Leprosy: Why does it persist among us?

Victor S. Santos[1]

Carlos D. F. de Souza[2]

Paulo R. S. Martins-Filho[3]

Luis E. Cuevas[4]

Affiliation

[1]Centre for Epidemiology and Public Health. Federal University of Alagoas, Arapiraca, Brazil.

[2]Department of Medicine. Federal University of Alagoas, Arapiraca, Brazil.

[3]Investigative Pathology Laboratory. Federal University of Sergipe, Aracaju, Brazil.

[4]Department of Clinical Science. Liverpool School of Tropical Medicine, Liverpool, United Kingdom.

Corresponding author

Victor S. Santos. Universidade Federal de Alagoas, Campus Arapiraca, Rodovia AL-115, Bom Sucesso, Arapiraca, Alagoas 57309-005, Brazil. Email: santosvictor19@gmail.com

Conflict of interest: The authors declare have no conflict of interest.

Funding source: This paper was not funded.

Key-words: Communicable disease control; Delayed diagnosis; Epidemiology; Infectious disease transmission; Leprosy; Social inequality.

Abstract

Despite a substantial reduction in its global prevalence since 1990s, leprosy transmission continues unabated and remains a significant public health problem. The causes for its persistence are multi-factorial, ranging from the lack of implementation of contact tracing, the skill-dependent diagnostic method with over reliance on clinical recognition; to its strong linkages to social inequality and inequity. Leprosy control and elimination is still an enormous challenge for governments and scientists and the answer for this complex problem needs to be multifaceted, which includes higher research investments to identify risk areas, novel and better diagnostics and therapeutic tools and a reduction of social inequalities.

Key-words: Communicable disease control; Delayed diagnosis; Epidemiology; Infectious disease transmission; Leprosy; Social inequality.

1. Introduction

Leprosy is a chronic condition caused by *Mycobacterium leprae* that affects the skin and peripheral nerves which causes severe physical disability and deformity [1] with psychological health consequences and poor quality of life [2]. Despite a substantial reduction in its global prevalence from the 1990 and 2000 onwards, however, since 2005 leprosy transmission has continued unabated and remains a significant public health problem that needs to be revisited. The causes of the persistence of leprosy are multi-factorial, ranging from the infrequent implementation of contact tracing, the skill-dependent diagnostic method and over reliance on its clinical recognition; to its strong linkages to social inequality and inequity.

2. A brief history of recent elimination efforts

In 1982 the World Health Organization (WHO) recommended the use of three antibacterial drugs combined, rifampicin, dapsone, and clofazimine, in response to the increasing numbers of dapsone-resistant cases [3]. This multidrug therapy (MDT) is more effective than the previous monotherapy by dapsone and its success reduced the number of prevalent cases and led to a decrease in the number of cases that needed to be treated at any one time from 5.3 million in 1985 to 3.1 million in 1991. The efficacy of MDT in reducing the prevalence of leprosy encouraged WHO to develop an strategy for leprosy elimination as a public health problem by 2000, which was defined as a prevalence of less than 1 case per 10,000 population [4]. This global target was achieved by 2000, with a 95% reduction of prevalent cases, although several countries had failed to reach their national targets, indicating that leprosy had persisted as a public health problem in country hotspots [5]. Despite the rapidly declining prevalence, incidence changes were less striking, with an estimated 200,000 incident cases still being reported annually, of which 9-10% occur in

children under 15 years, indicating ongoing and recent transmission [6]. Notably, a high proportion of incident cases already have physical disability and deformities at the time of diagnosis, denoting a late diagnosis that perpetuates transmission. Moreover, given the large number of late diagnosis, it is likely the true number of cases is higher than the numbers of cases reported [7].

In 2016, WHO launched the 2016-2020 Global Leprosy Strategy aiming to reduce grade 2 leprosy disability rates to less than one case per 1 million population and the number of leprosy-related disabilities among pediatric patients to zero [8], while maintaining the ultimate goal of transmission elimination of <1 new case per 10,000 population [4]. This strategy is reliant on the early detection and treatment of cases among high risk groups, although models to estimate the effectiveness of current interventions suggest that with the slow decline of incident cases and the substantial pool of undiagnosed cases, especially in endemic areas, the strategy will require many years to reach its targets [9].

3. The importance of contact tracing and coping methods

The 2016-2020 Strategy also highlights the need for strengthening active case finding, particularly targeting leprosy foci in hyperendemic areas, to identify and treat early other cases occurring within the household, potentially reducing its spread and decreasing disability through the detection of less severe cases. Several leprosy control programs have implemented active case finding through mass campaigns and screen household contacts. Household contacts are at a higher risk of leprosy than the general population and active screening has a higher yield than passive case finding - when patients notice symptoms and seek health care services. Contact tracing has similar performance identifying cases in hyperendemic and low endemic areas and may also result in an earlier diagnosis, with the detection of cases with less disease severity [10]. Despite its higher yield, contact tracing

requires a skilled clinical dermato-neurological examination, which depends on the health worker ability and training and simpler methods that are less operator dependent are needed. Serological and other laboratory tests have been developed to supplement a clinical diagnosis, but they have either a low diagnostic accuracy, especially for PB leprosy, or have limitations for implementation in primary health care facilities with limited laboratory infrastructure [10,11].

Recently, the WHO recommended the use of single dose rifampicin chemoprophylaxis for contacts, after excluding leprosy and tuberculosis, to prevent the development of leprosy [10]. WHO also recommends the introduction of chemoprophylaxis by control programs, particularly for contacts outside the family of an index case and after adequate management of household contacts and consent of the index case to disclose their disease, as leprosy is a highly stigmatizing disease [10]. Programs are still facing challenges to implement this new approach, and, once implemented, it will be necessary to monitor its effectiveness, especially for populations at high risk for leprosy.

A WHO position paper on the use of BCG to reduce the incidence of leprosy indicated that BCG at birth is effective at reducing the risk of leprosy and its use should be Maintained, at least in all leprosy high-burden countries or settings (good quality of evidence). A vaccine based on the non-pathogenic *Mycobacterium indicus pranii* appears to be protective, but evidence of its efficacy is based on only two randomized clinical trials (moderate quality of evidence) [10].

4. Challenges for leprosy diagnosis

The diagnosis of leprosy still relies on careful dermatological and neurological examinations to establish sensory loss in skin lesions or reddish skin patches, thickened or enlarged peripheral nerves or the identification of pleomorphic acid fast bacilli on slit skin smears or

histopathologic changes [10]. Leprosy has varied clinical, microbiological and histopathological manifestations, which are determined by the bacillary load and the cellular immune responses to *M. leprae* [12,13]. This variable presentation often results in misdiagnosis and delayed diagnoses, especially among individuals with low bacillary loads in which leprosy recognition is more challenging.

Serological and other laboratory assays currently have low sensitivity, especially in early disease stages and asymptomatic individuals. Although nucleic acid amplification tests (both single-gene and multiplex-PCR) have higher sensitivity and specificity than serological tests , they are difficult to perform in primary health care settings, because of their technical and laboratory infrastructure requirements [10,11], which contributes to a delayed diagnosis. Furthermore, individuals with early leprosy often have low leprosy awareness and disregard the symptoms, while its long history in endemic communities is associated with major fear of stigma, generating barriers to access health services, which compounded with the difficulties in diagnosis, leads to delayed diagnosis.

5. Treatment and challenges of leprosy classification

Similar to late diagnosis, leprosy treatment is also challenging. In 1982, WHO implemented a standard therapeutic regimen consisting of MDT with rifampicin, dapsone, and clofazimine, with doses varying with the clinical, histological and bacteriological information [3]. Accordingly, patients are divided into two groups: PB or MB leprosy. Patients with PB leprosy receive monthly rifampicin and dapsone doses and daily dapsone for 6 months. Patients with MB leprosy receive monthly rifampicin, dapsone and clofazimine and daily dapsone and clofazimine for 12 month [3]. Since this classification required laboratory technical expertise with well-trained professionals it was difficult to adopt by fieldworkers and in 1997, WHO recommended a simplified 'operational classification' based on the

number of skin and nerve injuries [14]. This classification has a weak to moderate agreement with the classification based on intra-dermal smear microscopy, with best outcomes achieved when using smear microscopy [13]. Despite the potential for misclassification, the 'operational classification' served the purpose of facilitating the allocating of patients to the MDT regimes in settings with limited technical and laboratory resources.

To further simplify the therapeutic regimens, reduce the duration of treatment for MB leprosy and avoid the impact of misclassification, several studies have proposed a Unified MDT (U-MDT) using the 3-drugs for 6 months for all leprosy patients [15]. A systematic review of U-MDT studies reported that although PB patients could benefit from the 3-drug regime compared to the previous 2-drug therapy, with concern about the potential skin discoloration due to clofazimine use, while there is not enough evidence to support the recommendation to shorten the duration of treatment for MB leprosy [10]. WHO therefore currently recommends the use of the 3-drug rifampicin, dapsone and clofazimine regimen for all patients, with a treatment duration of 6 months for PB leprosy and 12 months for MB leprosy [10]. Further well-designed trials to better define the benefits of shortening the MDT regimens for MB leprosy are needed, including its effect on bacteriological outcomes [10]. A further complication are leprosy reactions, which are the result of exacerbated immune responses and occur in 25% of PB and 40% of MB leprosy. Reactions can present at any time, independently of treatment, including long after treatment completion [16]. The WHO recommends following patients for several years, as reactions can lead to further damage of peripheral nerves with the development of physical disability and deformities. Type 1 lepra reactions are delayed hypersensitivity reactions that occur in both PB and MB leprosy; while Type 2 lepra reactions are associated with circulation and tissue deposition of

immune complexes an occur only in MB leprosy. Reactions are a consequence of the disease and are not involved in transmission or risk of transmission and their treatment requires the use of analgesics and corticosteroids [16].

6. Socioeconomic determinants of leprosy

Living conditions and socio-economic factors play a role enabling leprosy persistence. Spatiotemporal modeling and surveys have demonstrated a strong relationship between the persistence of leprosy and social and economic deprivation, with clusters of cases located in areas with high social vulnerability [17,18]. The more heterogeneous the distribution of resources in an area, the higher the odds that leprosy would persist as an important health problem [17].

7. Conclusion and perspectives

There is a complex interaction of factors that enables the persistence of leprosy. Here we highlight the challenges for an early diagnosis, for implementing contact tracing by control programs, and the coexistence of leprosy and social vulnerability.

Leprosy control and elimination is still an enormous challenge and the solution for this complex problem needs to be multifaceted. Public policies should: i) increase research investment to identify risk areas, factors associated with disease progression and novel and better diagnostics and therapeutics; ii) investment in local health networks for the timely identification and treatment of patients, increasing case detection; iii) the strengthening of guidance and policies for national and regional programs; iv) the implementation of mitigating and compensatory measures for individuals affected by the disease; and v) the reduction of social inequalities and improved living conditions for populations with high leprosy burden. For now, it is still not possible to say goodbye to leprosy.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

[1] de Paula HL, de Souza CDF, Silva SR, et al. Risk Factors for Physical Disability in Patients With Leprosy. JAMA Dermatology. 2019;1–9.

[2] Santos VS, Oliveira LS, Castro FDN, et al. Functional Activity Limitation and Quality of Life of Leprosy Cases in an Endemic Area in Northeastern Brazil. PLoS Negl Trop Dis. 2015;9:e0003900.

[3] World Health Organization Study Group on Chemotherapy of Leprosy for Control Programmes. Chemotherapy of leprosy for control programmes. World Health Organ Tech Rep Ser [Internet]. 1982;675:1–33. Available from: https://apps.who.int/iris/handle/10665/38984

[4] World Health Assembly. Leprosy resolution WHA 44.9: forty-fourth [Internet]. Geneva; 1991. Available from: https://www.who.int/neglected_diseases/mediacentre/resolutions/en/index1.html

[5] World Health Organization. Global leprosy situation, 2010. Wkly Epidemiol Rec [Internet]. 2010;85:337–48. Available from: https://www.who.int/lep/resources/who_wer8535/en/

[6] World Health Organization. Global leprosy update, 2017: reducing the disease burden due to leprosy. Wkly Epidemiol Rec [Internet]. 2018;35:445–56. Available from: https://apps.who.int/iris/handle/10665/274290

[7] Smith WC, van Brakel W, Gillis T, et al. The Missing Millions: A Threat to the Elimination of Leprosy. PLoS Negl Trop Dis. 2015;9:2–5.

[8] **World Health Organization. Global Leprosy Strategy 2016-2020: Accelerating towards a Leprosy-FreeWorld. Monitoring and Evaluation Guide [Internet]. 2016.

Available from: https://www.who.int/lep/resources/9789290225096/en/.

[9] Medley GF, Blok DJ, Crump RE, et al. Policy lessons from quantitative modeling of leprosy. Clin Infect Dis. 2018;66:S281–S285.

[10] **World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017. Available from: https://apps.who.int/medicinedocs/documents/s23543en/s23543en.pdf

[11] *Gurung P, Gomes CM, Vernal S, et al. Diagnostic accuracy of tests for leprosy: a systematic review and meta-analysis. Clin Microbiol Infect. 2019;25:1315–27.

[12] Nath I, Saini C, Valluri VL. Immunology of leprosy and diagnostic challenges. Clin Dermatol. 2015;33(1):90-8.

[13] Santos VS, Mendonça-Neto PT, Raposo OFF, et al. Evaluation of agreement between clinical and histopathological data for classifying leprosy. Int J Infect Dis. 2013;17:e189-92.

[14] World Health Organization. WHO Expert Committee on Leprosy. Seventh Report. Geneva; 1997. Available from: https://apps.who.int/iris/handle/10665/42060.

[15] *Penna GO, Bührer-Sékula S, Kerr LRS, et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients. PLoS Negl Trop Dis. 2017;11:1–19.

[16] Richardus JH, Nicholls PG, Croft RP, Withington SG, SmithWCS. Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. Int J Epidemiol. 2004;33(2):337-343.

[17] de Souza CDF, Rocha VS, Santos NF, et al. Spatial clustering, social vulnerability and

risk of leprosy in an endemic area in Northeast Brazil: an ecological study. J Eur Acad Dermatology Venereol. 2019;jdv.15596.

[18] Pescarini JM, Strina A, Nery JS, et al. Socioeconomic risk markers of leprosy in high-burden countries: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12:1–20.