Curr Infect Dis Rep (2017) 19: 23
DOI 10.1007/s11908-017-0577-6

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Leprosy in Children

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Published online: 25 April 2017

Abstract
Purpose of Review This manuscript aims to review the cutting-edge developments regarding to the diagnosis, management, and prevention of leprosy in children.
Recent Findings Leprosy transmission still occurs continuously in some endemic areas in the world. Leprosy in children below 15 years old is a robust indicator of active source of infection in the community where they live. A special focus on children to reduce disabilities and reduce transmission is one of the core areas of interventions of the global leprosy strategy 2016–2020. Ongoing research is trying to develop better diagnostic tests and to advance chemoprophylaxis and immunoprophylaxis approaches.
Summary Early diagnosis in children can be hard because of the wide range of clinical aspects of the skin lesions and mainly due to the difficulty of performing the clinical peripheral nerve evaluation. We must maintain leprosy expertise and improve the health professionals training for leprosy diagnosis, since we still have a long journey to reach leprosy elimination.

Keywords Leprosy · Early diagnosis · Children

Introduction

A special focus on children as a way to reduce disabilities and reduce transmission is one of the core areas of interventions of the global leprosy strategy 2016–2020, recently published by the World Health Organization (WHO) [1••]. The disease caused by the *Mycobacterium leprae* can be physically, psy-

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

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chologically, and socially devastating if not early diagnosed and treated. Despite the accentuated decline in the prevalence of leprosy worldwide since the multidrug therapy (MDT) was recommended by the WHO in 1981, leprosy detection remains stable during the last 5 years, with an average of 223,502 new cases reported per year, globally. This figure indicates that the transmission still occurs continuously in some endemic areas, particularly in India, Brazil, and Indonesia, which reported over 10,000 new cases and accounted for 81% of the global burden of leprosy in 2015 [2].

Leprosy in children younger than 15 years old is an important epidemiological indicator. It is correlated with recent disease and active foci of transmission in the community, reflecting the inefficiency of local control programs. In 2015, the proportion of children among new cases globally was 8.9%, or 18,796 cases. The range of child case proportions fluctuated between 38.1% in Comoros and 0.8% in Niger [2].

However, some independent studies have found very high hidden prevalence of leprosy among children in endemic areas [3, 4]. Up to 11% with grade 2 disability (G2D) at the time of diagnosis, increasing to 27.3% during follow-up have been reported [5–7]. These disability rates in children are worrying and unacceptable as they reflect long delays in the diagnosis of leprosy, highlighting a failure of the health services system and gaps in the approach to control the disease [8].

There is evidence that the knowledge and skills of leprosy diagnosis, treatment, and management by general health workers are unsatisfactory [9, 10]. As a consequence, there may be a large accumulation of people with leprosy in the community who remain undiagnosed [11]. Leprosy in children can be difficult to identify, particularly because of the peripheral nerve function evaluation. The younger the child, the more difficult the changes in sensitivity are to evaluate [12].

Given that one of the main targets of the global leprosy strategy is zero disabilities among new pediatric patients (children below the age of 15) by 2020 [1••], this study aims to review the cutting-edge developments regarding to the diagnosis, management and prevention of leprosy in children.

Clinical Diagnosis

Leprosy diagnosis is based on clinical signs and loss of sensation [13], associated or not with thickened nerves. Although there are no laboratory exams that can detect all cases of leprosy, the presence of acid-fast bacilli (AFB) in skin smears is conclusive for a leprosy diagnosis.

The clinical spectrum of leprosy is related to the complex process of *M. leprae*-Schwann cell interaction at the peripheral nerves, together with the immunological responses of the individuals. Ridley and Jopling classification based on clinical, histopathological, and immunological criteria [14] can be used for classifying leprosy in adults and children as well. Tuberculoid (TT) leprosy has a better cellular immune response, containing the dissemination and inhibiting bacilli growth and dissemination, while Lepromatous (LL) leprosy has a defective cellular immune response, with a huge, but innocuous, antibody production that permits bacilli multiplication and disease dissemination. Between those two poles, there is a Borderline form of the disease, that can be Borderline Tuberculoid (BT), Borderline Borderline (BB), or Borderline Lepromatous (BL), depending on the types of lesions, histopathology, and immune status (Fig. 1).

A restricted macular condition, with a few hypopigmented macules is defined as indeterminate leprosy, but all clinical forms might have hypopigmented lesions. TT leprosy present with papules or tubercles that may group in a few well-demarcated plaques or annular lesions, associated or not to erythema. A few children may present infantile nodular leprosy, a self-healing TT leprosy defined by a nodular lesion, usually unique, on the face [15]. LL patients have numerous nodular lesions and infiltrated areas disseminated through the skin and mucosa. Borderline cases show erythematous, infiltrated plaques, with poorly demarcated outer edges, usually presenting a depressed center resulting in a foveolar appearance, a classic borderline lesion. The presence of one or multiple foveolar lesions should define the case as BB, while the appearance of less infiltrated plaques, some dry resembling TT, favors BT diagnosis, and the existence of a more diffuse infiltration and nodules guides the diagnosis to BL (Fig. 2).

The hallmark of leprosy is the presence of lesions or areas with hypo or anesthesia, that can be accompanied by hypohidrosis, alopecia, nerve thickening, and/or ache. Hypohidrosis and alopecia in TT patients are restricted to the lesions, and may be quite conspicuous, while LL patients may have large areas of hypo or anhidrosis. Advanced cases may associate hair loss in different parts of the tegument (except the scalp) and madarosis. BT, BB, BL patients may have local or spread areas of hypohidrosis and alopecia, while in indeterminate cases they are absent.

Although highly important for leprosy diagnosis, nerve thickness is not an easy task to be determined by the examiner, and sometimes even skilled health personnel may differ on the palpation findings, especially in children. Nerve thickness is only to be considered when associated with any functional loss, as hypo or anesthesia on its territory, or any motor dysfunction, and usually a difference is found when left and right nerve trunks are compared. TT patients may have a thick, painful nerve trunk on the same territory of the lesions, while borderline typically have more nerves affected, accompanied or not by spontaneous or palpation derived pain. As the disease progress towards the LL pole, the number of thickened nerves increase and can present pain during the palpation.

Fig. 1 Summary of Ridley-Jopling classification of leprosy

Ridley-Jopling Five-group System	TT	Borderline			LL
		BT	BB	BL	
Number of skin lesions	←				→
Bacilli in lesions	←				→
Cell mediated immunity	→				←
Antibody response	←				→

Note: **TT** = Tuberculoid. **BT** = Borderline Tuberculoid. **BB** = Borderline Borderline. **BL** = Borderline Lepromatous. **LL** = Lepromatous.

Among the signs and symptoms of leprosy are paresthesia "in islets" or accompanying paths of the nerve trunks involved by leprosy. With a proper approach, children can define different "dormant," "damped," or "forgotten" areas on the skin. One or more of these sensations may be reported by the patient, more intense at night and cold, in the early with intermittent nature, lasting from weeks to months interspersed with long periods of calm, becoming more continuous and debilitating with the evolution of the disease.

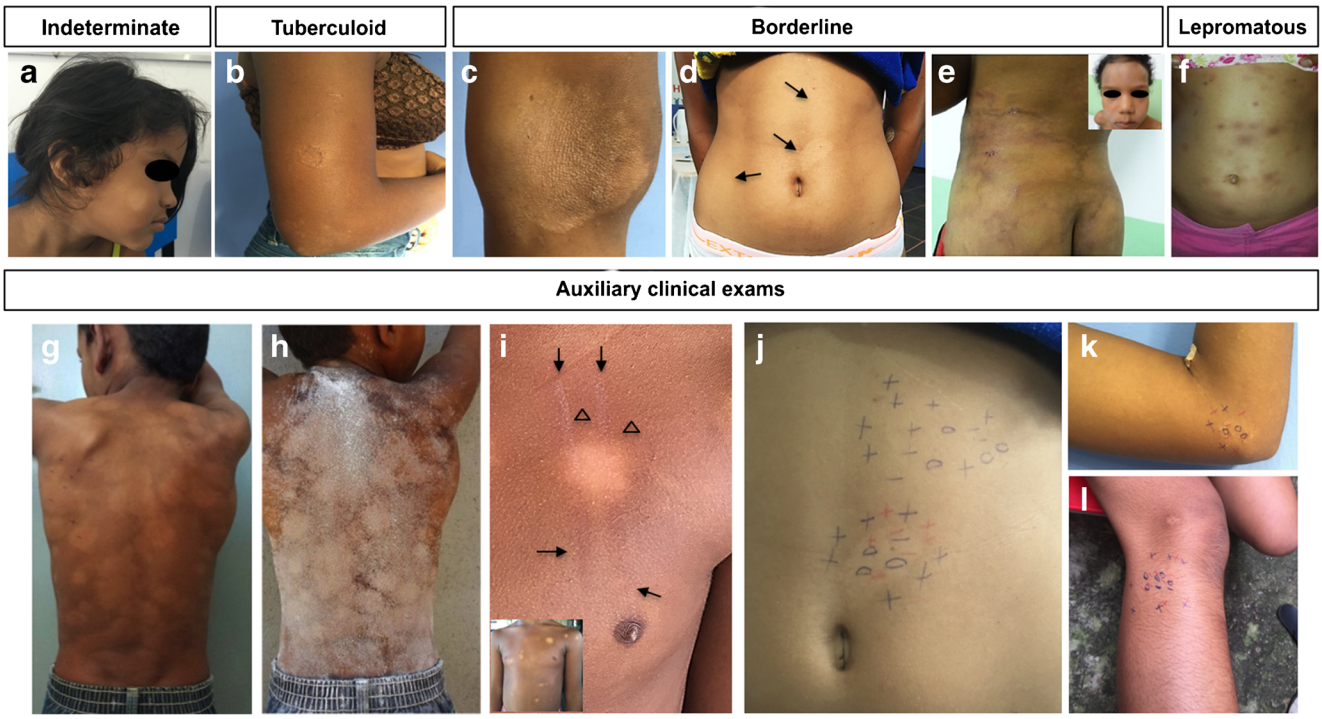

Fig. 2 Clinical manifestations in leprosy forms and auxiliary clinical exams. **a** Hypochromic macule on face (4 years old). **b** Annular plaque on right arm (12 years old). **c** Hypochromic plaque on left knee with infiltrated low edge (13 years old). **d** Multiple large hypochromic macules (*arrows*) on trunk (10 years old). **e** Multiple foveolar plaques on trunk and infiltrated face in close (7 years old). **f** Diffuse clofazimine impregnated areas (lepromas) after 3 months of multibacillary multi-drug therapy (11 years old). **g** Diffuse hypoesthetic hypochromic macules on trunk (6 years old). **h** Extensive hypo and anhidrotic areas on the back after 10 min of iodine-starch test. **i** Absence of secondary erythema reflex on leprosy hypochromic lesion as compare to its periphery areas (Δ) after strong scrawl (*arrows*) through the lesion in endogenous histamine test in hypochromiant dimorphous leprosy patient in close (8 years old). **j** Tactile (*blue* signs) and painful (*red* signs) sensitivity tests in hypoesthetic (−) and anesthetic (0) points in hypochromic areas surrounded by normoaesthetic (+) points on abdomen (10 years old). **k** Tactile and painful sensitivity tests in tuberculoid-borderline leprosy plaque left elbow (12 years old). **l** Tactile and painful sensitivity tests in alopecic hypochromic macule on right leg (12 years old)

Early lesions are characterized by hypochromic macule with hypo- or anesthesia. Several sensitivity evaluation techniques are described and used in clinical practice. In hypochromic spots with irregular borders, the tactile, thermal, and pain sensitivities should be tested, and assessments of vasomotor reflex and sweating must be conducted (Fig. 2).

For thermal change investigation, two test tubes containing cold and hot (±45 °C) water are used. The tubes should touch the lesioned skin lightly leaning, alternately and irregularly, while the patient is asked to infer the feeling that the tube elicits. Lukewarm information or "less hot" should be valued by setting thermal hypoesthesia, therefore, the test must be performed initially in normal skin and then in the suspected area, and should care about touching only the lower area of the tube surface, because in doing to a greater extent, the results may be falsely negative.

Likewise, pain sensitivity investigation is tested in healthy skin and in the suspected area with the tip or the base of a needle, alternately and randomly. The patient is asked to identify which part of the object (tip or base) is coming into contact with the skin. A limitation of this method is the need to use a perforating object, with the risk of needle stick injuries, besides the discomfort of physical examination for some patients, especially children, simply by the use of needles. Calm down the child showing the flick and make it clear that the sensitivity test is pain and not touch. Start your test on the suspect area where the child will be surprised by the absence or reduction of pain and then go to the periphery with normal sensitivity and greater pain, uncomfortable for continuity test; however, defining the island sensitivity alteration is a characteristic of leprosy.

To assess the tactile sensitivity and follow-up of patients with leprosy, a set of nylon monofilaments of varying thicknesses are widely used, called esthesiometer or Semmes Weinstein monofilaments (SWM). On the skin surface, the normal tactile sensitivity is defined by the green monofilament equivalent to 0.05 g-force. As described above, internal and external areas to suspected areas should be tested by applying monofilament for three consecutive times on the same point (Movie 1 - https://1drv.ms/v/s!AnFfwiJhUSs-gdsRWe1Xfo3S2tI3xA). It is possible to use SWM for leprosy diagnosis [16], and in our hands, children from 6 years old may respond well to SWM. It is mandatory to explain well the test for children, and if necessary to use other methods, like instead of answering, to point with their fingers where there is a touching sensation.

Vasomotor reflex may be evaluated using a 1:1000 solution of histamine. A drop of the solution is applied to the lesioned skin and another to the normal skin. After a few light punctures with a needle, the triple reaction of Lewis is incomplete on the lesioned skin, as follows. In both areas, an initial 3–15 s erythema due to capillary dilatation occurs. After 30–90 s, a reflecting erythema by axonal arteriolar dilatation is seen only on normal skin. Finally, after 2–3 min, urtica forms in both areas. In the leprosy spot, the secondary reflex erythema is absent or decreased by impairment of nerve endings.

As for sweating assessment in leprosy lesions, the iodine-starch or compound alizarin (compact brown staining of a part of alizarin, two parts of starch and one part of sodium carbonate) can be used. The patient is instructed to do some exercise to cause sweating. The sweat reaction to iodine-starch or alizarin compound alters the initial color of iodine from brown to dark brown or blueish (lugol reaction) or violet with alizarin. On the macula of leprosy, sweat is absent (anhidrosis) or decreased (hypohidrosis) maintaining the whitish and dried original color of the starch or the original color of the dried compound of alizarin due to impairment of the autonomic nerve endings [17].

During the course of leprosy, exacerbations of the disease may happen one or more times, in processes defined as leprosy reactions, type 1 or reversal reaction, and type 2 or erythema nodosum leprosum (ENL), that can occur alone or associated. Indeterminate leprosy patients never have reactions, while TT and BT may develop only type 1, BB, and BL types 1 and 2, and LL patients may develop only type 2. All, but indeterminate, may develop chronic neuritis during the course of the disease. Type 1 reaction is a highly aggressive cellular immunological reaction, with no systemic symptoms, that may cause important nerve pain and impairment resulting in permanent disabilities. Type 2 reaction is an aggressive neutrophilic inflammation leading to panniculitis and/or vasculitis resultant of the production of immune complexes and complement against *M. leprae* antigens which may be deposited on the vascular walls [18]. The process develops subcutaneous nodules, especially on arms and legs, associated with to fever and malaise, accompanying inflammation of different organs.

In summary, Ridley-Jopling classification is quite useful for adequate assessment of the patients who present very clear lesions of leprosy. However, school children lesions are very preliminary, and the present challenge is to diagnose them with very mild symptoms, with no reactions nor disabilities, still on PB form, breaking the transmission chain in order to control the leprosy endemics.

Laboratory Diagnosis

Diagnosis of those with early disease symptoms allowing treatment, is critical to preventing nerve damage and disability. Due to the incorporation of leprosy diagnosis into the general family health delivery system in many areas of the world, the number of trained leprologists and laboratory technicians focused on this disease has decreased, leading to an increase in misdiagnosis and a delay in providing treatment in a timely manner [10]. There is currently no laboratory test capable of diagnosing leprosy, so the development of a simple

and cheap test that could assist health professionals to correctly diagnose the disease based on metabolomic or immunologic biomarkers of infection is desirable.

Leprosy is a clinical spectrum with variation in the manifestations of skin lesions and nerve damage closely aligned with the ability of the host to mount an effective immune response, entirely dependent on the interplay of both cell mediated and humoral responses, and up to 80% of people worldwide have a natural immunity to mycobacterial infection [19]. The most widely used Ridley-Jopling classification system categorizes the disease into five forms based on histopathological features of skin lesions, ranging from organized granulomas with predominant lymphocytic infiltration with almost undetectable acid-fast bacilli (AFB) in the polar tuberculoid form (TT) progressing to completely disorganized aggregates of foamy histiocytes and $\geq 10^{10}$ bacilli per gram of tissue in the polar lepromatous form (LL), with immunologically unstable borderline forms in between (BT, BB, BL). The main features important for classification are the histological patterns of cellular infiltration and organization of hematoxylin and eosin stained skin biopsy sections, involvement of peripheral nerves, and observing AFB within nerves or in histiocytes using the Fite-Faraco modification of the carbol fuchsin staining technique [20]. Bacilloscopy of multiple skin biopsies can establish the bacillary index (BI) on a logarithmic scale, which can range from 0 (no AFB detected) to 6+ (>1000 AFB per field).

An important aim of many research groups would be the development of an improved diagnostic test allowing detection of *M. leprae* infection before clinical symptoms arise. Tests are being developed that can measure biomarkers that are the result of infection, and can include measuring antibody responses to mycobacterial antigens, cell mediated cytokine release assays (such as the detection of IFN-γ), amplification of mycobacterial DNA by PCR, or the use of metabolomics to detect molecular features specific to *M. leprae* infection in the blood or urine. Assays to assess leprosy patient antibody responses to the *M. leprae*-specific antigen, phenolic glycolipid-I (PGL-I) have been in use for over 30 years [21], and include ELISA assays and lateral flow devices. The protein antigen LID-1, composed of the fusion of two well-recognized *M. leprae* proteins, ML0405 and ML2331, is recognized almost as well as PGL-I by almost all lepromatous patients [22]. Another group has combined lateral flow assays with up-converting phosphor (UCP) reporter technology to detect anti-PGL-I responses along with detecting Th1 and Th2 cytokine responses (IFN-γ and IL-10, respectively) by T cells in a single sample. Since the outcome of *M. leprae* infection is determined by the interplay of cellular- and humoral immunity, these multiplex UCP-LFA test strips can provide more detail about the individual's immune response to *M. leprae* antigens [23, 24]. Molecular detection methods incorporating the amplification of the repetitive RLEP sequence by PCR have also been used to identify individuals infected with *M. leprae* [25•]. Recent evidence indicates that individuals who are RLEP PCR positive in ear lobe slit skin smears (SSS) or biopsies of the nasal turbinate or other skin lesion sites as well as having a positive anti-PGL-I titer likely have asymptomatic infection and are at the highest risk of developing disease [26]. Our studies in hyperendemic areas in Pará, Brazil support these findings. Initial results of several large families living in "hot spots" indicated that >80% of family members were positive for anti-PGL-I; >70% were positive for RLEP by PCR, with up to 65% being positive for both biomarkers, indicating extreme rates of infection, with one or more individuals in each household diagnosed with leprosy based on clinical signs (unpublished observations). Finally, metabolomics has been used to identify molecular features in the serum of leprosy patients, showing that there was an overabundance of polyunsaturated fatty acids and phospholipids linked to a high BI in lepromatous disease [27]. There is also a preliminary report of using mass spectrometry to identify molecular signatures of *M. leprae* picked up by silica plates pressed against leprosy skin lesions [28].

Despite recent advances, the diagnosis of leprosy must remain firmly in the hands of well-trained health professionals. Nevertheless, even with active surveillance and the possibility of chemoprophylaxis to treat larger cohorts of household contacts who demonstrate biomarkers of subclinical infection, mathematical modeling studies indicate that lowering new case detection rates in hyperendemic areas like Pará will likely take a long time [29, 30], especially given the complexities of registering diagnosed cases and getting them the treatment they deserve [31].

Treatment/Management

The treatment of leprosy is ambulatory, using standardized treatment regimens, according to the operational classification. Children weighing more than 50 kg use the same treatment prescribed for adults. Those between 30 and 50 kg should use the brown (MDT MB) or blue (MDT PB) children cards [32]. For children under 30 kg, the monitored monthly dose recommended is rifampicin in suspension 10–20 mg/kg, dapsone 1–2 mg/kg, and clofazimine 5.0 mg/kg. The daily doses of dapsone is 1–2 mg/kg and clofazimine 1.0 mg/kg. The most visible side effect of MB treatment is a brownish appearance of the skin, that can lead to avoid going to school and to stop treatment [33]. The estimated number of Glucose 6-phosphate dehydrogenase (G6PD) deficiency is high (330 million worldwide), and drug-induced acute hemolytic anemia may be life-threatening [34]. Dapsone-related anemia is one of the most referred side effects of MDT, varying from 2.4 [35] to 12% [36] of all patients—including children—on MDT, and health professionals must be aware of it.

Type 1 reaction can be treated using steroids, usually prednisone 1 mg/kg/day, with a gradual reduction of about 10–20% every 15 days after clinical improvement. A strict impairment evaluation and improvement analysis is mandatory during the course of steroids, that may have important collateral effects, as growth inhibition and Cushing syndrome. Type 2 reaction may be treated with thalidomide, an excellent drug that rapidly improves the clinical situation of the patient. The drug has been used to treat different pediatric conditions, from multiple myeloma to Graft versus Host Disease (GVHD) in dosages up to 800 mg per day [37]. In leprosy, there are no clinical trials on children, and a dosage of up to 9.5 mg/kg/day is described to be used as an attack dose, that may be decreased every 15 days [38]. In our experience, a maximum dosage of 300 mg/day is usually sufficient to control ENL in children, tapering off 20–30% every 15 days. Thalidomide is teratogenic, and pregnancy test together with two contraceptive methods is mandatory for women of fertile age, before starting the drug. Other immunosuppressive drugs have been used in clinical trials with good results.

Prevention

There is no specific protection against leprosy. Early diagnosis and prompt treatment with full course of MDT continue to be the key strategy to prevent the disease because it breaks the chain of transmission [1••]. Promoting active case-finding and continuous contact tracing are essential. In this way, geographical information systems (GIS) and spatial analysis have contributed to identify priority areas with higher risk for leprosy, increasing the efficiency of active strategies [39, 40••]. School children surveys, performed by well-trained health professionals, is imperative in highly endemic areas in order to increase the early detection of new cases [3, 41], actually this is one of the pillars of the WHO current recommendation [1••]. A review of childhood leprosy in India over the past two decades concluded that community survey is a more effective method to detect cases of leprosy among children than voluntary reporting and referral services, as it targets the hidden cases [42].

Nevertheless, leprosy elimination will not be accomplished by MDT alone, and new tools are required to prevent the disease. Past and ongoing research has made some progress in the areas of chemoprophylaxis and immunoprophylaxis to prevent leprosy [43], but the definitive intervention is not yet available. Bacillus Calmette–Guérin (BCG) vaccination or revaccination has been used in some countries, like Brazil, as a prophylactic measure. The best data available indicates that BCG has a wide-ranging protective efficacy with an average ≈50% and protection appears to be better against the MB than the PB form [44]. Even with the massive neonatal BCG vaccination in Brazil since 1976, leprosy continues to be a public health problem in this South American country.

Chemoprophylaxis trials to treat *M. leprae* infection before it develops into overt disease have been carried out since 1960s. Drugs such as dapsone, acedapsone, and rifampicin alone or in combination with other drugs (rifampicin-ofloxacin-minocycline) were tested. General population and mostly contacts were targeted by the studies. Data shows that chemoprophylaxis provides a relatively short protective effect, which is lost beyond 2 years [43, 44]. Currently, there is not enough evidence to support the widespread use of any chemoprophylaxis regimen to prevent leprosy, and it is not approved by any health authority.

A strategy using a combination of the immunoprophylaxis with BCG and chemoprophylaxis with single dose rifampicin to prevent leprosy in contacts of newly diagnosed leprosy cases is under ongoing investigation. The researchers hypothesize that the effects of both interventions may be complementary, causing the combined preventive outcome to be significant and long-lasting [45]. We argue that any chemoprophylaxis approach should be applied only after solving the questions related to the very high hidden prevalence of leprosy in endemic areas, detecting and treating all undiagnosed cases with MDT.

Conclusion

Early diagnosis and treatment is the fundamental strategy to prevent leprosy transmission. Leprosy in children below 15 years old is a robust indicator of active source of infection in the community where they live. Subclinical infection among children is considered a sentinel for hidden prevalence in the general population, as well. Large scale school children surveys performed in clusters of leprosy in hyperendemic municipalities with well-trained personnel can increase the detection rate and consequently decrease the *M. leprae* transmission. Early diagnosis in children can be hard, even for those with experience in dealing with this disease, because of the wide range of clinical aspects of the skin lesions and mainly due to the difficulty of performing the clinical peripheral nerve evaluation. The astonishing and sad high hidden prevalence of leprosy among children in some hyperendemic areas in the world means that we still have a long journey to reach leprosy elimination. Ongoing research is trying to develop better diagnostic tests and to advance chemoprophylaxis and immunoprophylaxis approaches. But for now, we must maintain leprosy expertise and improve the health professionals training for leprosy diagnosis.

Acknowledgements We would like to thank the following institutions for their support to the authors: CNPQ, CAPES, CAPES PROAMAZONIA, FAPESPA, SESPA, FAEPA-HCFMRP-USP, The Order of Malta (MALTALEP), The New York Community Trust (The Heiser Program for Research in Leprosy) and the J. William Fulbright Scholar to Brazil award.

Compliance with Ethical Standards

Conflict of Interest Drs Barreto, Frade, Filho, da Silva, Spencer, and Salgado declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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