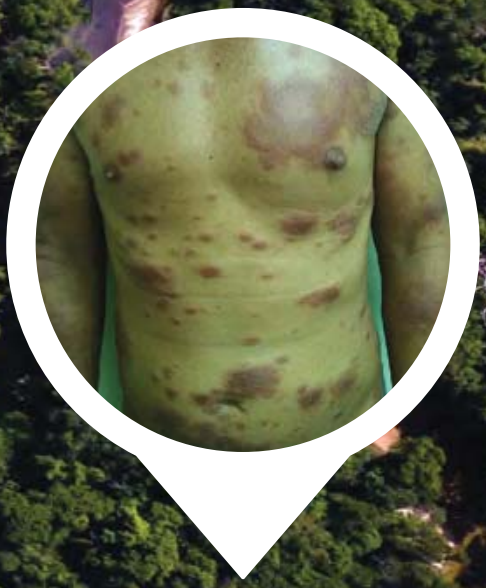
Strategies to reduce leprosy transmission in hyperendemic regions in Brazil and elsewhere in the world

Leprosy is a chronic disease of the skin and nerves caused by infection with the uncultivatable intracellular pathogen, *Mycobacterium leprae*. It is an ancient disease, the oldest known to be associated with humans, with osteological evidence of characteristic bone pitting and deformities found in burial sites in India as far back as 2000 BC. Although leprosy is completely curable today with chemotherapy, delays in diagnosis and receiving treatment frequently result in advanced cases of nerve damage, muscle loss, blindness, and bone deformity and resorption, with resulting disfigurement, disability and stigmatization.

Treatment with multidrug therapy (MDT) has been available since the mid-1980s, and by 2001 effective global leprosy elimination campaigns sponsored by the World Health Organization (WHO) had reduced the prevalence by 89%. Gaps exist in the knowledge of how *Myco. leprae* is transmitted, what genetic factors and innate and adaptive immune responses of the host lead to resistance or susceptibility to disease, the long incubation time prior to the slow development of diverse symptoms, and the very low rate of disease progression in infected individuals, that all create challenges to the development of ways to interrupt transmission. In 2015, 210,758 new cases were diagnosed worldwide, with 8.9% being detected in children less than 15 years old and 6.7% of those having grade 2 disability (G2D). Higher rates of G2D indicate a delay in the detection and diagnosis of leprosy and ranged from 1.8% in Micronesia to 42.1% in Somalia. Leprosy in children is an important epidemiologic indicator and is correlated with multiple active foci of disease transmission in the community. Three countries, India, Brazil and Indonesia, accounted for 81% of all new cases detected in 2015.

Brazil detected 26,395 new cases that year and remains the only country in the world that has not met the WHO goal of less than 1 new case per 10,000 population, and is currently at around 1.2/10,000. There is tremendous regional variation in the new case detection rates (NCDR) in Brazil, with low rates in the southern states like Rio Grande do Sul (0.1/10,000) while high or hyperendemic rates (defined as between 2 and more than 4 new cases per 10,000, respectively) are found in the central-western, northeast and northern regions of the country. States in the Amazon region have only around 17% of the total population of Brazil, but report over 50% of all of the new cases of leprosy. Recent data from Brazil's national disease notification database (SINAN) show that around 50% of the population living in 19 out of the 27 states of Brazil are exposed to either high or hyperendemic rates of infection. Mathematical modelling studies projecting trends to reach the goal of less than 1/10,000 in the state of Pará, based on NCDR available from SINAN, suggest that this will not be realized until at least 2030 or 2061. Although taking into account the present actual NCDR based on our active case-finding studies in multiple cities, achieving this goal may not realistically be attained until much later. Recent surveys in even supposedly low endemic regions in São Paulo state (0.23/10,000) and the Federal District in Brasilia (0.52/10,000) revealed unexpectedly high rates of hidden leprosy cases (24 new cases in 1,398 individuals in Jardinópolis, São Paulo [1.7%], and 44 new cases in 390 individuals in Brasilia, [11.3%]), which were only



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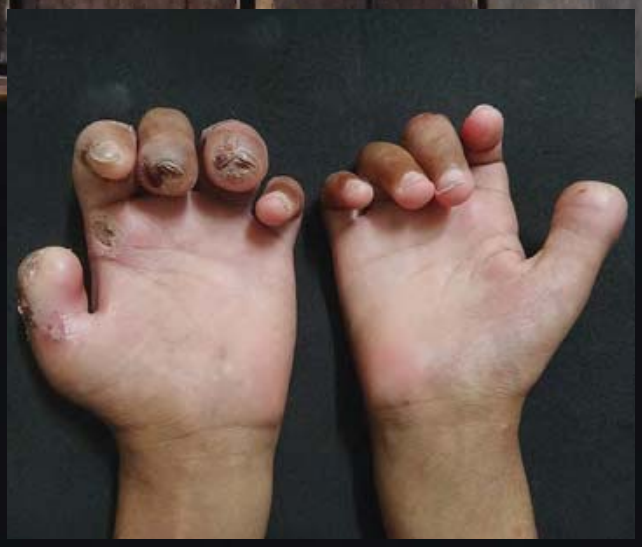
revealed with targeted surveillance in these areas. These findings illustrate the importance of active surveillance by experienced leprosy dermatologists and additional case-finding among the household contacts of newly diagnosed cases, since it is estimated that the number of hidden cases of leprosy is likely to be up to 8-fold higher than the prevalence in the area at any given time.

Recent studies in low- or medium-endemic regions of Brazil indicate that there has been a shift in those groups experiencing the highest risk of succumbing to leprosy, primarily with a much higher increase in older individuals (peaking at 60–69 years old), almost a 2-fold higher risk of multibacillary MB disease in men compared with women in all states regardless of economic class, and progressively higher rates of MB disease, indicating a higher bacillary load. These trends are similar to the reduction in the prevalence of leprosy in Norway in the 1920s prior to the availability of drug therapy, where improvements in economic growth, sanitary conditions, clean water, reduction in the housing density and improved hospital infrastructure gradually reduced the bacillary load in the general population and resulted in the eventual elimination of leprosy in that country by the mid-20th century. Although these trends appear to represent that leprosy is on the wane in some parts of Brazil, the integration of leprosy control into the family health strategy means that there are fewer trained professionals capable of recognizing classic symptoms of skin lesions and nerve damage resulting in higher yearly reports of MB disease and G2D, indicating delays in diagnosis that can only increase the rates of disability and transmission. Evidence has accumulated that there are large numbers of asymptomatic, undiagnosed or misdiagnosed cases, and that up to 4 million of these hidden cases may exist by 2020 worldwide, representing a major threat to efforts by endemic countries to interrupt transmission and reach the global elimination target set recently by the London Declaration.

The Human Development Index (HDI) is a composite numeric measurement established by the United Nations Development Programme in 1990 to assess three basic dimensions of human development, namely life expectancy at birth, mean years of schooling and standard of living based on Gross National Income per capita. The HDI in Brazil has improved 23.4% over the last 25 years (currently at 0.755, considered a high HDI). However, due to inequalities in the distribution of human development in different regions of the country, the northern states in the Amazon region, including Pará state, consistently rank near the bottom for the HDI index, which likely reflects issues of health and healthcare availability for people living in the area. Currently, the family health strategy provides basic health coverage for only about 50% of the population in Pará. As a result of integrating leprosy diagnosis into the family health strategy and reduced numbers of trained physicians capable of correctly diagnosing disease symptoms, new case detection relies mainly on passive detection of cases in most areas of the country, resulting in the relatively low numbers of new cases reported into the SINAN database for this region.

Over the last few years, the principal stakeholders, including the WHO, involved in promulgating strategies aimed at reducing the global burden of leprosy, particularly in hot spots or high to hyperendemic regions, agree that early diagnosis, contact tracing and treatment of all patients should be part of the overall strategy. Since 2009, our group has focused attention on over a dozen cities in the northern state of Pará, Brazil, which historically has had one of the highest NCDR in the country (>4.0/10,000), and based on current rates there will be 40,000 new cases in children diagnosed in the next decade in this state alone. Our strategy utilizes active surveillance of schoolchildren and the household contacts of newly diagnosed cases, averaging 4% in children and 8% in household contacts. Each team consists of an experienced leprologist, a physiotherapist to look for muscle weakness and nerve pain, a nurse, a phlebotomist to draw a blood sample to assess anti-PGL-I antibodies (a known biomarker of *Myco. leprae* infection) and laboratory and field personnel to collect demographic data. In addition, we strongly rely on assistance from the local community health agents and health authorities from the basic family health units who live in the area and can direct us to known or suspected cases living there. During our week-long visits, we bleed and examine between 500–1,000 children and household contacts. During the period 2013–2014, we visited seven different cities in the state of Pará, examining 4,617 individuals and diagnosing 387 new cases of leprosy (8.4%). In the laboratory, we used Geographic Information Systems (GIS) to map hot spots within cities so follow-up studies can be performed on families living in the most affected areas. We are also developing and evaluating new rapid diagnostic lateral flow tests and using PCR to screen individuals for *Myco. leprae* earlobe colonization that we hope will eventually be able to identify those individuals that are most at risk of progressing to disease, particularly in families living in these identified hot zones. In addition, there are large-scale clinical trials underway coordinated by national programmes that are examining the efficacy of the use of post-exposure prophylaxis (PEP), either single dose rifampicin (SDR) or other multidrug short-course therapy regimens in multi-country locations to evaluate the potential of accelerating the reduction of transmission in high and hyperendemic areas. There are strong hopes that the use of these kinds of aggressive strategies and rapid diagnostic tests will ultimately break the lines of transmission and successfully remove leprosy as a major health concern.



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John S. Spencer *Colorado State University,* left
Marco Andrey Cipriani Frade *Universidade de São Paulo,* centre
Claudio G. Salgado *Universidade Federal do Pará,* right