



## Summary of the Twenty-Eighth Meeting of the International Task Force for Disease Eradication (ITFDE) April 23, 2018

The 28<sup>th</sup> meeting of the International Task Force for Disease Eradication (ITFDE) was convened at The Carter Center, Atlanta, GA, USA on April 23, 2018 to review the status of the global efforts to eliminate Leprosy (Hansen's disease) and the need for improved diagnostic testing and treatment, the reduction of social stigma, and the exploration of the potential reservoir in armadillos. The Task Force members at the time of this meeting were Dr. Stephen Blount, The Carter Center (Chair); Dr. Gautam Biswas, World Health Organization (WHO); Dr. Peter Figueroa, The University of the West Indies, Jamaica; Dr. Donald Hopkins, The Carter Center; Dr. Julie Jacobson, Bill & Melinda Gates Foundation; Dr. Hamid Jafari, Centers for Disease Control and Prevention (CDC); Professor David Molyneux, Liverpool School of Tropical Medicine; Dr. Patrick Osewe, The World Bank; Dr. Stefan Peterson, UNICEF; Dr. David Ross, The Task Force for Global Health; Dr. Dean Sienko, The Carter Center; Dr. Nilanthi de Silva, University of Kelaniya, Sri Lanka/WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTDs); Dr. Laurence Slutsker, PATH; Dr. Ricardo Thompson, National Institute of Health (Mozambique), and Dr. Dyann Wirth, Harvard School of Public Health. Nine Task Force members (Figueroa, Jacobson, Hopkins, Jafari, Molyneux, Ross, Sienko, Slutsker, Thompson) attended this meeting, and two were represented by an alternate (Dr. Robert Kezaala for Peterson; Dr. Opopo Oyaka Tshivuila Matala for Osewe).

Presenters at this meeting, which was chaired by Dr. Dean Sienko, included Drs. Wim van Brakel, Netherlands Leprosy Relief (NLR); Erwin Cooreman, WHO; Thomas Gillis, RSTOP, The Leprosy Mission Canada; Mohan Gupte, Indian Council of Medical Research (ICMR); and Paul Saunderson, American Leprosy Missions.

### **Leprosy and its current extent**

Leprosy (Hansen's disease) is a slowly developing chronic disease caused by the bacterium *Mycobacterium leprae* and a newly discovered, closely related species, *M. lepromatosis*. Both organisms cause similar disease, are 90% identical genetically, and share the ability to infect nerves. Susceptibility to the disease and to its various manifestations varies, resulting in a wide clinical spectrum: indeterminate, tuberculoid, borderline tuberculoid, borderline lepromatous and lepromatous. Unlike tuberculosis, there is no evidence that HIV co-infection exacerbates leprosy. Skin lesions are common. Disability due to nerve damage is the most serious outcome, often leading to stigma and discrimination. The exact mechanisms of transmission are unknown, but the likely routes in human-to-human transmission are via respiratory (aerosol droplets) and/or skin contact. The disease has an extremely long incubation period of up to 2-10 or more years. Close contacts have increased risk of developing leprosy, especially household contacts, neighbors and persons having extended social contact with untreated leprosy patients. Research

suggests that reservoirs of infection may include untreated new and relapsed patients, unrecognized cases, healthy carriers of the bacilli (latent leprosy), as well as the environment (soil and water). Animal reservoirs for *M. leprae* have been confirmed in North America (armadillo) and the United Kingdom (red squirrel), and armadillos have been implicated in transmission to humans in North America. The relative importance of these reservoirs in transmission is not well understood. Genetic typing can be used to track strains of *M. leprae* and study transmission networks, and also to assess the role of animal reservoirs.

Clinical signs and symptoms are currently the main means of diagnosis. Demonstration of bacilli in slit-skin smears or biopsy material is also proof of leprosy. The bacterium cannot be grown on artificial media to confirm the diagnosis--although it can be grown in mouse footpads with difficulty—but point-of-care diagnostic aids to detect antibody and cytokine responses to infection have advanced over the past decade and are being vetted in experimental trials to establish sensitivity, specificity and operational utility. At present there is no reliable diagnostic test available, especially for pauci-bacillary leprosy. Mathematical modeling suggests that a diagnostic for detecting early infection (as opposed to disease) in combination with treatment of such pre-clinical infection would have the greatest impact on interrupting transmission. Modeling also suggests that at least 40 years of interventions may be required in order to stop transmission altogether.

Leprosy is treated with combinations of 2 drugs (dapson, rifampin) for 6 months (pauci-bacillary disease) or 3 drugs (dapson, rifampin, and clofazimine) for 12 months (multi-bacillary disease). Relapse rates following multi-drug therapy are around 1% and levels of resistance to rifampin and dapson appear to be relatively low (however, the current surveillance system is very limited). Patients become non-infectious within one month after beginning multi-drug therapy, and the number of bacteria is reduced by one log after a year of therapy. New research that has expanded understanding of the pathogenesis of nerve damage may provide new approaches for treating that pathology.

The World Health Organization (WHO) undertook the first global leprosy survey in 1961, which estimated there were 11-12 million cases of the disease globally. Treating patients with dapson alone elicited widespread resistance, which led to the introduction of multi-drug therapy in 1981 and reduction in duration of chemotherapy for multibacillary leprosy in 1994 (to two years) and in 1998 (to one year). A little more than 5 million cases were registered globally in 1985. Resolution WHA44.9 by the World Health Assembly in 1991 called for “elimination of leprosy as a public health problem”, defined as registered prevalence of less than one case on treatment per 10,000 population by 2000—a goal which WHO later declared achieved globally<sup>1</sup> with 600,000 cases reported in 2000 and nationally in most countries by 2005. The International Task Force for Disease Eradication (ITFDE) concluded in 2001 that commendable progress had been made over the past decade but that leprosy was not then eradicable.

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<sup>1</sup> World Health Organization. Global Leprosy Update, 2016: Accelerating Reduction of Disease Burden. *Wkly Epidem Rec* 92(35):501—519. Available at: <http://apps.who.int/iris/bitstream/handle/10665/258841/WER9235.pdf;jsessionid=8484232F40C4B56DE21E88F9C8615350?sequence=1>, accessed February 6, 2018.

Achieving elimination as a public health problem led to scaling down of leprosy programs in many countries. The number of new cases reported annually declined to ~300,000 by 2005 and ~200,000 since then. Published papers document dramatic progress against the disease in countries such as Japan, Republic of Korea, Mexico and Spain. WHO promoted the Enhanced Strategy for the Elimination of Leprosy in 2011-2015, followed by the Global Leprosy Strategy 2016-2020 “Accelerating towards a leprosy-free world”. The latter strategy advocates for active case detection and reduction of stigma, acknowledges the protective effect of BCG vaccination against leprosy, and promotes research on improved treatment, diagnostics, and chemo- and immuno-prophylaxis. WHO plans to issue new guidelines for diagnosis, treatment, and prevention of leprosy soon. American Leprosy Missions is promoting an initiative to help map disabling Neglected Tropical Diseases (NTDs), including critical leprosy indicators such as new cases, child cases, and disability, at low cost, using routine data, in order to improve provision of services.

The Task Force discussed the potential need for a new quantitative target, which more closely reflects true elimination (absence of local transmission), as well as a limited number of well-chosen indicators for monitoring program effectiveness, such as the disability rate per million population and age-specific rate of leprosy in children, for example. Some felt that registered prevalence figures are less useful to monitor interruption of transmission. The association of persistent endemic pockets of transmission associated with some areas of high population density and poor socio-economic status was noted, but these associations are diluted and sometimes lost in aggregate statistics from wider geographic areas.

According to WHO’s latest annual global update for 2016,<sup>2</sup> 143 countries reported surveillance data for leprosy, but 77 countries did not. During 2016, 217,968 new cases were reported (2.9 per 100,000 population), mostly residing in South-East Asia, Sub-Saharan Africa, and Brazil. The proportion of new patients with Grade 2 disability (visible disability) at the time of diagnosis has been stable at around 6% for the past decade.

## **Research**

Post-exposure prophylaxis (PEP) is a key to interrupting transmission of leprosy, since much transmission likely occurs during the incubation period before new infections are apparent. Single-dose rifampicin has been shown to reduce the risk of leprosy among contacts by about 50-60%. An enhanced post-exposure chemoprophylaxis (PEP++) trial will begin in 2018 to test the efficacy of rifampicin (600 mg) and moxifloxacin (400 mg) given together to contacts three times at 4-weekly intervals. BCG vaccination alone is estimated to have a protective effect of about 50% among household contacts; a study has shown that BCG and rifampicin used together have an estimated protective effect of about 80%.

A new experimental subunit vaccine against leprosy, LepVax, developed by the Infectious Diseases Research Institute, Seattle, with the support of the American Leprosy Missions, entered Phase 1 trial in the United States in September 2017. Earlier studies suggest that this vaccine

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<sup>2</sup> World Health Organization. Global Leprosy Update, 2016: Accelerating Reduction of Disease Burden. *Wkly Epidem Rec* 92(35):501—519. Available at: <http://apps.who.int/iris/bitstream/handle/10665/258841/WER9235.pdf;jsessionid=8484232F40C4B56DE21E88F9C8615350?sequence=1>, accessed February 6, 2018.

provides safe, effective pre- and post-exposure prophylaxis in armadillos, with lesser or delayed neurological side effects compared to BCG.

### **Conclusions and Recommendations**

1. Since the previous ITFDE review in 2001 global leprosy has made great progress operationally and in biological understanding: identifying a second species responsible for the infection; developing genotyping to track chains of transmission; discovering more about the disease's transmission, pathogenesis, multiple drug therapy and chemo-prophylaxis; and reducing annual reported global prevalence of the disease from about 600,000 cases in 2000 to about 200,000 cases annually since 2005. Much more progress is possible, using what we know now. The new WHO guidelines are expected to help programs incorporate new interventions and improve monitoring of program activities.
2. While the previous target set by WHO to reduce the registered prevalence of leprosy to less than 1 case on treatment per 10,000 population by the year 2000 has been reached in most countries at the national level, significant numbers of new cases are still occurring. WHO and its partners should consider establishing an appropriate new evidence-based quantitative target and a few key indicators that reflect the strongly clustered local nature of leprosy endemicity.
3. While much progress has, is, and can be made to reduce occurrence of leprosy, the Task Force believes that the disease cannot be eradicated--meaning interruption of transmission worldwide—with currently available tools, given the existence of a documented reservoir in wild armadillos in North America, no reliable diagnostic to detect infected persons before they can develop disease or become source of infection for others during a very long incubation period, and the inadequacy of epidemiologic and surveillance data.
4. The incompleteness of surveillance data to help describe, map and track occurrence of leprosy globally and define at-risk populations adequately is a major weakness. Given WHO's legal constraints in reporting data from member countries, it should work with national leprosy programs, the Global Partnership for Zero Leprosy or some other appropriate entities to help gather, assess, and report relevant information from multiple sources, including published data, research studies, historical material, and relevant observations by Non-Governmental Organizations. Mapping efforts should be expanded to help define global distribution and focality and guide programmatic activities.
5. The ITFDE commends the robust research agenda being pursued by WHO, the Global Partnership for Zero Leprosy and others. Developing a diagnostic to reliably detect persons as soon as possible after they become infected, in time to prevent them from infecting others, should be a high priority. Other urgent needs include better understanding of the logistics of implementation of recommended interventions, including in coordination with other interventions, and of the potential role of *M. leprae* in soil and water in transmission of the infection.
6. There is a need to identify additional funders for this program beyond the national governments, Novartis Foundation, The Nippon Foundation, and the International Federation of Anti-Leprosy Association (ILEP) members.