Innovative tools and approaches to end the transmission of Mycobacterium leprae

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Leprosy control has seen little innovation and only limited progress in the past decade. However, research on the disease has increased and important innovations are underway. Here, we comment on efforts to develop tools and approaches to detect leprosy and to stop the transmission of Mycobacterium leprae, the causative bacillus of the disease. The tracing and screening of contacts of known patients with leprosy promises to strengthen early diagnosis, while preventive chemotherapy will reduce the risk of contacts developing the disease by 50–60% within 2 years of administration. Until now, diagnosis has been mainly based on the presence of signs and symptoms, but efforts are underway to develop inexpensive, reliable, point-of-care tests to diagnose infection. Development of a leprosy-specific vaccine that boosts long-lasting T-cell responses is also a research objective. As for launching a programme to interrupt transmission, two interlinked tools—epidemiological modelling and the concept of an investment case—are being developed to explore the feasibility and costs of such a programme and its overall effect on individuals and society. We believe that sustained innovation is needed and that only a combination of tools and approaches holds promise to end M leprae transmission.

Introduction

According to a WHO report published in 2006, “leprosy, one of the most ancient, feared and disabling diseases of humankind, is on the verge of defeat”. However, the causative bacillus of the disease, Mycobacterium leprae, is still being transmitted to human beings in at least 122 countries, where more than 200000 new cases of leprosy, including around 25000 infections in children, are being discovered every year. Several factors are responsible for continuing transmission of the infection. Delayed diagnosis, which allows transmission to contacts and progression of the disease, leading to nerve function impairment, is the most common factor for continued transmission. Reasons for delayed diagnosis include disregard of early symptoms, difficulties in the differential diagnosis of leprosy, and fear of stigma from community members. As a result of the fear of stigma, many people with suspected signs or symptoms of leprosy do not seek health care. Misdiagnosis by health professionals also delays diagnosis and perpetuates transmission of the infection. Compounding these issues is the fact that most patients with leprosy live in poor and marginalised communities, where experienced staff and facilities required to establish a diagnosis are often absent. Once diagnosed and classified as paucibacillary or multibacillary leprosy, patients can be managed efficiently with multi-drug therapy.

Understanding the difficulties in diagnosing leprosy and stopping M leprae transmission is our incomplete understanding of the route and mechanism whereby M leprae enters the human body. Various routes of entry have been proposed, including human-to-human transmission via prolonged direct skin contact or through aerosols, direct inoculation through trauma, or direct or insect-mediated infection from zoonotic or environmental reservoirs. The most common route of transmission is thought to be direct contact or aerosols in the context of prolonged exposure to an untreated individual with M leprae infection, especially a patient with multibacillary leprosy and multiple lesions who is closely related to the contact. There is also evidence of zoonotic M leprae reservoirs, most notably the nine-banded armadillo (Dasyus novemcinctus) in southern states of the USA, but they are probably of negligible relevance for the global epidemiology of the disease. Of note, a high proportion of newly detected patients with leprosy in endemic areas are unable to identify the source of their infection. This phenomenon has been explained by the long incubation period of the disease and also by indirect transmission, such as from water or soil. Host factors, including genetic predisposition and immune and nutritional status, also appear to be important risk factors for M leprae infection. Improved socioeconomic conditions is also debated as a cause of the negative association between leprosy incidence and gross domestic product in several countries. However, the causal relationship between the socioeconomic development of a country and the risk to an individual of developing leprosy is much less clear. The scarcity of basic research tools is hampering attempts to improve the understanding of M leprae transmission: there is no way of growing M leprae in culture media, easily handled animal models of leprosy are unavailable, and the incubation period of M leprae is long.

In 1991, WHO passed a resolution to eliminate leprosy as a public health problem by 2000, defining elimination as a global prevalence of less than one patient with leprosy per 10000 population. Today, of the 122 countries in which leprosy is still endemic, 120 have reached the WHO elimination goal, not least due to a shortening of the standard treatment duration which resulted in a sharp drop in the number of people on treatment. A further reduction of the standard treatment duration is currently discussed. In 2012, WHO set a goal for global elimination of leprosy by 2020 in the frame of its roadmap “accelerating work to overcome the global impact of neglected tropical diseases”.

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The transmission. This Personal View summarises recent possibilities for studying, are needed to develop M. leprae and the risk factors for infection, as well as improved prevention.

Although interruption of transmission is part of the vision driving this new strategy, the strategy does not have a strong agenda for acceleration of leprosy diagnosis and prevention.

Improved understanding of M. leprae transmission and the risk factors for infection, as well as improved possibilities for studying M. leprae, are needed to develop more effective tools and interventions to interrupt transmission. This Personal View summarises recent work to develop new strategies and tools that we consider to be crucial for halting the transmission of M. leprae. These strategies and tools include targeted screening with diagnostic tools to identify patients with leprosy; innovative strategies for prevention of the disease, such as administration of chemoprophylaxis or immunoprophylaxis to individuals at risk of infection; and transmission models and investment cases for elucidation of new pathways to interrupt M. leprae transmission.

Identifying people infected with M. leprae and reducing the risk of transmission to contacts

Active case finding involves reaching out to contacts of index patients and screening them for signs of leprosy. Active case finding contributes to achieving early diagnosis and is thus an effective way to reduce the risk of disability in patients with leprosy and to curb the transmission of M. leprae. The risk of a contact of an index patient developing leprosy is related, among other factors, to the duration and closeness of the contact, consanguinity with the index patient, and the type of leprosy of the index patient. Screening should be confined to people whose contact with the index patient lasted for many hours per week over a period of several months. Contact tracing might be restricted to household members or include neighbours or social contacts of the index patient, depending on the resources available, local epidemiological factors, and the degree of stigma in the community. Contact tracing should be done as soon as possible after confirmation of leprosy in an index patient and after the first month of multidrug therapy. Contact tracing is ideally done by local staff who can readily identify and approach the contacts, examine them, and refer those suspected of being infected for confirmatory diagnosis. Alternatively, the contacts of all patients diagnosed in a certain period can be traced in the course of a campaign or special drive. This retrospective active case finding has previously been used for tuberculosis control in Cambodia, where it was found to increase case notification among contacts.

With regard to post-exposure chemotherapy, several anti-leprosy drugs given in different combinations and regimens have been tested in clinical trials for their ability to reduce the risk of contacts developing the disease. The most robust evidence to date to show the protective potential of post-exposure chemoprophylaxis in the contacts of index patients came from a cluster randomised, double-blind, placebo-controlled trial in Bangladesh. In that trial, a single dose of rifampicin given to contacts of patients with leprosy reduced the incidence of leprosy among the contacts by 57% (95% CI 33–72) in the first 2 years of the study. The protective effect differed between contact cohorts but persisted throughout the 6 year follow-up of the study.

The presumed risk that rifampicin prophylaxis given to patients with leprosy might induce or amplify tuberculosis resistance to rifampicin has been examined, found to be negligible, and therefore outweighed by the protective benefits of the drug. BCG vaccination at birth or later has been shown to provide a certain degree of protection against leprosy, adding to the protective effect of single-dose rifampicin.

The study in Bangladesh showed that single-dose rifampicin given to contacts who had received BCG vaccination during infancy reduced the risk of leprosy among the contacts by 80% (95% CI 50–92).

Evidence for the effectiveness of contact tracing followed by chemoprophylaxis in reducing the incidence of new case detection and grade 2 disability prompted the establishment of a Leprosy Post-Exposure Prophylaxis (LPEP) programme designed to study the effectiveness and feasibility of active contact tracing combined with single-dose rifampicin administration in various country settings with different leprosy programmes. The LPEP programme is currently operating in eight countries (Brazil, Cambodia, India, Indonesia, Myanmar, Nepal, Sri Lanka, Tanzania). Research groups in Brazil and Bangladesh are assessing the effectiveness of (re-)vaccinating contacts with BCG in addition to single-dose rifampicin administration and the benefits of a test to detect infected individuals among contacts is also under investigation. However, case finding, whether active or passive, can only identify a certain fraction of all patients with leprosy. Hence there is a need for integration of contact tracing and post-exposure prophylaxis interventions into national leprosy programmes capable of implementing these interventions, as well as reliable passive case detection and robust surveillance systems, including accurate recording, timely reporting, and regular monitoring.
Vaccines

Chemoprophylaxis for contacts of patients with leprosy has been partly successful in the prevention of leprosy. However, chemoprophylaxis is unable to protect contacts on subsequent exposure to the leprosy bacillus. Moreover, only a small number of anti-leprosy drugs are available and their excessive use could lead to drug resistance. By contrast, a specific vaccine to induce a long-lasting immune response would prevent future infections. Vaccines are generally seen as essential tools to eliminate a transmissible disease. The feasibility of inducing protective immunity with a vaccine is supported by the fact that 90% of people infected with *M leprae* mount a protective immune response to the bacillus. Several leprosy vaccine projects have recently been completed. Clinical trials have been done for *Mycobacterium indicus pranii*, *Mycobacterium vaccae*, *Mycobacterium kansasii*, killed *M leprae*, and BCG. Systematic reviews and meta-analyses have suggested that BCG has a protective efficacy of around 50% against leprosy, with greater protection against multibacillary than paucibacillary leprosy. In some countries, patients with leprosy who were vaccinated with BCG in childhood have been re-vaccinated with BCG on the basis of the strength of evidence from several studies showing that multiple BCG vaccinations can enhance protection against *M leprae*. However, this strategy has not been effective against tuberculosis, and WHO guidelines do not support BCG re-vaccination. Some studies have even suggested that BCG vaccination or re-vaccination might accelerate the onset of paucibacillary leprosy.

Historically, most adjuvants used in approved vaccines have been aluminium-based—ie, containing aluminium salts. Such adjuvants have been used safely to boost antibody responses for the past 70 years. However, an effective vaccine against leprosy is one that induces durable T-helper-1 (Th1) responses against *M leprae* antigens. The development of safe and effective adjuvants capable of inducing the desired responses has made possible a new generation of vaccines against intracellular pathogens. Innovative Th1-inducing adjuvants are already available for use in tuberculosis vaccines, and a whole new generation of adjuvants capable of enhancing T-cell responses is now in the advanced stages of development. A novel strategy for producing a new generation of leprosy vaccines combines both immunological and molecular techniques. Antigen-specific T cells have been used to screen hundreds of *M leprae* gene fragments for potential use in a vaccine. Owing to the sequencing of the entire *M leprae* genome, it is now possible to rapidly synthesise entire *M leprae* genes and to produce recombinant proteins. These advances have led to the development of the first defined leprosy vaccine, which will be ready for clinical testing in 2017. In a first step, the vaccine might be administered to contacts of patients with leprosy together with preventive chemotherapy in a bid to simultaneously rid them from *M leprae* infection and protect them from future re-infection. Vaccine safety has been studied in the armadillo model; the findings indicate that a defined vaccine is safe and actually delays nerve damage.

Diagnostic tools

Leprosy presents in several forms: the bacterial load is low in the tuberculoid form, whereas it is high in the lepromatous form. Available serological tests are sensitive for patients with a reasonably high bacterial load (ie, patients with multibacillary leprosy), but insensitive for patients with paucibacillary leprosy, for whom T-cell-based tests and molecular PCR tests are required to support the diagnosis of leprosy. Historically, the diagnosis of leprosy has relied on clinical evaluation of suspected leprosy lesions and the use of a slit-skin smear test that allows a health professional to determine the bacteriological index, which gives an indication of the bacterial load. Indeed, existing WHO guidelines refer to clinical diagnosis and classification as key diagnostic tools, but these methods have shortcomings. Clinical evaluation detects disease rather than subclinical infection, and bacteriological assays cannot reliably distinguish between asymptomatic infections and leprosy disease. Also, the slit-skin test is invasive and not sensitive for paucibacillary leprosy, determination of the bacteriological index requires robust training and quality control, and this index is not correlated with disease severity.

There is a clear need for inexpensive point-of-care diagnostic tests that are highly specific and sensitive, can detect subclinical infection, and could be used either to confirm diagnosis in people with suspected leprosy lesions or to screen contacts of index patients or other population groups at a high risk for leprosy. Serological test kits often rely on the measurement of antibodies against PGL-1. However, anti-PGL-1 antibody concentrations are often detected at low titres in patients with paucibacillary leprosy. A currently available ELISA based on the LID-1 and ND-O-LID is positive for most patients with multibacillary leprosy within 90 min. Studies of patients with leprosy from Colombia and the Philippines suggested that this test could eventually replace the slit-skin procedure to confirm multibacillary leprosy because of its good sensitivity (95·7%) and specificity (93·2%), although a laboratory was still required to do the test. By contrast, the sensitivity of an antibody-based test for paucibacillary leprosy was low in endemic regions, and a high rate of false-positive test results was observed in endemic populations. Efforts to interrupt *M leprae* transmission would greatly benefit from a diagnostic tool to detect infection rather than disease. For example, real-time PCR (rtPCR) is highly specific and sensitive and shows promise for diagnosis of both multibacillary and paucibacillary leprosy sufficiently early to ensure the
prompt treatment needed to prevent disabilities and reduce \textit{M leprae} transmission.\textsuperscript{79} However, no rtPCR test for the diagnosis of leprosy has yet been validated, and people who carry \textit{M leprae} without signs of disease are found in endemic areas. The PCR-based techniques that are used to detect pathogen RNA can also determine the viability and transmissibility of an \textit{M leprae} strain and could be used in contact screening and surveillance programmes.\textsuperscript{73} PCR amplification of \textit{M leprae} DNA can be done on a wide variety of tissue sources, including skin biopsy samples, oral or nasal swabs, and whole blood. However, optimal results are obtained by use of skin biopsies rather than readily collected samples. Additionally, clinical validation of the test and establishing the correlation of test results with those from serological tests are still to be done. Therefore, an approved PCR-based test to diagnose leprosy is not yet available.\textsuperscript{70,72}

Another approach for diagnosis of leprosy under investigation by several research teams is based on the host’s polarised T-cell immune response to \textit{M leprae}. The inflammatory cytokine-mediated Th1 cell response is elicited in response to \textit{M leprae} in paucibacillary leprosy. Th1-antigen-specific responses in patients with paucibacillary leprosy are detectable by use of in-vitro cell stimulation assays with protein-based and peptide-based derivatives. Th1-cell-based surrogate tests might detect asymptomatic \textit{M leprae} infections. Research on developing such a test focuses on the detection of interferon γ, other cytokines, and biomarker profiles.\textsuperscript{42,73–75}

Interest is growing among leprosy researchers in using nerve enlargement and inflammation in patients with suspected leprosy as a surrogate confirmatory diagnostic biomarker. Studies\textsuperscript{76,77} have used bilateral high-resolution sonography and colour doppler imaging to objectively measure nerve enlargement and inflammation in the ulnar, median, lateral popliteal, and posterior tibial nerves of patients with leprosy. The imaging and sonography procedures showed that the nerves of patients with leprosy were significantly thicker than those of healthy individuals. The clinical relevance of thickened peripheral nerves in the contacts of patients with leprosy is unclear. Sonography is not invasive and would be more cost-effective than MRI, which is currently used to determine nerve thickening in patients with suspected leprosy. Exploratory studies of the diagnostic potential of this technique are ongoing.\textsuperscript{77} but questions remain as to how any breakthroughs could be operationalised in endemic settings.

**Planning of \textit{M leprae} transmission interruption with epidemiological modelling and an eradication investment case**

Epidemiological modelling of \textit{M leprae} transmission and leprosy is essential in the design, guidance, and assessment of leprosy control policies. The NTD Modelling Consortium\textsuperscript{85} brings together an international team of disease modellers with an objective to provide quantitative model analyses to support efforts to achieve, among other goals, the WHO goal for leprosy elimination by 2020.\textsuperscript{20} Two leprosy compartmental models and one individual-based transmission model have been described in the literature.\textsuperscript{75} Both compartmental models investigate the course of leprosy in populations and the long-term effect of control strategies.\textsuperscript{83–85} The individual-based model (SIMCOLEP) focuses on the effect of case finding among contacts of newly diagnosed patients with leprosy.\textsuperscript{83,84} The SIMCOLEP model assesses whether leprosy could be eliminated at national and subnational levels by 2020 in different high-burden countries with WHO’s definition of elimination.\textsuperscript{85} Predictions indicated that country-level elimination as defined by WHO could be achieved in India, Brazil, and Indonesia by 2020, but that leprosy is likely to remain above the elimination threshold in most of the current high-endemic regions or districts within these countries. An analysis of the case detection rates in India with linear mixed-effects regression also suggested a very slow decline in endemic leprosy, with heterogeneity across states and districts.\textsuperscript{86}

In a study\textsuperscript{87} of Pará State, an area of high leprosy incidence in Brazil, modelling analyses with SIMCOLEP suggested that, under existing control activities, the number of cases of newly diagnosed leprosy will continue to decrease slowly and that elimination of leprosy as a public health problem could possibly be achieved by 2030 or thereafter if control programmes continue to implement passive case detection, multidrug therapy administration, and contact tracing at the current levels of intensity. Provision of chemoprophylaxis to contacts would further decrease the new case detection trend.\textsuperscript{87} This finding has been contested by another group who maintain that the current approach neglects a high proportion of the existing patients with leprosy and thus is unlikely to result in any substantial and lasting reduction of disease burden and transmission.\textsuperscript{83,85}

A detailed analysis of data from Thailand with an advanced back-calculation method suggested that the decrease in incidence of leprosy in that country over many years could be attributed to the efforts of the country’s control programme.\textsuperscript{82} Models can have an important role in testing various assumptions about the transmission of \textit{M leprae} because many uncertainties remain with respect to transmission dynamics. More importantly, models can also provide an indication of which interventions will have the greatest effect on halting transmission.

Efforts to eliminate a disease might be costly. Therefore, the decision to commit to elimination should be based on a robust analysis of the benefits, risks, and costs that accrue from such an undertaking.\textsuperscript{83} To meet this requirement, a so-called elimination or eradication investment case (EIC) procedure has been developed and applied to several neglected tropical diseases, including onchocerciasis, lymphatic filariasis, and human African trypanosomiasis.\textsuperscript{25–27} The EIC approach is particularly appropriate for diseases such as leprosy that incur a
high socioeconomic burden and for which multiple interventions exist or are being developed. An EIC for leprosy would help to judge whether sustainable interruption of transmission is feasible, what the most promising interventions for achieving that objective would be, and which long-term consequences the chosen interventions would entail. An EIC should also include an assessment of the changes required to the health system in leprosy-endemic countries, an analysis of the likely effect of zero leprosy transmission on economic productivity at the household and population levels and on social participation.15 The economic impact of leprosy elimination might turn out to be substantial at the household but not the societal level, given the generally low prevalence and highly focal occurrence of the disease among the poorest segments of the population. A 2016 systematic review98 identified a number of factors that might turn out to be widespread but mistaken belief that leprosy has been eliminated. The leprosy research community, together with other key players on the leprosy scene, have taken up the challenge of revitalising efforts to halt transmission of \textit{M lepra}. Research is underway on transmission and on the development of new tools and strategies needed to prevent transmission. Reaching this goal will not be achieved easily or quickly, and the tools to monitor progress towards zero transmission remain to be developed. Also, leprosy will remain a public health and social problem for decades after the successful interruption of transmission because of the long incubation period of \textit{M lepra}, leprosy reactions (ie, immunologically mediated episodes of acute or subacute inflammation), and the social and economic consequences of the disease.

Sustainability, perseverance, and constant innovation will be crucial to the success of a programme to halt transmission of \textit{M lepra}. Periodic reviews and

Conclusions
The drive to interrupt \textit{M lepra} transmission and finally eliminate leprosy is entering a crucial stage. The causative bacterium is still circulating freely within many communities and, since the turn of the century, the number of newly diagnosed patients with leprosy detected annually has stagnated. One reason is the dwindling of the political and financial commitment required to stop transmission, a development that resulted mostly from concerted efforts. The leprosy research community, together with other key players on the leprosy scene, have taken up the challenge of revitalising efforts to halt transmission of \textit{M lepra}. Research is underway on transmission and on the development of new tools and strategies needed to prevent transmission. Reaching this goal will not be achieved easily or quickly, and the tools to monitor progress towards zero transmission remain to be developed. Also, leprosy will remain a public health and social problem for decades after the successful interruption of transmission because of the long incubation period of \textit{M lepra}, leprosy reactions (ie, immunologically mediated episodes of acute or subacute inflammation), and the social and economic consequences of the disease.

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Panel: Key findings of a systematic review on constructing a leprosy elimination investment case
A 2016 systematic review98 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.29

Disease burden and elimination
- The proportion of newly detected leprosy cases in children younger than 15 years reflects the degree to which \textit{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,28 but its application is limited.
- The \textit{M leprae}-specific anti-PGL-I antibody test has limited applicability, because it is only reliably positive in multibacillary cases.20

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.22
- Contact tracing followed by administration of chemoprophylaxis, BCG vaccination, or both is currently the most promising approach to halting \textit{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.30

Biological and technical feasibility of transmission interruption
- Genome-based technology will probably facilitate the development of leprosy vaccines and diagnostic tests.23

Socioeconomic burden and public goods obtainable
- The disability-adjusted life-year is not a reliable indicator of the leprosy disease burden.102,104
- 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
adjustments will be needed as new tools and approaches are tested. Of particular relevance to efforts to interrupt *M. leprae* transmission is the need for these tools and strategies to be readily usable within existing health systems, even in the many countries that no longer have dedicated leprosy control programmes and that have thus lost the technical experience and deep understanding of the local epidemiology that were embedded in these programmes. The development and deployment of new tools and strategies calls for close collaboration between all actors on the leprosy scene, including the research community, international normative agencies such as WHO, national health authorities, non-governmental organisations, and the agencies and institutions that will catalyse the efforts to bridge the gap between hopes and realities.

**Contributors**
The concept of the paper was developed by FM and PS. Specific chapters were drafted by PS (Introduction, Identifying people infected with *M. leprae* and reducing the risk of transmission to contacts, and Conclusions). SGR (Vaccines), FM (Diagnostic tools), and TDH and JHR (Planning of *M. leprae* transmission interruption with epidemiological modelling and an eradication investment case). The full draft was developed by PS. All authors reviewed and approved the final draft.

**Declaration of interests**
We declare no competing interests.

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