience in community mobilization and organizing, skilled enough to work alongside health systems, and with capacity in consumer leadership. Most importantly, strong organisations of persons affected will facilitate and even accelerate the interruption of transmission of *M. leprae* and ultimately help achieve zero transmission.

Research recommendations

Following the symposium held in 2024, a gap analysis was undertaken to compare the current status of the gaps in understanding of transmission and identified needs from the 2014 symposium. The full analysis may be found in the Supplement; specific key research recommendations are shown in Table 2.

In summary, on the first day of the GPZL symposium, presentations on a wide range of topics within the area of *M. leprae* transmission and leprosy disease were given, the content of which forms the synthesis of evidence presented here. As well as this, during the symposium, several breakout groups took place during which both research and operational topics were discussed, and research and operational recommendations were given by the symposium participants. In this paper we have presented the progress since 2014 in the field of research into *M. leprae* transmission, as well as recommendations for future research. The accompanying paper[146] presents the operational approaches and recommendations from the symposium.

Table 2. Research recommendations

Topics	Research recommendations
Human reservoirs	Develop PCR-based diagnostics with a lower limit of detection so that full genotyping may be carried out with smaller amounts of *M. leprae* DNA. Develop field-based RNA-based viability assays, including advancement of freezing technology suitable for use in the field. Validate the available immunodiagnostic tests for prevalence of infection (anti-PGL-I IgM in FSB) on a global scale. Validate the available tests for detection infection at an individual level (qPCR of lesions) Develop an integrated protocol for testing (sero-)prevalence of infection of multiple NTD-causing pathogens that can be adapted based on local needs. Conduct surveys to determine prevalence of infection using molecular and serological tools.
Entry and exit route	Elucidate the importance of nasal swabs, positive for (viable) *M. leprae* particularly in the low endemic setting. Analyse MB patients with high numbers of bacilli in the nose and their relevance to transmission.
Roles of animals or vectors	Analyse the impact of armadillos as a source of infection for humans, particularly in areas where human leprosy is nonendemic and develop public health interventions to minimise transmission risk (for the Americas).
Role of poverty/social determinants	Map social determinants of health and conduct studies to determine which are more important for leprosy and how they interact. Link social determinant research to epidemiological mapping, because social determinants may be context specific.
Host-pathogen interactions	In settings where *M. lepromatosis* is not yet demonstrated, determine whether RLEP-negative MB patients are infected with *M. lepromatosis* to avoid the risk of not diagnosing leprosy. Multiplex qPCR for specific detection of both *M. leprae* and *M. lepromatosis* DNA is routinely applied in some laboratories.[9,145]
Transmission networks	**Overarching research proposal to address the questions:** • *Are asymptomatic individuals infectious and if so, when do they start transmitting?* • *How to identify the source of infection of new cases, especially those arising in the "non-contact" community in leprosy endemic areas?* • *In spatiotemporal hotspots, is transmission still ongoing?* • *Is there no transmission ongoing from more isolated cases?* Increase collection of genome-sequenced *M. leprae* strains complemented with detailed epidemiological data, seroprevalence data (in children), all preferably population-based longitudinal data. Investigate genetic diversity of *M. leprae* from different sources (patients, nasal carriers, zoonotic and environmental) to study transmission ecology. Determine the total bacterial burden in a population and when transmission events are likely to have occurred.
Enhanced epidemiological data	Estimate the number of cases being treated by the private sector. Implement mapping of new cases, contact tracing and active case-finding strategies to identify transmission hotspots, ideally integrated with molecular epidemiology. Investigate further the existence of geographic boundaries indicating higher risk of transmission. Investigate which individuals require PEP among groups that are possibly eligible – validate boundaries of risk of infection.

Conflict of interest

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Supplementary data

Supplemental information for this article can be found online at https://doi.org/10.47276/lr.96.2.2025034.

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