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GPZL Reports on Research Priorities

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The Global Partnership for Zero Leprosy Research Agenda Working Group comprised 8 subgroups, whose reports are presented here.

Subgroup on Epidemiologic Modeling and Socioeconomic Research

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Background

Epidemiologic modeling can play a key role in supporting efforts to reach zero transmission and zero disability of leprosy. It is an efficient and powerful tool for quantifying transmission patterns and for predicting future trends in leprosy detection and the potential impact of existing and novel interventions.[1] Transmission dynamics of leprosy are inherently nonlinear. Apart from host factors, an individual's risk for developing leprosy is determined by the number of cases in an area and the infectiousness of cases among their contacts. The number of newly detected cases is determined by past exposure of the individual to *M. leprae*. Moreover, leprosy is known for its long incubation time and delayed diagnosis due to difficulties in diagnosis and fear of stigma.[2,3] As a result, measuring the impact of changes in policy can be difficult because the impact of current changes may not be seen in the short run. Epidemiologic modeling can help to identify long-term impact of policy changes and optimal (endgame) strategies.[1]

At the same time, an investment case should be built to inform (local) policy makers and other donors on the importance of investing in new tools and strategies aimed for achieving zero leprosy. As the road to zero leprosy requires extensive use of resources, the decision to commit to zero leprosy initiatives should be based on a robust analysis of the benefits, risks, and costs to ensure value for money—especially in less developed settings.[4] To guide this process,

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an eradication investment case (EIC) for leprosy is recommended.[5] Such a framework would provide a systematic inventory of what is needed to achieve zero leprosy along with information about the challenges, risks, and sustainability of an initiative. An EIC is particularly appropriate for diseases such as leprosy that have a high socioeconomic burden and for which multiple interventions exist or are being developed. The EIC framework has been recently tailored to the context of leprosy by Tiwari and Richardus,[6] who outlined the following key domains:

- Disease burden and elimination.
- Current state of the leprosy program and recent technical advances.
- Available and new tools and their scope in interrupting transmission.
- Future requirements during and after transmission interruption.
- Biological and technical feasibility of transmission interruption.
- Socioeconomic burden and public goods obtainable.
- Financing leprosy elimination.
- Health systems and their capacity.

A leprosy EIC would help to determine whether zero leprosy is feasible, the capacity of the initiative to monitor and evaluate control programs, the most promising interventions for achieving that goal, and the long-term consequences of the interventions. It also includes an assessment of the health-system changes required in leprosy-endemic countries.[3]

In formulating their research agenda, the Subgroup on Epidemiologic Modeling and Socioeconomic Research of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group reviewed recent modeling work on leprosy and socioeconomic research and identified important key questions that support efforts to reach zero leprosy and contribute to the development of a leprosy EIC.

Current knowledge and key questions

Previous modeling work on leprosy has mainly focused on predicting future leprosy trends and evaluating the impact of various interventions. A leprosy EIC does not exist yet, but a recent literature review has identified current knowledge and key information gaps on constructing a leprosy EIC.[6] An overview of the key findings from this systematic review was published separately[3] and is presented in the Box below (Figure 1).

To develop a leprosy EIC, input is mainly required from epidemiologic modeling and socio-economic research. However, developments in research outlined by other subgroups of the GPZL Research Agenda Working Group (i.e., Diagnostics, Vaccines, PEP, and Operational Research) are also crucial.

The key findings and knowledge gaps in the field identified by the Subgroup on Epidemiologic Modeling and Socioeconomic Research are summarized below.

Epidemiologic modeling

FEASIBILITY OF GLOBAL INTERRUPTION OF LEPROSY TRANSMISSION

Interruption of leprosy transmission is unfeasible within two decades without additional efforts and new interventions.[7,8] A next step would be to provide a realistic time frame upon

Panel: Key findings of a systematic review on constructing a leprosy elimination investment case

A 2016 systematic review[98] identified a number of factors that should be considered when developing a case for investing in the elimination of leprosy. The findings listed below, adapted from that review, are grouped under eight headings, in accordance with an internationally recognised guide on preparing disease eradication investment cases.[99]

Disease burden and elimination

- The proportion of newly detected leprosy cases in children younger than 15 years reflects the degree to which *Mycobacterium leprae* transmission is occurring.
- The proportion of patients with grade 2 disability (visible deformity or damage) reflects the degree to which a health system is achieving early detection and prompt treatment of patients.
- Many leprosy cases escape detection by health systems.[2]

Current state of the leprosy programme and recent technical advances

- The new PCR test is capable of detecting the leprosy bacillus and its resistance to drugs,[100]but its application is limited.
- The *M. leprae*-specific anti-PGL-I antibody test has limited applicability, because it is only reliably positive in multibacillary cases.[101]

Available and new tools and their scope in interrupting transmission

- Tracing contacts of index leprosy patients can detect new cases more effectively than population-based approaches but faces operational and ethical challenges.[12]
- Contact tracing followed by administration of chemoprophylaxis, BCG vaccination, or both is currently the most promising approach to halting *M. leprae* transmission.

Future requirements during and after transmission interruption

- Linking leprosy elimination efforts with programmes working on other neglected tropical diseases ensures the sustainability, efficacy, and financial resilience needed to reach the WHO leprosy elimination goal.[2,25]

Biological and technical feasibility of transmission interruption

- Genome-based technology will probably facilitate the development of leprosy vaccines and diagnostic tests.[102]

Socioeconomic burden and public goods obtainable

- The disability-adjusted life-year is not a reliable indicator of the leprosy disease burden.[103,104]
- Leprosy is one of many neglected tropical diseases associated with poverty.[105]

Financing leprosy elimination

- Information about the costs of provision of leprosy services is scarce.

Health systems and their capacity

- Integration of a leprosy programme into the general health system reduces the level of anti-leprosy stigma in a country.
- Community-based rehabilitation is effective in integrated programmes but is used in few health systems.[106,107]

Figure 1.

which zero leprosy and zero disability can be reached. This information would also be relevant when developing a leprosy EIC. As zero leprosy has not been formally defined yet, modeling studies can assess various definitions, such as achieving zero new (child) cases or sustained zero new leprosy cases. Moreover, modeling studies could also assess the time frames for reaching intermediate targets.

- *Key questions:*
  - What would be a realistic time frame to achieve global interruption of transmission?
  - How long should programs be continued to achieve zero leprosy?
  - How should zero leprosy be defined?

POTENTIAL IMPACT OF NEW STRATEGIES AND TOOLS

Universally, studies have highlighted the need for earlier diagnosis and treatment of leprosy, preferably in the asymptomatic stage, in order to substantially reduce the new case detection rate (NCDR).[9–11] Innovative ways to prevent leprosy include administering post-exposure prophylaxis (PEP) to contacts of newly diagnosed leprosy patients and providing earlier diagnosis through screening with diagnostic tools. A modeling study on leprosy in Pará State in Brazil showed that administering a single dose of rifampicin (SDR) to household contacts, in addition to current controls, would lower the NCDR by 40%.[12] Another study showed that the use of a diagnostic test to detect subclinical leprosy cases could be a crucial step for interrupting transmission.[9] In high endemic settings, the use of a population survey as a testing strategy with a diagnostic is preferred over household contact testing. Another strategy to consider is poverty

reduction.[13] In Brazil and Mexico, research is being done on cash transfers in relation with diseases, including leprosy, with promising results.[14,15] Also, integrated strategies can be explored.[16] For example, joint detection of tuberculosis (TB) and leprosy could be considered in some areas,[17] with BCG treatment also effective in patients with leprosy. Another example is the use of skin camps for several neglected tropical diseases (NTDs).

- *Key questions:*
  - What is the potential long-term impact of available and new tools such as vaccines and diagnostics and their scope in interrupting transmission?
  - Which interventions are most promising?
  - Which strategy would yield the highest impact on transmission (both in terms of reduction in incidence and in time until lower infection levels are reached)?
  - How can modeling of the impact of poverty reduction on leprosy best be done?

GEOGRAPHICAL VARIATION AND POPULATION AT RISK

- ***Geographical variation***

  Current incidence trends show the geographical variability of leprosy. This is also evident in the predictions from modeling studies. Regions with lower incidence of leprosy are predicted to reach the 10 per 100,000 threshold within a few years, whereas those with higher incidence are predicted, with current interventions, to have only a small chance of reaching this threshold within 20 years.[7] This pattern is true at the national scale (e.g., India, Brazil, and Indonesia compared to other affected countries) and at a sub-national level (e.g., among Brazilian states),[7,8] and might be true of smaller spatial scales. Also, differences in breakdown between multi-bacillary and paucibacillary infections may impact the infection reservoirs and thus transmission.
  - *Key questions:*
    - To what extent does the impact of interventions differ among geographical regions?
    - Should interventions be tailored to specific endemicity levels, and, if so, how?
    - In which areas is zero leprosy feasible in a relatively short time span?
    - How should zoonotic transmission in the Americas be measured?
- ***Population at risk***

  The size of the population at risk for leprosy may determine the size of the problem and therefore could be used for advocacy, awareness raising, and program-planning activities. However, the population at risk in the context of leprosy is not defined or estimated yet because of several challenges in making such an estimate. A modeling study is ongoing to estimate the number of people needing PEP, as a proxy of the population at risk, in order to substantially reduce the newly detected cases.
  - *Key questions:*
    - How should we define population at risk?
    - What is the estimated population at risk?

IMPACT OF OTHER EPIDEMIOLOGICAL RISK FACTORS FOR TRANSMISSION

Geographical variation could be dependent on (as yet) largely understudied risk factors, including environmental reservoirs and host factors that may predispose an individual to

multibacillary infection.[2] Potential host factors include undernutrition and comorbidities/co-infections.[18] These risk factors could be identified through meta-analyses, accompanied by observational studies or trials.

- *Key questions:*
  - Which epidemiological risk factors are relevant?
  - How do we incorporate these types of risk factors into a model?

END-GAME SCENARIOS

No research has been conducted in this area. Endgame scenarios might already be considered in several regions in the world that report a very low number of new annual cases. These areas may serve as a blue print for others when they will reach this point. Using modeling, we can identify what is needed to achieve zero leprosy and what possible post-zero leprosy scenarios may look like.

- *Key questions:*
  - What is needed to achieve and sustain zero leprosy?
  - What are possible scenarios for a post-zero leprosy era?

TESTING HYPOTHESES

In the past, modeling has been used to explore the likelihood of certain hypotheses in the absence of empirical evidence. A good example is a study that assessed multiple hypotheses of susceptibility mechanisms in leprosy (genetic vs. non-genetic).[19] Epidemiologic modeling can be used to assess various hypotheses on issues such as transmission dynamics, migration, and/or drug resistance. Such studies may overlap with the research agendas prioritized by other subgroups of the GPZL Research Agenda Working Group and should align with those agendas.

- *Key questions:*
  - What efforts are needed to assess hypotheses regarding transmission dynamics?
  - What is the impact of migration on leprosy trends?
  - If drug resistance becomes a problem, how would that affect the course of leprosy incidence?

Economic research

AVAILABLE TOOLS AND THEIR ECONOMIC FEASIBILITY

Cost effectiveness and cost-benefit analyses are essential for identifying the best possible leprosy control strategy for a specific country or region. Two cost-effectiveness studies have been published: one on case detection strategies and one on chemoprophylaxis.[20,21] Currently, a modeling study on the cost-effectiveness of PEP taking into account future benefits is ongoing. To determine if an investment is sound, a cost-benefit analysis comparing the total expected cost of each option against their total expected benefits is recommended.

- *Key questions:*
  - What is the cost-effectiveness of current and new tools?
  - What are the results from cost-benefit analyses conducted in different settings (health system contexts)?

SOCIOECONOMIC BURDEN OF LEPROSY

- ***Disease burden***
  Estimates on the burden of disease due to leprosy rely on disability weights that underestimate the actual disadvantages resulting from leprosy. First, there is a need to identify leprosy-associated disability (social and mental issues are not considered currently), followed by a re-estimate of disability weights for endemic counties or WHO regions. The burden in children, including the impact of the disease on school dropout, lifelong stigma, and mental health, should also be considered.
  - *Key questions:*
    - What efforts are needed to estimate disability and assess disability weights of leprosy?
    - What efforts are needed to estimate the burden of morbidity due to leprosy and other NTDs or other diseases that share cross-cutting issues with leprosy?
- ***Socioeconomic risk factors of leprosy***
  Socioeconomic risk factors of leprosy include the length of time in poverty, level of education, and socioeconomic status of the family; nutritional factors; water, sanitation, and hygiene factors; housing conditions; and the presence of coinfection(s). Previous and ongoing studies have focused on several of these risk factors for transmission (related to hotspots). However, studies to determine the importance of each risk factor are still needed. This evidence may also contribute to epidemiologic modeling.
  - *Key questions:*
    - *What are the relevant socioeconomic risk factors of leprosy?*
    - *What is the potential impact of each risk factor?*
- ***Monetizing socioeconomic burden of leprosy and associated illness***
  The social burden of leprosy is hardly estimated but is important for leprosy prevention efforts due to high social negative impact. The prevalence of social consequences and public expenditure on social welfare (directly and indirectly related to leprosy) remain unknown. Also, an analysis of the likely effect of leprosy on economic productivity at the household and population levels and on social participation is unknown. Willingness-to-pay studies are needed to quantify/monetize the impact of social consequences (discrete choice experiment).
  - *Key questions:*
    - *What is impact of leprosy on economic productivity?*
    - *What is the impact of leprosy on social participation?*
    - *What is the estimated impact of social consequences due to leprosy?*

FINANCIAL AND COST ANALYSIS OF LEPROSY AND ASSOCIATED ILLNESS

- ***Cost analysis of leprosy and associated illness***
  A study has been published estimating the out-of-pocket expenditures for leprosy households.[21] Direct and indirect household expenditure on leprosy was estimated to be on

average $5·40–$6·50 and $8·70–$12, respectively. More such studies are needed from various countries to estimate the total societal cost of leprosy care.

- *Key question:*
  - What is the out-of-pocket expenditure on leprosy for affected households and individuals in different settings?

- ***Financial analysis of (global) leprosy programs***
  The *2015 WHO report on investing to overcome the global impact of NTDs* estimated that the investment in leprosy services would be on average $37 million annually.[22] This includes costs for contact tracing, treatment, and care. It is important for health systems to facilitate sustained leprosy control activities. However, with low numbers of leprosy cases, this may become difficult due to financial and human resource constraints and diminishing ability to diagnose leprosy. A recent study has also assessed the leprosy costs in two primary health settings in India.[23]
  - *Key questions:*
    - *What efforts are needed to develop a systematic method to estimate gross expenditure per country?*
    - *What is the gross total expenditure on leprosy per country/region?*

Subgroup on Digital Health

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Summary
The use of digital health-based interventions in leprosy is limited. Several examples have been compiled and outlined in this report. There are clearly many opportunities to apply digital interventions in the broader field of neglected tropical diseases (NTDs). Examples include digital diagnostics, surveillance, disease mapping, eLearning, policy and digital strategy, and monitoring and evaluation.

- Leprosy often goes undetected due to a lack of diagnostic tools, awareness of the disease, or effective screening methods.
- Low-income communities need better access to quality healthcare.
- Digital innovations are being made in the NTD and NCD fields through physician aids, eLearning and mapping.

National leprosy programs are showing willingness and taking action to incorporate national digital registries into their prevention efforts. These registries will help ensure accurate case detection and rates and improve targeting of resources.

Partnerships with the IT sectors could encourage and fuel innovation and funding for leprosy prevention. The use of digital diagnostics will lead to new research to enable more rapid diagnosis of disease. These advances will contribute to policy developments and help

build strategic partnerships for adoption and scale up of new and existing interventions, which can potentially serve as important models for other NTDs.

The Subgroup on Digital Health of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group identified several major gaps for digital health application for leprosy. These include lack of:

- Sufficient evaluations of digital health interventions.
- Interest in and use of digital technologies in the field of leprosy.
- Skilled workers and resources for digital health training and application.
- Scalable and sustainable digital health solutions that can be integrated into national health systems.
- Strategic planning for successful interventions to be scaled (and applied) to other NTDs.

The Subgroup identified the following digital health research priorities to fill these knowledge gaps and help reach zero leprosy:

- Geolocalization of cases.
- Digital diagnostics.
- eLearning and hands-on training (with accreditation).
- Policy research, implementation, and tracking.
- Independent evaluation of digital interventions (with scale-up plans).

Existing digital interventions in leprosy

NIKUSHTH FOR PATIENT REGISTRATION

In India, the National Leprosy Eradication Programme (*NLEP*) has commissioned a digital tool, called *Nikushth*, for registration of leprosy patients. This application was built by *HISP India* on the *DHIS2* platform from the University of Oslo, and is open source.

LEPROSY ALERT RESPONSE NETWORK AND SURVEILLANCE SYSTEM (LEARNS)

The Novartis Foundation and the Department of Health and Department of Science and Technology in the Philippines have worked together to build an enhanced leprosy referral and surveillance network among healthcare providers (HCPs). The goal of this project is to have a positive impact on the disease burden for leprosy in the Philippines by introducing a role-based tele-dermatology system that will enable health workers to consult with specialists by providing images of skin lesions and patient details and then get an expert diagnosis for the patient. The patient can then be referred through the system for further treatment and follow-up. The system allows for the storage of images and patient details, creation of alerts based on delayed response by HCPs, unusual case reporting (low or high) in a given region, failure of follow-up, and other capacities. The system also allows reports to be generated for evaluation of the regional health centers, system effectiveness, and other considerations. Importantly, the LEARNS tool has been evaluated for sensitivity and specificity in the clinic and in a 'real world' field setting.

Results of the evaluation have shown that when LEARNS is used new case detection rates increase while the time to diagnosis decreases (from approximately 2 months to 2·5 days; Figure 2).

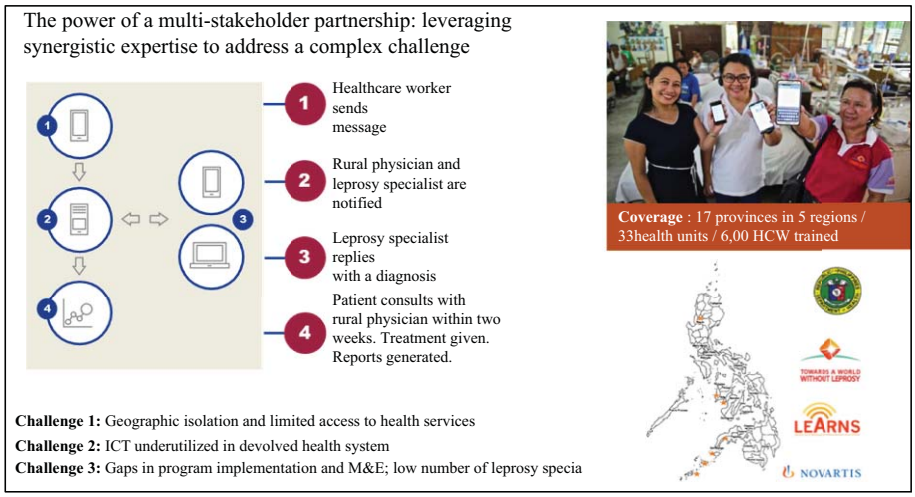

Figure 2. The LEARNS project in the Philippines.

GIS MAPPING APPLICATION

The Novartis Foundation has also worked with the University of Oslo and HISP India to develop a GIS mapping application that uses data from Nikushth to provide a visualization of cases over time at the level of the Indian "block," an area that includes approximately 50 000 people.

This is currently the most granular level of mapping available; while the name of the center where the patient was diagnosed is captured in the data, the location of each center has not yet been given map coordinates. This information will be available soon, however, and will enable the government to map cases to the location of the health centers and therefore provide targeted assistance for health worker education, medication provision, and resource mobilization to strengthen efforts to interrupt transmission. This application is also built with

Figure 3. Capturing an image for the Leprosy Intelligent Image Atlas at Fiocruz in Brazil.

the open-source DHIS2 platform and is therefore available in any country where a digital patient registration system is in operation.

DIGITAL DIAGNOSTICS

The Novartis Foundation and Microsoft are partnering to develop a proof-of-concept artificial intelligence (AI)-enabled digital health tool and a Leprosy Intelligent Image Atlas to aid in the early detection of leprosy. As part of *the collaboration*, Microsoft and the Novartis Foundation will work with local investigators from Oswaldo Cruz Foundation (Fiocruz) in Brazil to develop a protocol to examine anonymized images collected by Fiocruz. This will include a high-resolution image and metadata capture protocol to process the leprosy skin lesion images. The imagery and AI code will be publicly accessible at a later stage (Figure 3).

THE SKINAPP

Developed by Netherlands Leprosy Relief (NLR), the SkinApp is a smartphone app designed to support peripheral health workers in diagnosing and treating common, NTD- and HIV-related skin diseases. Although skin diseases are highly prevalent, the availability of dermatologists in many areas is limited (in Mozambique, there are 10 dermatologists for a population of 27 million people). Many public health centers are run by clinical officers or nurses who have very limited training in dermatology. NLR developed the SkinApp after field-testing an adapted version of *Mahé's algorithm* for diagnosis and treatment of common skin diseases in Nigeria. A first version of the app was field tested in Zambezia Province in Mozambique, in both urban and rural districts. Findings and feedback have led to an improved version of the SkinApp that can now be downloaded and in the *Google Play Store*. In April, NLR will field test this improved version of the SkinApp in Mozambique with the aim of improving the quality of diagnosis and treatment of skin diseases and enhancing early detection of skin-related NTDs as well as HIV-related skin diseases (Figure 4).

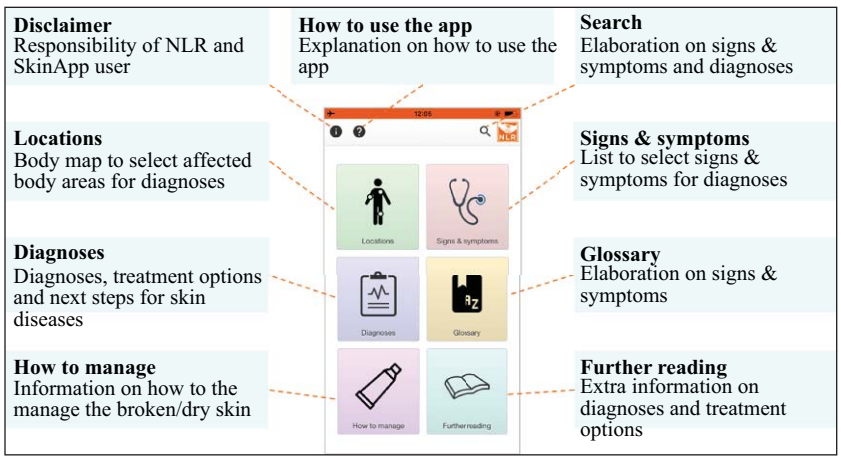

Figure 4. The NLR SkinApp - home screen.

BENEFITS OF SKINAPP

- A **simple tool to diagnose skin diseases** by check-boxes of signs and symptoms and affected body areas.
- An **easy-to-use database of skin diseases**, including signs and symptoms, pictures, and treatment options, which helps in making diagnoses and provides eLearning for community health workers.
- Available in rural settings since it **can be used offline.**

DIGITAL HEALTH POLICY

Despite the widespread use of mobile phones (with approximately 99·7% market penetration), the use of digital health-assisted interventions is uncoordinated and often fragmented. These interventions and applications rarely reach scale. The *Broadband Commission Working Group on Digital Health* has convened the world's top experts to develop recommendations on ways that policymakers and other stakeholders can develop sustainable digital health solutions to address national health priorities. This will help to accelerate universal health coverage and the achievement of the United Nations' *Sustainable Development Goal 3*.

The Working Group's 2017 report, *Digital Health: A Call for Government Leadership and Cooperation between ICT and Health*, created a blueprint for how information and communications technology (ICT) and health leaders and policymakers can collaborate to develop national digital health strategies.

The Working Group's 2018 report, *The Promise of Digital Health: Addressing Non-communicable Diseases to Accelerate Universal Health Coverage in LMICs*, builds on the earlier work. It provides practical recommendations and best practice examples of how policymakers can implement sustainable digital health solutions that address NCDs in low- and middle-income countries, therefore accelerating Universal Health Coverage and achieving Sustainable Development Goal 3. The report sets out six building blocks, accompanied by country examples, to help policymakers realize the full potential of digital technology to strengthen their health systems and accelerate universal health coverage:

1. Policy makers need to prioritize, formulate and coordinate national digital health strategies.
2. Legal frameworks are essential to protect patients while enabling innovation.
3. Standardized infrastructure allows information to be shared and used across the journey of patients with chronic diseases such as NCDs.
4. Interoperability between diverse digital health solutions and data sources is a must to enable coordinated NCD management.
5. Partnerships combine expertise, assets, and ideas to amplify the scale and impact of successful digital health solutions.
6. Sustained financing is mandatory to scale successful digital health solutions.

Subgroup on Operational Research

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Introduction

Operational research is a type of research that seeks to improve health outcomes by enhancing the efficiency or reach of currently available tools rather than by developing novel ones. The methodologies employed may be similar to those used in other types of research, such as comparing an intervention arm (e.g., through a new way of organizing one aspect of a program) with a control arm. Or, the method may be more specifically operational, e.g., examining the feasibility of expanding the use of a proven intervention such as post-exposure prophylaxis (PEP),[24] or examining the reasons behind a certain operational problem such as why some people do not complete treatment as prescribed.[25] Operational research can thus be applied to a wide range of program components.

Priority research topics

In discussing strategies to reach zero leprosy, the Operational Research Subgroup of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group recognized that certain operational issues assume greater significance. The Subgroup therefore focused on six priority topics: mapping, data management, monitoring and surveillance, health systems strengthening, drug-resistance surveillance, and active case-finding. While the use of digital tools and the use of mathematical modeling are also important aspects of operational research, these topics were examined by separate GPZL subgroups and are discussed in their respective reports.

MAPPING

Mapping disease incidence (to focus prevention) and prevalence (to focus treatment) has been widely used to display the geographical distribution of several neglected tropical diseases (NTDs). Analytic tools are increasingly available, but much of the hard work in mapping involves collecting reliable patient and disease data in an appropriate format and linking these to data relevant for operational research (e.g., data on transportation, logistics). Such data are often available from multiple sources and in multiple formats but can be linked via their geographic locations. Two enabling technologies include geographic information systems (GISs) and location-based services (e.g., global positioning systems [GPS]). GISs enable combination of disparate data by linking locations, while GPS links detailed and reproducible location data to observed health measures.[26,27]

In addition to technological support for mapping, the past several decades have seen a rapid increase in the development of statistical tools for the analysis of spatial and spatio-temporal data. Mapping incidence and prevalence at the level of small administrative regions and communities is particularly helpful for leprosy because of the highly focal nature of the disease, which can result in high incidence/prevalence areas being isolated and surrounded by lower background values.

Based on discussions with the Operational Research Subgroup, two general areas of spatial statistical tools are of particular interest for enabling operational research: (1) the detection of local concentrations of high local incidence/prevalence rates; and (2) given the scale of spatial clustering, the development of focused and adaptive sampling methods for efficient detection of local hot spots of disease. For the first category, two sets of spatial statistical tools are particularly useful in leprosy surveillance: methods to stabilize rates of a rare disease in small geographic areas and methods to detect spatial/spatiotemporal clusters of locally high disease rates (hot spots). Both categories extend traditional epidemiologic analyses into the spatial and spatiotemporal setting,[28] and tools are becoming available for their routine use in public health surveillance. Such methods are already used by the leprosy research and surveillance communities,[29–31] and a comprehensive review of the emerging literature in this area would help consolidate methods and computational tools and move results from the statistical/epidemiologic methodology literature into operational research for leprosy surveillance and response.

Regarding the second category, most NTD mapping to date has involved sample surveys of common diseases, which provide an estimated prevalence of disease for a given area (e.g., a district). However, leprosy is an uncommon disease, which usually occurs in clusters. While some mapping has been done using routinely reported data, this may not adequately reflect the true burden of disease because of the variable quality of case-finding in most programs. The challenge of efficiently sampling a large geographic area to identify isolated clusters of an outcome of interest motivates a class of methods known as *adaptive sampling*, which was originally developed as part of wildlife monitoring but has great potential for use in NTD surveillance. The basic concept involves ongoing broad surveillance along with increased efforts for areas indicating initial evidence of high rates, areas of historically high rates, or areas containing a signature of risk factors indicative of higher local rates. Research is needed to tailor such approaches to routine use for NTD surveillance, but promising applications exist for *Loa loa* detection,[32,33] and Chagas disease surveillance.[34]

Based on discussions within the Subgroup, the time is opportune for moving tools from the statistical and epidemiological methods research space into routine practice in leprosy and NTD surveillance to allow development of focused, actionable, and sustainable surveillance protocols for leprosy detection, treatment, and prevention.

DATA MANAGEMENT

Data management is an important subject for operational research. All health programs obtain, record, report, and analyze data for a variety of purposes, but this is rarely, if ever, done without complications. Problems include too much or too little data, missing data, data errors, reporting delays, and other issues. Even with good data, determining the best indicators to monitor progress can be difficult and regulations regarding privacy need to be incorporated in any system. The presentation of public health data for a wide range of users is

now often enhanced by geographic display, making such presentations closely linked with mapping (described above).

MONITORING AND SURVEILLANCE

Two kinds of monitoring are needed for leprosy prevention: program monitoring (to reflect indicators of process, outcomes, etc.) and epidemiological monitoring (with proper denominators and rigorous scientific inference).

The latter is essential to understand trends, without programmatic artifacts and errors. For leprosy, having an accurate estimate of the true DALYs lost would also help raise funding needed for impactful work. Epidemiological monitoring is also necessary to understand the extent to which current interventions are having an impact, so that adjustments and improvements can be made. This topic also overlaps with data management and mapping.

HEALTH SYSTEMS STRENGTHENING

Weak health systems can pose many barriers to effective leprosy control. All national programs should therefore analyze the weaknesses of their leprosy control and health care systems and identify challenges and the opportunities.

Health Systems Strengthening (HSS) in leprosy should aim to:

- Achieve effective and sustainable leprosy control towards zero leprosy among high and low endemic settings.
- Be integrated with general health care systems.
- Contribute to the broader goals of universal health coverage.

Operationally, health systems interact in all areas of leprosy control measures: case detection (including special efforts such as contact tracing, etc.), effective treatment (including follow up during the post-multi-drug therapy [MDT] period), improved implementation of quality disability interventions, and improved initiation of prevention activities (including chemoprophylaxis). Therefore, HSS research should be viewed as a cross-cutting issue in any kind of operational research undertaken to reach zero leprosy.

A WHO handbook describes six building blocks of health systems:[35]

- Service delivery.
- Health workforce.
- Health information systems.
- Access to essential medicines.
- Financing.
- Leadership/Governance.

Although the handbook focuses on the health system as a whole at national level, each component can (and should) be looked at more narrowly from the perspective of a particular program or locality. For example, data management and mapping are clearly part of the health information system, while case-finding activities depend on the skills and availability of the health workforce.

Other issues related to the health workforce with implications for leprosy include:

- Different case-finding methods, including contact examination and the provision of PEP.
- The increasing recognition of counseling as a necessary service, particularly for all new cases.
- The need for post-MDT surveillance and disability prevention.

Another important issue is surveillance. Research on the best methods will be a powerful tool for advocating for financing and the political commitment to achieve zero leprosy.

R2STOP, an NTD research initiative, has identified implementation research associated with contact management and chemoprophylaxis as their primary goal for stopping leprosy transmission. In recognition of that goal and to align with the overall operational research agenda of GPZL, the priority research areas of HSS should focus on these challenges, with leprosy a mainstreaming agenda in their objectives, processes, and outcomes.

In addition to specific components of each of the health systems building blocks, several major overall research areas for leprosy can be identified. These include

- Public and private partnerships (involving all providers) in implementing extended contact surveillance with integrated approaches of case detection, prevention of disability activities, follow-ups, and prophylaxis.
- Efforts to influence policy support to institute community participation (including co-financial support) in routine care (including referral, follow-ups, and counseling).
- Integration of leprosy information (individual and consolidated) into national digital platform (e.g., DHIS2) for monitoring and decision making.

Specific questions can be formulated for each area in conjunction with other priorities of operational research, suitable in the time and context.

DRUG-RESISTANCE SURVEILLANCE

Drug resistance is a potential disrupter of any communicable disease control/elimination program. Although the number of leprosy samples so far tested is low, results suggest that drug resistance is not currently a serious threat to leprosy control.[36] However, surveillance measures are urgently needed to recognize drug resistance and enable immediate treatment to prevent its spread and reduce its impact on efforts to attain zero leprosy.

Basic research is needed for improved methods of testing for drug resistance, especially methods that can be used in less sophisticated and more peripheral settings, such as district hospitals or health centers, as have been established with tuberculosis. Another research need is the development of a test for resistance to clofazimine. Whole genome sequencing will also be useful to identify further variations between drug-resistant and sensitive strains of *M. leprae* that may be useful as molecular signatures for drug resistance under routine conditions. Research could also be initiated to identify relevant genetic mutations in other genes such as rpoA, rpoC, and other mechanisms of drug resistance.

Operational research is needed in two key areas: first, the development of improved sampling procedures from new cases to properly monitor the rate of primary resistance to rifampicin; and second, improved monitoring of treatment outcomes in cases showing rifampicin resistance to determine the efficacy of second-line drug treatments for resistant cases.

ACTIVE CASE-FINDING

Finding incident cases of leprosy is currently the basis for control and elimination methods, as mapping leprosy trends and implementing chemoprophylaxis for contacts both depend on the identification of new cases. Many methods of active case-finding have been used in a variety of settings, so determining the best approach for leprosy prevention is the primary operational research question.

Contact examination has generally been a traditional component of leprosy control programs and is recommended by WHO. The study in Nigeria mentioned above found contact examination to be the most cost-effective method of identifying new cases. This approach is now widely used, especially in settings where chemoprophylaxis is being provided to contacts not found to have active leprosy.

More recently, attention has been paid to the possibility of integrated diagnosis and management of a range of skin diseases within the NTD field.[37,38] In this approach, community health workers could identify suspect cases (using a tool such as the NLR *SkinApp*, or the *WHO guide on recognizing skin NTDs*) for later confirmation and treatment by experienced staff.

Studies on how to overcome health workers' unfamiliarity with the basic signs of leprosy, particularly in low-endemic settings, are currently underway in Cambodia.[39,40] A new approach to early diagnosis— retrospective active case finding (RACF), which uses small mobile teams—was developed in the country. With RACF, previously diagnosed leprosy patients are traced and their contacts screened through "drives." This approach appears feasible and effective in detecting new leprosy patients among contacts of previously registered patients. However, a well-maintained national leprosy database is essential for successful contact tracing. Therefore, passive case detection through routine leprosy surveillance is a precondition for efficient RACF as the two systems are mutually enhancing. Together, these two approaches may offer a promising option for countries with low numbers of leprosy patients but evidence of ongoing transmission. The impact on leprosy transmission could be further increased by the administration of single dose rifampicin as PEP to eligible recipients.

The following six methods of active case detection* have been generally used:

- ***House-to-house approach.*** This approach is useful in high endemic areas. Its guiding principle is that every household should be visited and suspected cases defined in advance. Awareness activities with information directed to the public are needed before such a campaign can be conducted. Adequate resources should be allocated for information, education, and communication (IEC); for training (and honorarium) of staff performing case detection; and for confirmation. The search team should include a trained health worker plus two ASHA volunteers (one female and one male), who have been provided general tools for suspecting leprosy. The team should visit and examine suspected cases and refer them to the nearest (ideally within walking distance) health facilities for evaluation on the same day or within the next 1–2 days. Health facilities should include trained staff to examine individuals for confirmation; slit smear laboratory capacity should also be available.
- ***Campaign-based approach.*** The campaign approach may be helpful in moderate or low prevalence areas. As in a skin camp approach, in a campaign-based approach the public is

*Descriptions provided by Dr. Narayan Dharmshaktu.

informed of the outreach in advance and invited to a location such as an open-air market (haat bazaar), health camp, school, or other village site where individuals can be examined by a trained physician and a skin smear slide can (optimally) be taken. Advanced distribution of information to community members is essential under this approach. This approach can also be combined with active house-to-house search approaches.

- ***Index case-based active case detection.*** This approach is useful in low endemic areas, including areas where elimination is close to being achieved. The index case method can also be combined with the campaign approach in low endemic areas but good IEC must be conducted in advance to inform people when and where to report. This approach can also be applied in migrants populations, such as human settlement areas near industrial and construction projects. For large villages, this approach should aim to reach at least 100 households around index cases (25 households in each direction), including the relatives settled in the village. If a village is smaller than 100 households, the full village should be examined. For migrant and human settlement populations, the same strategies should apply. While the index-case approach is cost saving, it has the disadvantage of incomplete coverage and thus the likelihood of missing cases.
- ***Incentive-based case detection activities.*** For this approach, case detection is done throughout the year and can involve community level health care volunteers who are paid an incentive for each confirmed new case they identify. It can also involve patient motivation through monetary incentives if patients are confirmed as having leprosy at a health facility or with incentives for free evaluation and advice for patients suffering from other skin diseases. Incentives can also be provided to individuals who bring suspected cases for confirmation, which can serve as additional motivation for the general population to report to the health facility. This approach may be useful in areas with literate people and very good health infrastructure.
- ***Household healthy contact examination.*** This approach is generally recommended as part of both routine leprosy program activities and active and passive case detection approaches.
- ***Mixed approach.*** Combined approaches for active case detection can also be done by programs to enhance the yield and improve cost effectiveness. Examples include (1) a house-to-house approach, along with a campaign approach with or without incentive; (2) a house-to-house approach with index case-based approach with or without incentive; (3) an index case-based approach with a campaign approach with or without incentive; and (4) an index case-based approach with an incentive approach. Each approach may be useful if it is carefully planned and includes adequate supervision and monitoring within the available resources.

Operational research could help to identify which method(s) are best in various situations.

Additional suggested operational research questions

Subgroup members suggested several other questions on issues that could potentially be addressed through operational research, but these were not discussed in detail. Examples include the following:

- What is the best approach for monitoring and treating nerve function impairment during anti-microbial chemotherapy? (more applicable to discussions on disability).

- What strategies should be used for patients with anergy to *M. leprae* who are likely to require prolonged protection against re-infection or relapse?
- How can the concentration of environmental *M. leprae* be reduced in neighborhoods of patients newly started on MDT?
- What is the weight of disability among persons affected by leprosy, using the *Global Burden of Disease* (GBD) criteria?

Discussion and conclusions

Operational research can potentially cover a wide range of topics. The Subgroup has selected a few that seem of particular relevance to achieving zero leprosy. Data management is central to any public health program and is closely related to program monitoring and surveillance. New technology has made the display of geographical data an ideal way to present large amounts of information in a user-friendly manner for planning and decision-making. Therefore, the operational research agenda relating to data management and mapping is likely the area of most immediate importance to zero leprosy.

HSS is an overarching concern, related to important Sustainable Development Goals such as Universal Health Coverage and ending the epidemics of certain infectious diseases. Any studies working towards zero leprosy should be aligned with other efforts to strengthen health systems.

Monitoring and managing drug resistance is an important area for research to prevent the effectiveness of standard treatment from being compromised. While drug resistance in leprosy is not currently a problem, it has the potential to undermine any work unless recognized.

A final priority area for operational research is active case-finding, which should be designed to be as efficient as possible. Virtually all interventions on the road to zero leprosy depend on finding index cases as a first step, so even small improvements in this area may have beneficial outcomes.

Subgroup on Diagnostics

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Introduction

Although leprosy is caused by an infectious agent (*Mycobacterium leprae* or *M. lepromatosis*), most of the heavily exposed population—the household and family members of patients—will not develop leprosy during their lifetime. This group is considered at highest risk for developing leprosy, but only 3%–5% will progress to the disease. Inherent to the

current method of diagnosis of leprosy (i.e., detection of clinical symptoms such as skin patch with loss of sensation, enlarged peripheral nerves), the disease is often diagnosed late. Furthermore, although multidrug therapy (MDT) is effective, the number of new cases has been stationary for the past 15 years—indicating that treatment does not block transmission. In the past 25 years, immunoprophylaxis (with BCG vaccination) and, more recently, chemoprophylaxis (e.g., single-dose rifampin [SDR]) have proved effective in preventing leprosy in household contacts. Indeed, the *2018 WHO guidelines* support this chemoprophylaxis approach, which is likely to be a successful, short-term strategy aimed at identifying new cases and treating healthy social and household contacts to impact incidence. Nevertheless, efforts are clearly needed to improve early identification of leprosy patients and to identify and treat infected persons—especially in low-to-middle endemic areas where the use of large-scale chemoprophylaxis would not be cost-effective in controlling transmission and reducing incidence. To reach these goals and contribute to zero leprosy, progress is needed in clinical and laboratory-based diagnosis as well as translation of the latter to rapid, user-friendly field tests.

Overview and current activities regarding leprosy diagnostics

Over the past 40 years, biochemical studies identifying PGL-I, the sequencing of the *M. leprae* genome, and consortia such as the Initiative for Diagnostic and Epidemiological Assays for Leprosy (IDEAL) have been landmarks in the development of leprosy diagnostic tests. Initially, detection of humoral and cellular immune host-derived biomarkers with ELISAs were used for detection of antibodies and cyto/ chemokines, respectively,[41] whereas molecular diagnostic assays were applied to detect pathogen-derived molecular (DNA/RNA). More recently, for both host immune response-based assays as well as PCR-based assays, technological advances are enabling better performance as well as an improved, minimally invasive point-of-care (POC) format, through novel versions of the above-mentioned techniques.[42–45] Comparison of test platforms as well as large scale evaluation in multiple endemic areas have been widely investigated for antibody-based tests,[46] and the performance of anti-PGL-I Ab based assays has been extensively described in the literature over several decades.[47] However, for pathogen-based qPCR assays as well as cellular immunity-based rapid field-tests, although both field-tested in multiple areas with different levels of endemicity,[42,43,45] there have been few independent and consistently replicated results of large sample size in coherent experimental designs in multicenter studies.

In several studies, data have been presented on pathogen detection using qPCR with different targets,[48] host immunity-based serological assays based on using either PGL-I or NDO-LID,[49] or cellular assays based on cytokine/ chemokine release assays.[42,43] There is vast evidence indicating that anti-PGL-I IgM or NDO-LID can be used in multibacillary (meaning smear-positive, BL and LL cases) leprosy diagnosis, although seropositivity in endemic areas can be found in numerous individuals who will never develop leprosy. However, PCR improves identification of paucibacillary (meaning smear-negative, TT and BT cases) leprosy as complementary to histological analysis.[50] Moreover, combined detection of humoral (antibodies) and cellular (cytokines) biomarkers significantly improves their diagnostic potential, for both types of leprosy.[43] Although most of the current products/ tests have been developed "in house," large-scale (population-based) studies using a rapid test to detect anti-*M. leprae* antibodies are currently ongoing (for example, the EDCTP-

funded PEOPLE study). Notwithstanding the fact that rapid tests detecting cytokines/chemokines were field-tested in areas on three continents where leprosy is still endemic,[43] larger scale studies are needed to provide proper sensitivity and specificity data.

Among the challenges to leprosy diagnostics that should be the focus of research, the Subgroup on Diagnostics of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group outlined the following:

- The bacteria do not grow in vitro, in regular culture media.
- There is no definitive gold standard method for diagnosis.
- Bacteria silently infect nerves and skin cells, subverting immunological responses; hence, there are few clear early signs of the disease that could distinguish active disease from infection.
- There is no reliable marker to estimate infection and risk to disease progression.
- Among clinical forms of paucibacillary leprosy, the bacteria are virtually undetectable using any testing techniques, although qPCR has demonstrated advances in sensitivity. In addition, indirect methods based on simultaneous detection of host humoral as well as cellular immune response directed against the bacteria provide promise as new tools.
- Clinical presentations among persons with leprosy differ widely, and several other diseases present the same phenotypes—especially for the paucibacillary forms.

The Subgroup outlined two main diagnostic-related needs to achieve zero leprosy:

1. The ability to conduct early and specific diagnosis of leprosy and *M. leprae* infection to block transmission using affordable, rapid POC tests in low-resourced settings.
2. The ability to screen exposed individuals to detect those who are infected. The use of chemo- and immuno-prophylaxis (see report from Subgroup on Vaccines) in low-to-middle endemic areas could help identify this group more precisely in the future.

Research priorities and key questions

POTENTIAL USE OF DIGITAL TECHNOLOGIES TO HELP IMPROVE CLINICAL DIAGNOSIS

Five clinically recognized forms of leprosy are classified by Ridley and Jopling.[51] In a group of more than 1000 patients referred to a center with expert dermatologists, 90% were diagnosed based on clinical features without skin biopsies for histological or molecular analysis, indicating that intensive education is necessary to train experts for field identification.[52]

Laboratory tests are not currently available to confirm either tuberculoid (TT) or borderline-tuberculoid (BT) leprosy. The bacteria are not detected in slit skin smears from lesions or other sites (ear lobes, knee, or elbow). The detection of the bacilli is possible in mid-borderline (BB), borderline-lepromatous (BL), and lepromatous leprosy (LL) patients. Thus, when multibacillary leprosy is suspected and microscopy analysis is available, diagnosis is easier. Indeterminate leprosy is considered to be an early form of leprosy, which progresses towards either the tuberculoid or lepromatous pole.

- *Key questions*
  - Could the use of high-resolution images and artificial intelligence improve confirmation of suspected leprosy?
  - Could artificial intelligence be used to screen skin biopsies using hematoxylin and eosin (H&E) stains or slit skin smear slides for unrecognized patterns to help detect tissue patterns or bacilli to improve diagnosis?
  - Could cutaneous thermography be used as a complementary diagnostic method, with or without ultraviolet photography? Thermography is capable of rapidly and dynamically measuring the thermal energy of large areas of the skin through the generation of images up to 1 million tones, representing differences of up to 0·01°C. It is a non-invasive, safe, and inexpensive technique. It would also make it possible to remotely perform leprosy diagnosis in the most prevalent and poorest areas of the world by sending images to reference centers.

NUCLEIC ACID-BASED TESTS

qPCR is being tested to confirm disease among paucibacillary patients. However, two main issues need to be addressed to validate its use for disease confirmation: (1) several different targets are available; and (2) most of the published qPCR data use research reagents and not GMP products, which are designed for diagnostic purposes.

- *Key questions*
  - Is there a method that could improve sensitivity and specificity in qPCR, including reproduction of results? There is an urgent need for independent confirmation, larger sample sizes, and combination of the best methods or mechanisms to harmonize testing of different assays in different laboratories using external quality assessment (EQA). In this regard, minimal requirements for best practices in qPCR in leprosy diagnosis are needed. While specificities from different countries should be considered, tests should be globally validated.
  - Are better sampling methods available for direct/indirect detection of *M. leprae* or DNA/RNA for use in diagnostic confirmation? Current methods rely on slit skin smears and biopsies that are invasive and painful. Novel, less invasive, and affordable methods are needed.
  - Could other diagnostic methods be developed? The use of loop-mediated isothermal amplification (LAMP) in leprosy molecular diagnosis is a relatively new DNA amplification technique. Because of its simplicity, ruggedness, and low cost, LAMP could be soon the method of choice for molecular diagnosis of leprosy but needs extensive validation.

DRUG-RESISTANCE SURVEILLANCE

The development of primary resistance, especially for rifampicin, depends on treatment adherence and completion rates for multibacillary cases. It is estimated that resistance is increasing in different countries, although no systematic surveys/queries have been performed. PEP protocols are spreading, and their impact on drug resistance needs to be evaluated in the long term.

- *Key question*
  - Is the number of *M. leprae* resistant strains increasing, especially in endemic countries?
  - Are there other mechanisms for drug resistance, especially for clofazimine?

REACTIONS AND RELAPSES (INCLUDING IN THE CONTEXT OF RESISTANCE)

Leprosy is a phenotypically diverse disease, and patients can undergo reactional episodes. One of the most difficult issues is to discriminate relapses from reactions. Since reemergence of the disease could be associated with resistance, direct screening is necessary to ensure adequate treatment.

- *Key questions*
  - Since qPCR or other molecular available techniques could be developed to directly detect leprosy, as well as primary resistance to avoid ineffective treatment, is it possible to develop a duplex or triplex qPCR also targeting the most frequent resistant SNPs in rpoB?
  - Could a new test be developed to detect bacterial viability? The direct detection and estimation of molecular bacilli viability in fresh or fixed clinical samples would help improve management of relapse cases (live mycobacteria) by distinguishing from reactional states (dead mycobacteria).
  - Concerning reactions, is it possible to define markers or a score to estimate the patient's risk of developing reactions?

DIAGNOSTIC TEST BASED ON DETECTION OF HOST IMMUNITY

Serological methods of detecting antibodies against *M. leprae* antigens such as NDO-LID or PGL-I are not sensitive enough to detect paucibacillary leprosy. Besides, the presence of anti-*M. leprae* antibodies is not predictive for disease. Current strategies such as detection of blood-based cytokines by POC lateral flow assays offer diagnostic advantages and have been tested in different countries. These strategies should be further evaluated in larger study designs. For serological assays, some strategies can be used to achieve specificity and higher sensitivity. These include (1) employing conformational or linear immunodominant epitopes selected from products of the patient's immune response and (2) using these epitopes as bait for specific antibodies on label-free biotechnological platforms.[53]

- *Key questions*
  - Can large scale multi-center studies be undertaken to validate the diagnostic potential for MB and PB leprosy of POC lateral flow assays for (simultaneous) detection of multiple cytokines/ chemokines and provide proper data on specificity and sensitivity of lateral flow assays, using a defined biomarker signature, including markers for humoral and cellular immunity? Could treatment response be monitored in the same way?

OTHER DIAGNOSTIC ISSUES

The use of host genomics has pinpointed novel pathways that are activated or deactivated upon infection either in blood or tissue (skin and nerves). Also, host SNPs have been identified as being associated with disease outcome.[54]

- *Key questions*
  - Although a panel of blood-based host transcriptomic biomarkers has been described, can more extensive data be obtained (particularly data on infected individuals developing disease) in order to determine markers associated with (early) disease?
  - Can a panel of host SNPs be used to estimate the risk of developing disease?

There are no tools, culture media, or techniques available to aid *M. leprae* growth, making the identification and characterization of *M. leprae* difficult. Recently, tick-cell lines have been described as tools to grow *M. leprae*.[55]

- *Key question*
  - Would the use of tick-cell lines be feasible for confirmation of *M. leprae* diagnosis?
  - Would their use be feasible for antibiotic resistance and drug discovery screening?

TESTING FOR INFECTION

Achieving zero leprosy will require better tools for disease control. It will be necessary to predict among the at-risk population which individuals have the highest chance of progressing to disease. Defined markers are needed to test whether a specific panel, signature, or response could anticipate leprosy progression among contacts or the general population. It is important that these tools be used in the near future in low- and middle-endemicity countries/areas where screening of at-risk populations prior to chemo- and immunoprophylaxis would be cost-effective.

- *Key questions*
  - Could a panel of genetic polymorphisms or transcripts or metagenomic markers be defined to scrutinize high risk contacts?
  - Is it possible to have a next-generation skin test (for example, based on recombinant proteins) to screen for infected people?
  - Can novel, low-complexity lateral flow assays based on fingerstick blood provide a means for POC triage testing for infection by measuring both antibodies and cyto/chemokines in capillary blood?
  - Can a combined field-friendly test with a smartphone app be developed for follow up of at-risk individuals and patients to increase testing and population coverage in leprosy endemic areas.

NON-HUMAN RESERVOIRS

Issues surrounding non-human reservoirs for leprosy deserve attention and may impact diagnosis. Recently, armadillos and red squirrels were reported as natural hosts that also develop the disease after infection with *M. leprae* or *M. lepromatosis*. These results have

provided novel hypotheses concerning *M. leprae* transmission that could influence leprosy epidemiology and control.

- *Key questions*
  - Are there reservoirs and transmission routes other than human-human in leprosy? An improved and integrated view of the natural course of the disease could help establish life cycles.
  - Does leprosy in non-humans exhibit an infection stage and later an active disease stage (a two-step leprosy progression) that could be used as model of leprosy development?
  - Could non-human models be tested for leprosy progression?

Genomics could be used to better understand phylogeography and perhaps depict novel virulence factors. Whole, large-scale genomics could be used to help determine strains/SNP type/haplotype associations isolated from different clinical forms of the disease.

Conclusions and recommendations

Early diagnosis can help stop transmission and improve leprosy control. Although novel tools with the potential for use in leprosy control exist, they must be scalable, GMP produced, field friendly (i.e. low complexity), low cost, and adaptable to different levels of endemicity.

As research priorities to ensure the capability for early diagnosis needed to achieve zero leprosy, the Subgroup on Diagnostics recommends the following:

- Diagnostic assays (qPCR for pathogen, host immune response assays, host transcriptomic assays) should be harmonized and validated globally through multicenter studies. As part of this effort, standardization and quality assurance programs should be implemented to compare these tools, providing grants are available for these efforts.
- Less invasive sampling methods should be developed.
- Although reasonable sensitivity and specificity have been achieved with currently available methods, new methods using biomarker discovery, mycobacteria viability, cell culture, and risk factor modeling should be developed for improved (next-generation) diagnostic tools.
- Transmission research (intermediary host, vectors) may impact diagnostics, epidemiology, surveillance, and control and should be prioritized.
- Tools should be used either to confirm leprosy when patients present suspicious lesions or to screen and follow-up high risk individuals.

Longitudinal studies will allow identification of better markers associated with disease progression. Future studies should involve evaluation of several assays at different laboratories/field sites globally using identical protocols and allowing overall accessibility in open (multi-disease) platforms for independent confirmation and validation.

Subgroup on Post-Exposure Prophylaxis

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Introduction

Early case detection and prompt treatment with multi-drug therapy are the cornerstones of the World Health Organization (WHO) recommendations for leprosy control.[56,57] The more than 200,000 new leprosy patients detected each year,[58] of which 10% are children, indicate stable and ongoing transmission of *Mycobacterium leprae*. One of the main challenges to interrupting transmission is the disease's long incubation period: around 5 years until clinical and diagnostic symptoms appear.[59] The risk of developing leprosy varies across contact groups.[60] Household contacts have the highest risk, and neighbours of infected individuals have a risk more than four times higher than that of the general population. While no specific vaccine is currently available, work on the first leprosy-specific vaccine is advancing.

Transmission of *M. leprae* can best be interrupted by introducing new preventive interventions. Chemoprophylaxis in the form of single-dose rifampicin (SDR) given to close contacts of leprosy patients reduces their risk of developing leprosy by 60%; when combined with childhood Bacillus Calmette-Guérin (BCG) vaccination, this risk is reduced by 80%.[61] A large, double-blind randomized controlled trial in Bangladesh and a controlled trial in Indonesia have provided the bulk of evidence,[62–64] indicating that SDR may also reduce transmission by killing *M. leprae* in exposed contacts. Before SDR is provided to contacts of leprosy patients, they must be screened for signs and symptoms of leprosy and other exclusion criteria through a clinical, non-invasive examination of the skin. Because of this component, which is identical to active case finding, the implementation of a chemoprophylaxis intervention contributes to early case detection. The possibility of inducing rifampicin resistance in *M. tuberculosis* has been examined by a group of experts who concluded that this risk is negligible—both on theoretical grounds and on evidence from the long-standing worldwide practice of giving monthly doses of rifampicin for the treatment of leprosy.[65] Implementation research studies on how to best integrate contact screening and SDR distribution into routine leprosy control programmes are currently ongoing in several countries.

History of leprosy post-exposure prophylaxis

Systematic reviews with meta-analysis showed that several chemoprophylaxis projects had been conducted in the 1960s and 1970s using dapsone once or twice weekly for 2–3 years or acedapsone every 10 weeks for 7 months; since the 1990s, SDR has been used.[62,63] All studies showed superiority of the intervention over placebo, with an overall reduction of the leprosy new case detection rate (NCDR) of 40%–60% in contacts.

The most important results concerning the efficacy of SDR in leprosy post-exposure prophylaxis (PEP) were generated by the COLEP trial in Bangladesh.[66] This trial was a single-center, double-blind, cluster-randomised, placebo-controlled study that included 21 711 contacts of over 1000 recently diagnosed leprosy patients. The overall risk reduction for contacts during the first 2 years after SDR administration was 57%; no further risk reduction was found beyond those 2 years. The highest protective efficacy was found in non-blood-related contacts, but the study was underpowered to evaluate the impact on particular contact groups. The calculated number of contacts needed to be treated to prevent a single case of leprosy was 265 after 2 years and 297 after 4 years.[64] Childhood vaccination with BCG also had a protective effect of nearly 60%, and when combined with SDR an added benefit was observed resulting in a protective effect of 80%.[67] Thus, there are strong indications that SDR in leprosy PEP (SDR-PEP) helps to decrease the incidence of leprosy.[68]

Current and recent studies on leprosy PEP

INDONESIA (2014–2016)

A recent study in Indonesia has shown that in hyper-endemic foci SDR-PEP given to household contacts alone may not be effective.[69] For high-incidence pockets ('hotspots') or populations ('hotpops'), a "blanket" or mass drug administration approach for SDR-PEP may be more appropriate.[68] The feasibility of a population-wide administration of SDR was tested in a prospective follow-up study in a high endemic and isolated community in Indonesia. The feasibility could be proven, but the need for adequate planning and additional investments was highlighted.[70] A follow-up of this study is needed to observe the long-term effect and determine the conditions to sustain it.

LEPROSY POST-EXPOSURE PROPHYLAXIS (LPEP) (2015–2019)

The LPEP program is currently ongoing in India, Indonesia, Myanmar, Nepal, Sri Lanka, Tanzania, Brazil, and Cambodia. It is designed to evaluate effectiveness, impact, and feasibility of contact tracing and SDR-PEP for contacts of leprosy patients under routine program conditions.[71–73] The core LPEP study explores the feasibility and impact of combining three key interventions: (1) systematically tracing the contacts of newly diagnosed leprosy patients; (2) screening the traced contacts for signs of the disease; and (3) administering SDR to eligible contacts.[71] The activities are implemented through established structures of the national leprosy control programmes, with coordination and supervision support by international partners. Interim results based on data from 5941 index patients (89.4% of registered index cases) and 110 512 contacts eligible to receive SDR (785 refused) show that the intervention is feasible in different settings and under varying circumstances. However, for implementation of SDR-PEP on a greater scale and in multiple socio-epidemiological conditions, more field-level evidence is needed about its feasibility and impact in settings with different levels of leprosy endemicity, particularly low-endemic populations.

PEOPLE TRIAL (2018–2022)

The PEOPLE trial will evaluate different modalities of PEP for leprosy prevention in Madagascar and the Comoros,[74] with the goal of identifying optimal target populations for

PEP. It is planned as a cluster randomized trial aiming to:

- Test the safety and efficacy of a higher dose of rifampicin such as single-double dose (SDDR; 1200 mg rifampicin per adult compared to 600 mg rifampicin in the LPEP program).
- Identify which approach for selecting contacts eligible for PEP is most effective in reducing incident leprosy through four study arms:
  - Control (no PEP).
  - SDDR-PEP, only household contacts.
  - SDDR-PEP, household contacts and anti-PGL1 positive village contacts.
  - Blanket SDDR-PEP at village level.

In all four study arms, annual door-to-door surveys will be conducted covering entire villages. All permanent residents will be offered leprosy screening. Risk ratios will be calculated for leprosy based on (1) physical distance from the nearest index household, (2) proportions of phylogenetically clustered patients, and (3) proportions of patients belonging to the social network of another patient. Additionally, costs per person treated with SDDR-PEP for each study arm will be calculated, and genotyping of bacilli on samples from all incident leprosy patients will be conducted.

PEP4LEP (2018–2022):

The PEP4LEP trial is an implementation trial in Mozambique, Ethiopia, and Tanzania. This cluster randomized study will compare PEP effectiveness in terms of the rate of leprosy patients detected and the delay in case detection through two SDR prophylaxis interventions: (1) a community "skin camp" and (2) a health-center based approach that treats household contacts only. Additionally, it will compare the feasibility of the two chemoprophylaxis interventions in terms of cost effectiveness and acceptability. Both interventions will use an integrated skin disease approach and rely on a validated skin disease diagnosis app (*the SkinApp*) to facilitate diagnosis. Other skin issues, such as common skin diseases, other neglected tropical diseases (NTDs) manifesting with skin lesions, and HIV/AIDS-related skin diseases, will also be diagnosed and treated. A capacity assessment will be used to evaluate the skills of health workers in using the common skin approach in practice.

MALTALEP (2013–2019):

Maltalep is a cluster randomized controlled trial comparing immunization with BCG alone with BCG plus SDR in contacts of newly diagnosed leprosy patients. Contact groups of approximately 10 persons were established for each of the 1500 leprosy patients enrolled in the trial, resulting in around 15 000 contacts in total. BCG was administered to the intervention group followed by SDR 2 months later. The control group received BCG only. Follow-up was at 1 year and 2 years after intake. The primary outcome is the occurrence of clinical leprosy within 2 years. Simultaneously with vaccination and SDR, blood samples for *in vitro* analyses have been obtained from 300 contacts participating in the trial to determine the effect of these chemo- and immune-prophylactic interventions on immune and genetic

host parameters. Results of this trial will become available in 2019, after completion of 2 years follow-up for all participants.

PEP++ PROJECT (2017–2022):

The PEP++ Project uses a cluster-randomized trial design to compare the efficacy of an enhanced chemoprophylaxis regimen (PEP++) with that of SDR PEP in close contacts who are seropositive for antibodies against the leprosy-specific ND-O-LID conjugate. PEP++ is a multi-dose regimen comprising clarithromycin and rifampicin. The PEP++ intervention will complement a novel, cluster-based blanket implementation of SDR PEP. Clusters in the participating districts will be identified using geographic information system (GIS) technology. Both approaches will be supported by optimized leprosy case detection and treatment services, including health systems strengthening, contextualized community education on leprosy, stigma reduction interventions, and involvement of leprosy-affected persons in various roles in their communities.

Research priorities and key questions

BASIC EPIDEMIOLOGICAL DATA NEEDS

A detailed understanding of disease distribution is essential for planning interventions like PEP.

Leprosy prevalence and surveillance

While over 200,000 new cases of leprosy are reported each year, a number of countries to not report to WHO at all, or only irregularly;[58] in Brazil, India, and Africa high numbers of hidden cases were observed.[75–77] Leprosy control programmes are often insufficient in parts of these countries or not established at all. Being a focal disease, national statistics are also insufficient to identify priority areas for interventions. Activities like PEP should be integrated into local health services or combined with other disease control programmes to make them successful.[68] Thus, prevalence studies and surveillance activities are increasingly needed—especially in areas where leprosy reporting is insufficient.

- *Key questions*
  - Where are the leprosy endemic areas?
  - How do we define endemic, and how many hidden cases do we have?

Mapping of current and retrospective routine surveillance data

The *AIM Initiative* demonstrated that, based on routine (i.e., Ministry of Health) surveillance data of diagnosed leprosy patients, digital maps can be generated with village-level accuracy. These maps also enable the overlay of geo-referenced health facility locations to show the availability of services related to the distribution of the diseases. Establishing a detailed understanding of disease distribution is essential for planning PEP intervention.

- *Key question*
  - What is the geospatial distribution of leprosy patients in endemic countries?

LEPROSY PEP INTERVENTION

The most critical pending research questions for LPEP involve operational research on how to design and implement the intervention itself.

PEP intervention effectiveness

To make an intervention like PEP successful, effective and feasible active case-finding/contact-tracing approaches must be defined both for low- and high-endemic settings and for existing and novel approaches. PEP can be combined with different, active case-finding modes. Contact screening approaches that include households, neighbours, or social contacts could be done by actively visiting the houses or by asking the contacts to visit health care facilities. The screening could be done by volunteer health care workers or by experts on a case-by-case basis or during screening drives. PEP also could be given in a blanket approach, during "skin camps" or any other mass screening events. Many different interventions are and will be tested in the near future, and a periodically updated review of the evidence and coordination of studies is necessary to avoid duplication and identify optimal protocols for individual country/region or district settings.

- *Key question*
  - Which type of PEP intervention fits best with which epidemiological setting?

PEP effectiveness under routine conditions

Efficacy of PEP for contacts of leprosy patients has been proven in several studies under research conditions. As countries transition to implementing such interventions under routine program conditions, it is essential to monitor the effectiveness of this approach. Different routine conditions should be distinguished (integrated vs. vertical, and/or NTD integrated vs. TB integrated). Monitoring should also include good surveillance for adverse reactions.

- *Key question*
  - How effective is PEP under routine conditions?

Detailed cost studies

To encourage ministries of health to introduce PEP as a routine approach in their countries, cost-benefit information is essential. Evaluations should consider the costs for active case finding and for PEP along with the individual, societal, financial, and other benefits. Cost evaluation should be considered part of a wider elimination investment, as the long-term perspective and elimination potential will be major drivers of cost-effectiveness.

- *Key questions*
  - What are the costs of PEP?
  - How cost effective are the different implementation approaches?

Quality of leprosy screening by minimally trained staff

Active case finding and PEP interventions often rely on volunteer or paid community health workers (CHW) and other minimally trained staff. These individuals are expected to remain in their home village or neighbourhood, and usually work part-time. To assess their effectiveness, it is essential to study the diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) of their activities, to determine necessary training and re-training schedules, and to explore the problems and challenges they face in diagnosing leprosy.

- *Key questions*
  - Is the quality of leprosy screening by CHW sufficient to justify their use in PEP activities?
  - If so, under what conditions?

Surveillance for rifampicin resistance in leprosy

Although the possibility of inducing rifampicin resistance in *M. leprae* and *M. tuberculosis* has been estimated to be very low, surveillance to compare resistances in SDR and non-SDR areas is needed. Particularly, samples and data from patients who develop leprosy or tuberculosis after the SDR administration should be collected.

- *Key question*
  - Does implementation of PEP lead to development of rifampicin-resistant leprosy or tuberculosis?

Field-friendly diagnostic tests

The use of field-friendly, point-of-care (POC), rapid diagnostic test (RDTs) would facilitate the diagnosis of leprosy under field conditions, particularly by non-medical staff such as CHWs (see above). Issues surrounding the development, validation, and introduction of such tests were examined by the Subgroup on Diagnostics and are very relevant to the success of PEP activities.

- *Key question*
  - What efforts are needed to ensure the development and validation of a field-friendly, rapid diagnostic test to support minimally trained staff in the diagnosis of leprosy?

LEPROSY PEP FREQUENCY AND DRUG OPTIONS

Efforts are needed to address several research questions on PEP medication.

Frequency of SDR in high endemic settings

The efficacy of SDR has been shown to persist over a 2-year period, with no additional benefit thereafter. The re-administration of SDR after this 2-year period could improve the effect, but the true benefit of re-treatment remains unclear.

- *Key questions*
  - What is the additional benefit of SDR re-administration?
  - Under which epidemiological conditions is re-administration of SDR justified?

Other drugs for PEP

The potential of drugs like moxifloxacin and bedaquiline or drug combinations for PEP should be tested.

- *Key question*
  - How effective are other (new) drugs for single and repeated PEP?

PEP for high-risk contacts

The efficacy of SDR to reduce the risk of developing leprosy is lower among blood-related household contacts and other very close contacts compared to more distant contacts. Studies are ongoing to address this issue (e.g., PEP++ and PEOPLE, see above), but other interventions should also be explored.

- *Key question*
  - How can the efficacy of PEP for blood-related household contacts and other high-risk contacts be increased?

Disturbance of gut microbiome through PEP

The use of antibiotics can disrupt the ecology of the human gut microbiome. It would be useful to study the short- and long-term consequences of single-dose antibiotic use on the human gut microbiome and its effect on diseases such as malnutrition, obesity, diabetes, and bacterial co-infections.

- *Key question*
  - What are the effects of SDR on the gut microbiome?

Combination of SDR and vaccines

Immunization of newborns with BCG improves the protective effect of SDR. The effect of other vaccines, like newly developed TB vaccines, is unclear. The use of inactivated or recombinant vaccines would allow for possible co-administration with SDR PEP. Vaccine development issues were addressed by the Subgroup on Vaccines, but it is important to study their use in PEP activities.

- *Key question*
  - Which vaccines are useful in terms of immunoprophylaxis and could be combined with SDR?

TRANSMISSION

The impact of leprosy PEP interventions on transmission and thus toward zero leprosy can only be fully appreciated based on an improved understanding of *M. leprae* transmission. Increased knowledge on *M. leprae* transmission will also facilitate the design of targeted interventions to interrupt transmission that complement early case detection and PEP. The current state of knowledge on *M. leprae* transmission has been reviewed,[78] and related research priorities formulated.[79] An overview of tools and strategies to end *M. leprae* transmission, including through PEP, has also been published.[80] Based on the above, four research areas have been identified by the Subgroup as priority concerns for understanding *M. leprae* transmission:

Human-to-human transmission (human reservoir)

Areas of interest include (1) biomarkers for all clinical and subclinical cases of leprosy as well as biomarkers for asymptomatic carriers; (2) the role of colonization and route of entry of *M. leprae* into the human host; (3) roles of co-infections on the entry/exit of *M. leprae* from the human host; and (4) stages of pathogenicity of *M. leprae* to understand the migration (port of entry to the site of initial lesion to point of exit) of the bacterium inside the human host.

Non-human reservoirs

Areas of interest include (1) distribution of *M. leprae* in armadillos in the Americas and corresponding zoonotic potential; (2) role of other animals in *M. leprae* transmission; (3) biological relationship between *M. leprae* and amoeba as well as arthropods; (4) presence of *M. leprae* in the environment in different endemic settings; (5) genotyping to understand the role of *M. leprae* strains found in the environment and those found in the population; and (6) demonstrated viability of *M. leprae* in the environment.

Host–pathogen interactions

Areas of interest include (1) relationships between *M. leprae* genetic characteristic and virulence, growth kinetics, drug resistance, tropisms for nerves, and the tendency to cause reactions; (2) the role of host genetic risk factors in susceptibility and resistance to *M. leprae* infection, clinical progression of leprosy, and reactions; (3) understanding how the immune response affects the various manifestations of leprosy including establishment of infection, progression of disease, nasal carriage, and reactions; and (4) understanding of the similarities/differences between *M. leprae* and *M. lepromatosis*.

Transmission networks

Areas of interest include (1) collection of genome-sequenced *M. leprae* strains including isolates from various origins (e.g., worldwide, paucibacillary patients) complemented with detailed epidemiological data; and (2) genetic diversity of *M. leprae* from different sources (e.g., patients, nasal carriers, zoonotic and environmental sources) and various settings (e.g., high and low endemic regions) to understand the transmission ecology at the community level.

Subgroup on Vaccines

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Background

Several cultivatable mycobacteria have been evaluated for use in alternate leprosy vaccines. In the South India trial, a group of recruits was immunized with *Mycobacterium w*, which has been reported to provide protection in mice. Follow-up evaluations indicated that *M. w* provided only 25·7% protection, lower than all other groups evaluated. Despite this limitation, a large-scale, double-blind immunoprophylactic trial of an *M. w* vaccine was conducted among index cases and their household contacts in Uttar Pradesh, India, between 1992 and 2001. The vaccine consisted of 1×10^9 heat-killed *M. w* bacilli for the first dose, with a second, half dose given 6 months later. When index cases alone were vaccinated, protective efficacies of 43%, 31%, and 3% were reported after 3, 6, and 9 years, respectively. When contacts alone were vaccinated, protective efficacies of 69%, 59%, and 39% were observed for these time periods. When both patients and contacts were vaccinated, these protective efficacies were 68%, 60%, and 28%. As has been found in other studies, the vaccine efficacy was highest in children. Thus, the protective effect of the *M. w* vaccine was sustained in Uttar Pradesh for a period of about 7–8 years. Despite the reporting of these results in 2005 and the commercial availability of the vaccine ("Immuvac"), immunization with *M. w* does not appear to have been evaluated in other leprosy-endemic regions and it has not emerged as a common control or prevention strategy for leprosy.

Recent studies

- **Indian Cancer Research Center (ICRC) bacilli**
  ICRC bacilli, which are cultivable mycobacteria of uncertain origin, probably belonging to the *Mycobacteria avium* intracellulare complex, were also used in the South India trial as a live vaccine following reported use of this vaccine candidate to protect mice. ICRC immunization induced persistent lepromin conversion in LL patients, as well as inducing lepromin conversion in previously negative healthy subjects. Of all the immunization groups included in the South India trial, ICRC provided the best protection, at 65·5%, thus indicating that the ICRC vaccine might be useful for control of leprosy. Again, however, widespread use of ICRC for the prevention of leprosy has not been reported.
- ***Mycobacterium vaccae***
  Mycobacterium vaccae is a nonpathogenic species of the mycobacteria that lives naturally in soil. In a trial conducted in Vietnam involving vaccination with killed *M. vaccae* alone (10^8 bacteria), BCG alone, or BCG plus 10^7 killed *M. vaccae,* children living in close contact with leprosy were enrolled. Although a cumulative 53% protection was observed in the first 4 years and 81% in the second 4 years for the vaccine groups combined, there

were no significant differences in protection afforded by each of the three vaccines although it was suggested that immunization with killed *M. vaccae* alone provided protection. The addition of a preparation of killed *M. vaccae* to BCG did not enhance protection afforded over that observed by either vaccine alone.

- ***Mycobacterium habana***
  Based on the protection observed in mice and the induction of lepromin reactions in monkeys, *M. habana* has also been proposed as a leprosy vaccine candidate. Among individuals immunized with live *M. habana* vaccination in India, lepromin reactivity was reportedly augmented. Although this finding suggested that *M. habana* immunization stimulated specific cell-mediated immunity against *M. leprae* and indicated vaccine potential, there have been no subsequent reports regarding the protective efficacy of *M. habana* vaccination.

Taken together, several vaccine strategies centered on the use of whole mycobacteria have been attempted; however, to date, none besides BCG have advanced into common use. Although BCG vaccination has proven to be only partially effective, this important vaccine must be maintained and kept available for applications in both TB and leprosy, at least for the foreseeable future. As the number of BCG manufacturers continues to diminish, however, supply is becoming a serious issue.

Information to date indicates that the ideal vaccine against leprosy would need to induce strong, long-lasting T cell responses directed against *M. leprae* antigens, thereby limiting infection, preventing disease, and reducing bacterial transmission to others. Not until recently has it been practical to contemplate development and delivery of a new generation of vaccines for leprosy. Key technological and conceptual advances that put this strategy within reach stem from enabling antigen discovery through molecular cloning techniques, most notably the completion and publication of the *M. leprae* genome. Gene synthesis and antigen production, previously an insurmountable problem when dealing with an organism never cultured in the laboratory, are now achievable at scales appropriate for vaccine development. Of even more critical importance is the recent availability of adjuvants to enable a new generation of T cell vaccines. Evidence supporting the development of a defined leprosy vaccine came in part from studies showing that immunization with crude antigen preparations derived from the *M. leprae* cell wall, cell membrane, and cytosol can provide protection—building on data using whole *M. leprae* for prophylactic immunization. Although developing usable vaccine from whole cells or fractions thereof is not practical, these earlier studies demonstrated the potential, at least in experimental models, of developing a vaccine against leprosy.

Over the past several decades, the number of examples of effective immunotherapy for cancer and infection has been increasing. Concepts have evolved, along with more effective diagnostic tools, from using immunotherapy primarily for treatment of disease to its use in prevention approaches including post-exposure prophylaxis (PEP). This latter example is particularly applicable to the development of leprosy vaccines for which susceptible populations can be effectively targeted for introduction of safe and effective intervention measures to prevent progression to disease as well as transmission to others.

Partially effective vaccine applications for leprosy have been employed for decades, primarily in the form of different BCG vaccine products that vary widely in their composition and potency. Nonetheless, such vaccines have been used in cases of paucibacillary disease and, more recently, in contacts of multibacillary patients.

Key outcomes

As better tools are now becoming available for early detection of infection with *M. leprae* and as some degree of efficacy has been achieved using single-dose rifampin (SDR) for PEP, it is urgent that new approaches to augment or replace chemo-prophylaxis to prevent disease progression and transmission in exposed individuals. Until recently, immunotherapy options were limited to BCG, which being a live vaccine is generally limited to a single application. Furthermore, BCG availability has become a challenge as various facilities have stopped production.

Beginning in the 1990s, there has been a renewed effort to develop better leprosy vaccines and two inactivated vaccines for *M. leprae* are now advancing: MIP, a whole-cell vaccine of heat-killed mycobacteria (*M. pranii*, previously known as *M. w*); and LepVax, a multi-valent recombinant protein formulated in a modern adjuvant. The latter contains a modern adjuvant that has been used in more than a dozen vaccine candidates and is a safe and effective inducer of durable T-cell responses.

Ideal properties of a leprosy vaccine include its:

- Safety in *M. leprae*-infected and -uninfected individuals.
- Capacity to induce both *M. leprae*-specific immune responses and durable anti *M. leprae* immunity.
- Ability to be used in contacts, together with SDR, to inhibit transmission and disease progression.

Potential applications of a leprosy vaccine include:

- Treatment shortening for paucibacillary (PB) treatment.
- PEP in leprosy contacts.

As of early 2019 the MIP vaccine candidate is undergoing further evaluations in India, and the LepVax candidate will enter into Phase 2 evaluations in Brazil this year. Thus, including BCG, there are now three potential vaccine candidates for use in a zero leprosy campaign. As further clinical studies are designed and implemented, it will be important to carefully evaluate safety and efficacy endpoints, including changes in neurological function.

Conclusions

In summary, never before have there been so many tools for the diagnosis, prevention, and treatment of leprosy. The time is clearly right for a comprehensive and multi-faceted approach to zero leprosy. Based on their reviews and discussions, members of the Vaccines Subgroup of the Global Partnership for Zero Leprosy (GPZL) Research Agenda Working Group have made the following observations regarding vaccine research towards zero leprosy:

1. Safety monitoring will be a critical component for evaluation of any vaccine/immunotherapy procedure in a PEP/therapeutic setting.
2. Regular updates are needed on the current status of the MIP vaccine and LepVax.
3. Coordination is needed with WHO regarding criteria used to make recommendations for vaccine implementation.

4. Inclusion of a range of early diagnostic tests will be important in vaccine trial design and interpretation. Initially, these tests should be used not to include or exclude contacts from vaccine trials but rather to advance understanding of disease, the diagnostic tests themselves, and the optimal utility of a vaccine/immunotherapy.
5. Evaluation of clinical trial sites is critical to ensure adequate design/execution of studies in areas where the need is highest and where a path towards approval has been defined.
6. Clarification is needed for study design and for the parameters used to evaluate vaccine safety/efficacy.
7. One or more *Target Product Profiles* should be developed for vaccines, e.g., one for shortening the duration of treatment for PB disease and another for disease prevention in contacts.

Subgroup on Disability

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Summary
Leprosy is an important cause of preventable disability. Leprosy-related disability is not limited to physical dysfunction but includes activity limitations, stigma, discrimination, and social participation restrictions. Within the Research Agenda Working Group of the Global Partnership on Zero Leprosy (GPZL), two subgroups were formed to address these issues. The agenda for stigma and discrimination research was defined by the Subgroup on Stigma; the Subgroup on Disability focused their work in the following two areas:

I. Preventing disabilities among persons affected by leprosy
II. Minimizing the impact of living with impairments due to leprosy

Much is known about these two main components of leprosy-related disability. Early detection and treatment of both the disease and the reactions and nerve function impairment it causes are critical to prevent disabilities. Effective strategies for preventing disability and its worsening are known, and successful rehabilitation techniques are available. However, there is much room for improvement in areas such as accessibility of services, effectiveness (including cost effectiveness) of available services, and novel tools to improve current practices. Increased understanding of the causes of disabilities and ways to optimize disease management and improve inclusion is definitely needed to work towards zero leprosy.

The Subgroup identified several priority research topics under the two focus areas:

I. *Preventing disabilities among persons affected by leprosy:*
- Early detection of leprosy to prevent disability:
  - Assessing the impact of case finding/contact tracing strategies on the prevalence of leprosy-related disabilities among new cases.
- Pathophysiology, detection, and management of reactions:

  - Research on pathophysiological/immunological mechanisms of Type 1 and Type 2 reactions and nerve damage.
  - Development and validation of diagnostic tools for the detection and measurement of nerve function impairment.
  - Promotion and facilitation of the use of available treatment for reactions and nerve function impairment and identification of new treatment options.

II. *Minimizing the impact of living with impairments due to leprosy:*

- Number of people with disability due to leprosy and categorization and quantification of their needs:
  - Estimating the burden of disability due to leprosy.
- Prevention of disability and its worsening (POD):
  - Research on the feasibility, effectiveness, and impact of POD strategies, including self-care, physiotherapy, occupational therapy, and combined approaches.
- Rehabilitation services:
  - Assessing the accessibility and effectiveness of physical rehabilitation services and the provision of assistive devices.
- Community-based rehabilitation (CBR):
  - Research on the effectiveness, feasibility, and social and economic impact of CBR programs.

Some of these research needs can be addressed by large, population-based surveys. Such surveys could be added to ongoing multi-center studies, if resources were added to ensure sufficient capacity. Studies of reactions and nerve function impairment would require basic pathophysiological/immunological lab research. Efforts to minimize the impact for people living with impairments would require a targeted approach in areas with large numbers of people affected by leprosy or where people are affected by multiple neglected tropical diseases (NTDs).

Introduction

Although most leprosy-related disabilities are preventable, an estimated 2–3 million people live with leprosy-related impairments. These impairments may or may not cause activity limitations or restrict social participation, depending on the degree of severity and of social stigma. If the psychosocial consequences of leprosy, such as exclusion, anxiety, and depression were also considered, the number of persons affected could be much higher. This is certainly the case if the impact on family members is taken into account.

Disability is more than physical dysfunction; it includes activity limitations, stigma, discrimination, and social participation restrictions in interaction with contextual factors. This is reflected in the WHO International Classification of Functioning, Disability and Health (ICF) model of disability, which shows the relatedness of body structure and function (and impairment thereof), activity (and activity restrictions), and participation (and participation restrictions) (Figure 5). Future research therefore should address major challenges at the national and international levels to ensure prevention of disabilities and to minimize the impact of people living with disabilities by managing these in such a way that their participation and inclusion in society is optimized.

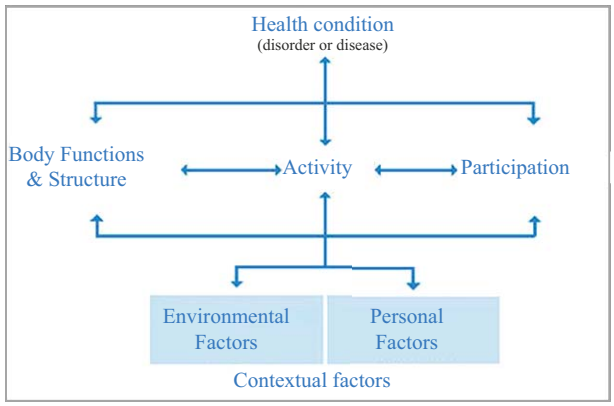

Figure 5. WHO ICF model of disability.

The Subgroup on Disability identified key research areas related to disability that are needed to prevent and reduce leprosy and the consequences of the disease. As a basis of their work, the Subgroup reviewed multiple strategies, including the *Triple Zero Campaign of ILEP*, the *ILEP Global Strategy*, and the *WHO Global Leprosy Strategy 2016–2020*, along with documents and developments in the field of neglected tropical diseases (NTDs) and disability. The developments in the various disability-related task groups of the *NNN Disease Management, Disability and Inclusion (DMDI) Working Group* were also considered. The Subgroup also examined the recent work done by the *Leprosy Research Initiative* (LRI) to draft an updated set of research priorities aligned with current developments in the field of leprosy. For this effort, the LRI completed an extensive exercise that involved an inquiry panel, focus group discussions, an e-survey, and a Delphi panel and included a wide range of stakeholders (e.g. persons affected by leprosy, organizations working in the field of leprosy, medical staff, policy makers, researchers etc.).

Goal of the disability subgroup

The goal of the research recommended by the Subgroup on Disability is to contribute to:

- Preventing disabilities among persons affected by leprosy.
- Minimizing the impact for people living with impairments due to leprosy by:
  - Ensuring that persons with permanent impairments due to leprosy or other NTDs can effectively manage their impairments and disabilities and have access to medical, rehabilitation, and social services when needed.
  - Improving social inclusion of all persons affected by leprosy through disability-inclusive development.

Research priorities

I. PREVENTING DISABILITIES AMONG PERSONS AFFECTED BY LEPROSY

- **Early Detection of Leprosy to Prevent Disability**
  - *Assessing the impact of case finding/contact tracing strategies on the prevalence of leprosy-related disabilities among new cases*
  - The impairment status of a leprosy patient at diagnosis is known to be the most important determinant for future impairment.[81] However, the extent to which different active case finding and contact tracing strategies contribute to a reduction of leprosy related disabilities is unknown.
    - *Key question*
      - What is the impact of case finding/contact tracing strategies on the prevalence of leprosy-related disabilities?
    - *Research to address the issue*
      - Operational research to assess the (cost-) effectiveness of case finding strategies
      - Mapping studies of leprosy patients and leprosy-related disabilities
- **Pathophysiology, Detection, and Management of Nerve Function Impairment and Reactions**
  - *Pathophysiology of reactions and nerve function impairment*
    Research is needed on the pathophysiological/immunological mechanisms of Type 1 and Type 2 reactions and nerve damage (as well as neuropathic pain) in leprosy, including the identification of factors associated with increased risk of reactions and nerve function impairment. Some of these factors are known, such as the type of leprosy and the time since completion of treatment.[82,83] However, a better and more specific understanding of mechanisms and risk factors is needed to improve management of reactions.[84–86] In addition, as neuropathic pain also importantly contributes to disability, early recognition and improved management of such pain is needed.
    - *Key questions*
      - What are the pathophysiological/immunological mechanisms associated with increased risk of reactions, nerve function impairment, and neuropathic pain?
      - What new and effective treatment options are available for the management of neuropathic pain?
    - *Research to address the issue*
      - Basic pathophysiological/immunological lab research to identify risk factors for reactions and nerve involvement
  - *Detection of nerve function impairment*
    Development and validation of diagnostic tools is needed to detect and measure nerve function impairment (including silent neuritis) and reactions. Detecting nerve damage as early as possible will greatly contribute to the prevention of disability. Nylon monofilaments (Semmes-Weinstein monofilaments) and voluntary muscle testing are current state-of-the-art tools that have been shown to correlate well with sophisticated neurophysiological measures.[87–93] Newer instruments have recently been evaluated.[94] Definitions for clinically relevant nerve function impairment are needed to determine meaningful change.

- *Key questions*
  - How can the identification of Type 1 and Type 2 reactions be improved?
  - Which simple, existing or new tools can provide the earliest detection of neurological signs of leprosy and/or measure nerve function impairment?
  - How can the use of these tools best be promoted and the capacity of health care staff to use them be ensured?
- *Research to address the issue*
  - Clinical research to test and compare new and existing tools to detect nerve function impairment
  - Implementation research to ensure the use of tools to detect nerve function impairment by different health care providers

○ *Management of reactions and nerve function impairment*

Efforts are needed to promote and facilitate the use of available treatment for reactions and nerve function impairment and to identify new treatment options. Given that reactions and neuropathy remain the leading cause of disability in leprosy, promoting and facilitating the use of available treatment (steroids) remain top priorities. Recent trials have established that a steroid regimen of 32 weeks to treat nerve damage does not give added benefit over a 20-week regimen.[95,96] A parallel trial established that steroid treatment of newly diagnosed leprosy patients with sub-clinical, small fibre neuropathy at the time of diagnosis does not reduce the risk of long-term clinical nerve damage. Alternative drug treatments for Type 1 and Type 2 reactions may improve prognosis and reduce the risks inherent in long-term steroid treatment. Research has shown that households affected by erythema nodosum leprosum (ENL) face significant economic burden and are at risk of being pushed further into poverty.[97] However, more research is needed to explore this area and identify solutions. Research on armadillos suggested that LepVax treatment might restore some early sensory axonal function: when used as post-exposure prophylaxis, it alleviated and delayed the neurologic disruptions caused by *M. leprae* infection.[98]

- *Key questions*
  - What efforts are needed to ensure that steroids are available and used properly and in a timely manner for the treatment of reactions?
  - What are alternative, effective treatment options for the management of reactions?
  - What are mechanisms of increased financial burden on leprosy patients and their families due to reactions, and what are possible solutions to address them?
  - What could the role of LepVax be in the prevention and treatment of nerve function impairment?
- *Research to address the issue*
  - A survey to assess 1) the (national) guidelines on steroid use and the steroid availability at national and peripheral levels and 2) the capacity of health workers to use them.
  - Qualitative research to examine patient and health care provider behaviour when treatment of reactions is needed.
  - A new Cochrane review of steroid and other drug trials for management of reactions.
  - An assessment on the benefits of alternatives to corticosteroids.

- Health economics research to determine the risks for an increased financial burden due to reactions.
- Qualitative research to determine solutions to prevent an increase of the financial burden.
- Clinical trials to learn more about the effects of LepVax.

II. MINIMIZING THE IMPACT OF LIVING WITH IMPAIRMENTS DUE TO LEPROSY*

- **Number of People with Disability due to Leprosy**
  - *Estimating the burden of disability due to leprosy and other NTDs or other diseases that share cross-cutting issues with leprosy*

    Efforts to improve disability prevention and management for persons affected by leprosy are hindered by the lack of data on the number of persons with disabilities in general as well as the number with disabilities related to leprosy or other NTDs. The disability grade at the time of diagnosis is usually the only disability factor that is recorded in leprosy control. The type of disability and the worsening of disability during and after treatment is usually not included in reports. A better understanding of the magnitude of the problem and the needs of the people living with impairments is required to properly address them through program planning, using baselines for monitoring outcome and impact of interventions as well as for advocacy and fundraising.
    - *Key question*
      - What is the burden of disability due to leprosy and other NTDs or other diseases that share cross-cutting issues with leprosy?
    - *Research to address the issue*
      - Cohort study to determine the quantity of the increase of disability during and after treatment.
      - Mapping studies of people with disabilities due to leprosy and other related diseases such as NTDs.
- **Prevention of Disability and Its Worsening (POD):**
  - *Research on the feasibility, effectiveness, and impact of POD strategies (including self-care, physiotherapy, occupational therapy, and combined approaches)*

    Limited evidence is available on the added value of self-care groups and family support for POD.[99,100] More evidence, however, is needed on various POD approaches in different settings and with other disabling diseases, especially regarding feasibility and effectiveness, including cost-effectiveness. The local context, gender roles, living conditions, existing barriers, and other factors for persons affected by leprosy all determine the feasibility of disability prevention strategies. Novel techniques used in wound care in general and in diabetic foot-care specifically can be beneficial for persons with ulcers due to leprosy. Development of a protocol for combined self-care of persons with leprosy-related and diabetic neuropathy would be important.
    - *Key questions*
      - What are the most feasible, (cost-) effective strategies for POD in various settings?

*Stigma and discrimination are addressed in the report from the Subgroup on Stigma.

  - What new, effective treatment options for ulcers are available?
  - Could alternative therapies contribute to increasing the quality of life for people with leprosy?
- ➢ *Research to address the issue*
  - Operational research; piloting of best practices for combined skin and wound care, including M-Health approaches and self-management.
    Qualitative research on the application of alternative practices to alleviate pain symptoms and increase quality of life.
  - Qualitative research on the perception and acceptability of POD strategies and ulcer treatment options.
    Health economics research to assess the cost-effectiveness of POD strategies.
  - Operational research piloting different wound treatment.

- **Inclusive Rehabilitation Services**
  - *Assessing the accessibility and effectiveness of physical rehabilitation services and the provision of assistive devices for persons with leprosy-related disabilities within a health system context*

    Rehabilitation services and the provision of assistive devices for persons with leprosy-related disabilities are often organized in parallel to the existing general health services. Evidence showing the (cost-) effectiveness and feasibility of integrated services would help to convince stakeholders of the benefit of providing persons affected by leprosy with the services they need within the existing health system.
    - ➢ *Key question*
      - How can rehabilitation services for persons affected by leprosy be organized most effectively within the existing health system?
    - ➢ *Research to address the issue*
      - Health systems research to determine the best way to integrate rehabilitation services for persons affected by leprosy.
        Health economics research to determine the cost-effectiveness of integrated services.
        Mapping of rehabilitation services.
- **Community-based Rehabilitation**
  - *Research on the effectiveness, feasibility, and social and economic impact of CBR programs*

    The evidence base related to the impact of CBR remains limited, both in terms of quantity and strength of design.[101]
    - ➢ *Key question*

      What are the characteristics of sustainable, effective, feasible, and impactful CBR programs to address the needs of persons affected by leprosy?
    - ➢ *Research to address the issue*

      Qualitative research to determine the needs of persons affected by leprosy.
      Operational research piloting different CBR approaches.

Baseline information needed

An inventory of the existing leprosy research structures (e.g., the research groups involved in studies on leprosy, disability, and related issues) would help to clarify the capacity needed to address the research priorities on leprosy-related disability. It would also help identify ways to address various research needs through integrated studies.

Access to certain baseline data would be very useful for the research agenda on disability. To help attain these data, the GPZL's Operational Excellence Working Group could include the following issues in an assessment of leprosy control programs:

- Post-multi-drug treatment surveillance.
- Availability of and accessibility to steroids; the use of thalidomide.
- The use of nerve function assessment tools.
- Geographic overlap with other NTDs.
- The accessibility to and the use of devices, such as prosthetics, orthoses, and auxiliary devices.
- Best practices to address POD and minimizing the impact of living with impairments due to leprosy.

Subgroup on Stigma

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Introduction

Compared with other leprosy-associated issues, the topic of stigma and discrimination has received little attention from the International Federation of Anti-Leprosy Associations (ILEP) members, the World Health Organization (WHO), and national programs. Yet, it is consistently the number one issue and challenge described by persons affected by leprosy in most areas of the world. Discrimination and attitudinal biases are often mentioned as the primary barrier to inclusion for persons with other disabilities and are a key topic in the United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD). Stigma is often the factor that turns an impairment into a disability and causes social exclusion. The mental health consequences of living with disabilities and the associated stigma and discrimination are increasingly an area of interest in the neglected tropical disease (NTD) field.

Stigma is highly relevant in the context of the Global Partnership for Zero Leprosy (GPZL), as zero discrimination is a declared goal. Moreover, stigma is a barrier to zero leprosy due to its effect on leprosy prevention, treatment, case management, and prevention of disabilities.

To achieve zero leprosy and to have a meaningful impact on stigma and discrimination, future research should address major challenges at the national and international levels. The priorities for this research should fit with or optimally integrate with those of the *ILEP's Triple Zero Campaign, the WHO Global Leprosy Strategy 2016–2020*, and the aspirations of the GPZL and the Neglected Tropical Disease NGO Network (NNN). The GPZL Research Agenda Working Group's Subgroup on Stigma examined these reports to make an inventory of needs related to leprosy stigma and discrimination. The Subgroup also drew on the report of a global research priority review conducted by the Leprosy Research Initiative (LRI) in 2018 and considered the work of the various task groups of the NNN's *Disease Management, Disability and Inclusion (DMDI) Working Group*, which has a Task Group on Mental Wellbeing and Stigma that works on related issues.

Based on this review, the following were identified as important needs and challenges to be addressed in the leprosy field related to stigma:

- Documenting (and mapping) the level of stigma in communities and health services.
- Addressing community stigma as a barrier to zero transmission, e.g., as a barrier to:
    - Treatment seeking, early diagnosis, and disclosure.
    - Treatment adherence.
    - Prevention of disabilities.
- Addressing negative attitudes and behaviours against persons affected by leprosy as barriers to inclusion in the community, with special reference to women and girls, and in access to health services.
- Documenting the impact of stigma and discrimination on the mental health of persons affected by leprosy (and other NTDs) and identifying and evaluating ways to prevent and mitigate this impact.
- Mitigating the effects of stigma and discrimination among persons affected by leprosy (especially internalized stigma) and among their family members.
- Validating stigma and mental health assessment tools from the *NTD Disability and Morbidity Toolkit* in more leprosy-endemic countries.
- Applying the health-related stigma concept:[102] pioneering joint stigma reduction interventions for persons with NTDs and/or disability groups.

GOALS OF THE RESEARCH PRIORITIZED BY THE STIGMA SUBGROUP

The goals of the research recommended by the Stigma Subgroup are to:

- Reduce stigma as a barrier to treatment seeking, case detection, diagnosis, treatment adherence, self-care, and rehabilitation.
- Mitigate the impact of stigma and discrimination on mental wellbeing and all aspects of social participation among persons affected by leprosy.
- Increase active participation of persons affected by leprosy in leprosy services.
- Improve social inclusion of all persons affected by leprosy through disability-inclusive development.

Research priorities, current knowledge, and key questions

In 2018 the Leprosy Research Initiative (LRI), a combined venture of several ILEP partners and other NGOs supporting work in the field of leprosy, conducted an extensive review of leprosy research priorities that had been defined in 2013. Their efforts involved an inquiry panel, focus group discussions, a global e-survey, and a Delphi panel. The purpose was to draft an updated set of research priorities aligned with the current developments and challenges in the field of leprosy. The effort involved a wide range of stakeholders, including persons affected by leprosy, representatives from organizations working in the field of leprosy, medical staff, policy makers, and researchers. The main questions identified were 1) which leprosy-related research topics are considered to be the most important and (2) how are they ranked according to priority by the stakeholders?

The LRI results were grouped according to the three zeros in the ILEP Strategy: Zero Transmission, Zero Disability, and Zero Discrimination. The Stigma Subgroup reviewed these results and did not identify any major missing topics. The Subgroup then took the top eight research priorities for Zero Discrimination from the LRI study and grouped them into four major priority themes that could be studied together in large, coordinated multi-country projects. Changes were made to the wording and emphasis of several of the topics. The four priority themes are listed below, together with key research questions for each.

1. INTERVENTIONS TO REDUCE STIGMA AS A BARRIER TO ZERO LEPROSY

Several stigma interventions such as contact intervention, peer counseling, and socioeconomic development have been tested.[103,104] Also, the effectiveness of using "champions" and involving persons affected by leprosy in stigma reduction have been demonstrated.[105,106] The positive effects of a sustained social marketing campaign in Sri Lanka have been shown, but results in terms of stigma reduction were never measured.[107,108] The effects of a multi-media modified leprosy elimination campaign in India were measured but never published in a peer-reviewed journal.* The interventions described in these studies should be tested in additional settings and cultures, and ways to scale up such interventions should be investigated through operational research. A few surveys have been done in recent years to document the types, prevalence, and severity of stigma in leprosy-endemic countries.[103,109–114] However, such studies are needed in all leprosy-endemic countries and in countries and areas where leprosy-related stigma is known to be a problem. Baseline data are needed for monitoring the effect of interventions. It is important that such baseline and stigma monitoring studies use standard tools. The Participation Scale[115] and the 5-Question Stigma Indicators are recommended in the *Monitoring and Evaluation Guide* that accompanies the WHO Global Leprosy Strategy 2016–2020. These and a number of stigma-assessment tools have been validated cross culturally,[116–123] but additional validation studies are needed—especially validation of the short 5-Question Stigma Indicators in the Monitoring and Evaluation Guide and the SARI Stigma Scale.[121] Stigma levels are known to vary significantly, even at local levels, which has direct repercussions for targeting interventions.[124] Stigma baseline studies should also address health services-related stigma, which is still a common, but rarely studied

* http://www.comminit.com/bbcmediaaction/content/impact-data-bbc-world-service-trust-leprosy-project

phenomenon in many leprosy-endemic countries. An instrument for this purpose was recently developed and validated to assess attitudes of health care providers towards persons affected by leprosy in southern India.[125]

Guidelines for participation in research studies have been formally adopted by WHO,[126] but the implementation often has been rudimentary. It is essential for research projects to include persons affected by leprosy among the investigators, where possible, and on steering committees. Similarly, these persons should be involved in decisions that may impact them and in the implementation of leprosy services. Studies examining how this can best be done in various situations and the effects of this involvement are urgently needed.

Research into the effectiveness of stigma reduction interventions should include feasibility, acceptability, and the impact of community involvement, skills building, and empowerment and participation of persons affected by leprosy. Such studies should also include cultural validation of tools to determine the level and type of stigma in communities and health services and among persons affected by leprosy and to monitor and evaluate the effect of the interventions.

- *Key questions*
  - What is the effectiveness of various stigma-reduction interventions in different settings, and which interventions can be used on a large scale?
  - What is the prevalence of different types of stigma and their geographic distribution in leprosy-endemic areas?
  - How often and in what ways do stigma and discrimination against persons affected by leprosy occur in the health services? How do stigma experiences develop over time?
  - What are the effects of the participation of persons affected by leprosy in research and health services? What are best practice models to implement this?

2. UNDERSTANDING PERCEPTIONS OF LEPROSY AND THE REASONS BEHIND THEM

Patient and community knowledge, beliefs, fears, and practices play major roles in the perception of leprosy,[116,127,128] in the perceived need for early diagnosis and treatment, and in the prevention and management of disabilities.[129–134] These factors need to be well understood so that interventions targeted to specific beliefs and attitudes can be used instead of generic messages.

Research is needed on the perceptions of the disease and explanatory models (personal conceptualization of the cause, course, and consequences of leprosy). Research into experiences with the disease and its consequences is also needed as a basis for developing optimal communication and behaviour change approaches. A standard toolkit using mixed methods should be cross-validated and adopted for studying the perceptions and explanatory models regarding leprosy.

- *Key question*
  - What do patients and community members know, believe, fear, and do concerning leprosy that would be relevant for developing tools for health education and behaviour change regarding stigma, disclosure, treatment seeking, treatment adherence, and prevention of disabilities?

3. MENTAL WELLBEING OF PERSONS AFFECTED BY LEPROSY

The negative impact of having leprosy and leprosy-related visible and other disabilities and especially of experiencing stigma and discrimination on the mental wellbeing of persons affected by leprosy has long been recognized.[135–139] However, population-based studies of mental distress, anxiety, and depression among this population and their family members are scarce. There is evidence that various forms of counseling can help greatly to mitigate the mental health impact of leprosy.[140–142] Studies are needed to examine the association between mental distress, anxiety, and depression and various health and programmatic outcomes, such as case detection, treatment adherence, self-care, and rehabilitation.

Studies are also needed on mental wellbeing of persons affected by leprosy and on the associations between mental health, health care-seeking behaviour, and accessibility of services (e.g., diagnostic or treatment delay, treatment compliance, participation in self-care groups). Such studies should be part of or directly linked to intervention studies to prevent a negative impact on and/or to improve mental wellbeing among those suffering from anxiety, depression, or other mental health conditions.

- *Key questions*
  - What is the prevalence of mental distress, anxiety, and depression among persons affected by leprosy and their family members?
  - What is the impact of mental distress, anxiety, and depression on health care and programmatic outcomes, such as case detection, treatment adherence, self-care and rehabilitation?
  - How can a negative impact on mental wellbeing be mitigated once it has occurred?

4. UN PRINCIPLES AND GUIDELINES FOR THE ELIMINATION OF DISCRIMINATION

The UN Human Rights Council adopted *Principles and Guidelines for the Elimination of Discrimination against Persons Affected by Leprosy and Their Family Members* in 2010. However, very few studies have addressed the implementation of this important document. Studies are needed to assess the (local) implementation and impact of these principles and guidelines, and interventions should be developed to improve this practice.

- *Key questions*
  - What is the status of the implementation of the UN *Principles and Guidelines for the Elimination of Discrimination Against Persons Affected by Leprosy and Their Family Members?*
  - What is the impact of these principles and guidelines?

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