Global Partnership for Zero Leprosy

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Research Agenda Working Group
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) (1) or examining the reasons behind a certain operational problem such as why some people do not complete treatment as prescribed (2). 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 (3,4).

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 (5) 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 (6-8), 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 (9,10) and Chagas disease surveillance (11).

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 (12):

- 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 (13). 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 (14,15). 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 (16,17). 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[1] 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 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

[1] Descriptions provided by Dr. Narayan Dharmshaktu

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.

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