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Leprosy in children - a Cuban perspective

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Review article**Title:** Leprosy in children-a Cuban perspective.**Authors:** Ruiz-Fuentes, JL^{1*}; Rumbaut, R²; Hurtado, L³; Pastrana, F⁴.

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Review article

Title: Leprosy in children-a Cuban perspective.

ABSTRACT

Background: Children are believed to be the most vulnerable group for leprosy. Childhood leprosy reflects disease transmission in the community as well as the efficiency of ongoing disease control programs. In Cuba, leprosy isn't a national health problem, however new childhood leprosy cases are diagnosed every year. **Objectives:** Clinic-epidemiological pattern of childhood leprosy in Cuba over the past two decades were analyzed. We also evaluated the effectiveness of new intervention strategies developed in the country. **Results:** In the last 18 years, a total of 103 children in Cuba have been diagnosed, showing that active transmission of cases is maintained in 13 of the 15 Cuba's provinces. The majority of cases were multibacillary (66%). Paucibacillary cases were 34%. Clinically 60% of children have more than five lesions in all body. Voluntary reporting was the principal method of case detection. The presence of familial and extra-familial contact with leprosy cases may be a cause of concern, as it implies continuing transmission of the disease. Only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disability). A set of national investigations have been developed to intervene in a timely manner. Intervention strategies that combine clinical surveillance and laboratory test could be an option for early detection of childhood leprosy. **Conclusions:** Early detection of cases due to effective health education campaign, regular and complete treatment with MDT and contact tracing may be important in reducing the burden of leprosy in the community.

INTRODUCTION

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Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (Hansen's bacillus). It affects the skin, mucous membranes and peripheral nerves (1). It is associated with significant morbidity, as alongside the neurological damage, there are social, psychological and economic problems for the patient (2, 3).

Leprosy has been a major public-health problem in many developing countries for centuries. The World Health Organization (WHO) reports that in 2017, 210 671 new cases were diagnosed (4). The number of new cases in the Americas (29,101) [13.8 percent of the global burden] is surpassed only by Southeast Asia. (4, 5).

The household contacts of a baciliferous focus can show a variable response to the infection. Some acquire the disease in its benign form; others do so in its most serious form and others resist the entry and multiplication of the bacillus (6). In children any of the clinical forms of leprosy may occur (7), and they appear to be the most vulnerable group to *Mycobacterium leprae* infection (8). The number of new cases detected in children under fifteen years of age continues to be high. In 2017 children constituted 8.1% new cases worldwide, with 16 979 children diagnosed and 238 children with grade 2 disabilities (4). The diagnosis of a new case in children and adolescents shows the active circulation of bacillus. It also indicates the magnitude of the transmission of the disease that is directly related to the proportion of infection sources (multibacillary forms) without treatment and the efficacy of the actions of control programs (9).

In Cuba, leprosy stopped being a national health problem in 1993 when the rate of registered prevalence of less than 1 case per 10 000 inhabitants was reached. Despite the progress made in the control of the disease the detection of new cases has remained constant (10). Every year new cases of childhood leprosy are reported. The frequency of cases with disabilities is not significant, but the multibacillary clinical forms predominate. The early diagnosis of new leprosy cases continues to be a central point in the development of control strategies to reduce the time of exposure of children to these untreated infectious sources.

The present review addresses the characteristic of the diagnosis of childhood leprosy in Cuba in the last 18 years. It also evaluates the effectiveness of new intervention strategies developed in the country.

Archived documents, medical records, disease prevalence censuses conducted since 2000, epidemiological survey, Mandatory Notification Cards and leprosy morbidity and mortality statistics for 2000–2017 from the National Statistics Office of the Ministry of Public Health (MINSAP) were reviewed, along with scientific publications and National Guidelines for Leprosy Control (NGLC).

OPERATIONAL DEFINITIONS

Early diagnosis is carried out before symptoms appear, or within 11 months after their appearance, when there are still no signs of disability.

Late diagnosis occurs after 11 months of symptom onset or when the patient already has some disability.

Disability is classified as grades 0, 1 and 2, and applied separately to extremities and eyes (11). Table 1.

Table 1: World Health Organization leprosy disability grading system

Disabilities 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 (anesthesia) in 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 meters away)
2	Cases with both anesthesia and complications such as trophic ulcers, claw deformities and bone resorption in extremities	Involves severe vision impairment (vision worse than 6/60; inability to count fingers from 2 to 6 meters away) also includes lagophthalmos, iridocyclitis and corneal opacities.

Household contact any and every person who lives or has lived with a leprosy patient at least during a year.

CLINICAL MANIFESTATIONS OF LEPROSY

Childhood leprosy does not differ from adult leprosy but has characteristics that are specific to it. Children at an early age, from three to four years old, suffer from the initial or infantile form of the disease (12, 13). The first symptoms are usually at the neural level with a tingling sensation (paresthesia or acroparesthesia), especially in the extremities. In its initial stages macules or hypochromic and / or erythematous spots appears, which are usually of variable size, number and location, with diffuse or well-defined borders or contours. They may be associated with disorders of superficial sensitivity (thermal, tactile and painful) and may be accompanied by alteration of sweating or alteration of hair growth(14).

In older children, around adolescence, where there is supposed to be a longer time of exposure to the bacillus, other symptoms may appear more similar to those described for the polar forms of the disease. Occasionally, the only manifestation of the disease is the thickening of superficial nerves, especially the auricular, superciliary and ulnar muscles (15).

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3 Tuberculoid and childhood nodular leprosy are the most common presentations in
4 children. Tuberculoid leprosy presents with papulo-lichenoid lesions, characterized
5 by micronodules with acute plaques, single and small. Childhood nodular leprosy is
6 characterized by erythematous nodules on the face or limbs, usually a single lesion.
7 Both forms are of benign prognosis. Some authors suggest that this two types of
8 leprosy can disappear spontaneously and reappear over time installing the disorder
9 of sensitivity with involvement of one or more peripheral nerves, the face, buttocks
10 and extremities (16, 17).
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13 Less common presentations in childhood include indeterminate and lepromatous
14 leprosy. Indeterminate leprosy consists of a single macula of non-precise edges with
15 sensory disturbance located mainly on the face, limbs and buttocks. Lepromatous
16 leprosy is occasionally seen in children older than 5 years. The incidence of the
17 disease increases with age with diffuse infiltration of the skin, skin lesions and
18 internal organs. It is usually seen in children in countries with high endemicity of
19 the disease. The clinical manifestations involve the infiltration of large cutaneous
20 areas, especially in the cartilaginous areas of the nose and ears. The mucous
21 membranes of the nose are invaded by a large number of microorganisms. The
22 lesions can be hypochromic or hyperchromic, from small and single to multiple and
23 large including nodules (18)
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27 In cases in which a neural lesion appears, this is usually irreversible, the loss of
28 sensory, sympathetic and motor function end in severe disability of the hands, feet
29 and muscles. This leads to mutilation and deformity (19).
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32 Late diagnosis can lead to the appearance of disabilities ranging from lack of
33 sensitivity to motor paralysis of a limb. It can also give rise to secondary lesions that
34 are not specific to the pathology, such as burns and wounds, which, if not treated
35 properly, will lead to bone destruction or reabsorption. Reaction complications are
36 rare in children (20).
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39 **EPIDEMIOLOGY**

40 In the last five years (2013-2017), there has been a slight decrease in the number of
41 cases diagnosed annually, with 190 new cases in 2017 (4) Figure 1. This diminution
42 may suggest apparent progress. However each year new cases of childhood leprosy
43 are diagnosed in Cuba, which shows that active transmission of cases is maintained
44 in almost all the provinces of the country (13 of the 15 Cuba's provinces). In the last
45 18 years, a total of 103 children in Cuba have been diagnosed. Figure 1 shows the
46 number of cases of childhood leprosy and the total number of new cases diagnosed
47 in Cuba between 2000 and 2017. In 2013, the largest number of cases of childhood
48 leprosy was diagnosed with 11 children (21).
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51 The provinces that have the most frequently reported cases in the period 2000-2017
52 are Granma, Santiago, Guantánamo, Ciego de Ávila and Havana (21-25).
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56 The age group most commonly affected by the disease among children under 15
57 years old was that between 10 and 14 years of age (Table 2). This is due to the
58 disease's long incubation period of approximately three to five years (26, 27). The
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youngest patients diagnosed in Cuba were three years old. An equal number of boys and girls have been affected (25).

Table 2. Distribution by age of children diagnosed with leprosy in Cuba.

Years /Age	0-4	5-9	10-14	Total
2000		1	4	5
2001		2	3	5
2002			2	2
2003			3	3
2004		2	1	3
2005		1	7	8
2006			1	1
2007			2	2
2008		1	3	4
2009		3	5	8
2010		2	5	7
2011		1	9	10
2012		4	5	9
2013		4	7	11
2014	1		7	8
2015		4	5	9
2016		1	2	3
2017	1	2	2	5
Total	2	28	73	103

The last decade has seen an increase in multibacillary forms. Figure 2 (27, 28).

This is evidence, in our opinion of the greater exposure of these children to the bacillus, due largely to the maintenance in the community of sick people, especially multibacillary patients, without treatment.

Regarding the number of lesions, we found that 62 children had more than five lesions in all the body. This is different to that reports from others countries where children and adolescents usually have had a single lesion in exposed areas (29, 30). We have also found that in this period one children was diagnosed with musculoskeletal manifestations, such as arthralgia and myalgia, on presentation. Additionally another important indicator is the percentage of children with disability grade 1 and 2 among the new cases of childhood leprosy. In this period only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disability). Neder *et al.* reported that 14% of 50 children with leprosy in Cuiabá, Brazil, examined had musculoskeletal manifestations with asymmetric polyarthritis of the small articulations of the hands (31).

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3 In Cuban children the average range in terms of the time of evolution of the skin
4 lesions and the first consultation is less than a year, in almost cases, according to
5 parents. This fairly short time between the start of the disease and the consultation
6 is probably due to the easy access of patients to primary care (32). Others authors
7 refer to a time of 18 month between presentation and diagnosis (8). However this
8 indicator shows an inconsistent behavior taking into account that in children the
9 initial manifestations of the disease are observed predominantly in the skin and the
10 multibacillary form requires many years of evolution (33, 34). Some authors suggest
11 that in the pediatric ages the skin alterations take years to establish and many times
12 in the initial or benign forms of the leprosy they present as nonspecific chronic
13 dermatitis. It is clear that we are facing a situation of little perception of risk of both
14 the population and health personnel. Due undoubtedly to the drastic decrease of
15 new cases experienced in Cuba in the last decade. On the other hand, 89% of the
16 cases diagnosed have at least one case of leprosy diagnosed in their family, so they
17 must be diagnosed by household contacts tracing.

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25 It is accepted that the main transmission for leprosy are the upper airways. The
26 multibacillary patients without treatment are the largest source of expelling
27 bacillus. That's why leprosy patients' household contacts have the highest
28 probability of acquiring the disease (35, 36). In Cuba some of the children presenting
29 with leprosy are considered Index Case. The source of infection is diagnosed after
30 examining the children's household contacts. In a retrospective study conducted
31 over 20 years (1989-2006) at the pediatric Hospital Juan Manuel Marquez, 60% of
32 children with leprosy had a known source of infection in the family and in 48% of
33 the cases were grandparents(27). The behavior in the last decade has not changed
34 because it is recognized in the literature that especially in the case of children; family
35 contact is the primary source of the infection (34). It is almost always an
36 intradomicilliary family member. Special attention to this epidemiological pattern
37 can help in the identification of new cases. Children do not have a mature immune
38 system (37) and considering that predisposition to developing the disease is
39 inherited (38, 39), they are in the most vulnerable group. Active surveillance on this
40 age group is therefore essential.

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48 Romero-Montoya et al. in a study of 12 children with leprosy in Colombia found that
49 nine of them had a household contact leprosy patient. They also reported that the
50 children appear to be more prone to illness than other family members (40). The
51 risk of a person developing leprosy is nine times greater among household contacts
52 and up to four times greater among contacts with neighbors(41). Durães et al. in
53 Brazil, demonstrated a risk of illness of 2.4 times greater than the case index in
54 household contacts as compared to household perimeter contacts, and 2.05 if the
55 contacts were first degree relatives. Considering the same type of household contact,
56 the higher incidence among blood relatives within a nuclear family, as compared to
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3 the other blood relatives, demonstrates the component of genetic predisposition,
4 which has been widely reported in prior literature (42).
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7 All described data indicates that the strategies designed to reduce cases of childhood
8 leprosy are still insufficient and that children who are at risk of developing the
9 disease still escape from active surveillance. This situation has shown the need to
10 develop strategies to improve surveillance and active search among suspected
11 cases.
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14 15 **DIAGNOSIS**

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17 The diagnosis of leprosy is essentially clinical. A complete general and
18 dermatological examination regarding the morphology, number, size, site, color,
19 anesthesia, margins, surface, satellite lesions and general clearing of skin lesions and
20 involvement of peripheral truncal nerves, and cutaneous nerves must be done,
21 called thermal sensitive test (20). This test is very difficult to conduct particularly in
22 children. Reactions and deformities must be also noted.
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27 The diagnosis requires good clinical skill, as many skin lesions can be asymptomatic
28 and often simulate other dermatoses, common or rare that can be confused or
29 coexist with leprosy (28). It is important to make the differential diagnoses with
30 other dermatoses (43). For this reason is necessary complement the evaluation with
31 the skin smear microscopy and a biopsy with a histopathological study of the
32 cutaneous lesion (44).
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37 Slit-skin smear (SSS) examination is the test for microscopic detection of acid-fast
38 bacilli (AFB). In Cuba, for the diagnosis of a new case, a total of six or seven samples
39 (bilaterally at the ear lobes and elbows lymph, in addition to extended nasal mucus
40 of both pits and the lymph of one or two skin lesions)(45).
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44 The sample should be taken from the edges of the lesion. To obtain dermal fluid
45 samples, a clamp should be made with both fingers to decrease blood flow. With a
46 sheet of sterilized scalpel a small incision is made. Lymph obtained is smeared onto
47 a microscopic slide sheet and air dried (they are not useful samples with blood)(46).
48 These preparations are heat fixed and stained with the Ziehl-Neelsen carbol fuschin
49 stain and graded as per Ridley's scale for bacteriological index (BI) (47).
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53 Taking a sample for smear microscopy is painful. Some authors suggest conducting
54 this exam only in children 10 years and older (9). It is very difficult to observe
55 Hansen bacilli on the smear, so the finding of positive smear microscopy is rare in
56 children. Some authors reported that almost 10% of children under 15 years of age
57 had a positive smear microscopy (13, 48). However, Samaniego et al., (2006) found
58 positive smear microscopy in 22% (19/88) of children under 15 years old who were
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3 submitted to the exam, while Palit et al found between 5.42-25% of positive smear
4 microscopy in a review of at least 12 Indian studies that included more than 1 000
5 children (49, 50). In Cuba since 2000 there has been an increase of positive smear
6 microscopy in children. Between 2012 and 2017, 27/39 children diagnosed had
7 positive smear microscopy (69%).
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11 For children a biopsy, together with a histopathological study of the cutaneous
12 lesions, seems to be the more appropriate choice to increase the chance of finding the
13 bacillus in the lesion (51).
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16 **ACTIVE SEARCH OF NEW CASES**

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19 The NLCP in agreement with other Cuban health institutions (Tropical Medicine
20 Institute Pedro Kourí, Pediatric Hospital Juan Manuel Marquez and Provincial
21 Center for Hygiene, Epidemiology and Microbiology of Havana) have developed
22 intervention projects with the objective to identifying those children who are
23 contacts of patients with leprosy earlier and proposing a follow-up strategy that
24 allows early diagnosis.
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29 A set of national investigations have been developed to intervene in a timely
30 manner. Some projects considered improve clinical dermatological evaluation of all
31 children contacts of patients. Other strategies combine conventional methods with
32 the use of serological method based on phenolic glycolipid I and molecular methods
33 using PCR-Rlep, to perform an initial assessment of all children which are contacts
34 of patients with leprosy.
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39 In Cuba several studies have been carried out using the UMELISA-Hansen kit for the
40 detection of IgM antibodies against the phenolic glycolipid I (52). In a study
41 conducted in three Cuban's provinces between 2013 and 2015, a serological follow-
42 up was carried out every six months during two years in children household
43 contacts of patients with leprosy. In this period a total of 151 children were included
44 in the study, of whom 44 (29%) were positive for phenolic glycolipid. Of these
45 children, 11 were diagnosed in the three years of the project (52). The results could
46 serve as a basis to evaluate the use of this tool as a possible strategy for active
47 searching for new cases of leprosy among children contacts of patients. Currently,
48 studies have been conducted using the anti-PGL-I to evaluate the seroprevalence of
49 household and school contacts in hyperendemic areas. Barreto et al. conducted a
50 study with school children in the Amazon region and found that 777 (48.8%) of the
51 1,592 school children proved to be seropositive for anti-PGL-I (53). This
52 seroprevalence suggested the possibility of undiagnosed cases and subclinical
53 infections among children in the Amazon region. The importance of the study on
54 these school children was the early diagnosis of the disease (53).
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3 Despite the active search for new cases among contacts in the last 18 years in Cuba,
4 in 23% of leprosy cases in children, the source of infection has not been found
5 because no family history was recognized and no case was diagnosed during the
6 evaluation of the contacts. This is unusual, because it is recognized that in children
7 the prolonged and narrow social interactions are much lower than in adults (54), so
8 research studies should be able to determine the source of infection of these minors.
9 Is evident that the development of new strategies and the integration of several tools
10 in order to reduce the late diagnosis of new leprosy cases is necessary to reduce
11 leprosy burden and to limit the infection.
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16 In Cuba in 2014, eight children were diagnosed. All cases presented with the MB
17 form including two children with a late diagnosis of more than two years of
18 symptoms. One of them had a grade 2 disability. A comprehensive study was carried
19 out with household contacts of leprosy children with the objective of identifying the
20 infection source. Laboratory test included SSS of ear lobes and elbows, serological
21 test (UMELISA-Hansen) (52) and PCR-Rlep from lymph smear (55). The suspected
22 source of infection was identified in 6 of the 8 children.
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27 We describe the characteristics of the families that were part of the study. **Case**
28 **number 1:** masculine 4 years old. It presented one nevus type macule,
29 bacteriological index 1, phenolic glycolipid I serology positive, PCR-Rlep positive
30 and was diagnosed as multibacillary patient. His mother was diagnosed with MB
31 leprosy in 1992 and diagnosed again in 2014. His grandmother and great-
32 grandmother were diagnosed in 2014 and 1992 respectively. And also found that a
33 great grandmother has also tuberculosis. **Case number 2:** masculine 13 years old.
34 It presented nasal bleeding, nodules, falls of the tails of the eyebrows and eyes
35 lashed, leonine fascias, bacteriological index 1, phenolic glycolipid I serology
36 negative, PCR-Rlep positive and was diagnosed as multibacillary patient. His uncle
37 and his grandmother both from mother branch where diagnosed after the child.
38 **Case number 3:** feminine 12 years old. It presented numerous hypochromic macules
39 and cramps. Bacteriological index zero, PGL-I serology positive, PCR-Rlep positive
40 and was diagnosed as MB patient. She lived during her birth with three no relative
41 persons; they have a diagnosis of multibacillary leprosy since 2000. **Case number**
42 **4:** masculine 15 years old. He presented lower limb pain, epistaxis, grade two
43 disability, tenar atrophy and cramps, preacher hand. Bacteriological index 1, PGL-
44 I serology negative, PCR positive. Both maternal grandparents, a brother of his
45 grandfather and an aunt had also a diagnosis of multibacillary leprosy between 1998
46 and 2010. **Case number 5:** feminine 15 years olds. It presented nasal and bleeding
47 obstruction, nodules and cramps. Bacteriological index 5, PGL-I serology negative,
48 PCR-Rlep positive, diagnosed as multibacillary patient. Her mother was diagnosed
49 as paucibacillary patient after her diagnosis. **Case number 6:** masculine 10 years
50 olds. Hyperchromic macules, cramps, nasal obstruction. Bacteriological index 2,
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3 PGL-I serology negative, PCR-Rlep positive, multibacillary patient. His parents and
4 an uncle were diagnosis as multibacillary cases four years ago.
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7 In four cases the infectious source were previously diagnosed and treated person.
8 In two other children the sources of infection were first degree blood relatives who
9 were new cases diagnosed and treated. Only in two children we were not able to
10 find out the sources of infection. However they live in Cuba`s regions with high
11 incidence of leprosy so we believe that contacts who do not live with children could
12 be the sources of infection. That`s why the new strategies now include school
13 contacts and neighbors.
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18 In 2018 Ramasamy studied 358 household contacts of 117 childhood leprosy cases
19 in a tertiary referral center in India. They found that 17 (4.8%) were diagnosed as
20 new cases of leprosy, 30 (8.4%) were known cases currently on treatment and 46
21 (12.8%) had been previously treated for leprosy (54). They concluded that a
22 household contact survey is an effective method for case detection in leprosy control
23 programmes.
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27 **CONCLUSIONS**

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30 The diagnosis of childhood leprosy in Cuba shows the relevance of leprosy control
31 activities even in areas with low prevalence to sustain the elimination of leprosy.
32 The intervention strategies used in Cuba have made it possible to increase the
33 effectiveness of the active search for cases of childhood leprosy. Early detection of
34 cases due to effective health education campaign, regular and complete treatment
35 with MDT and contact tracing may be important in reducing the burden of leprosy
36 in the community.
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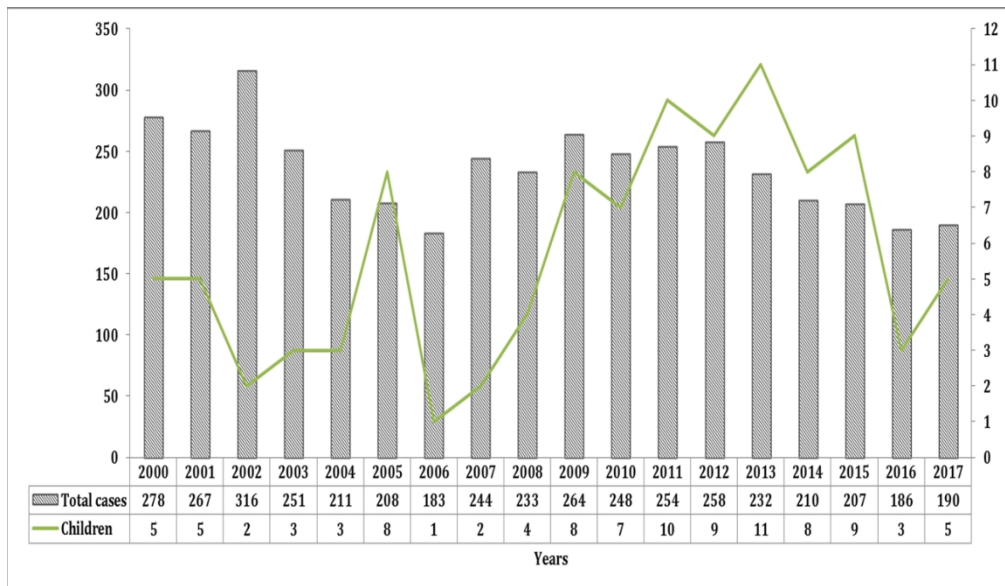
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58 **Figure Legends**
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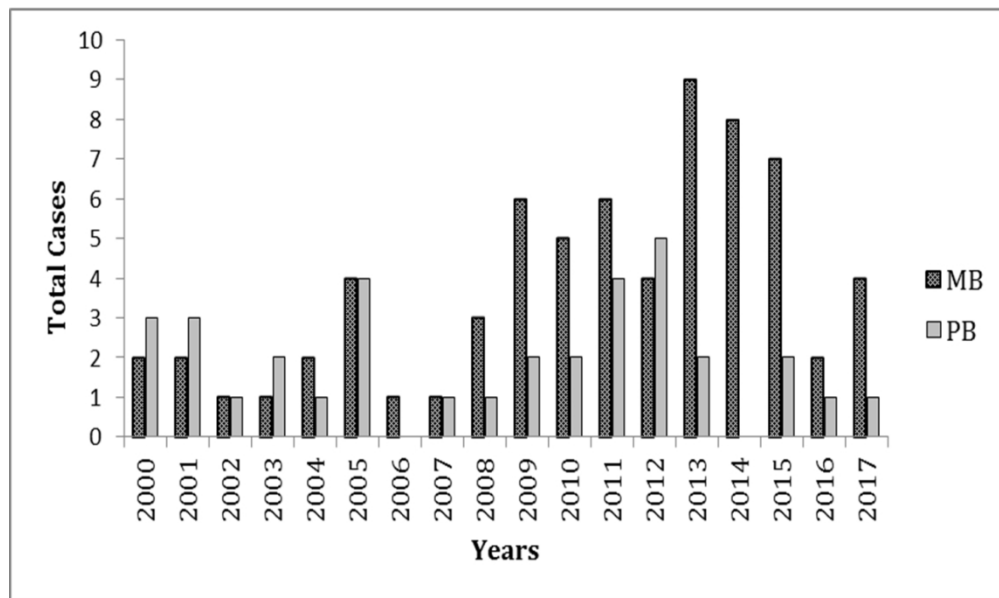
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3 Figure 1. Number of cases of childhood leprosy for years and the total number of
4 new leprosy cases diagnosed. Cuba 2000-2017. Left vertical axis represents total of
5 new cases diagnosed in the country. Right vertical axis represents total cases of
6 childhood leprosy diagnosed in Cuba in the same period
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11 Figure 2. Distribution of cases of childhood leprosy per year according to
12 operational classification. PB: paucibacillary patients; MB: multibacillary patients.
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Review article

Title: Leprosy in children-a Cuban experience on leprosy control.

ABSTRACT

Background: Children are believed to be the most vulnerable group for leprosy. Childhood leprosy reflects disease transmission in the community as well as the efficiency of ongoing disease control programs. In Cuba, leprosy isn't a national health problem, however new childhood leprosy cases are diagnosed every year. **Objectives:** We summarize the historical experience of childhood leprosy control in Cuba over the past two decades. **Results:** In the last 18 years, a total of 103 children have been diagnosed in Cuba, showing that active transmission of cases is maintained in 13 of the 15 Cuba's provinces. The majority of cases were multibacillary (66%). Paucibacillary cases were 34%. Clinically 60% of children have more than five lesions in all body. Voluntary reporting was the principal method of case detection. The presence of familial and extra-familial contact with leprosy cases may be a cause of concern, as it implies continuing transmission of the disease. Only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disability). A set of national investigations have been developed to intervene in a timely manner. Intervention strategies that combine clinical surveillance and laboratory test could be an option for early detection of childhood leprosy. **Conclusions:** Early detection of cases due to effective health education campaign, regular and complete treatment with MDT and contact tracing may be important in reducing the burden of leprosy in the community.

Keywords: childhood, Cuba, epidemiology, leprosy

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It affects the skin, mucous membranes and peripheral nerves (1). It is associated with significant morbidity, as alongside the neurological damage, there are social, psychological and economic problems for the patient (2, 3).

Leprosy has been a major public health problem in many developing countries for centuries. The World Health Organization (WHO) reports that in 2017, 210 671 new cases were diagnosed (4). The number of new cases in the Americas (29,101 [13.8 percent of the global burden]) is surpassed only by Southeast Asia. (4, 5).

The household contacts of a baciliferous patient can show a variable response to the infection. Some acquire the disease in its benign form; others do so in its most serious form and others resist the entry and multiplication of the bacillus (6). In children, any of the clinical forms of leprosy may occur (7), and they appear to be the most vulnerable group to *Mycobacterium leprae* infection (8). The number of new cases detected in children under fifteen years of age continues to be high. In 2017 children constituted 8.1% new cases worldwide, with 16 979 children diagnosed and 238 children with grade 2 disabilities. Table 1 (4). The diagnosis of a new case in children and adolescents shows the active circulation of bacillus. It also indicates the magnitude of the transmission of the disease that is directly related to the proportion of infection sources (multibacillary forms) without treatment and the efficacy of the actions of control programs (9).

In Cuba, leprosy stopped being a national health problem in 1993 when the rate of registered prevalence of less than 1 case per 10 000 inhabitants was reached. Despite the progress made in the control of the disease, the detection of new cases has remained constant (10). Every year new cases of childhood leprosy are reported. The frequency of cases with disabilities is not significant, but the multibacillary clinical forms predominate. The early diagnosis of new leprosy cases continues to be a central point in the development of control strategies to reduce the time of exposure of children to these untreated infectious sources.

The present review summarized the Cuban experience of childhood leprosy control in the last 18 years.

Archived documents, medical records, disease prevalence censuses conducted since 2000, epidemiological survey, Mandatory Notification Cards, and leprosy morbidity and mortality statistics for 2000–2017 from the National Statistics

Office of the Ministry of Public Health (MINSAP) were reviewed, along with scientific publications and National Guidelines for Leprosy Control (NGLC). The data included in this review was collected by the National Program for Leprosy Control as part of their monthly analysis of leprosy situation in the country.

Table 1: World Health Organization leprosy disability grading system

Disabilities 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 (anesthesia) in 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 meters away)
2	Cases with both anesthesia and complications such as trophic ulcers, claw deformities and bone resorption in extremities	Involves severe vision impairment (vision worse than 6/60; inability to count fingers from 2 to 6 meters away) also includes lagophthalmos, iridocyclitis, and corneal opacities.

CLINICAL MANIFESTATIONS OF LEPROSY

The diagnosis of leprosy is essentially clinical. Childhood leprosy does not differ from adult leprosy but has specific characteristics. Children at an early age, from three to four years old, suffer from the initial or infantile form of the disease (12, 13). The first symptoms are usually at the neural level with a tingling sensation (paresthesia or acroparesthesia), especially in the extremities. In its initial stages, macules or hypochromic and/or erythematous spots appears, which are usually of variable size, number, and location, with diffuse or well-defined borders. They may be associated with disorders of superficial sensitivity (thermal, tactile and painful) and may be accompanied by alteration of sweating or alteration of hair growth(14).

In older children, around adolescence, where there is supposed to be a long time of exposure to the bacillus, other symptoms may appear more similar to those described for the polar forms of the disease. Occasionally, the only manifestation of the disease is the thickening of superficial nerves, especially the auricular, superciliary and ulnar muscles (15).

Tuberculoid and childhood nodular leprosy are the most common presentations in children. Tuberculoid Leprosy (TL) presents single and small lesions. Elevated

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3 erythema with dry surface and alopecia may be present. Childhood nodular
4 leprosy is characterized by erythematous nodules on the face or limbs, usually a
5 single lesion. Both forms are of benign prognosis. Some authors suggest that this
6 two types of leprosy can disappear spontaneously and reappear over time
7 installing the disorder of sensitivity with the involvement of one or more
8 peripheral nerves, the face, buttocks, and extremities (16, 17).
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12 Less common presentations in childhood include Indeterminate and Lepromatous
13 Leprosy.
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15 Indeterminate Leprosy (IL according to Ridley and Jopling classification) (18)
16 consists of a single macula of non-precise edges with sensory disturbance located
17 mainly on the face, limbs, and buttocks. Lepromatous Leprosy (LL) is occasionally
18 seen in children older than 5 years. The incidence of the disease increases with age.
19 It is usually seen in children in countries with high endemicity of the disease. The
20 clinical manifestations involve the infiltration of large cutaneous areas, especially
21 in the cartilaginous areas of the nose and ears. The mucous membranes of the nose
22 are invaded by a large number of microorganisms. The lesions can be hypochromic
23 or hyperchromic, from small and single to multiple and large including nodules
24 (19)
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28 In cases in which a neural lesion appears, this is usually irreversible, the loss of
29 sensory, sympathetic and motor function ends in severe disability of the hands,
30 feet, and muscles. This leads to mutilation and deformity (20).
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35 Late diagnosis can lead to the appearance of disabilities ranging from lack of
36 sensitivity to motor paralysis of a limb. It can also give rise to secondary lesions
37 that are not specific to the pathology, such as burns and wounds, which, if not
38 treated properly, will lead to bone destruction or reabsorption. Reaction
39 complications are rare in children (21).
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43 In Cuba regarding the number of lesions, we found that 62 children of 103
44 diagnoses in this period, had more than five lesions in all the body. We have also
45 found that in this period one child was diagnosed with musculoskeletal
46 manifestations, such as arthralgia and myalgia, on presentation. The child wasn't in
47 reaction. Additionally, another important indicator is the percentage of children
48 with disability grade 1 and 2 among the new cases of childhood leprosy. In this
49 period only four children had disabilities (one with grade 2 disabilities and three
50 with a grade 1 disabilities).
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52 53 54 **EPIDEMIOLOGY**

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56 In the last five years (2013-2017), there has been a slight decrease in the number
57 of leprosy cases diagnosed annually, with 190 new cases in 2017 (4) Figure 1. This
58 diminution may suggest apparent progress. However each year new cases of
59 childhood leprosy are diagnosed in Cuba, which shows that active transmission of
60

cases is maintained in almost all the provinces of the country (13 of the 15 Cuba's provinces). Figure 1 shows the number of cases of childhood leprosy and the total number of new cases diagnosed in Cuba between 2000 and 2017. In 2013, the largest number of cases of childhood leprosy was diagnosed with 11 children (2).

The provinces that have the most frequently reported cases in the period 2000-2017 are Granma, Santiago, Guantánamo, Ciego de Ávila and Havana (22-26).

The age group most commonly affected by the disease among children under 15 years old was that between 10 and 14 years of age (Table 2). This is due to the disease's long incubation period of approximately three to five years (27, 8). The youngest patients diagnosed in Cuba were three years old. An equal number of boys and girls have been affected (26).

Table 2. Distribution by age of children diagnosed with leprosy in Cuba.

Years /Age	0-4	5-9	10-14	Total
2000		1	4	5
2001		2	3	5
2002			2	2
2003			3	3
2004		2	1	3
2005		1	7	8
2006			1	1
2007			2	2
2008		1	3	4
2009		3	5	8
2010		2	5	7
2011		1	9	10
2012		4	5	9
2013		4	7	11
2014	1		7	8
2015		4	5	9
2016		1	2	3
2017	1	2	2	5
Total	2	28	73	103

The last decade has seen an increase in multibacillary forms (BL and LL). Figure 2 (8, 9). This is evidence, in our opinion of the greater exposure of these children to the bacillus, due largely to the maintenance in the community of sick people, especially multibacillary patients, without treatment.

CUBAN' STRATEGIES FOR LEPROSY CONTROL

All described data indicates that the strategies designed to reduce cases of childhood leprosy are still insufficient. Children who are at risk of developing the disease still escape from active surveillance. This situation has shown the need to develop strategies to improve surveillance and active search among suspected cases.

The National Program for Leprosy Control in agreement with other Cuban health institutions (Tropical Medicine Institute Pedro Kourí, Pediatric Hospital Juan Manuel Marquez and Provincial Center for Hygiene, Epidemiology and Microbiology of Havana) have developed intervention projects with the objective to identifying those children who are contacts of patients with leprosy earlier and proposing a follow-up strategy that allows early diagnosis.

A set of national investigations have been developed to intervene in a timely manner. Some projects considered improve clinical dermatological evaluation of all children contacts of patients. Other strategies combine conventional methods with the use of serological method based on phenolic glycolipid I and molecular methods, to perform an initial assessment of all children which are contacts of patients with leprosy.

In general terms, the most important methods for early diagnosis is the dermatological examination regarding signs and symptoms of leprosy in children and adult. In children, this test is very difficult to conduct. If some of the children appear to be suspicious, a bacteriological and pathological analysis is recommended. In Cuba, for children diagnosis, a total of six samples of lymph smears are taken and a biopsy of the cutaneous lesions for histopathological study. The new case is classified according to the WHO's classification. The treatment is according to WHO's recommendation (5) and is controlled and supervised by the local health structures (family doctors and nurses). Those professionals along with local dermatologist are responsible for clinical surveillance of family and non-family contacts of the new case, every year during five years. This clinical surveillance combine with a serological follows up of suspicious children shows interesting results in terms of early diagnosis. Also, the integration of molecular methods of diagnosis could be a great strategy for leprosy control in Cuba. Moreover, the presence in Cuba of regions with a high incidence of leprosy makes us believe that contacts that do not live with children could be an important source of infection. That's why the new strategies now include school contacts and neighbors.

CUBAN EXPERIENCE IN CONTEXT WITH OTHERS AMERICAN COUNTRIES

The Cuban public health system has a recognized robustness so, for children with leprosy the average range in terms of the time of evolution of the skin lesions and the first consultation is less than a year, according to parents. This fairly short time between the start of the symptoms and the consultation is probably due to the easy access of patients to primary care (30). In other countries, authors refer to a time of 18 months between presentation and diagnosis (8). However, this indicator, at least in Cuba, shows an inconsistent behavior taking into account that in children the initial manifestations of the disease are observed predominantly in the skin and the multibacillary form requires many years of evolution (31, 32). Some authors suggest that in the pediatric ages the skin alterations take years to establish and many times in the initial forms of leprosy, they present as nonspecific chronic dermatitis. It is clear that in Cuba we are facing a situation of little perception of risk of both the population and health professionals. Due undoubtedly to the drastic decrease of new cases experienced in Cuba in the last decade. On the other hand, 89% of the cases diagnosed have at least one case of leprosy diagnosed in their family, so they must be diagnosed by household contacts tracing.

It is accepted that the main transmission for leprosy is the upper airways. multibacillary patients without treatment are the largest source of expelling bacillus. That's why leprosy patients' household contacts have the highest probability of acquiring the disease (33, 34). In Cuba, some of the children presenting with leprosy are considered Index Case (first case in a family). The source of infection is diagnosed after examining the children's household contacts. In a retrospective study conducted over 20 years (1989-2006) at the pediatric Hospital Juan Manuel Marquez, 60% of children with leprosy had a known source of infection in the family and in 48% of the cases were grandparents(28). The behavior in the last decade has not changed because it is recognized in the literature that especially in the case of children; family contact is the primary source of the infection (32). It is almost always an intra-familial member. Special attention to this epidemiological pattern can help in the identification of new cases. Children do not have a mature immune system (35) and considering that predisposition to developing the disease is inherited (36, 37), they are in the most vulnerable group. Active surveillance on this age group is therefore essential.

Romero-Montoya et al. in a study of 12 children with leprosy in Colombia found that nine of them had a household contact leprosy patient. They also reported that the children appear to be more prone to illness than other family members (38). The risk of a person developing leprosy is nine times greater among household contacts and up to four times greater among contacts with neighbors(39). Durães et al. in Brazil, demonstrated a risk of illness of 2.4 times greater than the case

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3 index in household contacts as compared to household perimeter contacts, and
4 2.05 if the contacts were first degree relatives. Considering the same type of
5 household contact, the higher incidence among blood relatives within a nuclear
6 family, as compared to the other blood relatives, demonstrates the component of
7 genetic predisposition, which has been widely reported in prior literature (40).
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11 In Cuba, several studies have been carried out using the UMELISA-Hansen kit for
12 the detection of IgM antibodies against the phenolic glycolipid I (41). In a study
13 conducted in three Cuban's provinces between 2013 and 2015, a serological
14 follow-up was carried out every six months during two years in children
15 household contacts of patients with leprosy. In this period a total of 151 children
16 were included in the study, of whom 44 (29%) were positive for phenolic
17 glycolipid. Of these children, 11 were diagnosed in the three years of the project
18 (41). The results could serve as a basis to evaluate the use of this tool as a possible
19 strategy for active searching for new cases of leprosy among children contacts of
20 patients. Currently, studies have been conducted using the anti-PGL-I to evaluate
21 the seroprevalence of household and school contacts in American's hyperendemic
22 areas. Barreto et al. conducted a study with school children in the Amazon region
23 and found that 777 (48.8%) of the 1,592 school children proved to be seropositive
24 for anti-PGL-I (42). This seroprevalence suggested the possibility of undiagnosed
25 cases and subclinical infections among children in the Amazon region. The
26 importance of the study on these school children was the early diagnosis of the
27 disease (42).
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35 The Cuban experience about leprosy control in America's region is relevant in
36 terms of control programs strategies that could be economically sustainable for
37 developing countries.
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42 **CONCLUSIONS**

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45 The diagnosis of childhood leprosy in Cuba shows the relevance of leprosy control
46 activities even in areas with low prevalence to sustain the elimination of leprosy.
47 The intervention strategies used in Cuba have made it possible to increase the
48 effectiveness of the active search for cases of childhood leprosy. Early detection of
49 cases due to effective health education campaign, regular and complete treatment
50 with MDT and contact tracing may be important in reducing the burden of leprosy
51 in the community.
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Conflict of interest statement

The authors declare there are no conflicts of interest

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Jenny Laura Ruiz Fuentes made substantial contributions to the conception and design of the work; carried out the analysis and interpretation of data, drafting the work and made the Final approval of the version to be published

Raisa Rumbaut carried out the acquisition, analysis and interpretation of data for the work, made critical revision for important intellectual content, made the final approval of the version to be published

Laura Hurtado carried out the acquisition, analysis and interpretation of data for the work, made critical revision for important intellectual content, made the final approval of the version to be published

Fernanda Pastrana Carried out the revision of the manuscript critically for important intellectual content; made the final approval of the version to be published and ensured that questions related to the accuracy or integrity of the work were appropriately investigated and resolved.

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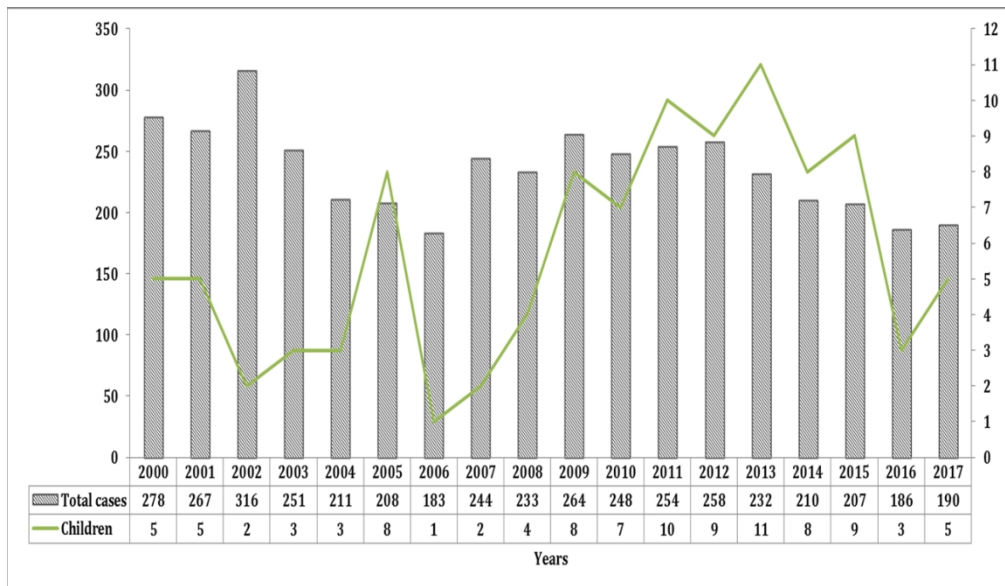
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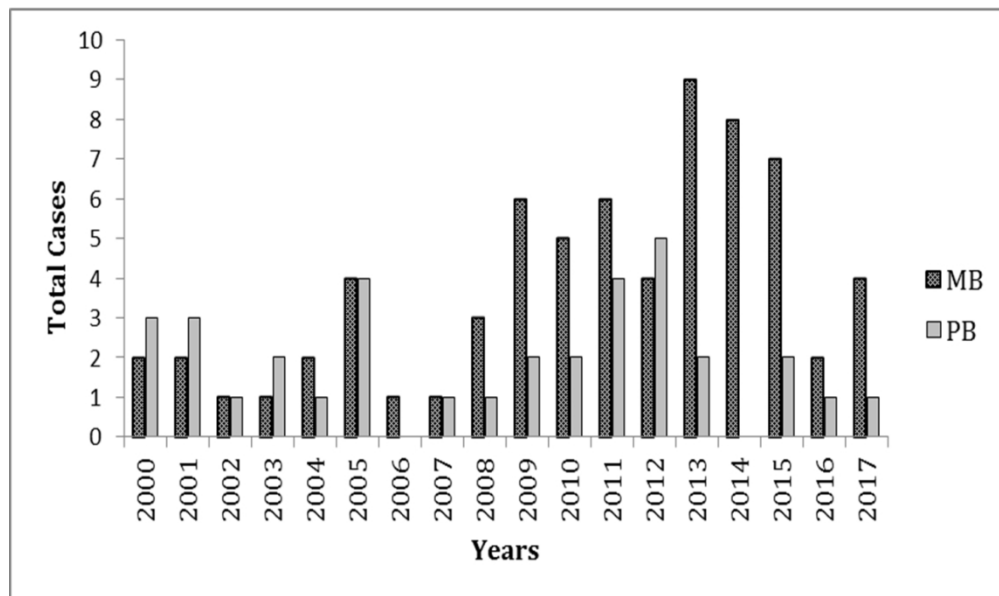
Figure 1. Number of cases of childhood leprosy for years and the total number of new leprosy cases diagnosed. Cuba 2000-2017. Left vertical axis represents total of new cases diagnosed in the country. Right vertical axis represents total cases of childhood leprosy diagnosed in Cuba in the same period

Figure 2. Distribution of cases of childhood leprosy per year according to operational classification. PB: paucibacillary patients; MB: multibacillary patients. Cuba 2000-2017

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Leprosy in children- a Cuban experience on leprosy control

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Review article

Title: Leprosy in children- a Cuban experience on leprosy control.

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Review article

Title: Leprosy in children-a Cuban experience on leprosy control.

ABSTRACT

Background: Children are believed to be the most vulnerable group for leprosy. Childhood leprosy reflects disease transmission in the community as well as the efficiency of ongoing disease control programs. In Cuba, leprosy isn't a national health problem, however new childhood leprosy cases are diagnosed every year. **Objectives:** We summarize the past experience of childhood leprosy control in Cuba over the past two decades. **Results:** Between the years 2000 and 2017, a total of 103 children have been diagnosed in Cuba, showing that active transmission of cases is maintained in 13 of the 15 Cuba's provinces. The majority of cases were multibacillary (66%). Paucibacillary cases were 34%. Clinically 60% of children have more than five lesions in all bodies. Voluntary reporting was the principal method of case detection. The presence of familial and extra-familial contact with leprosy cases may be a cause of concern, as it implies continuing transmission of the disease. Only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disability). A set of national investigations have been developed to intervene in a timely manner. Intervention strategies that combine clinical surveillance and laboratory test could be an option for early detection of childhood leprosy. **Conclusions:** Early detection of cases due to effective health education campaigns, regular and complete treatment with MDT and contact tracing may be important in reducing the burden of leprosy in the community.

Keywords: childhood, Cuba, epidemiology, leprosy

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It affects the skin, mucous membranes and peripheral nerves (1). It is associated with significant morbidity, as alongside the neurological damage, there are social, psychological and economic problems for the patient (2, 3).

Leprosy has been a major public health problem in many developing countries for centuries. The World Health Organization (WHO) reports that in 2017, 210 671 new cases were diagnosed (4). The number of new cases in the Americas (29,101 [13.8 percent of the global burden] is surpassed only by Southeast Asia. (4, 5).

The household contacts of a baciliferous patient can show a variable response to the infection. Some acquire the disease in its benign form; others do so in its most serious form and others resist the entry and multiplication of the bacillus (6). In children, any of the clinical forms of leprosy may occur (7), and they appear to be the most vulnerable group to *Mycobacterium leprae* infection (8). The number of new cases detected in children under fifteen years of age continues to be high. In 2017 children constituted 8.1% new cases worldwide, with 16 979 children diagnosed and 238 children with grade 2 disabilities, see Table 1 (4). The diagnosis of a new case in children and adolescents shows the active transmission of bacillus. It also indicates the magnitude of the transmission of the disease that is directly related to the proportion of infection sources (multibacillary forms) without treatment and the efficacy of the actions of control programs (9).

Table 1: World Health Organization leprosy disability grading system

Disabilities 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 (anesthesia) in 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 meters away)
2	Cases with both anesthesia and complications such as trophic ulcers, claw deformities and bone resorption in extremities	Involves severe vision impairment (vision worse than 6/60; inability to count fingers from 2 to 6 meters away) also includes lagophthalmos, iridocyclitis, and corneal opacities.

In Cuba, leprosy stopped being a national health problem in 1993 when the rate of registered prevalence of less than 1 case per 10 000 inhabitants was reached. That

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3 is the goal of WHO to define the elimination of the disease and serves as a guide for
4 the work of the control programs at countries. Despite the progress made in the
5 control of the disease, the detection of new cases has remained constant (10).
6 Every year new cases of childhood leprosy are reported. The frequency of cases
7 with disabilities is not significant, but the multibacillary clinical forms
8 predominate. The early diagnosis of new leprosy cases continues to be a central
9 point in the development of control strategies to reduce the time of exposure of
10 children to these untreated infectious sources.
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15 The present review summarized the Cuban experience of childhood leprosy
16 control between the years 2000-2017.
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20 Archived documents, medical records, disease prevalence censuses conducted
21 since 2000, epidemiological survey, Mandatory Notification Cards, and leprosy
22 morbidity and mortality statistics for 2000–2017 from the National Statistics
23 Office of the Ministry of Public Health (MINSAP) were reviewed, along with
24 scientific publications and National Guidelines for Leprosy Control (NGLC). The
25 data included in this review was collected by the National Program for Leprosy
26 Control as part of their monthly analysis of the leprosy situation in the country.
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30 **CLINICAL MANIFESTATIONS OF LEPROSY**

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32 The diagnosis of leprosy should be based on cardinal features of leprosy.
33 Childhood leprosy does not differ from adult leprosy but has specific
34 characteristics.
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37 Children at an early age, from three to four years old, suffer from the initial or
38 infantile form of the disease (12, 13). Table 2. The first symptoms are usually at
39 the neural level with a tingling sensation (paresthesia or acroparesthesia),
40 especially in the extremities. In its initial stages, macules or hypochromic and/or
41 erythematous spots appears, which are usually of variable size, number, and
42 location, with diffuse or well-defined borders. They may be associated with
43 disorders of superficial sensitivity (thermal, tactile and painful) and may be
44 accompanied by alteration of sweating or alteration of hair growth(14).
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49 In older children, around adolescence, where there is supposed to be a long time of
50 exposure to the bacillus, other symptoms may appear more similar to those
51 described for the polar forms of the disease. Occasionally, the only manifestation of
52 the disease is the thickening of superficial nerves, especially the auricular,
53 superciliary and ulnar muscles (15).
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56 Tuberculoid and childhood nodular leprosy are the most common presentations in
57 children. Tuberculoid Leprosy (TL) presents single and small lesions. Elevated
58 erythema with dry surface and alopecia may be present. Childhood nodular
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3 leprosy is characterized by erythematous nodules on the face or limbs, usually a
4 single lesion. Both forms are of benign prognosis. Some authors suggest that these
5 two types of leprosy can disappear spontaneously and reappear over time
6 installing the disorder of sensitivity with the involvement of one or more
7 peripheral nerves, the face, buttocks, and extremities (16, 17).
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10 Less common presentations in childhood include Indeterminate and Lepromatous
11 Leprosy.
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14 Indeterminate Leprosy (IL according to the Indian classification system) consists
15 of a single macula of non-precise edges with sensory disturbance located mainly
16 on the face, limbs, and buttocks. Lepromatous Leprosy (LL according to Ridley and
17 Jopling classification) (18) is occasionally seen in children older than 5 years. The
18 incidence of the disease increases with age. It is usually seen in children in
19 countries with high endemicity of the disease. The clinical manifestations involve
20 the infiltration of large cutaneous areas, especially in the cartilaginous areas of the
21 nose and ears. The mucous membranes of the nose are invaded by a large number
22 of microorganisms. The lesions can be hypochromic or hyperchromic, from small
23 and single to multiple and large including nodules (19)
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28 In cases in which a neural lesion appears, this is usually irreversible, the loss of
29 sensory, sympathetic and motor function ends in severe disability of the hands,
30 feet, and muscles. This leads to mutilation and deformity (20).
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Table 2. Three Leprosy classification using Cuban Program for Leprosy Control (18, 21, 22)

Leprosy Classification			Brief Description		
WHO operational system (1987)	Ridley-Jopling (1966)	Madrid (1953)	Number of skin lesions	Neurological damage	Bacteriology: Microscopic criteria
Paucibacillary 1 skin lesions	Tuberculoide (TT)	Tuberculoide (TT)	Unique and infiltrated lesions	No neurological damage	Negative
	Borderline tuberculoide (BB)	Indeterminate	Stasis and hypopigmented lesions	Little neurological damage	Negative
Paucibacillary 2-5 skin lesions	Borderline lepromatous (BL)		Borderline (IND)	Few or many lesions of varying size	Little or no neurological damage
		Multibacillary >5 lesions		Lepromatous (LL)	Multiple lesions, maculopapular
Lepromatous (LL)	Multiple lesions, maculopapular, nodules		Late thickening of the nerves		> 2+
	Multiple lesions, maculopapular, nodules		Late thickening of the nerves		> 2+

Negative: No acid fast bacilli observed

1+ or 2+: microscopic criteria when observed acid fast bacilli using Zielh-Neelsen stained

Late diagnosis can lead to the appearance of disabilities ranging from lack of sensitivity to motor paralysis of a limb. It can also give rise to secondary lesions that are not specific to the pathology, such as burns and wounds, which, if not treated properly, will lead to bone destruction or reabsorption. Reaction complications, are immune-mediated reactions causing by hyperreactivity or immune complex and are considered rare in children (23).

EPIDEMIOLOGY

In the last five years (2013-2017), there has been a slight decrease in the number of leprosy cases diagnosed annually, with 190 new cases in 2017 (4) Figure 1. This

diminution may suggest apparent progress. However each year new cases of childhood leprosy are diagnosed in Cuba, which shows that active transmission of cases is maintained in almost all the provinces of the country (13 of the 15 Cuba's provinces). It is accepted that the main transmission for leprosy is the upper airways. Multibacillary patients without treatment are the largest source of expelling bacillus. That's why leprosy patients' household contacts have the highest probability of acquiring the disease. Children have a lower level of socialization that's why in the populations where cases of childhood leprosy are diagnosed, the presence of sick adults without treatment becomes evident. It is important to note that once a patient is diagnosed and treated with polychemotherapy, the disease transmission chain is eliminated due to the high effectiveness of the treatment. Figure 1 shows the number of cases of childhood leprosy and the total number of new cases diagnosed in Cuba between 2000 and 2017. In 2013, the largest number of cases of childhood leprosy was diagnosed with 11 children (2).

The provinces that have the most frequently reported cases in the period 2000-2017 are Granma, Santiago, Guantánamo, Ciego de Ávila and Havana (24-28).

The age group most commonly affected by the disease among children under 15 years old was that between 10 and 14 years of age (Table 3). This is due to the disease's long incubation period of approximately three to five years (8). The youngest patients diagnosed in Cuba were three years old. An equal number of boys and girls have been affected (27).

Table 3. Distribution by age of children diagnosed with leprosy in Cuba.

Years /Age	0-4	5-9	10-14	Total
2000		1	4	5
2001		2	3	5
2002			2	2
2003			3	3
2004		2	1	3
2005		1	7	8
2006			1	1
2007			2	2
2008		1	3	4
2009		3	5	8
2010		2	5	7
2011		1	9	10
2012		4	5	9
2013		4	7	11
2014	1		7	8
2015		4	5	9
2016		1	2	3
2017	1	2	2	5

Total	2	28	73	103
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In Cuba regarding the number of lesions, we found that 62 children of 103 diagnoses in this period, had more than five lesions in all the body. We have also found that in this period one child was diagnosed with musculoskeletal manifestations, such as arthralgia and myalgia, on presentation. Additionally, another important indicator is the percentage of children with disability grades 1 and 2 among the new cases of childhood leprosy. In this period only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disabilities).

The last decade has seen an increase in multibacillary forms (BL and LL). Figure 2. This is evidence, in our opinion of the greater exposure of these children to the bacillus, due largely to the maintenance in the community of sick people, especially multibacillary patients, without treatment.

CUBAN' STRATEGIES FOR LEPROSY CONTROL

Leprosy was a health problem in Cuba until 1993. Between 1960 and 1990, research and surveillance actions were carried out to reduce the incidence of the disease. These actions were based on the development of an Inclusive Control Program that allowed for active surveillance in both rural and urban populations on the island (29). These actions were based on the Cuban Public Health System (10). The beginning of the application of polychemotherapy in Cuba in 1988 and its inclusion in the control program guaranteed a dramatic decrease in the incidence of the disease. As of 2003, when the rate of <1 case per 10 000 inhabitants at the province level is reached, a new stage begins that requires the implementation of novel strategies that allow the active search for new cases to be sustainable. All described data indicates that children who are at risk of developing the disease still escape from active surveillance. This situation has shown the need to develop strategies to improve surveillance and active search among suspected cases.

The National Program for Leprosy Control in agreement with other Cuban health institutions (Tropical Medicine Institute Pedro Kourí, Pediatric Hospital Juan Manuel Marquez and Provincial Center for Hygiene, Epidemiology and Microbiology of Havana) have developed intervention projects with the objective to identifying those children who are contacts of patients with leprosy earlier and proposing a follow-up strategy that allows early diagnosis.

A set of national investigations have been developed to intervene in a timely manner. Some projects considered improve clinical dermatological evaluation of all children's contacts of patients (30, 31). Other strategies combine conventional methods with the use of serological methods based on phenolic glycolipid I and

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3 molecular methods, to perform an initial assessment of all children which are
4 contacts of patients with leprosy.
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7 In general terms, the most important method for early diagnosis is the
8 dermatological examination regarding signs and symptoms of leprosy in children
9 and adults. In children, this test is very difficult to conduct. If some of the children
10 appear to be suspicious, a bacteriological and pathological analysis is
11 recommended. In Cuba, for children diagnosis, a total of six samples of lymph
12 smears are taken and a biopsy of the cutaneous lesions for histopathological study.
13 The new case is classified according to the WHO's classification. The treatment is
14 according to WHO's recommendation (5) and is controlled and supervised by the
15 local health structures (family doctors and nurses). Those professionals along with
16 local dermatologist are responsible for clinical surveillance of family and non-
17 family contacts of the new case, every year for five years (32). This method has
18 been effective in maintaining the incidence of the disease, however it has been
19 ineffective on the way to eliminating the disease. For this reason, strategies that
20 combine this clinical surveillance with a serological follow up of suspicious
21 children show interesting results in terms of early diagnosis.
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29 Also, the integration of molecular methods of diagnosis could be a great strategy
30 for leprosy control in Cuba. Moreover, the presence in Cuba of regions with a high
31 incidence of leprosy makes us believe that contacts that do not live with children
32 could be an important source of infection. The new strategies now include school
33 contacts and neighbors. The options of the National Control Program have been to
34 monitor the suspicious contacts by combining several methods, clinical serological
35 and molecular for a period never less than three years.
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39 As part of the Cuban Programs, communication strategies have been included that
40 include active education in populations with a high and low incidence of the
41 disease with the objective of encouraging the active search for typical injuries
42 among people and increasing the perception of risk.
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46 **CUBAN EXPERIENCE IN CONTEXT WITH other AMERICAN COUNTRIES**

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49 The Cuban public health system has recognized robustness so, for children with
50 leprosy the average range in terms of the time of evolution of the skin lesions and
51 the first consultation is less than a year, according to parents. This fairly short time
52 between the start of the symptoms and the consultation is probably due to the easy
53 access of patients to primary care (33). In other countries, authors refer to a time
54 of 18 months between presentation and diagnosis (8). However, this indicator, at
55 least in Cuba, shows an inconsistent behavior taking into account that in children
56 the initial manifestations of the disease are observed predominantly in the skin
57 and the multibacillary form requires many years of evolution (34, 35). Some
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3 authors suggest that in the pediatric ages the skin alterations take years to
4 establish and many times in the initial forms of leprosy, they present as nonspecific
5 chronic dermatitis. It is clear that in Cuba we are facing a situation of little
6 perception of risk of both the population and health professionals. Due
7 undoubtedly to the drastic decrease of new cases experienced in Cuba in the last
8 decade. On the other hand, 89% of the cases diagnosed have at least one case of
9 leprosy diagnosed in their family, so they must be diagnosed by household
10 contacts tracing.
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15 In Cuba, some of the children presenting with leprosy are considered Index Case
16 (first case in a family). The source of infection is diagnosed after examining the
17 children's household contacts. In a retrospective study conducted over 20 years
18 (1989-2006) at the pediatric Hospital Juan Manuel Marquez, 60% of children with
19 leprosy had a known source of infection in the family and in 48% of the cases were
20 grandparents (30). The behavior in the last decade has not changed because it is
21 recognized in the literature that especially in the case of children; family contact is
22 the primary source of the infection (35). It is almost always an intra-familial
23 member. Special attention to this epidemiological pattern can help in the
24 identification of new cases. Children do not have a mature immune system (36)
25 and considering that predisposition to developing the disease is inherited (37, 38),
26 they are in the most vulnerable group. Active surveillance on this age group is
27 therefore essential.
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34 Romero-Montoya et al. in a study of 12 children with leprosy in Colombia found
35 that nine of them had a household contact leprosy patient. They also reported that
36 the children appear to be more prone to illness than other family members (39,
37 40). The risk of a person developing leprosy is nine times greater among
38 household contacts and up to four times greater among contacts with neighbors
39 (41). Durães et al. in Brazil, demonstrated a risk of illness of 2.4 times greater than
40 the case index in household contacts as compared to household perimeter
41 contacts, and 2.05 if the contacts were first degree relatives. Considering the same
42 type of household contact, the higher incidence among blood relatives within a
43 nuclear family, as compared to the other blood relatives, demonstrates the
44 component of genetic predisposition, which has been widely reported in prior
45 literature (42).
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52 In Cuba, several studies have been carried out using the UMELISA-Hansen kit for
53 the detection of IgM antibodies against the phenolic glycolipid I (43). In a study
54 conducted in three Cuban provinces between 2013 and 2015, a serological follow-
55 up was carried out every six months during two years in children's household
56 contacts of patients with leprosy. In this period a total of 151 children were
57 included in the study, of whom 44 (29%) were positive for phenolic glycolipid. Of
58 these children, 11 were diagnosed in the three years of the project (43). The
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3 results could serve as a basis to evaluate the use of this tool as a possible strategy
4 for active searching for new cases of leprosy among children's contacts of patients.
5 Currently, studies have been conducted using the anti-PGL-I to evaluate the
6 seroprevalence of household and school contacts in American's hyperendemic
7 areas. Barreto et al. conducted a study with school children in the Amazon region
8 and found that 777 (48.8%) of the 1,592 school children proved to be seropositive
9 for anti-PGL-I (44). This seroprevalence suggested the possibility of undiagnosed
10 cases and subclinical infections among children in the Amazon region. The
11 importance of the study on these school children was the early diagnosis of the
12 disease (44). The proposal of this investigation in the Cuban experience is to use
13 this analysis not only as a tool in seroprevalence studies but also in supporting the
14 active search for new cases at least among patient contacts.
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21 The Cuban experience about leprosy control in America's region is relevant in
22 terms of control programs strategies that could be economically sustainable for
23 developing countries. The use of phenolic glycolipid serology I as a monitoring
24 tool for suspects can be useful and sustainable even in low-income countries.
25 However, although this proposal is not entirely new, the positive results of the
26 Cuban experience rest on the solidity of the public health system that is completely
27 inclusive and reaches every person in the country. Besides being unique in its
28 operation and staggered in its structures, it allows the use of networks and
29 strategies designed to deal with other diseases, integrated and adapted to the
30 surveillance of leprosy.
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37 CONCLUSIONS

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39 The diagnosis of childhood leprosy in Cuba shows the relevance of leprosy control
40 activities even in areas with low prevalence to sustain the elimination of leprosy.
41 The intervention strategies used in Cuba have made it possible to increase the
42 effectiveness of the active search for cases of childhood leprosy. Early detection of
43 cases due to effective health education campaigns, regular and complete treatment
44 with MDT and contact tracing may be important in reducing the burden of leprosy
45 in the community.
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56 Conflict of interest statement

57 The authors declare there are no conflicts of interest
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59

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6

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8 Jenny Laura Ruiz Fuentes made substantial contributions to the conception and
9 design of the work; carried out the analysis and interpretation of data, drafting the
10 work and made the final approval of the version to be published
11

12 Raisa Rumbaut carried out the acquisition, analysis, and interpretation of data for
13 the work, made critical revision for important intellectual content, made the final
14 approval of the version to be published
15

16 Laura Hurtado carried out the acquisition, analysis, and interpretation of data for
17 the work, made critical revision for important intellectual content, made the final
18 approval of the version to be published
19

20 Fernanda Pastrana Carried out the revision of the manuscript critically for
21 important intellectual content; made the final approval of the version to be
22 published and ensured that questions related to the accuracy or integrity of the
23 work were appropriately investigated and resolved.
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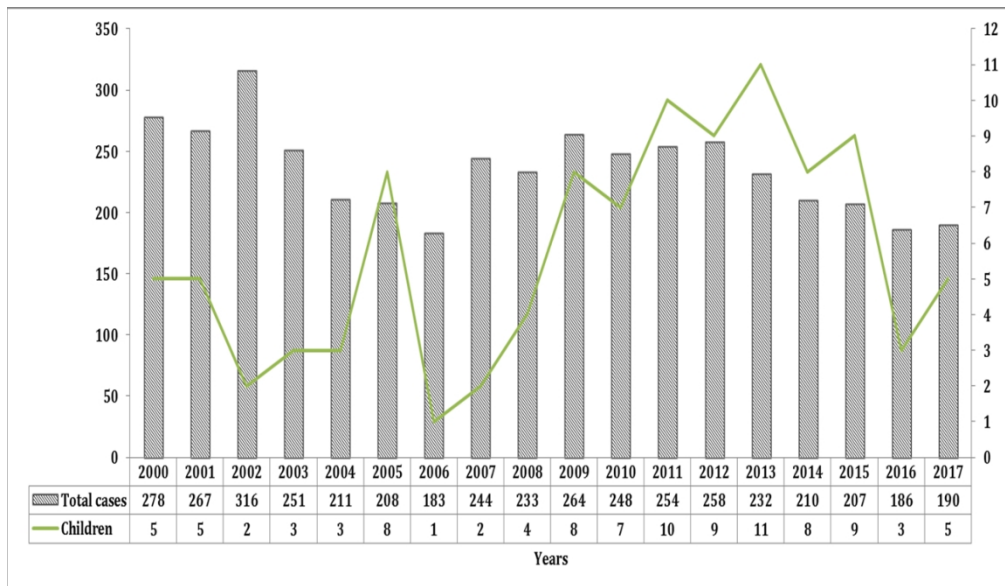
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Figure Legends

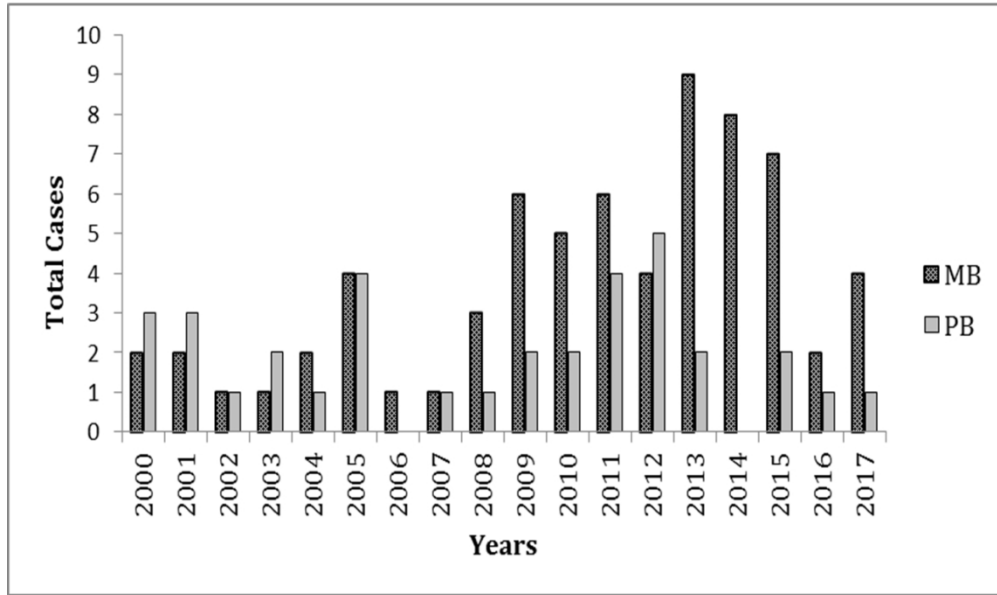
Figure 1. Number of cases of childhood leprosy for years and the total number of new leprosy cases diagnosed. Cuba 2000-2017. The left vertical axis represents total of new cases diagnosed in the country. The right vertical axis represents total cases of childhood leprosy diagnosed in Cuba in the same period

Figure 2. Distribution of cases of childhood leprosy per year according to operational classification. PB: paucibacillary patients; MB: multibacillary patients. Cuba 2000-2017

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BMJ Paediatrics Open

Leprosy in children- a Cuban experience on leprosy control

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Review article

Title: Leprosy in children- a Cuban experience on leprosy control.

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Review article

Title: Leprosy in children-a Cuban experience on leprosy control.

ABSTRACT

Background: Children are believed to be the most vulnerable group for leprosy. Childhood leprosy reflects disease transmission in the community as well as the efficiency of ongoing disease control programs. In Cuba, leprosy isn't a national health problem, however new childhood leprosy cases are diagnosed every year. **Objectives:** We summarize the past experience of childhood leprosy control in Cuba over the past two decades. **Results:** Between the years 2000 and 2017, a total of 103 children have been diagnosed in Cuba, showing that active transmission of cases is maintained in 13 of the 15 Cuba's provinces. The majority of cases were multibacillary (66%). Paucibacillary cases were 34%. Clinically 60% of children have more than five lesions in all bodies. Voluntary reporting was the principal method of case detection. The presence of familial and extra-familial contact with leprosy cases may be a cause of concern, as it implies continuing transmission of the disease. Only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disability). A set of national investigations have been developed to intervene in a timely manner. Intervention strategies that combine clinical surveillance and laboratory test could be an option for early detection of childhood leprosy. **Conclusions:** Early detection of cases due to effective health education campaigns, regular and complete treatment with MDT and contact tracing may be important in reducing the burden of leprosy in the community.

Keywords: childhood, Cuba, epidemiology, leprosy

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It affects the skin, mucous membranes and peripheral nerves (1). It is associated with significant morbidity, as alongside the neurological damage, there are social, psychological and economic problems for the patient (2, 3).

Leprosy has been a major public health problem in many developing countries for centuries. The World Health Organization (WHO) reports that in 2017, 210 671 new cases were diagnosed (4). The number of new cases in the Americas (29,101 [13.8 percent of the global burden] is surpassed only by Southeast Asia. (4, 5).

The household contacts of a baciliferous patient can show a variable response to the infection. Some acquire the disease in its benign form; others do so in its most serious form and others resist the entry and multiplication of the bacillus (6). In children, any of the clinical forms of leprosy may occur (7), and they appear to be the most vulnerable group to *Mycobacterium leprae* infection (8). The number of new cases detected in children under fifteen years of age continues to be high. In 2017 children constituted 8.1% new cases worldwide, with 16 979 children diagnosed and 238 children with grade 2 disabilities, see Table 1 (4). The diagnosis of a new case in children and adolescents shows the active transmission of bacillus. It also indicates the magnitude of the transmission of the disease that is directly related to the proportion of infection sources (multibacillary forms) without treatment and the efficacy of the actions of control programs (9).

Table 1: World Health Organization leprosy disability grading system

Disabilities 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 (anesthesia) in 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 meters away)
2	Cases with both anesthesia and complications such as trophic ulcers, claw deformities and bone resorption in extremities	Involves severe vision impairment (vision worse than 6/60; inability to count fingers from 2 to 6 meters away) also includes lagophthalmos, iridocyclitis, and corneal opacities.

In Cuba, leprosy stopped being a national health problem in 1993 when the rate of registered prevalence of less than 1 case per 10 000 inhabitants was reached. That

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3 is the goal of WHO to define the elimination of the disease and serves as a guide for
4 the work of the control programs at countries. Despite the progress made in the
5 control of the disease, the detection of new cases has remained constant (10).
6 Every year new cases of childhood leprosy are reported. The frequency of cases
7 with disabilities is not significant, but the multibacillary clinical forms
8 predominate. The early diagnosis of new leprosy cases continues to be a central
9 point in the development of control strategies to reduce the time of exposure of
10 children to these untreated infectious sources.
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15 The present review summarized the Cuban experience of childhood leprosy
16 control between the years 2000-2017.
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20 Archived documents, medical records, disease prevalence censuses conducted
21 since 2000, epidemiological survey, Mandatory Notification Cards, and leprosy
22 morbidity and mortality statistics for 2000–2017 from the National Statistics
23 Office of the Ministry of Public Health (MINSAP) were reviewed, along with
24 scientific publications and National Guidelines for Leprosy Control (NGLC). The
25 data included in this review was collected by the National Program for Leprosy
26 Control as part of their monthly analysis of the leprosy situation in the country.
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30 **CLINICAL MANIFESTATIONS OF LEPROSY**

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32 The diagnosis of leprosy should be based on cardinal features of leprosy.
33 Childhood leprosy does not differ from adult leprosy but has specific
34 characteristics.
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37 Children at an early age, from three to four years old, suffer from the initial or
38 infantile form of the disease (12, 13). Table 2. The first symptoms are usually at
39 the neural level with a tingling sensation (paresthesia or acroparesthesia),
40 especially in the extremities. In its initial stages, macules or hypochromic and/or
41 erythematous spots appears, which are usually of variable size, number, and
42 location, with diffuse or well-defined borders. They may be associated with
43 disorders of superficial sensitivity (thermal, tactile and painful) and may be
44 accompanied by alteration of sweating or alteration of hair growth(14).
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49 In older children, around adolescence, where there is supposed to be a long time of
50 exposure to the bacillus, other symptoms may appear more similar to those
51 described for the polar forms of the disease. Occasionally, the only manifestation of
52 the disease is the thickening of superficial nerves, especially the auricular,
53 superciliary and ulnar muscles (15).
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56 Tuberculoid and childhood nodular leprosy are the most common presentations in
57 children. Tuberculoid Leprosy (TL) presents single and small lesions. Elevated
58 erythema with dry surface and alopecia may be present. Childhood nodular
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3 leprosy is characterized by erythematous nodules on the face or limbs, usually a
4 single lesion. Both forms are of benign prognosis. Some authors suggest that these
5 two types of leprosy can disappear spontaneously and reappear over time
6 installing the disorder of sensitivity with the involvement of one or more
7 peripheral nerves, the face, buttocks, and extremities (16, 17).
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10 Less common presentations in childhood include Indeterminate and Lepromatous
11 Leprosy.
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14 Indeterminate Leprosy (IL according to the Indian classification system) consists
15 of a single macula of non-precise edges with sensory disturbance located mainly
16 on the face, limbs, and buttocks. Lepromatous Leprosy (LL according to Ridley and
17 Jopling classification) (18) is occasionally seen in children older than 5 years. The
18 incidence of the disease increases with age. It is usually seen in children in
19 countries with high endemicity of the disease. The clinical manifestations involve
20 the infiltration of large cutaneous areas, especially in the cartilaginous areas of the
21 nose and ears. The mucous membranes of the nose are invaded by a large number
22 of microorganisms. The lesions can be hypochromic or hyperchromic, from small
23 and single to multiple and large including nodules (19)
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28 In cases in which a neural lesion appears, this is usually irreversible, the loss of
29 sensory, sympathetic and motor function ends in severe disability of the hands,
30 feet, and muscles. This leads to mutilation and deformity (20).
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Table 2. Leprosy classification using Cuban Program for Leprosy Control (18, 21, 22)

Leprosy Classification			Brief Description		
WHO operational system (1987)	Ridley-Jopling (1966)	Madrid (1953)	Number of skin lesions	Neurological damage	Bacteriology: Microscopic criteria
Paucibacillary 1 skin lesions	Tuberculoide (TT)	Tuberculoide (TT)	Unique and infiltrated lesions	No neurological damage	Negative
	Borderline tuberculoide (BB)	Indeterminate	Stasis and hypopigmented lesions	Little neurological damage	Negative
Paucibacillary 2-5 skin lesions	Borderline lepromatous (BL)		Borderline (IND)	Few or many lesions of varying size	Little or no neurological damage
		Multibacillary >5 lesions		Lepromatous (LL)	Multiple lesions, maculopapular
Lepromatous (LL)	Multiple lesions, maculopapular, nodules		Late thickening of the nerves		> 2+
	Multiple lesions, maculopapular, nodules		Late thickening of the nerves		> 2+

Negative: No acid fast bacilli observed

1+ or 2+: microscopic criteria when observed acid fast bacilli using Zielh-Neelsen stained

Late diagnosis can lead to the appearance of disabilities ranging from lack of sensitivity to motor paralysis of a limb. It can also give rise to secondary lesions that are not specific to the pathology, such as burns and wounds, which, if not treated properly, will lead to bone destruction or reabsorption. Reaction complications, are immune-mediated reactions causing by hyperreactivity or immune complex and are considered rare in children (23).

EPIDEMIOLOGY

In the last five years (2013-2017), there has been a slight decrease in the number of leprosy cases diagnosed annually, with 190 new cases in 2017 (4) Figure 1. This

diminution may suggest apparent progress. However each year new cases of childhood leprosy are diagnosed in Cuba, which shows that active transmission of cases is maintained in almost all the provinces of the country (13 of the 15 Cuba's provinces). It is accepted that the main transmission for leprosy is the upper airways. Multibacillary patients without treatment are the largest source of expelling bacillus. That's why leprosy patients' household contacts have the highest probability of acquiring the disease. Children have a lower level of socialization that's why in the populations where cases of childhood leprosy are diagnosed, the presence of sick adults without treatment becomes evident. It is important to note that once a patient is diagnosed and treated with polychemotherapy, the disease transmission chain is eliminated due to the high effectiveness of the treatment. Figure 1 shows the number of cases of childhood leprosy and the total number of new cases diagnosed in Cuba between 2000 and 2017. In 2013, the largest number of cases of childhood leprosy was diagnosed with 11 children (2).

The provinces that have the most frequently reported cases in the period 2000-2017 are Granma, Santiago, Guantánamo, Ciego de Ávila and Havana (24-28).

The age group most commonly affected by the disease among children under 15 years old was that between 10 and 14 years of age (Table 3). This is due to the disease's long incubation period of approximately three to five years (8). The youngest patients diagnosed in Cuba were three years old. An equal number of boys and girls have been affected (27).

Table 3. Distribution by age of children diagnosed with leprosy in Cuba.

Years /Age	0-4	5-9	10-14	Total
2000		1	4	5
2001		2	3	5
2002			2	2
2003			3	3
2004		2	1	3
2005		1	7	8
2006			1	1
2007			2	2
2008		1	3	4
2009		3	5	8
2010		2	5	7
2011		1	9	10
2012		4	5	9
2013		4	7	11
2014	1		7	8
2015		4	5	9
2016		1	2	3

2017	1	2	2	5
Total	2	28	73	103

In Cuba regarding the number of lesions, we found that 62 children of 103 diagnoses in this period, had more than five lesions in all the body. We have also found that in this period one child was diagnosed with musculoskeletal manifestations, such as arthralgia and myalgia, on presentation. Additionally, another important indicator is the percentage of children with disability grades 1 and 2 among the new cases of childhood leprosy. In this period only four children had disabilities (one with grade 2 disabilities and three with a grade 1 disabilities).

The last decade has seen an increase in multibacillary forms (BL and LL). Figure 2. This is evidence, in our opinion of the greater exposure of these children to the bacillus, due largely to the maintenance in the community of sick people, especially multibacillary patients, without treatment.

CUBAN' STRATEGIES FOR LEPROSY CONTROL

Leprosy was a health problem in Cuba until 1993. Between 1960 and 1990, research and surveillance actions were carried out to reduce the incidence of the disease. These actions were based on the development of an Inclusive Control Program that allowed for active surveillance in both rural and urban populations on the island (29). These actions were based on the Cuban Public Health System (10). The beginning of the application of polychemotherapy in Cuba in 1988 and its inclusion in the control program guaranteed a dramatic decrease in the incidence of the disease. As of 2003, when the rate of <1 case per 10 000 inhabitants at the province level is reached, a new stage begins that requires the implementation of novel strategies that allow the active search for new cases to be sustainable. All described data indicates that children who are at risk of developing the disease still escape from active surveillance. This situation has shown the need to develop strategies to improve surveillance and active search among suspected cases.

The National Program for Leprosy Control in agreement with other Cuban health institutions (Tropical Medicine Institute Pedro Kourí, Pediatric Hospital Juan Manuel Marquez and Provincial Center for Hygiene, Epidemiology and Microbiology of Havana) have developed intervention projects with the objective to identifying those children who are contacts of patients with leprosy earlier and proposing a follow-up strategy that allows early diagnosis.

A set of national investigations have been developed to intervene in a timely manner. Some projects considered improve clinical dermatological evaluation of all children's contacts of patients (30, 31). Other strategies combine conventional

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3 methods with the use of serological methods based on phenolic glycolipid I and
4 molecular methods, to perform an initial assessment of all children which are
5 contacts of patients with leprosy.
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9 In general terms, the most important method for early diagnosis is the
10 dermatological examination regarding signs and symptoms of leprosy in children
11 and adults. In children, this test is very difficult to conduct. If some of the children
12 appear to be suspicious, a bacteriological and pathological analysis is
13 recommended. In Cuba, for children diagnosis, a total of six samples of lymph
14 smears are taken and a biopsy of the cutaneous lesions for histopathological study.
15 The new case is classified according to the WHO's classification. The treatment is
16 according to WHO's recommendation (5) and is controlled and supervised by the
17 local health structures (family doctors and nurses). Those professionals along with
18 local dermatologist are responsible for clinical surveillance of family and non-
19 family contacts of the new case, every year for five years (32). This method has
20 been effective in maintaining the incidence of the disease, however it has been
21 ineffective on the way to eliminating the disease. For this reason, strategies that
22 combine this clinical surveillance with a serological follow up of suspicious
23 children show interesting results in terms of early diagnosis.
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30 Also, the integration of molecular methods of diagnosis could be a great strategy
31 for leprosy control in Cuba. Moreover, the presence in Cuba of regions with a high
32 incidence of leprosy makes us believe that contacts that do not live with children
33 could be an important source of infection. The new strategies now include school
34 contacts and neighbors. The options of the National Control Program have been to
35 monitor the suspicious contacts by combining several methods, clinical serological
36 and molecular for a period never less than three years.
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41 As part of the Cuban Programs, communication strategies have been included that
42 include active education in populations with a high and low incidence of the
43 disease with the objective of encouraging the active search for typical injuries
44 among people and increasing the perception of risk.
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48 **CUBAN EXPERIENCE IN CONTEXT WITH other AMERICAN COUNTRIES**

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50 The Cuban public health system has recognized robustness so, for children with
51 leprosy the average range in terms of the time of evolution of the skin lesions and
52 the first consultation is less than a year, according to parents. This fairly short time
53 between the start of the symptoms and the consultation is probably due to the easy
54 access of patients to primary care (33). In other countries, authors refer to a time
55 of 18 months between presentation and diagnosis (8). However, this indicator, at
56 least in Cuba, shows an inconsistent behavior taking into account that in children
57 the initial manifestations of the disease are observed predominantly in the skin
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3 and the multibacillary form requires many years of evolution (34, 35). Some
4 authors suggest that in the pediatric ages the skin alterations take years to
5 establish and many times in the initial forms of leprosy, they present as nonspecific
6 chronic dermatitis. It is clear that in Cuba we are facing a situation of little
7 perception of risk of both the population and health professionals. Due
8 undoubtedly to the drastic decrease of new cases experienced in Cuba in the last
9 decade. On the other hand, 89% of the cases diagnosed have at least one case of
10 leprosy diagnosed in their family, so they must be diagnosed by household
11 contacts tracing.
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16 In Cuba, some of the children presenting with leprosy are considered Index Case
17 (first case in a family). The source of infection is diagnosed after examining the
18 children's household contacts. In a retrospective study conducted over 20 years
19 (1989-2006) at the pediatric Hospital Juan Manuel Marquez, 60% of children with
20 leprosy had a known source of infection in the family and in 48% of the cases were
21 grandparents (30). The behavior in the last decade has not changed because it is
22 recognized in the literature that especially in the case of children; family contact is
23 the primary source of the infection (35). It is almost always an intra-familial
24 member. Special attention to this epidemiological pattern can help in the
25 identification of new cases. Children do not have a mature immune system (36)
26 and considering that predisposition to developing the disease is inherited (37, 38),
27 they are in the most vulnerable group. Active surveillance on this age group is
28 therefore essential.
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35 Romero-Montoya et al. in a study of 12 children with leprosy in Colombia found
36 that nine of them had a household contact leprosy patient. They reported that in a
37 family where there are cases of undiagnosed leprosy, children are the ones most
38 likely to get sick (39, 40). Among the household contacts, the risk of developing the
39 disease was up to nine times more, while for the neighborhood contacts the risk
40 was four times more (41). Durães et al. in Brazil, demonstrated a risk of illness of
41 2.4 times greater than the case index in household contacts as compared to
42 household perimeter contacts, and 2.05 if the contacts were first degree relatives.
43 Considering the same type of household contact, in a nuclear family it was
44 observed that blood relatives had a higher incidence of the disease than other non-
45 blood relatives, illustrating the genetic predisposition described in other studies.
46 (42).
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53 In Cuba, several studies have been carried out using the UMELISA-Hansen kit for
54 the detection of IgM antibodies against the phenolic glycolipid I (43). In a study
55 conducted in three Cuban provinces between 2013 and 2015, a serological follow-
56 up was carried out every six months during two years in children's household
57 contacts of patients with leprosy. In this period a total of 151 children were
58 included in the study, of whom 44 (29%) were positive for phenolic glycolipid. Of
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3 these children, 11 were diagnosed in the three years of the project (43). The
4 results could serve as a basis to evaluate the use of this tool as a possible strategy
5 for active searching for new cases of leprosy among children's contacts of patients.
6 Currently, studies have been conducted using the anti-PGL-I to evaluate the
7 seroprevalence of household and school contacts in American's hyperendemic
8 areas. Barreto et al. conducted a study with school children in the Amazon region
9 and found that 777 (48.8%) of the 1,592 school children proved to be seropositive
10 for anti-PGL-I (44). The results suggest that in these regions there may be children
11 with subclinical or undiagnosed infections. That is why early diagnosis is
12 important (44). The proposal of this investigation in the Cuban experience is to use
13 this analysis not only as a tool in seroprevalence studies but also in supporting the
14 active search for new cases at least among patient contacts.
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21 The Cuban experience about leprosy control in America's region is relevant in
22 terms of control programs strategies that could be economically sustainable for
23 developing countries. The use of phenolic glycolipid serology I as a monitoring
24 tool for suspects can be useful and sustainable even in low-income countries.
25 However, although this proposal is not entirely new, the positive results of the
26 Cuban experience rest on the solidity of the public health system that is completely
27 inclusive and reaches every person in the country. Besides being unique in its
28 operation and staggered in its structures, it allows the use of networks and
29 strategies designed to deal with other diseases, integrated and adapted to the
30 surveillance of leprosy.
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37 CONCLUSIONS

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39 The diagnosis of childhood leprosy in Cuba shows the relevance of leprosy control
40 activities even in areas with low prevalence to sustain the elimination of leprosy.
41 The intervention strategies used in Cuba have made it possible to increase the
42 effectiveness of the active search for cases of childhood leprosy. Early detection of
43 cases due to effective health education campaigns, regular and complete treatment
44 with MDT and contact tracing may be important in reducing the burden of leprosy
45 in the community.
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56 Conflict of interest statement

57 The authors declare there are no conflicts of interest
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2
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4 commercial or not-for-profit sectors
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7 **Contributorship Statement**

8 Jenny Laura Ruiz Fuentes made substantial contributions to the conception and
9 design of the work; carried out the analysis and interpretation of data, drafting the
10 work and made the final approval of the version to be published
11

12 Raisa Rumbaut carried out the acquisition, analysis, and interpretation of data for
13 the work, made critical revision for important intellectual content, made the final
14 approval of the version to be published
15

16 Laura Hurtado carried out the acquisition, analysis, and interpretation of data for
17 the work, made critical revision for important intellectual content, made the final
18 approval of the version to be published
19

20 Fernanda Pastrana Carried out the revision of the manuscript critically for
21 important intellectual content; made the final approval of the version to be
22 published and ensured that questions related to the accuracy or integrity of the
23 work were appropriately investigated and resolved.
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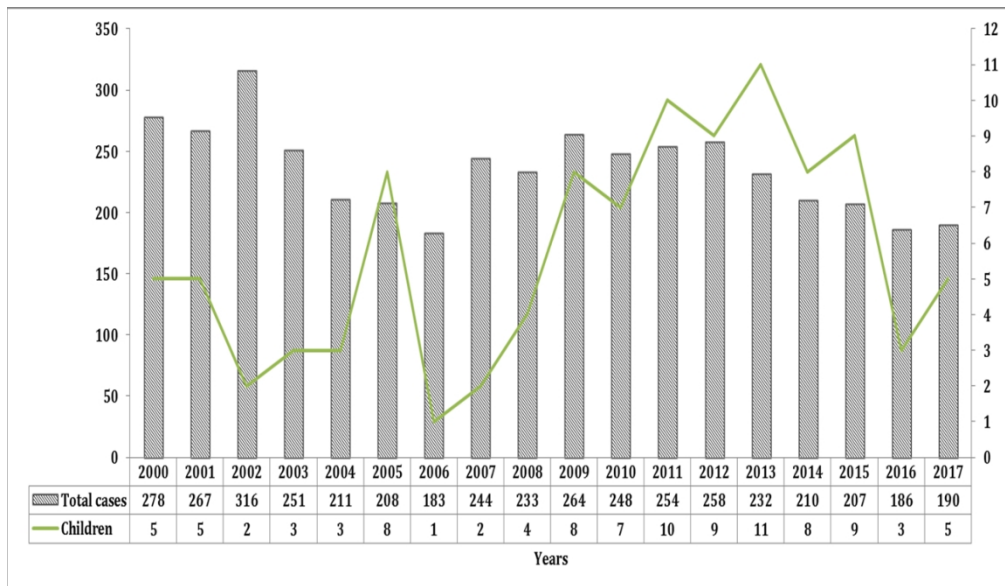
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Figure Legends

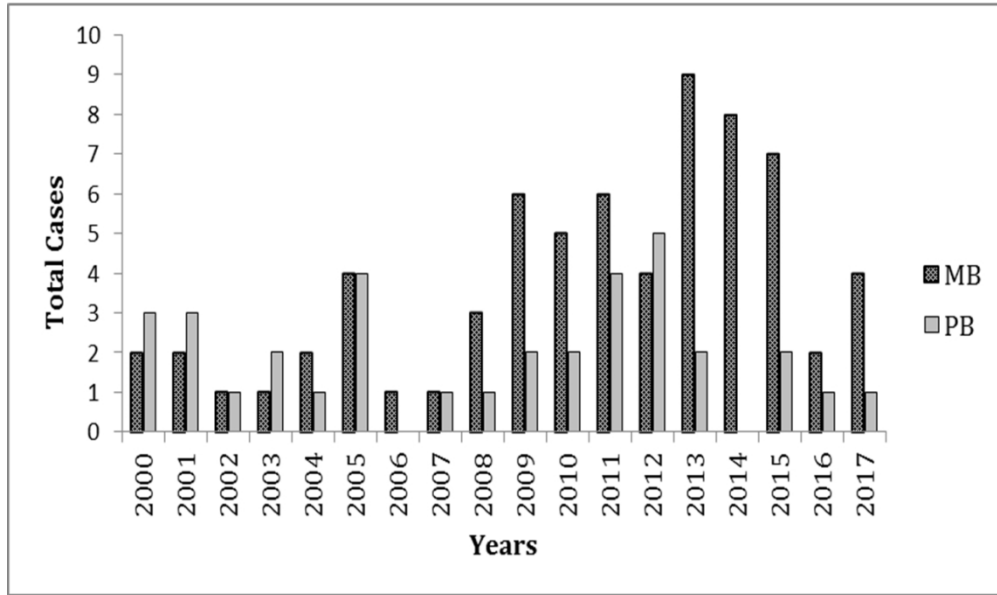
Figure 1. Number of cases of childhood leprosy for years and the total number of new leprosy cases diagnosed. Cuba 2000-2017. The left vertical axis represents total of new cases diagnosed in the country. The right vertical axis represents total cases of childhood leprosy diagnosed in Cuba in the same period

Figure 2. Distribution of cases of childhood leprosy per year according to operational classification. PB: paucibacillary patients; MB: multibacillary patients. Cuba 2000-2017

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