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Symposium Report: Developing Strategies to Block the Transmission of Leprosy

DEBORAH MENSAH-AWERE*, MARTIN W. BRATSCHI**,***, PETER STEINMANN**,***, JESSICA K. FAIRLEY**** & THOMAS P. GILLIS*
**effect:hope, Markham, Canada*
***Swiss Tropical and Public Health Institute, Basel, Switzerland*
****University of Basel, Basel, Switzerland*
*****Emory School of Medicine, Atlanta, GA, USA*

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Context

Remarkable progress has been made in the treatment and management of leprosy over the last 60 years. Current control strategies rest on early detection of disease and appropriate multidrug therapy (MDT) to cure the patient and halt transmission within the community. These strategies are built on a solid understanding of therapeutics for mycobacterial diseases but suffer from an incomplete understanding of transmission of *Mycobacterium leprae* and a shortage of tools that can truly diagnose leprosy at an early stage. Accordingly, transmission continues in many areas of the world.

To clarify the current state of our knowledge of *M. leprae* transmission and to establish a research agenda to address gaps in our understanding of transmission, an international symposium entitled "*Developing Strategies to Block the Transmission of Leprosy*" was organized and sponsored by effect:hope (The Leprosy Mission Canada) and held on May 29–30, 2014. The meeting was hosted by the National School of Tropical Medicine, Baylor College of Medicine in Houston, Texas.

GOALS AND OBJECTIVES OF SYMPOSIUM

The goal of the symposium was to establish a research agenda, aimed at bridging the gaps in our understanding of *M. leprae* transmission, which will complement a global research strategy focused on eliminating leprosy.

Correspondence to: Thomas P. Gillis, Effect:hope, Markham, Ontario, Canada (e-mail: tom.gillis48@gmail.com; tgillis@effecthope.org)

 0305-7518/15/064053+09 $1.00

The objectives were:

1. To identify the key gaps in our understanding of *M. leprae* transmission
2. To organise gaps into priority areas
3. To propose specific areas of investigation to address these priority areas

SYMPOSIUM CONTENT

Keynote speakers

"*The NTDs: Prospects for Elimination."* Peter Hotez, National School of Tropical Medicine, USA.

Peter Hotez presented an overview of the global burden of Neglected Tropical Diseases (NTDs) and their impact on health and on exacerbating the effects of poverty. Dr. Hotez discussed the current strategies in place for NTD control and elimination such as Mass Drug Administration and the impact it has had on reducing NTD prevalence. He highlighted the issues surrounding Disability-Adjusted Life Years (DALY) and how leprosy's very low DALY may not accurately reflect its sustained effect on people affected by leprosy. Dr. Hotez suggested that the London Declaration[1] may be overly simplistic when considering leprosy with regard to its road map and he supports focusing efforts on interrupting transmission for eventual elimination of leprosy.

"Tracing Our Path to Today." Paul Fine, London School of Hygiene and Tropical Medicine, UK.

Paul Fine described the history of leprosy as a disease including its disappearance from Northern Europe and the first attempts to estimate the global burden of the disease. Prof. Fine also shared current data on leprosy prevalence citing India, Brazil and Indonesia as the countries that account for 80% of new cases as of 2012. Prof. Fine discussed some of the possible theories related to *M. leprae* transmission and the reasons for the decline in leprosy prevalence globally. He also shared some of the issues related to semantics facing those working in the leprosy field and the impact this has on addressing *M. leprae* transmission.

"Systematic literature review on current knowledge regarding the transmission of leprosy (Hansen's disease)." Martin Bratschi, Swiss Tropical and Public Health Institute, Switzerland.

Martin Bratschi presented the findings from the systematic review of the peer-reviewed literature pertaining to *M. leprae* transmission which was carried out to assess the current state of knowledge on this topic. Dr. Bratschi showed that the systematic literature review identified a total of 79 relevant articles providing solid evidence for *M. leprae* transmission among contacts and for zoonotic leprosy in the Southern States of the USA. He also reported that based on the extant evidence, skin-to-skin contact, aerosols/droplets and shedding of bacteria into the environment and subsequent infection, all remain possible options and there is no study which has unequivocally demonstrated the mechanisms by which *M. leprae* bacteria are transmitted. The full literature review entitled "Current knowledge on *Mycobacterium leprae* transmission: a systematic literature review" is published concurrently with this article.[2]

"Modeling Leprosy: How mathematical models help us understand transmission and the effect of interventions." Jan Hendrik Richardus, Netherlands.

Jan Hendrik Richardus stated that the primary purposes of current leprosy models are to predict the course of leprosy incidence and to analyse the impact of various intervention strategies. He gave an overview of the Lechat, SIMLEP and SIMCOLEP mathematical models used for leprosy. He also highlighted some of the results from current leprosy modeling efforts including the cost-effectiveness of single-dose rifampin chemoprophylaxis and the impact of early diagnosis and treatment.

ENDEMIC COUNTRIES PRESENTATIONS

Representatives from five countries discussed the current trends in *M. leprae* transmission and control in their respective countries.

Brazil (Rosa Castillia Soares, Ministry of Health, Sao Paulo, Brazil)
India (Sunil Anand, TLMI India, Delhi, India)
Ethiopia (Abraham Aseffa, AHRI/ALERT, Addis Ababa, Ethiopia)
Bangladesh (Shaikh Hossain, ICDDR,B, Bangladesh)
Philippines (Marivic Balagon, LWM Center for TB & Leprosy Research, Cebu, Philippines)

The general themes were:

1. Leprosy control programmes have become decentralised and integrated into general health systems
2. Reduced numbers of cases were reported in the early 2000's
3. A high proportion of MB cases remain in Ethiopia and the Philippines
4. All five countries noted stable transmission in children
5. The rate of grade 2 disabilities overall has shown no significant change
6. There is decreasing expertise in case finding
7. High endemic pockets remain in most countries and appear to be related to lack of access to care, and poverty

BREAKOUT SESSIONS

Breakout sessions were held to discuss the following key topics related to *M. leprae* transmission: reservoir, parasite and host. Each breakout session began with a panel of experts speaking on key topics related to the session. Discussion groups were then formed around specific sub-topics and a rapporteur for each group was selected. Dr. Edith Bahmanyar of the Novartis Foundation then facilitated plenary discussions around the key findings presented by each rapporteur. The goal of the sessions was to identify and define the gaps in knowledge and needs within the key topic areas that would lead to an improved understanding of *M. leprae* transmission and provide new tools and strategies to block *M. leprae* transmission.

RESERVOIR

Expert Panel: Active cases (*Paul Saunderson),* Occult human reservoir (*Cairns Smith),* Animal reservoir (*Richard Truman)* and Environmental reservoir *(Ravindra Turankar)*

Sub-topics: 1. Active cases/occult human reservoirs (Saunderson/Smith)
2. Animal/Environmental reservoirs (Truman/Turankar)

PARASITE

Expert Panel: *M. leprae* genome *(Pushpendra Singh); M. lepromatosis (Xiang-Yang Han)*

Sub-topics: 1. Pathogen characteristics (Singh/Han)
2. Genotyping (Singh/Han)

HOST

Expert Panel: Genetics *(Erwin Schurr),* Immunology *(Tom Hawn)*, Vaccines (*Steve Reed),* Diagnostics *(Annemiek Geluk)*, Portal of exit/entry of *M. leprae (Eric Brenner)*

Sub-topics: 1. Genetics, Immunology (Shurr, Hawn)
2. Vaccines/Diagnostics (Reed, Geluk)
3. Portals of exit-entry of *M. leprae* (Brenner)

PARTNERS

Partners from an array of government and nongovernment research and research funding organizations presented their current research priorities and funding commitments as well as successful projects related to leprosy research and control. The partners represented were; National Institute of Allergy and Infectious Disease (NIAID, USA), Pan-American Health Organization (PAHO), The Leprosy Research Initiative (LRI) and Novartis Foundation (Switzerland).

GAPS IN OUR UNDERSTANDING OF *M. leprae* TRANSMISSION AND IDENTIFIED NEEDS

Based on the breakout sessions and the literature review on *M. leprae* transmission (see Keynote Speakers and 2) the following gaps in our understanding of *M. leprae* transmission and needs to fill these gaps were identified.

1. Human-to-human transmission of M. leprae

Studies have clearly shown that close proximity to leprosy patients increases the risk of contracting the disease. However, other members of endemic communities who are potentially asymptomatically infected carriers may also contribute to the transmission of *M. leprae*.

Gap 1: Human Reservoirs

We do not understand the full extent of the human reservoir of *M. leprae*; specifically the roles of undiagnosed patients, patient contacts and other members of endemic communities in perpetuating *M. leprae* transmission are unknown.

Needs to fill gap 1:

a) Discovery of biomarkers for: all clinical cases of leprosy, subclinical infections and asymptomatic carriers.
b) Develop platforms for field-friendly diagnostic tests.

2. Route of entry/exit of M. leprae *in humans*

A series of case reports appear to show that injection of *M. leprae* at the site of skin trauma (e.g. by tattoo or accident) can lead to localised as well as disseminated manifestations of leprosy. For most leprosy cases, there is however no clear sign that entry of the pathogen occurred through skin trauma, and the available evidence points more towards the involvement of the upper respiratory tract.

Gap 2: Entry and exit route

We do not understand the route of entry and exit of *M. leprae* in humans.

Needs to fill gap 2:

a) Assess the role of colonization and route of entry (e.g. nasal-oral mucosa, skin and gastrointestinal tract) of *M. leprae* into the human host.
b) Investigate potential roles of co-infections on the entry/exit of *M. leprae* from the human host (e.g. amoebiasis).
c) Study the stages of pathogenicity of *M. leprae* to understand the migration (port of entry to the site of initial lesion to point of exit) of *M. leprae* inside the human host.

3. Role of animals, the environment or insects in the transmission of M. leprae

In the Southern USA, leprosy has been shown to exist as a zoonosis, based on *M. leprae* strain identification, indicating that there is transmission of *M. leprae* between armadillos and humans. However, in other parts of the world, the role of animals as reservoirs or vectors in *M. leprae* transmission remains unclear. It is also unknown how the recently described existence of *M. leprae* in the environment contributes to the spread of the disease.

Gap 3a: Roles of animals or vectors

We do not understand the role animals (armadillos outside of the southern USA and other animals) or vectors (e.g. insects or amoeba) play in the transmission of *M. leprae*.

Needs to fill gap 3a:

a) Investigate how the distribution of *M. leprae* infection in armadillos is spreading in the Americas and how this affects the occurrence of human leprosy.
b) Investigate the genetic diversity of *M. leprae* in armadillos to better understand zoonotic and cross-species transmission.
c) Systematically investigate the possible role of animals (e.g. by serological surveillance) other than armadillos in *M. leprae* transmission in different endemic areas worldwide.
d) Investigate the biological relationship between *M. leprae* and amoeba.

Gap 3b: Role of environmental sources

We do not understand the source and relevance for transmission of *M. leprae* in the environment (e.g. in soil or water).

Needs to fill gap 3b:

a) Systematically investigate the presence of *M. leprae* in the environment in different endemic settings.
b) Use genotyping to characterize environmental *M. leprae* to determine how it relates to genotypes found in human infections in the same area.
c) Demonstrate viability and role in transmission of environmental *M. leprae*.

4. Role of Poverty in Transmission

It has been demonstrated that the socio-economic status of an individual appears to affect the risk of contracting leprosy. However, the driver of this correlation is not clear. Whilst there was not a breakout session dedicated to the topic of poverty and *M. leprae* transmission, it was a reoccurring theme discussed in several sessions of the symposium.

Gap 4: Role of poverty

We do not understand how poverty acts as a risk factor for *M. leprae* transmission.

Needs to fill gap 4:

a) Investigate the role of poverty-related factors, such as nutrition, hygiene and crowding on *M. leprae* transmission.

5. Role of Host-Parasite Interaction in Transmission

Despite recent advances in our understanding of *M. leprae* genetic diversity and the cellular immune response of leprosy patients, there are considerable gaps in our understanding of the interaction between *M. leprae* and the human host.

Gap 5: Host-pathogen interaction

We do not sufficiently understand the impact of the interaction between *M. leprae* and the human host on *M. leprae* transmission.

Needs to fill gap 5:

a) Investigate relationship between *M. leprae* genetic characteristics and virulence, growth kinetics, drug resistance, tropism for nerves and the tendency to cause reactions.
b) Understand the role of host genetic risk factors in susceptibility and resistance to *M. leprae* infection, clinical progression of leprosy and reactions.
c) Understand how the immune response affects the manifestation of the *M. leprae* infection (including establishing of infection, progression of disease, nasal carriage and reactions) and eventually transmission of *M. leprae*.
d) Increase understanding of similarities/differences between *M. leprae* and *M. lepromatosis*.

6. Transmission Networks

Recent evidence has shown that depending on the endemic setting, there are various types of *M. leprae* transmission networks.

Gap 6: Transmission networks

We do not understand the diversity and relevance of the various *M. leprae* transmission networks.

Needs to fill gap 6:

a) Increase collection of genome sequenced *M. leprae* strains with isolates from various origins (e.g. worldwide, PB patients) which are complemented with detailed epidemiological data.
b) Investigate genetic diversity of *M. leprae* from different sources (patients, nasal carriers, zoonotic and environmental) and various settings (e.g. high and low endemic) to study the transmission ecology at the community level.
c) Develop molecular epidemiology tools which are customised to a region to allow for fine typing from primary samples and investigation of transmission links.

7. Improving Epidemiology Data

Despite the elimination of leprosy in many countries, hot-spots of transmission with more than 1 case per 10 000 inhabitants and active transmission remain.

Gap 7: Enhanced epidemiological data

We do not fully understand the geographic distribution of leprosy, especially at a sub-national level.

Needs to fill gap 7:

a) Improve the quality of national epidemiological surveillance data including sub-national geographic variation and prevalence data based on local population densities.
b) Implement contact tracing and active case finding strategies to identify transmission hot-spots.
c) Digitalize leprosy surveillance to improve data access and timely identification of areas with high case numbers.

Conclusion and way forward

The *Developing Strategies to Block the Transmission of Leprosy* symposium brought together a broad spectrum of expertise in the field of infectious diseases (Table 1), in order to identify the key gaps that exist in our knowledge of *M. leprae* transmission as well as associated needs to close those gaps. Key overarching research principles that will help to improve our

understanding of *M. leprae* transmission were further identified from both the literature review on *M. leprae* transmission and during discussions at the symposium. These research principles are related to study design, the type of data to be collected in the course of studies and the capacity to conduct research in endemic areas. Specifically, it was concluded, that it is of great importance that long-term studies are performed and aspects of *M. leprae* transmission are monitored over several years. Only such longitudinal studies will have the potential to demonstrate how any novel tool, intervention or control measures can potentially affect the transmission of *M. leprae*. Furthermore, the degree of detail and types of data collected in different studies vary considerably and make comparison between findings from different studies difficult. The leprosy research and control communities should strive to define a minimal and standardised set of high quality clinical and demographic data that should be collected about participants in all studies. Researchers should further consider establishing a biobank of samples relevant for *M. leprae* transmission research. Finally, for the long-term research efforts required to eventually block the transmission of *M. leprae* it is of utmost importance to continue to support, expand and maintain research infrastructure and capacity in leprosy endemic areas. Likewise, government entities involved in leprosy control should continue to receive technical and other support so as to collect high quality epidemiological data about trends in the number of leprosy cases detected and how interventions are affecting the spread of the disease.

The key gaps and needs identified during this symposium and reported here are essential in shaping a global research agenda designed to block transmission of *M. leprae* and move toward eliminating the disease. These research priorities will form the foundation of the Transmission Research Initiative (TRI) which will be launched in October 2015 by effect:hope and partners, with a goal to support research aimed at closing gaps in our understanding of *M. leprae* transmission.

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Table 1. List of Participants affiliations

Participant	Affiliation
Erwin Schurr	McGill University, Montreal, Canada
Thomas Hawn	University of Washington, Seattle, WA, USA
Steve Reed	Infectious Disease Research Institute, Seattle, WA, USA
Annemiek Geluk	Leiden University Medical Center, Leiden, The Netherlands
Pushpendrah Singh	Ecole Polytechnique Federale de Laisanne (EPFL), Lausanne, Switzerland
Gerd Pluschke	Swiss Tropical and Public Health Institute, Basel, Switzerland
W. Cairns Smith	University of Aberdeen, Aberdeen, Scotland
Paul Fine	London School of Hygiene and Tropical Medicine, London, UK
Peter Hotez	National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, USA
Jan Hendrik Richardus	Erasmus MC, University Medical Center, Rotterdam, The Netherlands
Eric Brenner	University of South Carolina, Columbia, SC, USA
Masanori Matsuoka	Leprosy Research Center, National Institute of Infectious Diseases, Tokyo, Japan
Ravindra Turanka	The Leprosy Mission India and Stanley Browne Laboratory, Delhi, India
Marivic Balagon	Leonard Wood Memorial Center for TB and Leprosy Research, Cebu, The Philippines
Edith Bahmanyar	Novartis Foundation, Basel, Switzerland
Rosa Castalia Soares	Leprosy Program, Ministry of Health, Sao Paulo, Brazil
Sunil Anand	The Leprosy Mission Trust India, Delhi, India
Ruth Butlin	Nilphamari, Bangladesh
Abraham Aseffa	Armauer Hansen Research Institute and ALERT, Addis Ababa, Ethiopia
Shaikh Shahed Hossain	International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
Jessica Fairley	Emory School of Medicine, Atlanta, GA, USA
Martin Bratschi	Swiss Tropical and Public Health Institute, Basel, Switzerland
Anna Wickenden	effect:hope (The Leprosy Mission Canada), Markham, Canada
Peter Derrick	effect:hope (The Leprosy Mission Canada), Markham, Canada
Tom Gillis	effect:hope (The Leprosy Mission Canada), Markham, Canada
Kenneth Wong	effect:hope (The Leprosy Mission Canada), Markham, Canada
Paul Saunderson	American Leprosy Mission, Greenville, SC, USA
Christa Kasang	German Leprosy and TB Relief Association, Wurzburg, Germany
Wim van Brakel	Netherlands Leprosy Relief, Amsterdam, The Netherlands
Tamara Prinsenberg	Netherlands Leprosy Relief, Amsterdam, The Netherlands
Ken Gibson	The Leprosy Mission Ireland, Dublin, Ireland
Xiang-Yang Han	MD Anderson, Houston, TX, USA
Bide Landry	WHO-AFRO, Brazzaville, Republic of Congo
David Scollard	National Hansen's Disease Programs, Baton Rouge, LA, USA
Rahul Sharma	National Hansen's Disease Programs, Baton Rouge, LA, USA
Richard Truman	National Hansen's Disease Programs, Baton Rouge, LA, USA
Christine Sizemore	NIAID, National Institutes of Health, Bethesda, MD, USA
Terry Williams	Houston Department of Health and Human Services, Houston TX, USA
Steven Mays	Houston Department of Health and Human Services, Houston TX, USA