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Taylor Rae Landay **Date**

Trends and Characteristics of Pediatric Leprosy Cases in Minas Gerais, Brazil

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B.S. University of Maryland, 2015

Thesis Committee Chair: Jessica K Fairley, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Master of Public Health in Global Health
2020

Abstract

Trends and Characteristics of Pediatric Leprosy Cases in Minas Gerais, Brazil

By Taylor Landay

Background: Cases of leprosy around the world have steady declined, yet there is still active transmission in pediatric cases around the world, such as Minas Gerais, Brazil. We hypothesized that although the incidence of pediatric cases has declined, areas with lower health care service access would show active transmission of *Mycobacterium leprae* as measured by incidence and grade 2 disability in pediatric cases. **Methods:** A cross-sectional study was conducted using the Brazilian Notifiable Diseases Surveillance System, Minas Gerais division (SINAN-MG). Data were collected by passive reporting by health centers across the state upon initial diagnosis during 2002-2017. For this analysis, cases were included if they resided in a municipality that reported pediatric cases. Additionally, municipalities were further stratified based on their medical facility accessibility. Time periods were also assessed by creating two time groups: Time period 1 (2002-2009) and Time period 2 (2010-2017). Incidence was calculated for pediatric cases in the years 2002, 2009, and 2017. Incidence was then calculated for the year 2017 in municipalities with different levels of health services access. Statistical analyses conducted included univariate analysis, Chi-square testing, t-tests, and adjusted odds ratios. A logistic regression was applied to assess the association between health care access and disability. **Results:** This study had a total of 27,725 cases. Of those, 1,611 were pediatric cases. When time periods were compared time period 2 showed an increase in proportion of pediatric multibacillary leprosy (38.39%) compared to time period 1 (34.42%). There was also an increase in proportion of grade 2 disability in pediatric cases (2.58%) in time period 2 compared to time period 1 (1.91%). Average age of diagnosis in pediatric cases was younger in time period 2 (10.06; 95% CI [9.77-10.35]) than time period 1(10.43; 95% CI [10.27-10.60]). Municipalities with low access to health services reported 857 (53.20%) of all pediatric cases. In 2017, the incidence of pediatric cases in municipalities with low access to health services was 0.95 per 100,000 compared to 0.23 per 100,000 in municipalities with high access to health services (p=0.009). There was significantly higher odds of disability among municipalities with low access to health (OR 1.88 95% CI [1.37-2.59]). **Conclusion:** This study showed there is still active transmission of *Mycobacterium leprae* in Minas Gerais, Brazil. The increased proportion of multibacillary in time period 2 and average age of diagnosis highlight ongoing transmission. The increase in proportion of grade 2 disability in time period 2 supports a delay in diagnosis and treatment, suggesting more potential transmission prior to diagnosis. More surveillance is needed in municipalities with lower access to health services since over 50% of pediatric. All cases included in this study resided in those regions, and the odds of disability upon diagnosis in those regions is 1.88 times higher than regions with better access to health care facilities.

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I will like to start by first and foremost giving my greatest gratitude to Dr. Jessica Fairley, my thesis committee chair. Your support, guidance, and overall mentorship has been invaluable. I would also like to thank Lúcia Fraga, José Ferreira, and all of the medical students in Minas Gerais, Brazil who supported me during my time there and helped me fall in love with their beautiful country. Additionally, thank you to Dr. Julie Clennon for all your help and support during this process.

To my friends and family, I can't express how much your support and love has meant to me. To my mom, my rock and biggest cheerleader, thank you for always telling me to chase my dreams and reach for the starts. Thank you for teaching me to care about others and always do what is right. You have always shown me how to be a strong woman. To my late dad, thank you for demonstrating what it meant to be the change you wish to see in the world, and to always root for the underdog. To my partner Jeremy, thank you for unconditional support, love, and constant pep talks throughout this process.

Table of Contents

Chapter 1: Introduction

Leprosy, now often referred to as Hansen's disease, has circulated throughout human history for as long as humans can remember. Ancient Egyptian and Indian texts from 600 BCE described this disease among its people (1). It has been shown to follow human migrations patterns and evolve coincidingly with human evolution (2). While leprosy may seem a disease of the past, it is still prevalent in various parts of the world. Globally, there are over 200,000 new cases detected each year, of which 18,000 are in children under the age of 15 (3).

In 2000, when the World Health Organization (WHO) declared leprosy eliminated as a public health concern, the global prevalence of leprosy was under 1 case per 10,000 people. However, this statistic was misleading. In the 13 countries that host 94% of all remaining cases, they have not yet reached this level (4). As of 2017, India, Brazil and Indonesia accounted for 80.2% of the cases reported globally (5). Brazil hosts the second largest number of cases, after India (6) with a case detection rate of 12.1 per 100,000 inhabitants (7). While the rate continues to decrease each year, it remains a public health concern.

To truly understand the transmission of *Mycobacterium leprae*, it is critical to better understand the characteristics of pediatric cases and the areas in which they live. The detection of new cases in children under 15 years of age indicates that active bacilli are in circulation, thus leading to continued transmission and the presence of endemic disease. It is widely regarded that surveillance of new cases under the age of 15 is indicative of wider spread in the community (8).

Additionally, presence of disability at the time of diagnosis reflects inactive surveillance systems. In leprosy cases, disability, often marked by loss of nerve sensation and ocular impairment, can take years to develop (9). The severity, or grade of disability, also acts as a reflection of the disease burden, since it signifies late diagnosis of disease and likely

missed cases in the community. Many national programs for diagnosis of leprosy rely on screening of grade 2 disability as a surrogate marker of late diagnosis (10).When pediatric cases have a grade 2 disability at the time of diagnosis, it shows a lack of capacity for the health system to recognize and treat leprosy from the earliest stages. It shows a flaw in the surveillance system and in indicative of undiagnosed cases in the community (11). The World Health Organization (WHO) has set forth goals to completely eliminate grade 2 disability among pediatric cases by 2020 (12).

A major part of disease surveillance in Brazil relies on local health centers in endemic areas. The Unified Health System (Sistema Único de Saúde (SUS)) is the Brazilian government health system the provides care to it citizens. Due to political turmoil, and lack of public funding, there has been a large disparity in the access of care to citizens, disproportionately affecting those of poorer regions (13). For many municipalities in Brazil, their primary health clinics are the first line of active surveillance. The economic crisis has severely impacted the resources being allocated to health facilities, leaving the poor with even greater burden (14). Leprosy is known to affect areas of greater social vulnerability and poor living conditions (15).

The objective of this cross-sectional study was to better understand the demographic characteristics of pediatric cases of leprosy and the change in disability proportions over time in Minas Gerais, Brazil. This study can be used to better understand the demographics of cases under the age of 15, the level of health services communities have access to, and help prevent future disability.

Chapter 2: Literature Review

Overview

Leprosy is a universally known disease, but it may surprise some to find that there is still sparse information regarding its transmission patterns and pathogenicity. Human to human transmission is likely through droplets from the nasal mucosa (16). Most notably, infection is believed to happen over extended exposure to airborne nasal droplets released by infected individuals. It is also transmitted zoonotically though armadillos (17), although the exact mechanism of this is not fully understood. Additionally, a systematic literature review by Bratschi et al. found six studies that highlighted ecological risk factors such as water supply, food shortage and housing, indicating that there could be potential exposure to environmental transmission or environmental reservoirs (18).

Unfortunately, *Mycobacterium leprae* remains non-cultivable, leading to a great lack of information of its biological makeup (19). Symptoms are often subtle, so much so that sometimes patients are unaware they have contracted the disease (20). While more research and information on leprosy is becoming available as public health campaigns and destigmitization campaigns have become better funded and wider reaching, there remains much to be learned about *Mycobacterium leprae's* transmission and host susceptibility. Medly et. al described the importance of "interruption of transmission" in the process to fully eradicate leprosy. (3) To fully make global eradication a possibility, it will be critical to identify undiagnosed cases. Through modeling, it has been shown that the number of undiagnosed cases is likely double the number of currently diagnosed cases (3). Because these pools of undiagnosed people contribute to the spread of Hansen's disease over their lifetime, their treatment is critical for the eradication of leprosy.

Classifications

The manifestation of leprosy depends greatly on the host immune response and pathological characteristics in the tissues. Initially, leprosy was first classified into dichotomous categories; tuberculoid and lepromatous (8). Over time, three more classification levels were added between these (borderline tuberculoid, borderline borderline, and borderline lepromatous), each representing a bacterial load and immune response. In 1982, the World Health Organization grouped these into two main categories; paucibacillary (PB) and multibacillary (MB), for ease of diagnosis and treatment. A patient is classified as paucibacillary when the number of skin lesions is less than five and a negative bacilloscopy. Multibacillary is classified when there are greater than five lesions, a positive bacilloscopy (typically) and at least one area with nerve damage (21-23). When a bacilloscopy is unavailable, classification is dependent on clinical presentations, which can be subject to the skills of the diagnosing physician and requires specific medical training.

Presentation

The range of clinical symptoms depends on the immune system of the host. Some patients may present with only minor skin lesions while others can have severe nerve damage and deformities (24). Leprosy can affect the skin, peripheral nervous system, upper respiratory track, joints, eyes, vision, reproductive organs and adrenals glands (4). The most common symptoms include erythematous patches with low sensation, nerve damage (especially in extremities) and ocular involvement (10).

Damage to the nerves and eyesight are used to classify disability grade on a scale of grade 0, grade 1, and grade 2. The WHO classifies disability as: Grade 0 showing no impairment; Grade 1 as loss of sensation in the hand or foot; and Grade 2 as visible

impairment along with, but not always, loss of sensation in the hand or foot (25)(Figure 1). Disability grade is a strong indicator of how long a patient has been infected with *Mycobacterium leprae* and to what degree the are affected by the disease. Disability, and more specifically grade of disability, is an important epidemiological and operational indicator. Grade 2 can indicate potentially hidden endemic circulation (26). Even though incidence globally decreases each year, in 2017, Grade 2 disability was present in 6% of all cases worldwide. Delays in diagnosis leads to a greater number of undiagnosed cases. Without treatment, patients continue to spread the disease and contribute to active transmission of the bacillus. A low case count with high disability grades is indicative of an ineffective health system. This shows a global delay of diagnosis and need for surveillance systems that enable case identification and diagnosis(10).

Figure 1: The WHO Leprosy Disability Grading System (27)

Disability Grading	Extremities	Eyes
0	Patients with no functional impairment	No eye problem due to leprosy, no evidence of leprosy-related vision loss
1	Loss of sensitivity (anaesthesia) in the hands or feet, but no visible deformity or damage	Some vision impairment, but not severe (vision 6/60 or better; patients can count fingers from 2 to 6 m away).
2	Cases with both anaesthesia and complications such as trophic ulcers, claw deformities and bone resorption in the extremities.	Involves severe vision impairment (vision worse than 6/60; inability to count fingers from 2 to 6 m away); also includes lagophthalmos, iridocyclitis and corneal opacities.

Risk Factors and Treatment

Risk factors for leprosy are not as straight forward as one may think. According to White et al., 95% of the world's population are not "genetically susceptible" to contracting the disease (1). However, there is a higher prevalence in certain demographic groups that share common identities. White et al. states that this could be in relation to genetic factors

and ancestral exposure to the bacilli (1). Further research is needed to investigate risk of disease in contacts of cases to better understand an individuals' predisposition to contracting leprosy and expressing symptoms.

Stigma may hinder early diagnosis of leprosy. Rao et al. argue that prevalence of leprosy is underreported due to the comprehensive stigmatization surrounding the disease (28). Many cases go unreported or are only identified the later, more debilitating, stages of the disease (29). Additionally, because leprosy can leave permanent skin marks and deformations, it has been strongly associated with decreased self-esteem and social stigma (30). In 2019, Rao conducted a systematic literature review on implications of stigma interventions surrounding leprosy. They found that interventions that aimed at reducing stigma led to better health outcomes and community acceptance (31). While leprosy disease has many long-term sequelae, disability should be preventable. Treatment has been standardized by the World Health Organization since 1982. The treatment consists of combinations of three different drugs: dapsone, rifampicin, and clofazimine (16). There are different treatment regimens depending on the classification of Hansen's. Treatment has proven to be extremely effective and if caught early, can lead to a full recovery. However, complications called leprosy reactions, are characterized by acute inflammatory episodes, which in some cases can be triggered by treatment. These can extend all the way to the peripheral nerves, which requires immediate medical attention (32). Reactions are manageable as long as patients have access to health services.

Pediatric Cases

The question at hand is to estimate the incidence of leprosy cases under the age of 15 is and identify factors that are contributing to the ongoing burden in this population. The detection of new cases among children under 15 years of age indicates that active bacilli are

in circulation, thus leading to continued transmission and the presence of an endemic disease. Additionally, the proportion of children among newly infected cases shows a lack of early detection communities. If children contract the disease and are not diagnosed, they risk spreading the disease unknowingly, potentially causing a hidden epidemic.

In 2017, 150 countries reported new cases of pediatric leprosy. There were 16,979 new cases diagnosed under the age of 15 years old, making up 8.1% of all new cases worldwide (27). In Brazil, in 2011, 2,287 new cases of leprosy under the age of 15 were reported, making up 6.7% of all new cases, with a detection coefficient of 4.89 per 100,000 inhabitants. That was in-line with average epidemic levels (8). In 2017, the total number of new pediatric cases in Brazil went down to 1,718. However, the percentage of pediatric cases among all new cases went up to 7.5%, with a detection rate of 3.72 cases per 100,000 inhabitants (33). Clusters of pediatric cases have been show in in the Midwest, North and Northeastern regions of the country, indicating active transmission in those states (34).

Leprosy typically has an incubation period of 3-5 years but can be as long as 20 years (8). When cases under the age of 15 are diagnosed, it shows that not only is there active transmission of the bacteria, but that is has occurred recently (35). Furthermore, when there is detection of cases with grade 2 disability, it indicates the magnitude of disease transmission of disease. A cross-sectional study conducted by Ruiz-Fuentes and colleagues analyzed two decades of Cuban national leprosy data. They found the age group most commonly affected by leprosy is between the ages of 10-14. The youngest case reported was 3 years old (27) As recently as 2019, in Sergipe, Brazil six cases were found in children less than one year old (36).

A literature review was conducted by Vieira et al. reviewed 22 articles pertaining to leprosy in children under the age of 15 among the years 2001-2016. Out of 22 articles, 13

reported grade 2 disability proportions in the range of 1.7% to 5.5%. Ruiz-Fuentes et al. reported that the 16,979 new pediatric cases diagnosed in 2017, 238 had grade 2 disability at the time of diagnosis (27). These proportions of disability among pediatric cases indicate children are being infected at a young enough age to allow disability to progress to this advanced state. It is indicative of a strong circulation of the bacillus and lack of early detection in the age group (33). It further suggests an underreporting of pediatric cases and underreporting of cases in general.

Health Care

Brazil's Unified Health System, Sistema Único de Saúde (SUS), was created in 1989 to give universal health care access to all of its citizens. Primary healthcare is the responsibility of the government. The Family Health Program is responsible for the first level of care among patients. It has rapidly expanded over the years, from 2,000 to 43,000 teams between 1998 and 2018 (32). This covers roughly 130 million people, or 62.5% of the total Brazilian population. Massuda et al. explains in detail how the political turmoil and economic crises have led to severe defunding of public health programs. They report that as of 2018, Brazil spends 46%, one of the lowest, on health compared to the average of 51.28% among Latin American and Caribbean countries (37). Additionally, Brazil is still faced with a shortage of medical professionals, especially specialists such as those trained in specifically diagnosing leprosy (13).

In the state of Minas Gerais, there are three active reference centers dedicated to treating leprosy: Hospital Eduardo de Menezes, Center for Sanitary Dermatology and Leprosy (CREDESH), and Centro de Referência de Doenças. Endêmicas e Programas Especiais (CREDENPS). Aside from these main clinics, leprosy has to be diagnosed and treated by primary care centers. For many citizens in Brazil, their primary care center is the only medical clinic they visit. This proves challenging because leprosy is difficult to diagnose

and many physicians are not trained to recognize the early signs and symptoms of the disease. Specialists have become more concentrated to private sectors and left a major void in the primary care level in rural areas (38). With these issues, access to care could have an important effect on early diagnosis of leprosy and prevention of transmission.

Surveillance

It is known that the time between the onset of symptoms and diagnosis is one of the factors associated with the presence of physical disability, therefore, it is necessary for priority municipalities to develop active detection measures (11). Unfortunately, in lower resource areas, there is either not enough funding or awareness to properly train physician's in leprosy's diagnosis. Furthermore, the burden of leprosy among children is thought to be severely underestimated. A 2012 study in the Amazon randomly sampled 1,592 school children from high burden municipalities in Pará (PA) and conducted serological testing. Four percent of children were diagnosed with leprosy and 48% of the cohort tested positive for antibodies to anti-phenolic glycolipid-I (PGL-I), a specific *M. leprae* antigen. If they expand this proportion to the general population of the state, they estimate nearly 80,000 undiagnosed cases (39). This is thought to apply broader to other highly endemic areas in the country.

Underreporting of leprosy cases results from lack of control by public and local health system and also lack of funding and monitoring of the disease (8). When leprosy affects children, it can cause serious developmental delays, hospitalizations and emotional distress (40). This is a problem that deserves serious attention to prevent the ongoing spread of this globally debilitating disease.

Future Goals

The World Health Organization is still committed to the fight to eradicate leprosy. Their original goal was to eliminate leprosy as a global problem by 2000, which they

achieved. However, they have failed to achieve their new goal of eliminating leprosy at the country level (28). Their 2015 goal was to reduce the number of pediatric cases and "achieve a 35% reduction in the new cases detection rate with grade 2 deformity" (41). These are the indicators they have set forth to monitor the Leprosy Eradication Program (25). Their new pillars for the *Global Leprosy Strategy 2016–2020* are:

- Strengthen government ownership, coordination and partnership
- Stop leprosy and its complications
- Stop discrimination and promote inclusion

Each of these pillars highlights an area of growth for Brazil (12).

While the WHO is concerned with leprosy from a macro level, Brazil has taken their own steps to reduce the disease burden within their country. The Ministry of Health in Brazil prioritized cities of concern in 2010. Cities were labeled as priority if they had:

- a detection coefficient greater than 20 per 100,000
- A minimum of 10 cases in the general population and 1 new case diagnosed under the age of 15 years old
- 50 newly diagnosed cases in the metropolitan areas and out of risk areas and at least 5 cases in children under 15 years old and all capital cities

From this, each priority area received additional funding when surveillance measures were met. Additional financial resources were offered when an area was listed as following the epidemiological surveillance measures set forth. (35). Minas Gerais, Brazil was among the states that contained priority municipalities (11).

Study Relevance

After studying the literature for potential indicators of continued transmission of leprosy among children, it became clear that certain indicators such as disability grade and low resourced settings, largely support the hypothesis that there is still rapidly ongoing transmission of this disease. This study is in line with the literature suggestions of better understanding pediatric transmission to eliminate leprosy as a neglected tropical disease.

Chapter 3: Manuscript

Abstract:

Background: Cases of leprosy around the world have steady declined, yet there is still active transmission in pediatric cases around the world, such as Minas Gerais, Brazil. We hypothesized that although the incidence of pediatric cases has declined, areas with lower health care service access would show active transmission of *Mycobacterium leprae* as measured by incidence and grade 2 disability in pediatric cases. **Methods:** A cross-sectional study was conducted using the Brazilian Notifiable Diseases Surveillance System, Minas Gerais division (SINAN-MG). Data were collected by passive reporting by health centers across the state upon initial diagnosis during 2002-2017. For this analysis, cases were included if they resided in a municipality that reported pediatric cases. Additionally, municipalities were further stratified based on their medical facility accessibility. Time periods were also assessed by creating two time groups: Time period 1 (2002-2009) and Time period 2 (2010-2017). Incidence was calculated for pediatric cases in the years 2002, 2009, and 2017. Incidence was then calculated for the year 2017 in municipalities with different levels of health services access. Statistical analyses conducted included univariate analysis, Chi-square testing, t-tests, and adjusted odds ratios. A logistic regression was applied to assess the association between health care access and disability. **Results:** This study had a total of 27,725 cases. Of those, 1,611 were pediatric cases. When time periods were compared time period 2 showed an increase in proportion of pediatric multibacillary leprosy (38.39%) compared to time period 1 (34.42%). There was also an increase in proportion of grade 2 disability in pediatric cases (2.58%) in time period 2 compared to time period 1 (1.91%). Average age of diagnosis in pediatric cases was younger in time period 2 (10.06; 95% CI [9.77-10.35]) than time period 1(10.43; 95% CI [10.27-10.60]). Municipalities with low access to health services reported 857 (53.20%) of all pediatric cases. In 2017, the incidence of pediatric cases in municipalities with low access to health services was 0.95 per 100,000 compared to 0.23 per 100,000 in municipalities with high access to health services (p=0.009). There was significantly higher odds of disability among municipalities with low access to health (OR 1.88 95% CI [1.37-2.59]). **Conclusion:** This study showed there is still active transmission of *Mycobacterium leprae* in Minas Gerais, Brazil. The increased proportion of multibacillary in time period 2 and average age of diagnosis highlight ongoing transmission. The increase in proportion of grade 2 disability in time period 2 supports a delay in diagnosis and treatment, suggesting more potential transmission prior to diagnosis. More surveillance is needed in municipalities with lower access to health services since over 50% of pediatric. All cases included in this study resided in those regions, and the odds of disability upon diagnosis in those regions is 1.88 times higher than regions with better access to health care facilities.

Introduction:

Leprosy, now often referred to as Hansen's disease, has circulated throughout human history for as long as humans can remember. Ancient Egyptian and Indian texts from 600 BCE described this disease among its people (1). It has been shown to follow human migrations patterns and evolve coincidingly with human evolution (2). While leprosy may seem a disease of the past, it is still prevalent in various parts of the world. Globally, there are over 200,000 new cases detected each year, of which 18,000 are in children under the age of 15 (3).

In 2000, when the World Health Organization (WHO) declared leprosy eliminated as a public health concern, the global prevalence of leprosy was under 1 case per 10,000 people. However, this statistic was misleading. In the 13 countries that host 94% of all remaining cases, they have not yet reached this level (4). As of 2017, India, Brazil and Indonesia accounted for 80.2% of the cases reported globally (5). Brazil hosts the second largest number of cases, after India (6) with a case detection rate of 12.1 per 100,000 inhabitants (7). While the rate continues to decrease each year, it remains a public health concern.

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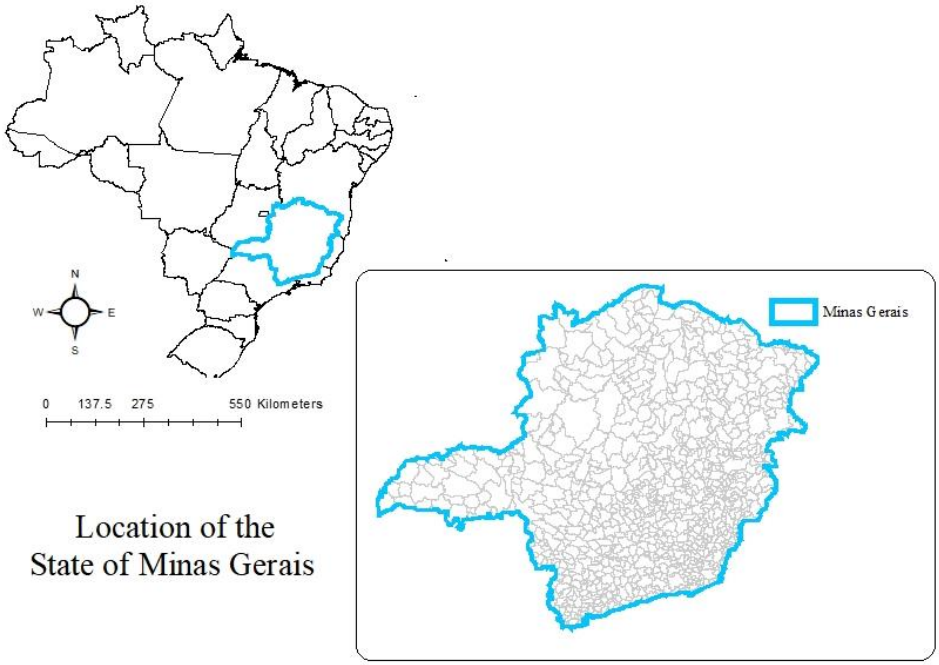
The objective of this cross-sectional study was to better understand the demographic characteristics of pediatric cases of leprosy and the change in disability proportions over time in Minas Gerais, Brazil. This study can be used to better understand the demographics of cases under the age of 15, the level of health services communities have access to, and help prevent future disability.

Methods:

Study Region

The data for this study is from Minas Gerais, a state in the southeast of Brazil with endemic leprosy (Figure 2). This inland state has a population of over 20 million people, and is known for its hilly nature, with an average elevation of 2,600 feet.

Figure 2: Minas Gerais, Brazil



Data collection

This cross-sectional study contains data from all across that state over a 15-year period. Data were collected over the years 2002-2017 through the Brazilian Notifiable Diseases Surveillance System, Minas Gerais division (SINAN-MG). Over 70 variables were collected in this dataset by questionnaire at time of diagnosis, filled out by medical professionals upon patient in-take. For purposes of this study, only cases from municipalities

that have both adult and pediatric cases were used in the analysis. Relevant variables considered for the purpose of this study are age of diagnosis, gender, race, municipality, grade of disability, accessibility, and operational classification of leprosy.

Records with diagnostic error or that were duplicated records were excluded. Due to the nature of the study, all adult cases were included if they lived in a municipality that also reported pediatric cases. Population data for each municipality were collected from census data collected by the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE).

Data Analysis

The data analysis was multipronged. Descriptive statistics were conducted using frequency tables on all patients under the age of 15 who were diagnosed with leprosy during the years 2002-2017. For comparison, they were also conducted for all adults diagnosed over the age of 15 during that same time period. Variables of interest include age of diagnosis, gender, disability grade, and operational classification. Operational classification was determined by the WHO standards set in 1984 and included paucibacillary and multibacillary. Differences in proportions were verified using bivariate analysis and a chi-squared test. An alpha of 0.05 and a 95% confidence interval were considered in all tests. A further sub-analysis explored the comparison of characteristics among pediatric cases by their operational class of leprosy. Paucibacillary and multibacillary were used as groupings to compare characteristics such as gender, race, and disability grade.

Cases were divided into two periods: cases from the years 2002-2009 (Time period 1), and all cases from 2010 to 2017 (Time period 2). The incidence of leprosy in patients diagnosed under the age of 15 and adult patients were calculated for both time period 1 and time period 2. A comparison of disability grade to time periods and health care access was analyzed using Odds Ratios and Chi-square analysis.

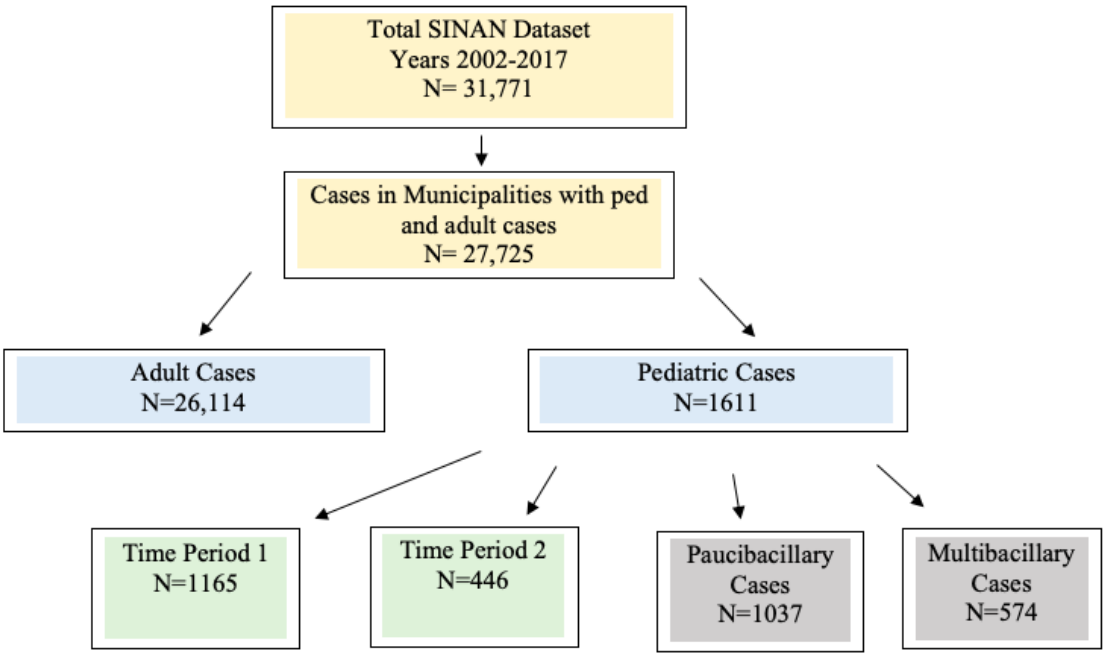
The demographic characteristics of the municipalities that contained pediatric cases were also analyzed. Data from the Humanitarian Data Exchange was used to enumerate the total number of health facilities operating in each municipality (42). Data included health facilities such as: dentist, doctor's office, hospital, pharmacy, and clinic. For the purposes of this analysis the following health facilities were included in the dataset: clinics, hospitals, and pharmacies. Doctor's offices were grouped with clinics. The sums of total clinics in each municipality were sorted into one of the three categories. Natural Jenks in ArcGIS 10.3 software were used to create three categories of access and municipalities were sorted into either, low, medium, or high access. This was determined to be the most optimal class range naturally found in this dataset. Municipalities in the low category had less than 5 health facilities. Municipalities in the medium had between health 5-17 facilities, and municipality in the high category had more than 18 health facilities.

Incidence of leprosy was calculated for each municipality in 2002, 2009 and then again in 2017 to assess change over time. A logistic regression was conducted using access to health services as an exposure and presence of disability as an outcome, using 95% confidence interval and an alpha of 0.05. All data analyses in this study were conducted using SAS version 9.4, ArcGIS 10.3 and OpenEpi Version 3.01.

Results

The dataset (Figure 3) includes data from 31,771 patients diagnosed with leprosy from the years 2002-2017. Of those cases, 27,725 live in municipalities that had reported pediatric cases between the years 2002-2017. There were 26,114 adult cases and 1,611 pediatric cases. Among the pediatric cases, 1,165 were reported in time period 1 and 446 were reported in time period 2. Of all pediatric cases, 1,037 were reported as paucibacillary, and 574 were reported as multibacillary.

Figure 3: Dataset



Of all adults who were diagnosed with leprosy between the years 2002 and 2017 the average age of diagnosis was 47.14 years old ± 16.77 years (95% CI [46.94-47.35]) (Table1). There was a slight majority of adult male (53.93%) (n=12,082) compared to 45.81% of pediatrics (n=738).

Figure 4: Municipalities included in dataset

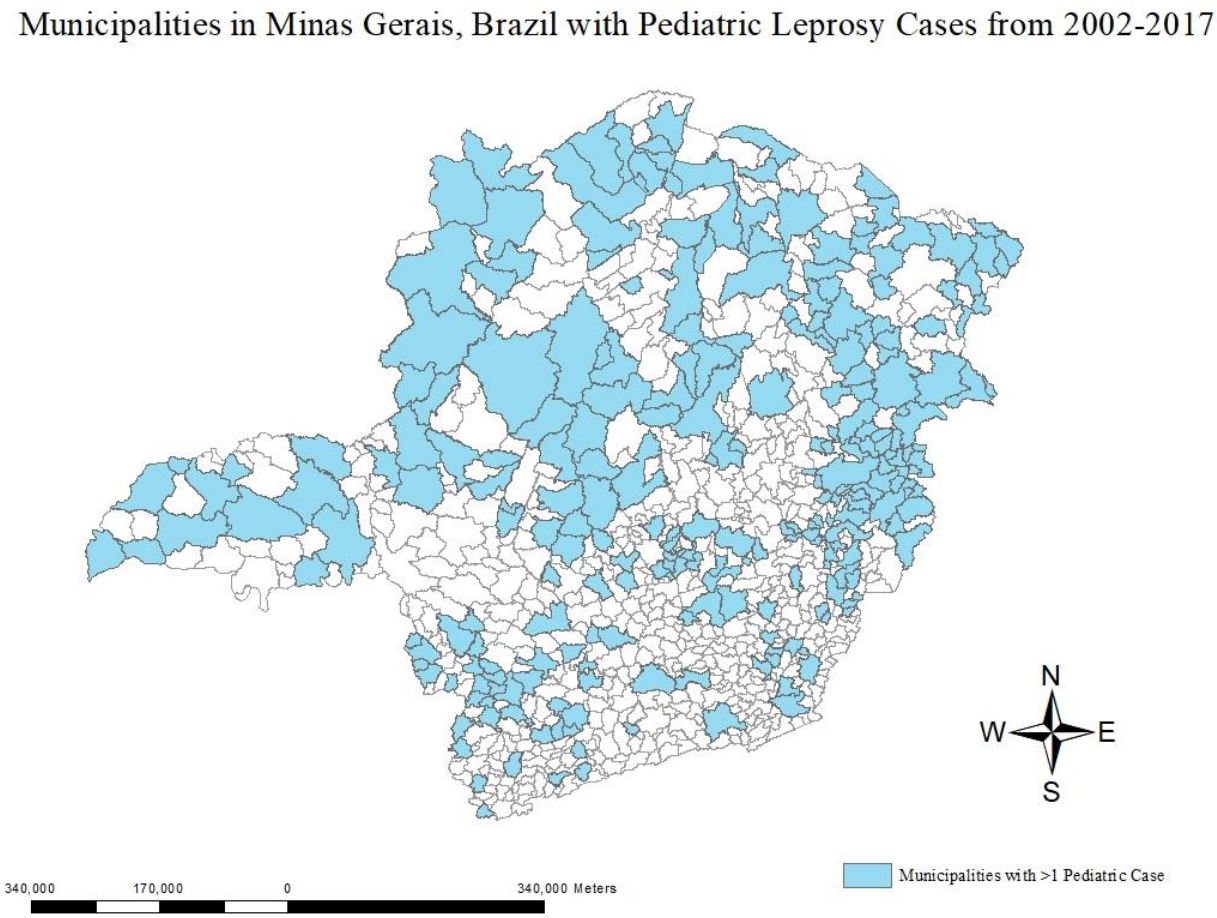


Table 1: Demographic characteristics of all cases of leprosy in Minas Gerais, Brazil from 2002-2017, who reside in municipalities that have reported pediatric cases

Variable	**Adults n=26,114 (94.19%)**	**Pediatrics ** n=1,611 (5.81%)**	**P-Value (Chi-sq)**
Age			
Mean 95% CI	47.14 (46.94-47.35)	10.33 (10.19-10.48)	<0.0001
std	±16.77	±2.95	
Range	15-103	1-14	
Sex, n (%)			
Male	14,082 (53.93)	738 (45.81)	<0.0001
Female	12,032 (46.07)	873 (54.19)	
Disability, n (%)			
No Disability	14,874 (58.88)	1,382 (87.58)	<0.0001
Grade 1	7,698 (30.47)	163 (10.33)	
Grade 2	2,691 (10.65)	33 (2.09)	
Race, n (%)			
White	10,371 (41.72)	496 (32.38)	<0.0001
Black	3,746 (15.07)	252 (16.45)	
Asian Descent	379 (1.52)	18 (1.17)	
Mixed	9,690 (38.98)	717 (46.80)	
Indigenous	52 (0.21)	8 (0.52)	
Did not answer	621 (2.50)	41 (2.68)	

Table 2: Characteristics and disability grade of all pediatric leprosy cases by operational classification

Variable	Paucibacillary N= 1,037 (64.3%)	Multibacillary N= 574 (35.63%)	P-Value (Chi-sq)
Age			
Mean 95% CI	10.09 (9.90-10.30)	10.78 (10.55-11.01)	0.003
SD	±3.02	±2.78	
Range	1-14	1-14	
Sex n %			
M	467 (45.03)	271 (47.21)	0.20
F	570 (54.97)	303 (52.79)	
Disability at time of diagnosis, n %			
No Disability	967 (94.71)	415 (74.51)	<0.001
Grade 1 +	49 (4.80)	114 (20.47)	
Grade 2++	5 (0.49)	28 (5.03)	
STD	±1.12	±6.74	
range	0-13	0-50	

+Disability grade 1 defined as eye problems with vision not severely affected (can count fingers up to 6 meters)

++Disability grade 2 defined as severe visual impairment (cannot count fingers up to 6 meters)

As shown in Table 2, the average age among pediatric cases who were diagnosed with paucibacillary leprosy was 10.09± 3.02 (95% CI 9.90-10.30). Most of these cases (94.71%, n=967) showed no sign of disability. Of those that did have disability at the time of diagnosis, 4.80%, (n=49) had grade 1 and 0.49% had grade 2 (n=5) ($p<0.0001$).

The average age of diagnosis among pediatric patients with multibacillary leprosy was 10.78 ± 2.78(95% CI 10.55-11.01). In contrast to patients with paucibacillary, patients

with multibacillary leprosy had an increased percentage of disability presence upon diagnosis. Grade 1 disability made up 20.47% (n=114), and grade 2 made up 5.03% (n=28) of all disability at time of diagnosis ($p<0.0001$). There was a significant slight increase in percentage of male pediatric cases (45.03%) (95% CI 9.90-10.30) with paucibacillary compared to multibacillary (47.21%) ($p<0.0001$).

Table 3: Characteristics, disability grade, and operational classification of all pediatric leprosy between two time periods

	Time period 1 Years 2002-2009	**Time period 2 Years 2010-2017**	**OR (CI)**	**P-Value (Chi-sq)**
Total Pediatric Cases				
N, %	1165 (72.1)	446 (27.9)		
Age				
Mean 95% CI	10.43 (10.27-10.60)	10.06 (9.77-10.35)		<0.022
STD	± 2.87	± 2.78		
Range	1-14	2-14		
Sex n %				
Male	519 (44.55)	219 (49.10)	.83 (0.67-1.04)	<0.100
Classification N %				
Paucibacillary	764 (65.58)	273 (61.21)	1.21 (0.97, 1.51)	<0.0001
Multibacillary	401 (34.42)	173 (38.79)	0.82 (0.66-1.03)	
Disability				
None				
N % Proportion T2 v T1	1004 (87.23)	378 (88.52) 1.01		0.013
Grade 1				
N % Proportion T2 v T1	125 (10.86)	38 (8.90) 0.82	0.81 (0.55-1.18)	0.136
Grade 2				
N % Proportion T2 v T1	22 (1.91)	11 (2.58) 1.35	5.31 (2.57-11.46)	<0.0001

Table 4: Incidence in all leprosy cases and all pediatric leprosy cases in Minas Gerais, Brazil in the years 2002, 2009, and 2017

Year	All Cases Per 100,000	Pediatric Cases Per 100,000
2002, n 95% CI p-value	34.79 (25.74 -43.84) <0.0001	2.59 (1.70 -3.47) <0.0001
2009, n 95% CI p-value	23.35 (17.88- 28.82) <0.0001	1.59 (0.72 -2.46) 0.0004
2017, n 95% CI p-value	13.55 (6.31 -20.78) 0.0003	0.84 (0.25- 1.44) 0.0056

Pediatric cases were compared among two time periods (Table 3). There was a total of 1,165 (72.1%) pediatric cases of leprosy from the years 2002-2009 and 446 (27.9%) cases from the years 2010-2017. Grade 2 disability accounted for 1.91% (n=22) of overall disability among pediatric cases in time period 1 and 2.58% (n=11) in time period 2. The proportion of cases with grade 2 disability in time period 2 was 1.35 times that of no disability in time period 1 (OR=1.35 p=0.013).

The overall leprosy incidence decreased over time from for both total cases and pediatric cases over the years 2002, 2009, and 2017 (Table 4). Pediatric cases also followed a downward trend. The incidence for pediatric cases in 2002 was 2.59 per 100,000 for pediatric cases ((95% CI (1.70 -3.47) p<0.0001). This then decreased to 1.59 per 100,000 ((95% CI (0.72 -2.46) (p=0.0004) in 2009 and then to 0.84 per 100,000 ((95% CI (0.25- 1.44) p=0.0056) in 2017.

Table 5: Health facilities and leprosy distribution in varying health service access municipalities in Minas Gerais, Brazil 2017

	Low health service access +	**Medium health service access ++**	**High health service access +++**	**P-Value (Chi-square**
Municipalities				
n. %	204 (84.30)	29 (11.98)	9 (3.72)	
Health Clinics per municipality				
Total, n %	86 (14.48)	251 (42.26)	257 (43.27)	<0.0001
Mean	0.43	9	29	
Cases				
Pediatric n, %	857 (53.20)	615 (38.18)	139 (8.62)	<0.0001
Adult Cases n, %	13,885 (53.30)	8,453 (32.45)	3,714 (14.27)	
Incidence				
Pediatric cases (per 100,000)	0.95	0.31	0.23	
std	±5.10	±0.80	±0.69	
p-value	0.0087	0.047	0.35	
CI	0.24- 1.65	0.0038-0.610	0.30- 0.76	
+ indicates < 5 medical facilities ++ indicates 5-18 medical facilities +++ indicates > 18+ medical facilities				

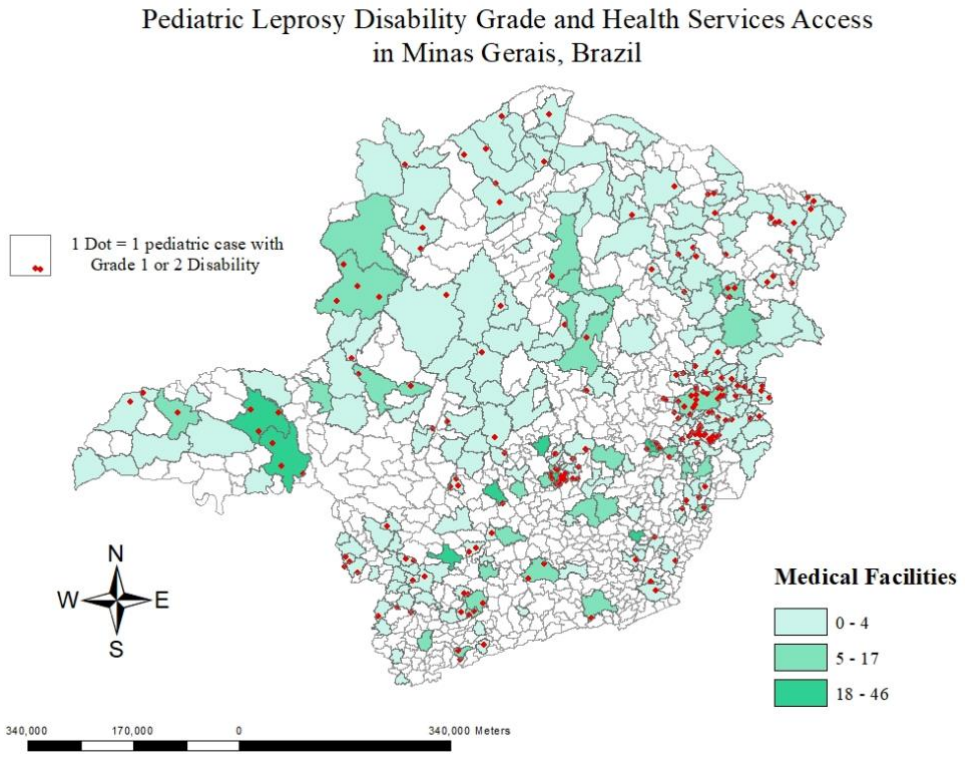
Table 5 explores the municipality-level association of leprosy burden with accessibility of health services. There were 204 municipalities that classified as low health service access, 29 as medium health service access, and 9 as high health service access. Within the low category, the total number of clinics was 89 (14.48%), with average number of clinics per municipality of 0.43. In the medium category, there was a total of 251 (42.26%) clinics with an average of 9 per municipality. In the high category, there was a total of 257 (43.27%), with an average of 29 clinics per municipality. There is an inverse relationship between number of cases per municipality and level of health services. As the level of health

service accessibility increases, the number of cases decrease. Table 6 summarizes the results of logistic regression analysis conducted to assess the association between access of care as the exposure and presence of grade 1 or 2 disability as the outcome. The best model had an Akaike information criterion (AIC) of 1151.84, and it included variables under consideration. This model, also, performed better than other models that adjusted for age and sex separately.

Table 6: Multivariate analysis of disability and health service among pediatric leprosy cases in Minas Gerais, Brazil after controlling for age and sex

Variable	Lower health service access × aOR	CI	P-value
Disability**	1.88	1.37-2.59	<0.0001
Age	1.15	1.08-1.22	<0.0001
Sex	0.99	0.74-1.35	0.99
**indicates a disability grade of 1 or 2 × indicates < 5 medical facilities			

Figure 5: Health Service Access and Disability in Pediatric Cases



Discussion:

Leprosy continues to be an important public health issue globally, and especially in many areas of Brazil, including Minas Gerais. Active transmission is ongoing and the presence of grade 2 disability among pediatric cases over time indicates hidden cases and a persistent level of infectious bacteria in the community. As noted by the WHO expert committee on leprosy, prevention of disability is dependent on early detection (21).

Additionally, the mean age of diagnosis for pediatric cases has decreased between time periods, indicating that children are contracting the disease at a younger age, suggesting more bacillus in circulation. While the difference between these two ages is small, if anything, we should be seeing an upward trend of mean age at diagnosis in later years. It is worth noting that the proportion of female to males increased among the years 2010-2017, although unclear why.

Notably, there was an increased proportion of multibacillary cases compared to paucibacillary cases in time period 2. Additionally, there was a higher proportion of Grade 2 disability in time period 2 versus time period 1. Grade 2 disability made up 1.91% of all cases in time period 1 whereas in time period 2, it made up 2.58%, an increase of 35.08%. This is consistent with findings from Raposo et al., who analyzed cases from Bahia, a northern state in Brazil and found an increased proportion of grade 2 disability from 2006 to 2015; their conclusions indicated delay in diagnosis and that grade 2 disability can be an indicator for hidden endemic transmission (26).

The results from this study are in line with the literature, as it is suggestive of a hidden epidemic in regions with a growing proportion of grade 2 disability among pediatric leprosy cases. This provides support to the study conducted by Vieria et. al.. They found 13 articles which reported grade 2 disability proportions in the range of 1.7% to 5.5%. These

proportions of disability among pediatric cases indicate that they are being infected at a young enough age to allow disability to progress to this advanced state. It is indicative of a strong circulation of the bacillus and lack of early detection in the age group (33). This shows the disease is reaching further stages before being diagnosed, indicating a need for a stronger surveillance system.

A study conducted by Monteiro addressed disability grade and detection rates in Tocantins, Brazil, a hyperendemic state for leprosy, covering a 12-year time period. In Monteiro's analysis, through bivariate analysis they found a lower proportion of grade 2 disability associated with increased detection of cases. Areas that had better trained professionals and greater access to Family Health Services (FHS) were able to prevent the progression of disease (15). The increase in proportion of grade 2 disability from time period 1 to time period 2 suggest there are undiagnosed cases and a potential hidden epidemic. This also provides justification that more active surveillance is needed and can greatly reduce disability burden.

The accessibility of medical facilities in each municipality in the dataset was assessed. Half of all pediatric cases and all cases in the dataset were from municipalities in the low access category, with 4 or less clinics. Additionally, the distribution of incidence of pediatric cases and all cases for the year 2017 among the three tiers of access to medical facilities supports this. In municipalities with pediatric cases, there was a direct relationship with having a greater pediatric case count and lower health care facilities per municipality. The incidence of leprosy among pediatric cases in 2017 was highest for those in low access municipalities compared to those in a higher access municipality. As mentioned previously, Brazil does not spend nearly as much of their gross domestic product as other Latin American countries on public health (37). More funding is needed in areas with fewer medical facilities as shown by these statistics.

Areas with fewer health clinics is a potential risk factor for increased disability among pediatric leprosy cases as well as likely a risk of increased transmission of the bacillus. A logistic regression identified a significant association of living in a municipality with lower access to health care services and having disability at the time of diagnosis. The finding of disability amongst patients living in lower access municipalities compared to no signs of disability amongst patients living in municipalities with higher access to health care, after controlling for age and sex is consistent with findings that being of a lower socioeconomic status is a potential risk factor for leprosy and increases the chance of delayed diagnosis. Cases of disability are more likely to be in municipalities with lower health care access.

The findings of this study are in alignment with previous literature examining pediatric cases of leprosy. The presence of grade 2 disability in pediatric cases is a reflection of the control activities in place and suggestive of a breakdown in the surveillance of new pediatric leprosy cases. Transmission is still ongoing in these communities and more so in areas with lower access to health services. It is the hope that these findings inspire future research and further exploration of pediatric cases and transmission of leprosy in Brazil.

Chapter 4: Implications and Recommendations

For further implications and ongoing policy, government officials should focus their energy on better surveillance among pediatric cases in lower accessible municipalities to ensure early detection and reduction of spread among the community. The first pillar the WHO set forth in their *Global Leprosy Strategy 2016–2020* encompassed governmental commitment to adequate resources for leprosy programs, and strengthening of surveillance (12). This study provides evidence of the need for ongoing work towards reaching that goal.

As mentioned in the review of the literature, there are not enough trained physicians to conduct widespread leprosy screening in Brazil. More highly trained specialists are needed if there is hope to catch the disease early, before it progresses to grade 1 or 2 disability. This is imperative to stop community transmission of the virus and reduce incidence among children. Health education measures among the population where there are concentrated new pediatric cases would also be recommended. Undiagnosed cases may be unaware of signs and symptoms to look for. Additionally, overall water sanitation and hygiene (WASH) educational programming and resources would benefit these communities from a general infectious disease standpoint.

Further research is needed on the transmission of leprosy in areas with lower access to health services. Health service funding for primary care centers is on the decline (13). For many citizens of Brazil, their community health clinic is their first line of defense.
The WHO stated specific target goals in their Operational Manual for their *Global Leprosy Strategy 2016–2020*: Zero disabilities among new pediatric patients and a grade-2 disability rate of less than 1 case per 1 million people. This study adds to current literature to further support the need for efforts to focus on the prevention of any new pediatric case being diagnosed with grade 2 disability. The municipalities with greatest risk of disability in pediatric cases should be prioritized. Resources should be allocated to better support

activities aimed at active surveillance of children in endemic areas of leprosy. Furthermore, municipality wide screening should be conducted in areas where there are fewer medical clinics and lower access to health services. An overall strengthening of the health care systems in municipalities with pediatric cases is critical to full reach the WHO's goal of a world without new cases of leprosy.

References

1. White C, Franco-Paredes C. Leprosy in the 21st century. Clin Microbiol Rev. 2015;28(1):80-94.

2. Paredes CF, Montes de Oca Sanchez G, White C. Global Leprosy Status in 2020: Still Losing Touch. Ann Acad Med Singapore. 2020;49(1):1-2.

3. Medley GF, Blok DJ, Crump RE, Hollingsworth TD, Galvani AP, Ndeffo-Mbah ML, et al. Policy Lessons From Quantitative Modeling of Leprosy. Clin Infect Dis. 2018;66(suppl_4):S281-S5.

4. Barbosa CC, Bonfim CVD, de Brito CMG, Ferreira AT, Gregorio V, de Oliveira ALS, et al. Spatial analysis of reported new cases and local risk of leprosy in hyper-endemic situation in Northeastern Brazil. Trop Med Int Health. 2018;23(7):748-57.

5. de Assis IS, Berra TZ, Alves LS, Ramos ACV, Arroyo LH, Dos Santos DT, et al. Leprosy in urban space, areas of risk for disability and worsening of this health condition in Foz Do Iguacu, the border region between Brazil, Paraguay and Argentina. BMC Public Health. 2020;20(1):119.

6. Lima ES, Roland Ide A, Maroja Mde F, Marcon JL. Vitamin A and lipid peroxidation in patients with different forms of leprosy. Rev Inst Med Trop Sao Paulo. 2007;49(4):211-4.

7. Freitas LR, Duarte EC, Garcia LP. Leprosy in Brazil and its association with characteristics of municipalities: ecological study, 2009-2011. Trop Med Int Health. 2014;19(10):1216-25.

8. Oliveira MB, Diniz LM. Leprosy among children under 15 years of age: literature review. An Bras Dermatol. 2016;91(2):196-203.

9. Srinivas G, Muthuvel T, Lal V, Vaikundanathan K, Schwienhorst-Stich EM, Kasang C. Risk of disability among adult leprosy cases and determinants of delay in diagnosis in five states of India: A case-control study. PLoS Negl Trop Dis. 2019;13(6):e0007495.

10. Maymone MBC, Laughter M, Venkatesh S, Dacso MM, Rao PN, Stryjewska BM, et al. Leprosy: Clinical Aspects and Diagnostic Techniques. J Am Acad Dermatol. 2020.

11. Chu T, Liu D, Huai P, Chen X, Han S, Chen S, et al. Comprehensive measures succeeded in improving early detection of leprosy cases in post-elimination era: Experience from Shandong province, China. PLoS Negl Trop Dis. 2020;14(2):e0007891.

12. Diseases WSDoCoNT. Guidelines for the diagnosis, treatment and prevention of leprosy. 2018 87.

13. Tasca R, Massuda A, Carvalho WM, Buchweitz C, Harzheim E. [Recommendations to strengthen primary health care in BrazilRecomendaciones para el fortalecimiento de la atencion primaria de salud en Brasil]. Rev Panam Salud Publica. 2020;44:e4.

14. Watts J. Brazil's health system woes worsen in economic crisis. Lancet. 2016;387(10028):1603-4.

15. Monteiro LD, Mota RMS, Martins-Melo FR, Alencar CH, Heukelbach J. Social determinants of leprosy in a hyperendemic State in North Brazil. Rev Saude Publica. 2017;51:70.

16. Fischer M. Leprosy - an overview of clinical features, diagnosis, and treatment. J Dtsch Dermatol Ges. 2017;15(8):801-27.

17. Ooi WW, Moschella SL. Update on leprosy in immigrants in the United States: status in the year 2000. Clin Infect Dis. 2001;32(6):930-7.

18. Bratschi MW, Steinmann P, Wickenden A, Gillis TP. Current knowledge on Mycobacterium leprae transmission: a systematic literature review. Lepr Rev. 2015;86(2):142-55.

19. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev. 2006;19(2):338-81.

20. Duarte-Cunha M, Marcelo da Cunha G, Souza-Santos R. Geographical heterogeneity in the analysis of factors associated with leprosy in an endemic area of Brazil: are we eliminating the disease? BMC Infect Dis. 2015;15:196.

21. World Health O. WHO Expert Committee on Leprosy. World Health Organ Tech Rep Ser. 2012(968):1-61, 1 p following

22. Negera E, Walker SL, Girma S, Doni SN, Tsegaye D, Lambert SM, et al. Clinico-pathological features of erythema nodosum leprosum: A case-control study at ALERT hospital, Ethiopia. PLoS Negl Trop Dis. 2017;11(10):e0006011.

23. Souza AD, el-Azhary RA, Foss NT. Management of chronic diseases: an overview of the Brazilian governmental leprosy program. Int J Dermatol. 2009;48(2):109-16.

24. Han XY, Aung FM, Choon SE, Werner B. Analysis of the leprosy agents Mycobacterium leprae and Mycobacterium lepromatosis in four countries. Am J Clin Pathol. 2014;142(4):524-32.

25. WHO. Enhanced global strategy for further reducing the disease burden due to leprosy (2011–2015). 2009.

26. Raposo MT, Reis MC, Caminha AVQ, Heukelbach J, Parker LA, Pastor-Valero M, et al. Grade 2 disabilities in leprosy patients from Brazil: Need for follow-up after completion of multidrug therapy. PLoS Negl Trop Dis. 2018;12(7):e0006645.

27. Ruiz-Fuentes JL, Rumbaut Castillo R, Hurtado Gascon LC, Pastrana F. Leprosy in children: a Cuban experience on leprosy control. BMJ Paediatr Open. 2019;3(1):e000500.

28. Rao D, Elshafei A, Nguyen M, Hatzenbuehler ML, Frey S, Go VF. A systematic review of multi-level stigma interventions: state of the science and future directions. BMC Med. 2019;17(1):41.

29. Forno C, Hausermann P, Hatz C, Itin P, Blum J. The difficulty in diagnosis and treatment of leprosy. J Travel Med. 2010;17(4):281-3.

30. Gomez LJ, van Wijk R, van Selm L, Rivera A, Barbosa MC, Parisi S, et al. Stigma, participation restriction and mental distress in patients affected by leprosy, cutaneous leishmaniasis and Chagas disease: a pilot study in two co-endemic regions of eastern Colombia. Trans R Soc Trop Med Hyg. 2020.

31. Chattree V, Khanna N, Rao DN. Alterations in T cell signal transduction by M. leprae antigens is associated with downregulation of second messengers PKC, calcium, calcineurin, MAPK and various transcription factors in leprosy patients. Mol Immunol. 2007;44(8):2066-77.

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

33. Vieira MCA, Nery JS, Paixao ES, Freitas de Andrade KV, Oliveira Penna G, Teixeira MG. Leprosy in children under 15 years of age in Brazil: A systematic review of the literature. PLoS Negl Trop Dis. 2018;12(10):e0006788.

34. Teixeira CSS, Pescarini JM, Alves FJO, Nery JS, Sanchez MN, Teles C, et al. Incidence of and Factors Associated With Leprosy Among Household Contacts of Patients With Leprosy in Brazil. JAMA Dermatol. 2020.

35. Freitas B, Xavier DR, Cortela D, Ferreira SMB. Leprosy in individuals under the age of fifteen in priority cities, Mato Grosso, Brazil. Rev Bras Epidemiol. 2018;21:e180016.

36. Santos MB, Santos ADD, Barreto AS, Souza MDR, Goes MAO, Barreto Alves JA, et al. Clinical and epidemiological indicators and spatial analysis of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil: an ecological and time series study. BMJ Open. 2019;9(7):e023420.

37. Massuda A, Hone T, Leles FAG, de Castro MC, Atun R. The Brazilian health system at crossroads: progress, crisis and resilience. BMJ Glob Health. 2018;3(4):e000829.

38. Oliveira APC, Gabriel M, Poz MRD, Dussault G. Challenges for ensuring availability and accessibility toin health care services under Brazil's Unified Health System (SUS). Cien Saude Colet. 2017;22(4):1165-80.

39. Barreto JG, Guimaraes Lde S, Frade MA, Rosa PS, Salgado CG. High rates of undiagnosed leprosy and subclinical infection amongst school children in the Amazon Region. Mem Inst Oswaldo Cruz. 2012;107 Suppl 1:60-7.

40. Gomes LC, Cortela D, Silva EA, Silva A, Ferreira SMB. Leprosy: prevalence and factors associated with seropositivity for anti-NDO-LID antibodies in children under 15 years of age. An Bras Dermatol. 2019;94(4):405-10.

41. Lana FC, Fabri Ada C, Lopes FN, Carvalho AP, Lanza FM. Deformities due to Leprosy in Children under Fifteen Years Old as an Indicator of Quality of the Leprosy Control Programme in Brazilian Municipalities. J Trop Med. 2013;2013:812793.

42. The Humanitarian Data Exchange HDX; 2020 [cited 2020. Available from: https://data.humdata.org/.