Neglected Tropical Diseases

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José Ignacio Santos-Preciado *Editors*

Neglected Tropical Diseases - Latin America and the Caribbean

Springer

Neglected Tropical Diseases

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Neglected Tropical Diseases - Latin America and the Caribbean

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ISSN 2194-8275 ISSN 2194-8283 (electronic)
Neglected Tropical Diseases
ISBN 978-3-7091-1421-6 ISBN 978-3-7091-1422-3 (eBook)
DOI 10.1007/978-3-7091-1422-3

Library of Congress Control Number: 2015939275

Springer Wien Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer-Verlag GmbH Wien is part of Springer Science+Business Media (www.springer.com)

Foreword

Increasing evidence mostly emerging over the last decade indicates that neglected tropical diseases (NTDs) are widespread in Latin America and the Caribbean (LAC) region, especially among the regions' poorest people. Today among the almost 600 million people who live in LAC, close to 100 million people live on less than $2 per day, of whom about one-half live below the World Bank poverty figure of $1.25 day (Hotez et al. 2013).

Virtually every person living at this level of poverty is infected with one or more NTDs, led by the intestinal helminth infections—ascariasis (86 million people), trichuriasis (72 million), and hookworm infection (30 million) (Pullan et al. 2014)—and Chagas disease (7–8 million). Moreover, dengue fever has become widespread both among the poor and middle-class populations, with some estimates indicating that there are more than 50 million incident cases (Bhatt et al. 2013). Other NTDs such as lymphatic filariasis (LF), leishmaniasis, and schistosomiasis are still common in some focal areas of the LAC region.

The consequences of such high disease burdens go beyond public health. The NTDs have been shown to reinforce and promote poverty through their long-term and debilitating features. They affect both agricultural and urban productivity and block children from growing to their full intellectual potential. The NTDs also disproportionately affected girls and women. Indigenous populations in the LAC region are especially vulnerable.

This volume, coedited by Dr. Carlos Franco-Paredes and Dr. Jose Ignacio Santos-Preciado, attempts to do a "deep dive" on the problems of NTDs in the LAC region. He has pulled together experts on all of the major NTDs highlighted above, as well as those we often do not hear about frequently, such as bartonellosis, cysticercosis, and fascioliasis. The volume will also provide useful updates on efforts to control or even eliminate some key NTDs in the Western Hemisphere, such as leprosy, LF, onchcoerciasis, and vivax malaria. Some of these efforts are

being conducted under the auspices of achieving 2012 London Declaration for NTDs targets and a 2013 World Health Assembly resolution for the NTDs.

There is much written here about some of the major forces that currently promote the emergence or reemergence of key NTDs, including physical and environmental factors such as deforestation, as well as social forces of poverty, conflict, urbanization, and human migrations.

This volume is a great opportunity for readers to obtain an in-depth overview of the problems of NTDs in the LAC region. I congratulate Dr. Franco-Paredes and his colleagues for their efforts!

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Contents

The Neglected Tropical Diseases in Latin America and the Caribbean: Burden of Disease and Approaches for Elimination and Control

Carlos Franco-Paredes and José Ignacio Santos-Preciado

Contents

Abstract Neglected tropical diseases (NTDs) have afflicted humankind since time immemorial, and their impact has impacted, and continues to do so, leading to disabling, deforming, stigmatizing diseases. This group of diseases decreases the freedoms and capabilities of individuals leading to economic poverty and underdevelopment. In Latin America and the Caribbean, the toll associated with many neglected tropical diseases is similar, if not higher, than that of HIV/AIDS and tuberculosis in this region. Fortunately, through the use of stepped-up advocacy, partnerships, resource mobilization, capacity enhancement, and careful allocation of resources, a number of NTDs can be controlled and potentially eliminated in Latin America and the Caribbean.

Keywords Neglected tropical diseases (NTDs) • Latin America • Caribbean • Chagas disease • Leprosy • Schistosomiasis • Soil-transmitted helminthes • Leptospirosis • Bartonellosis • Trichuriasis • Lymphatic filariasis • Hookworm • Cysticercosis • Leishmaniasis • Onchocerciasis • Yellow fever

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_1

1 Overview of the Neglected Tropical Diseases in Latin America and the Caribbean

Map is not the territory. This phrase coined by the Polish–American scientist and philosopher Alfred Korzybski may be interpreted from different perspectives. If we choose to focus on infectious pathogens, assessing geopolitical divisions may only cloud our perception of the ecological reach and biological determination of microbes, and it may also impair our appreciation of the biosphere (Lapo and Vladimir 2001). The Neglected Tropical Diseases (NTDs) illustrate the importance of Korzybski's dictum by impacting more than one billion people across the globe, and by placing at least 2 billion at risk (Ault 2007, 2008; Gyapong et al. 2010; Hotez et al. 2008a; Holveck et al. 2007). This geographic dilemma is exemplified in borders such as that of northern Mexico and the southern United States where populations sharing the same terrain and similar culture and history are also at risk of the same NTDs (Hotez et al. 2012). Similarly, there is a blurring of arbitrarily chosen borders in maps as demonstrated by the distribution of some NTDs in the Western Hemisphere corresponding with the legacy of the slave trade by Europeans (Lammie et al. 2007; Ault and Roses Periago 2011). In addition, due to international migration of populations latently infected with *Trypanosoma cruzi*, the cause of Chagas disease, from endemic areas in Latin America migrating to nonendemic areas (i.e., Europe), illustrates the potential globalization of previously geographically restricted NTDs.

Indeed, across most territories and regardless of the cartography chosen, impoverished people embedded in social failures may suffer from one or more NTDs. This group of infectious diseases is defined by the occurrence of chronic parasitic, bacterial, or other diseases that promote poverty because of their impact on child growth and cognitive development, pregnancy, and people's economic capabilities (productivity as an adult, low literacy, people being too sick to work, and parents taking time off work to care for sick children—frequently all this leading to premature death) (Table 1) (Ault 2007). As a result, the disease burden due to the major NTDs has been estimated to be 57 million disability-adjusted life years (DALYs) lost per year (Gyapong et al. 2010; Hotez et al. 2008a; Holveck et al. 2007; Ault 2008).

In Latin American and Caribbean region (LAC), many people currently live in poverty (more than 100 million people live on less than US$2 per day) (World Bank 2005). Most of the poor in this region live as subsistence farmers in rural areas and urban slums placing this large number of individuals at risk of infection and the disease consequences of NTDs (Hotez et al. 2012). Furthermore, the burden of disease resulting from the NTDs in LAC may exceed that of HIV/AIDS (Ault 2007). Health inequities are directly responsible for placing individuals at risk of NTDs: unsafe water, poor sanitation, refuse disposal, lack of access to health services, low literacy levels, and inadequate nutrition among other social determinants (Franco-Paredes et al. 2007a, b; Conteh et al. 2010; Montenegro and Stephens 2006). Concomitantly, NTDs represent important, yet often unrecognized, reasons of why the poorest people in the Americas cannot escape poverty (Hotez

Table 1 Ranking of neglected tropical diseases in Latin America and the Caribbean by prevalence and distribution

Disease	Population currently infected in LAC	Population at risk in LAC	Major vulnerable populations or geographic areas	No. LAC countries infected	Percentage of LAC population infected (% poor people infected)	Percent global disease burden in LAC
Trichuriasis	100 million	523 million	Poor Rural & Urban Slums	27	17.8 % (46.9 %)	16.6 %
Ascariasis	84 million	514 million	Poor rural & Urban slums	27	15.0 % (39.4 %)	10.4 %
Hookworm	50 million	346 million	Poor rural	26	8.9 % (23.5 %)	8.7 %
Chagas disease	8–9 million	25–90 million	Poor rural & Urban slums	13	1.6 % (4.1 %)	99.8 %
Schistosomiasis	1.8 million	36 million	Poor rural	4 with >1000 cases	0.3 % (0.8 %)	0.9 %
Blinding Trachoma	1.1 million	ND	Poor rural	3	0.2 % (0.5 %)	1.3 %
Lymphatic Filariasis	720,000	8.9 million	Urban slums & Poor rural	7	0.1 % (0.3 %)	0.6 %
Dengue fever	552,141 reported in 2006	ND	Urban slums	23	0.1 % (0.2 %)	ND
Cysticercosis	400,000	75 million	Poor rural	15	<0.1 % (0.2 %)	ND
Cutaneous (CL) and Visceral (VL) Leishmaniasis	62,000 CL 5,000 VL	ND	Urban slums & Poor rural	18	ND	ND
Leprosy	47,612 new cases	ND	Poor rural & Urban slums	22	<0.1 % (<0.1 %)	11.4 %

(continued)

Table 1 (continued)

Disease	Population currently infected in LAC	Population at risk in LAC	Major vulnerable populations or geographic areas	No. LAC countries infected	Percentage of LAC population infected (% poor people infected)	Percent global disease burden in LAC
Onchocerciasis	64 new cases in 2004	515,675	Poor rural	6	<0.1 % (<0.1 %)	0.3 %
Jungle yellow fever	86 new cases in 2004	ND	Jungle & Urban slums	4	<0.1 % (<0.1 %)	<0.1 %

From: Hotez et al. (2008a)

et al. 2008a; Lammie et al. 2007). LAC accounts for 8.8 % or 1.5–5 million DALYs of the global disease burden due to NTDs (Hotez et al. 2008a).

The NTDs in the Americas are concentrated not only within pockets of intense poverty but also among selected vulnerable populations, especially among indigenous populations (Hotez et al. 2008a). In some areas, women and children may be considered neglected populations due to their limited access to health and social support services (Franco-Paredes et al. 2007a, b). There is also mounting evidence that populations in conflict areas are disproportionately impacted by NTDs. Other vulnerable groups impacted by poverty and heavily affected by communicable and noncommunicable diseases include periurban communities (e.g., slum and shantytown dwellers) and the rural poor (e.g., migratory workers in agriculture, miners, and fishers) (Hotez et al. 2008a; Franco-Paredes et al. 2007a).

In Guatemala and southern states in Mexico, indigenous populations suffer from some of the highest rates of soil-transmitted helminth infections in the Americas, as well as high rates of onchocerciasis and Chagas disease (Hotez et al. 2008a; Conteh et al. 2010; Montenegro and Stephens 2006; Beltrame et al. 2002). Similarly, the indigenous people of Bolivia and Peru experience high rates of fasciolasis, cysticercosis, and plague; those in Colombia are at elevated risk for leishmaniasis, Chagas disease, and yellow fever; and in Brazil, high levels of soil-transmitted helminth infections and subsequent growth stunting occur among indigenous populations (Hotez et al. 2008a; Montenegro and Stephens 2006; Beltrame et al. 2002). In Guatemala and Mexico, the indigenous populations who live in coffee plantations are most at risk for onchocerciasis, whereas in Ecuador and Colombia the disease affects those living on the banks of river shores, primarily people of African and indigenous descent (Montenegro and Stephens 2006; Beltrame et al. 2002). In addition to LAC's indigenous populations, poor communities of African descent, such as those found in parts of the Caribbean, Central America, and Brazil, suffer from high prevalence rates of NTDs, especially hookworm infection, lymphatic filariasis, onchocerciasis, and schistosomiasis (Beltrame et al. 2002; Sauerbrey 2008; Hotez et al. 2008b; Maciel et al. 2008). Besides the major NTDs summarized in Table 1, there are other infectious diseases that are prevalent in LAC but that precise estimates are not available (Table 2).

The epidemiology of some NTDs, such as Chagas disease, is shifting partly due to urbanization, migration patterns of the rural poor, and an increase in urban poverty (Hotez et al. 2008a; World Bank 2005). Demographic trends suggest that the urbanization of poverty will continue: if poverty rates remain unchanged, by 2015 two-thirds of the poor in LAC will be living in cities (World Bank 2005), which may impact transmission patterns of some NTDs including Chagas and leishmaniasis due to urban migration. Many urban slums are built on unsecured land, often located in areas prone to natural disasters, such as flooding and landslides, or in close proximity to environmental hazards, such as landfills (Maciel et al. 2008), all of which can create environments that make the urban poor more susceptible to NTDs. In LAC, leptospirosis is an important cause of morbidity, especially in urban slums (Hotez et al. 2008a). In Brazil alone, more than 10,000 cases of severe leptospirosis cluster in the slum settlements, which lack adequate sewage systems and refuse collection services (Maciel et al. 2008). In South

Table 2 Major NTDs in Latin America and the Caribbean where there is no reliable data on disease burden and estimates

Helminth infections	Protozoan infections	Bacterial infections	Fungal infections and Ectoparasitic infections	Viral infections
Echinococcosis	Amebiasis	Bartonellosis	Mycetomas	Hemorrhagic Fevers
Cysticercosis	Giardiasis	Buruli ulcer	Paracoccidioidomycosis	Rabies
Fascioliasis		Leptospirosis	Myiasis	
Strongyloidiasis		Plague	Scabies	
Toxocariasis		Treponematoses (nonvenereal)	Tungiasis	

From: Hotez et al. (2008a)

America, visceral leishmaniasis is increasingly a periurban disease (Hotez et al. 2008a; World Bank 2005). In these settings, lack of sanitation with abundant rodents and large numbers of stray dogs and sporadic garbage collection provide sandflies-breeding sites and increase the risk for leishmaniasis (Alvar et al. 2006).

NTDs disproportionately result in negative health outcomes for girls and women (Hotez et al. 2008a; Alvar et al. 2006; Hotez 2009; Friedman et al. 2007). In Latin America, hookworm infection is a major contributor to anemia and iron loss in pregnancy (Hotez et al. 2008b). There is also some evidence that schistosomiasis in pregnancy causes: increased maternal morbidity and low birth weight (Hotez et al. 2008a; Beltrame et al. 2002). It has also been noted that congenital infections with some NTD pathogens can commonly occur (Montenegro and Stephens 2006). Congenital toxoplasmosis and malaria are the best-known examples, but now there is also evidence that congenital Chagas disease occurs with higher frequency among pregnant mothers infected with *T. cruzi* (Franco-Paredes et al. 2007a, b).

Although poverty has contributed to the proliferation of NTDs, evidence is mounting for associations between increased prevalence of diseases, conflict, and systematic human rights violations (Franco-Paredes et al. 2007a, b; Alvar et al. 2006). The emergence of cutaneous leishmaniasis in Colombia is linked to several decades of armed and guerilla internal conflict fueled by cocaine production and trafficking (Beyrer et al. 2007). In Colombia, more than 25 % of leishmaniasis cases reported in 2004 affected military personnel patrolling conflict areas, representing a three-time increase from the 2003 rate (Beyrer et al. 2007). For civilians living in conflict areas in Colombia, the size and pattern of disease incidence are unknown (Beyrer et al. 2007). In addition, the cycle of poverty, disease, inequality, and underdevelopment has at times led to social disruption and civil strife, as was the case in Chiapas, Mexico in 1994 with the Zapatista movement (Franco-Paredes et al. 2007a), which saw a concurrent reemergence of the Chagas disease (Ault 2008). Conflicts can break down community-health infrastructures, restrict access to health care, limit surveillance, prevention, treatment, and vector control, hamper outbreak investigations due to safety concerns, and reduce donor interest in research (Beyrer et al. 2007). Moreover, the conditions created by war and conflict further perpetuate the neglect of NTDs and marginalization of poor and internally displaced persons with these diseases.

2 Control and Elimination of NTDs in Latin America and the Caribbean

A major aspiration of public health interventions is that of attaining global health equity (Dowdle and Cochi 2011; Hopkins 2013). Given the fact that infectious diseases continue to cause a high burden of disease in many settings, disease-eradication efforts offer the opportunity to foster global health equity. Smallpox eradication framed this concept as a monumental global achievement with lasting societal benefits. As attractive as it may be, and after smallpox, the eradication of other infectious pathogens has proven difficult to accomplish (White and Franco-Paredes 2015; Tarantola and Foster 2011; Lockwood et al. 2014).

The principles of disease eradication rely on four factors: biologic feasibility, adequate public health infrastructure, funding, and sustained political and societal will (Dowdle and Cochi 2011). Global decisions on disease eradication require consideration of prioritization and costs in order to achieve the most appropriate, cost-beneficial, and equitable outcome of disease control (Hopkins 2013). Based on these premises, today, we have tools to effectively target the NTDs group including safe and inexpensive antihelminthics, rapid test kits for confirming the infection of several parasites, and community-based and integrated approaches to control these maladies. Therefore, it has become an ethical imperative to work toward the control and elimination of NTDs (Ault 2008; Ault and Roses Periago 2011). Furthermore, the World Health Organization (WHO) has identified some NTDs for elimination with three main targets for Latin America by the year 2015: Rabies, onchocerciasis, and Chagas disease transmission through transfusion of blood products. By the year 2020, WHO's elimination targets include leprosy, Chagas in most Latin American countries, lymphatic filariasis, and the endemic treponematoses (Ault and Roses Periago 2011).

LAC countries have had important success in eliminating infectious diseases in the region including smallpox, poliomyelitis, and measles (Ault 2007; Ault and Roses Periago 2011). In 2009, the Directing Council of the Pan-American Health Organization (PAHO) put forward a mandate in the form of a resolution (CD49-R19) to support countries in LAC to achieve elimination or substantially reducing the burden of disease associated with 12 NTDs. PAHO and the LAC countries have demonstrated that a number of NTDs can be eliminated in the region through the use of existing tools, political commitment, stepped-up advocacy, development of private–public partnerships, and resource mobilization (Ault and Roses Periago 2011). Onchocerciasis transmission has been eliminated in 8 of 13 foci among the six endemic countries in the region by the end of 2010. Additionally, a significant reduction in the burden of disease of Chagas disease has been achieved by a reduction in domestic vector transmission of (*Rhodnius prolixus* and *Triatoma infestans*) through the use of systematic indoor spraying concomitantly with a decline in blood transfusion associated infection.

In summary, there has been important achievement in controlling some NTDs in LAC including onchocerciasis and lymphatic filariasis in children and adults,,

malaria in Haiti and Dominican Republic, trachoma in school-age children, schistosomiasis in St Lucia and Suriname. With regard to Chagas disease, continuing interventions to maintain and expand programs using domestic vectoral transmission and transfusional Chagas efforts for elimination are under way (Ault and Roses Periago 2011). For some other disease whose burden can be drastically reduced with available tools, including schistosomiasis and soil-transmitted helminthiasis, ongoing efforts in LAC include mass drug administration to reduce intensity of infection or by preventive chemotherapy to prevent new infections (Salam et al. 2014). The use of spatial analysis and risk maps targeting of soil-transmitted helminthiasis maybe particularly useful but there is a lack of prevalence estimates of infection in many countries of LAC (Chammartin et al. 2013). Despite these limitations, current evidence suggests that effective community-based strategies exist and deliver a range of preventive and therapeutic interventions to decrease the burden of disease caused by helminthic NTDs.

Despite these achievements, health equity goes beyond providing health care. Preventing, treating, and rehabiliting those suffering an NTD may foster social equity in LAC. By decreasing health inequities linked with NTDs, our ultimate goal is to promote people's freedom and capabilities and to return a sense of dignity and self-realization into their lives (Franco-Paredes and Santos-Preciado 2011). Many gaps remain in reducing inequities and inequalities in health in LAC. Pursuing community participation and intersectoral partnerships is crucial to maintain gain and make interventions to control NTDs sustainable in the region. Furthermore, there is an urgent need for pursuing horizontal cooperation among countries that share problems or borders and to execute joint actions and develop intercountry plans. Finally, control and elimination of NTDS require multiple parallel interventions including mass drug administration of antiparasitic or antibacterial drugs, improvements in sanitation, and other integrated programs. However, the development of preventive or therapeutic vaccines to control major NTDs may play a crucial synergistic role in decreasing their burden of disease. In this context, the development of hookworm vaccine is in the pipeline, and there are existing partnerships for the development of vaccines against leishmaniasis and Chagas disease.

In collaboration with Springer–Verlag, the core objective of this collection of volumes is to generate a regional and unique approach to address the impact of the major neglected tropical diseases. In this regard, this volume brings attention to the substantial burden of diseases associated with NTDs in Latin America and the Caribbean. In addition, each chapter provides a discussion of potential approaches to their control and elimination. Some topics such as control or elimination strategies of echinococcosis, leptospirosis, endemic treponematosis, and soil-transmitted helminthes will be discussed in detail in other volumes of this collection. A selected group of hands-on international experts contributed to this volume. These topics are written by local experts with ample field experience and clinical expertise to discuss their perspectives in controlling and eliminating some of the major NTDs in LAC.

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Schistosomiasis in America

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_2

Abstract Schistosomes are parasitic flatworms that cause schistosomiasis, a Neglected Tropical Disease affecting at least 249 million people worldwide. It is the most important waterborne disease in America introduced to this continent during the time of the African slave trade. Of the seven species that infect humans, only *Schistosoma mansoni* is present in America. Schistosomiasis is endemic in Brazil, Suriname, Venezuela, Dominican Republic, Guadeloupe, and St. Lucia. Around 1.8 million people in the region, mostly in Brazil, are thought to be infected, with 25 million living at risk of contracting the disease. The main risk factor for infection is skin exposure through household, work, or recreational activities in water bodies contaminated with cercariae, the infective larval stage of the parasite, released by freshwater mollusks of the genus *Biomphalaria*, that eventually enter the human skin. Adult worms in the porto-mesenteric venous system release hundreds of eggs which leave the body by stools or remain trapped in the intestine and liver, causing intestinal and hepatic pathology progressing to portal hypertension. Initially, schistosomiasis control was based on snail elimination with chemical moluscicides; since 1984 the strategy was reoriented to selective or mass chemotherapy and, since 2006, to preventive chemotherapy with praziquantel. Migration of rural populations, socioeconomic improvement, potable water supply, sanitation, increased exposure of flowing populations toward water bodies during weekends, invasion of exotic snails, chemotherapy program, and persistence of susceptible *Biomphalaria* species in endemic countries are factors that have modified the epidemiology in different ways in the six countries affected in America where prevalence varies.

Keywords Schistosomiasis • *Schistosoma mansoni* • *Biomphalaria* • Latin America • Caribbean • Venezuela • Dominican Republic • St. Lucia • Suriname • Brazil

1 Introduction

Schistosomiasis is a chronic parasitic disease caused by trematodes of the genus *Schistosoma* present in tropical and subtropical areas. Seven species: *Schistosoma mansoni, S. intercalatum, S. guineensis, S. japonicum, S. mekongi, S. malayensis,* and *S. haematobium* infect humans; the first six species cause the intestinal clinical form and the seventh causes the urogenital form of the disease.

Fig. 1 Distribution of schistosomiasis in America

Schistosomiasis is the most important waterborne disease in America that was introduced to this continent during the time of the African slave trade between the sixteenth and nineteenth centuries (Morgan et al. 2005), but only the African species *Schistosoma mansoni* (Sambon 1907a) was able to infect local snail species of the genus *Biomphalaria* (*B. glabrata*, *B. straminea*, *B. kuhniana, B. prona, and B. tenagophila*) (PAHO 1968; Malek 1980; De Jong et al. 2001). In America, schistosomiasis is endemic in Suriname, Venezuela, Dominican Republic, Guadeloupe, St. Lucia, and large areas of Brazil (Fig. 1). This trematode infection behaves

1. Initial phase:
Acute form
a. asymptomatic
b. symptomatic

2. Late phase
Chronic phases – according to the most affected organs:
a. Hepatic-intestinal
b. Hepatic: periportal fibrosis without splenomegaly
c. Hepatosplenic: periportal fibrosis with splenomegaly
d. Complicated forms: i. vasculopulmonary
ii. glomerulopathy
iii. neurological
iv. other localizations: eye. skin. urogenital. etc.
v. pseudoneoplasic
vi. lymphoprolific disease

3. Associated diseases that modify the course of schistosomiasis
a. prolonged salmonellosis
b. liver abscess
c. in immunosuppressed cases (SIDA. HTLV. use of immunosuppressive drugs. etc.)
d. other hepatic disorders : viral, alcoholic. etc.

This clinical classification was elaborated by a group of Brazilian specialists, who gathered in 2008, at the occasion of the 44th Congress of the Brazilian Society of Tropical Medicine, at the request of the Ministry of Health (Katz, 2014)

Chart 1 Classification of clinical forms of Schistosomiasis mansoni

as a real antroponosis having limited ability to maintain the infection only in wild reservoirs in southeast Brazil (*Nectomys squamites*) (D'Andrea et al. 2000) and Guadeloupe (*Rattus rattus*) (Théron and Pointier 1995; Alarcón de Noya et al. 1997). Around 1.8 million people in the region, mostly in the coastal states of Brazil, are thought to be infected, with 25 million living at risk of contracting the disease in America (PAHO 2010).

The main contributing factor to the maintenance of schistosomiasis transmission in a community is the contamination of water sources mainly with human feces from people suffering from schistosomiasis, containing parasite eggs that hatch in water. These eggs release ciliated miracidiae infecting freshwater snails that later on eliminate tailed larvae (cercariae) which penetrate the human skin during contact with infested water. In humans, larvae migrate through blood vessel to the lungs and the portal system where they mature to adult worms. Hundreds of eggs released daily by each female adult worm must either leave the body by stools or become trapped in nearby tissues causing pathology (WHO 2014a; Colley et al. 2014). Inflammatory response to eggs trapped in intestine and liver tissues results in pathology, associated with intestinal manifestations (intestinal form) and liver fibrosis that progress to portal hypertension (hepatointestinal and hepatosplenic forms). More explicit clinical forms are summarized in Chart 1. In

consequence, infected individuals develop anemia, malnutrition, stunted growth, impaired cognitive development, and reduced capacity to work (Gryseels 2012).

The main risk factor for infection is skin exposure through household, work, or recreational activities in water bodies contaminated with feces from infected humans (WHO/PAHO 2014). In consequence, schistosomiasis is considered a disease of poverty, associated with the lack of basic health services (domestic potable water and wastewater treatment) and poor education for health.

Initially, schistosomiasis control was based on snail elimination with chemical moluscicides; since 1984 the strategy was reoriented to selective or mass chemotherapy with praziquantel (Pzq) and oxamniquine and, since 2006, to preventive chemotherapy with Pzq (WHO 2013). The preventive chemotherapy strategy for schistosomiasis control is based on the reduction of morbidity and transmission through periodic groups targeted for treatment with Pzq. These groups are school-aged children and adults at risk due to occupation or domestic tasks associated with water contact and entire communities living in highly endemic areas. The frequency of treatment is determined by the prevalence of infection in school-aged children (WHO 2006).

In recent decades, there have been significant epidemiological changes in America, such as socioeconomic improvement and increased health activities, which have conditioned disappearance of transmission in Puerto Rico; invasions of new competitor snail species (*Marisa cornuarietis* and *Melanoides tuberculata* (Pointier et al. 2011), management of the environment, and the migration of rural population to cities where there is limited water contact and pollution of the local rivers and other water bodies have decreased the possibility of water contact and transmission. This latter demographic factor adds to the fact that rural population has moved to urban places leaving the rural transmission foci of schistosomiasis and the numbers of reduced rural population have favored schistosomiasis control. The percentage of rural population decreased in Brazil from 70.5 % in 1950 to 15 % in 2013, from 59.5 to 1 % in Puerto Rico, and from 70.5 to 6 % in Venezuela, in the same period of time. (World Bank 2013; Negociado del Censo de los EE.UU. Puerto Rico 2010). This simple demographic factor has been underestimated and has quite possibly been one of the key factors in the decline of transmission in most countries of this continent. Noteworthy in contrast, in certain countries as Venezuela, is the increased exposure of urban tourist populations toward courses and water bodies in nearby endemic areas during weekends which is a risk for acquiring the infection and producing undetectable new cases, underestimating the true prevalence, and allowing maintenance and dispersion of the parasite.

This silent and chronic neglected tropical disease has become of secondary importance for Health Ministries due to the increasing relevance of other vector-borne diseases such as dengue, malaria, and chicungunya among others, in addition to administrative and political changes in most of the endemic countries of the region. However, ecological changes (pollution of infested rivers and water bodies), demographic changes (migrations from rural to urban areas), and improvement of socioeconomic standards (housing, domestic water supplies, and sanitation) might have had the most important impact on the control of schistosomiasis. The

elimination of transmission in Puerto Rico and the almost disappearance in Antigua, Dominican Republic, Martinique, Guadeloupe, and Montserrat from the Caribbean islands, together with a similar trend of control in Brazil, indicate that when there is a proper political decision associated with socioeconomic amelioration, it is possible and realistic to carry out its elimination in America.

One of the important aspects that are usually not mentioned in the data provided by the surveillance control programs of different countries is the degree of morbidity. Partial data are provided in this chapter from Brazil and Venezuela. It is noticeable that because of the decreasing intensity of the disease, there is a progressive and sustained diminution in morbidity severity and consequently in mortality. Moreover, it is necessary to improve the diagnostic tests for schistosomiasis, since low parasite burden usually courses with asymptomatic or oligosymptomatic forms of the disease, limiting clinical and classical laboratory diagnosis, underestimating in this way the true prevalence from each country (Alarcón de Noya et al. 2000; Noya et al. 2002; Enk et al. 2008; Colley et al. 2013).

The main epidemiological aspects of schistosomiasis are described as follows in the Caribbean islands and the mainland countries, Brazil, Suriname, and Venezuela.

2 Schistosomiasis in Brazil

2.1 Historical Background

Schistosomiasis was introduced in Brazil due to the traffic of African slaves. Between 1550 and 1850, it is estimated that 3.5–4 million Africans disembarked in Brazil, coming from regions where today's Angola, Benin, Nigeria, Ivory Cost, Guinea, Mali, and Mozambique are situated. Initially, this slave labor was introduced in the northeast of Brazil (Pernambuco and Bahia) in the sixteenth century. In the eighteenth century, with the discovery of gold and diamond in Minas Gerais, the migration was intense and it is estimated that 1/5 of the country's population migrated to this region (Lambertucci et al. 1987).

The introduction and dissemination of schistosomiasis was always linked to the economic development in the country. Thus, in the middle of the nineteen and the twentieth centuries, the migration to São Paulo and to the north of Paraná was initiated, where several foci of schistosomiasis were created. The same occurred in Fordlândia (Amazonas State), a city created by Ford Company to explore gum during the Second World War, counted with the labor of northeastern migrants.

A large number of the African slaves were certainly infected by *Schistosoma mansoni* and *Schistosoma haematobium*. *Schistosoma mansoni* found at least three species of snails of *Biomphalaria* genus as intermediate hosts: *B. glabrata, B. straminea,* and *B. tenaghophila*. It seems that these intermediate hosts were already in Brazil for over 1–2 million years, while the genus Bulinus was not present, not allowing the transmission of *S. haematobium* (Paraense 2008).

Otto Wucherer in 1866, who worked in Bahia, examined dozens of urine samples from patients at the request of Wilhelm Griesinger in 1866. Wucherer and Theodor Bilharz, who discovered the *Schistosoma haematobium* in Egypt, were classmates in the School of Medicine in Tubingen, Germany (Katz 2008). Wucherer did not find *S. haematobium* eggs in urine, although in August 4th 1866 he found microfilariae of a new species of parasite named later on as *Wuchereria bancrofti* (Coni 1952). The first cases of schistosomiasis mansoni in Brazil were reported in 1908 by Manoel Pirajá da Silva, with a description of 20 cases diagnosed by means of stool examination, where he found eggs with lateral spine (Pirajá da Silva 1909). Pirajá da Silva performed necropsies in three patients, and found 1 worm in the first two necropsies, in the third one he found 24 worms, describing adults and lateral-spined eggs in the female uterus. This description was decisive to differentiate *S. mansoni* from *S. haematobium* (Falcão 1959).

Although Sambon (1907a, b) named the new species as *S. mansoni* in honor of Patrick Manson, it was Pirajá da Silva who really described for the first time the worms of this species, since Sambon had examined a sole male worm incompletely in poor condition. Nevertheless, this important description by Pirajá da Silva was never recognized by Robert Leiper, when in 1915 he reproduced experimentally the life cycle of both parasites (Falcão 1953, 1959; Katz 2008). Lutz was responsible for the first description of Brazilian planorbids, intermediate hosts of schistosomiasis, and published a series on the life cycle of *Schistosoma mansoni* in *B. glabrata* and *B. straminea* snails, in Brazil (Lutz 1919). Brazilian researchers have contributed very much to the knowledge of schistosomiasis, in all fields, life cycle, treatment, clinical studies, pathology, diagnosis, epidemiology, control, genome, etc. (Katz 1992; Carvalho and Katz 2008).

The Integrated Program for Schistosomiasis (PIDE), at the Oswaldo Cruz Foundation, started in 1986, and 13 International Symposia on Schistosomiasis have been achieved every other year (Katz 2006).

2.2 Prevalence

To evaluate the prevalence of schistosomiasis in Brazil, two national surveys were previously conducted. The first one by Pellon and Teixeira (1950) and another one referring to the Special Program for Schistosomiasis Control "Programa Especial de Controle da Esquistossomose" (PECE 1976).

In the first survey, the prevalence of schistosomiasis was around 10 % in the states examined. The states of north, mid-west, south, and São Paulo were not included in this survey (Table 1) (Fig. 2). In PECE (1977) the prevalence was 6.6 %; all the states were examined, except the northern territories and Bahia (Table 1). In 2011, the Ministry of Health by means of the Oswaldo Cruz Foundation initiated the third National Survey on Prevalence of Schistosomiasis mansoni and Geo-helminthes ("Inquérito Nacional de Prevalência da Esquistossomose mansoni e Geo-helmintoses"), which is almost concluded. Approximately,

Table 1 National prevalence of schistosomiasis in Brazil between 1949 to 2014

Region	States	Pellon and Teixeira (1949)			PECE (1975–1977)			Katz et al. (2011–2014)		
		Examined	Positive	%	Examined	Positive	%	Examined	Positive	%
North	Acre	ND	ND	ND	ND	ND	ND	2,476	0	0.0
	Amazonas	ND	ND	ND	ND	ND	ND	2,857	0	0.0
	Amapá	ND	ND	ND	ND	ND	ND	1,686	0	0.0
	Pará	ND	ND	ND	28,227	124	0.35	2,558	8	0.23
	Rondônia	ND	ND	ND	ND	ND	ND	2,961	0	0.0
	Roraima	ND	ND	ND	ND	ND	ND	2,244	0	0.0
Northeast	Pernambuco	50,031	12,635	21.34	23,495	3,072	6.62	20,744	457	1.94
	Ceará	40,314	380	1.08	19,867	599	1.81	9,054	0	0.0
	Alagoas	14,966	3,065	19.17	70,040	14,712	19.06	12,735	307	2.66
	R.G. do Norte	18,662	433	2.19	11,870	70	0.6	9,648	5	0.04
	Bahia	74,015	12,237	15.38	ND	ND	ND	27,923	824	4.97
	Sergipe	14,675	4,423	27.46	6,085	1,926	31.49	11,735	740	6.55
	Paraíba	21,305	1,584	6.8	10,294	603	5.28	8,377	52	0.5
	Piauí	10,420	4	0.03	8,518	0	0.0	6,975	1	0.01
	Maranhão	12,716	59	0.45	13,754	446	2.82	9,415	21	0.24
South-East	Minas Gerais	162,176	7,953	6.51	55,605	5,656	6.98	34,606	850	0.89
	São Paulo	ND	ND	ND	ND	ND	ND	3,668	4	0.11
	E. Santo	12,822	209	2.39	11,057	290	1.37	7,084	61	0.86
	R. de Janeiro	ND	ND	ND	24,253	128	0.61	4,388	2	0.06
East-Center	Distrito Federal	ND	ND	ND	ND	ND	ND	2,722	0	0.0
	Goiás	ND	ND	ND	13,318	17	0.16	4,205	0	0.0
	Mato Grosso	ND	ND	ND	9,881	48	0.29	1,064	0	0.0
	Mato Grosso do Sul	ND	ND	ND	7,678	5	0.15	1,358	4	0.18
	Tocantins	ND	ND	ND	3,866	2	0.03	1,603	0	0.0

South	Paraná	ND	ND	ND	81,825	1,579	0.52	5,858	0	0.0
	Santa Catarina	ND	ND	ND	14,522	0	0.0	4,721	0	0.0
	Rio Grande do Sul	ND	ND	ND	29,222	1	0.0	2,127	0	0.0
	Brazil	432.102	42.982	9.94	443.377	29.278	6.60	204.153	3.336	1.63

ND, Not done

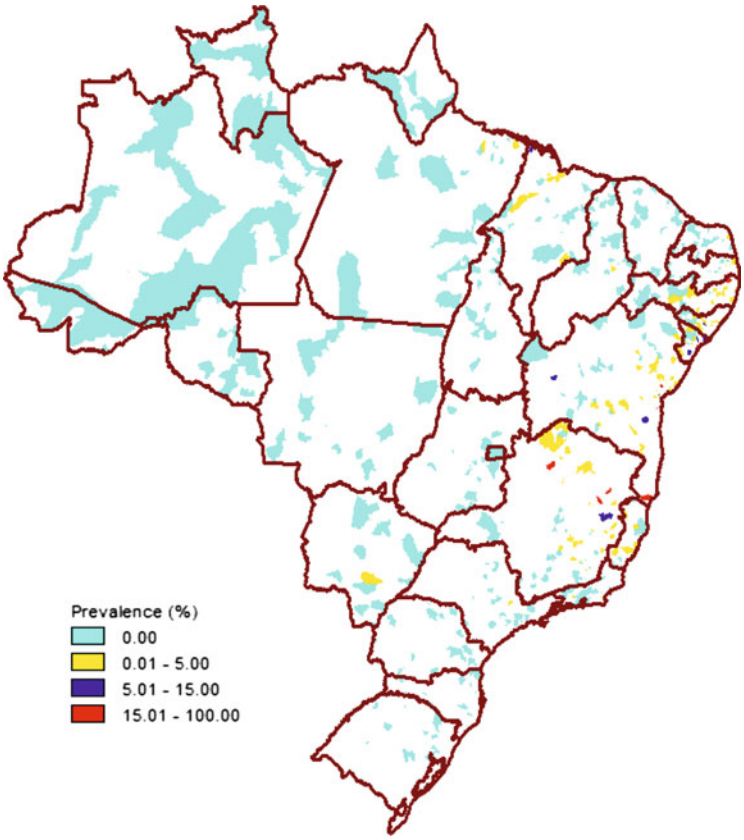

Fig. 2 Prevalence of Schistosomiasis mansoni in Brazil

200,000 school children (7–14-year old) have been examined by Kato Katz stool examination (Katz et al. 1972). This survey was conducted in 27 states of the Federation, including the Federal District and 540 municipalities. Schistosomiasis was found in 13 endemic states; since the cases from Mato Grosso do Sul were not autochthonous (Table 1) (Fig. 2). The states with higher prevalence were Sergipe (6.55 %), Bahia (4.97 %), Alagoas (2.66 %), and Pernambuco (1.94 %) (Katz et al. 2014).

Currently, the total prevalence in the country is 0.7 %, showing a significant decrease, when compared with the previous surveys (Table 1). When these numbers are extrapolated to the meso-regions for each state, an estimated number of 1.5 million people would be infected in the country. This kind of survey, although valid to show the prevalence in the country as a whole, does not allow the detection of isolated foci or areas that have not been selected. Some isolated foci with very low prevalence must be mentioned: one in the State of Rio Grande do Sul; two in the State of Santa Catarina; and several foci in Ceará, Paraná, and others (Fig. 2).

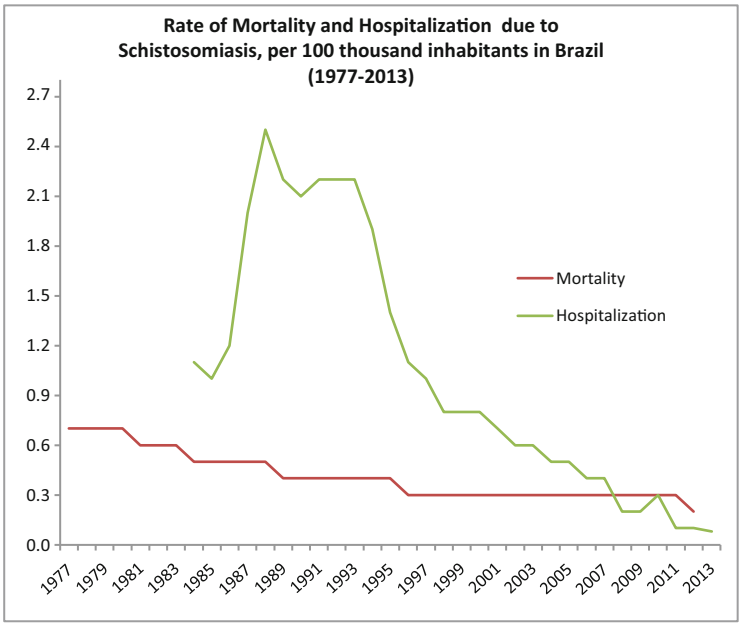

Fig. 3 Rate of mortality and hospitalization in Brazil due to schistosomiasis in Brazil 1977–2013 (*Source* Katz et al. 2014)

2.3 Morbidity, Mortality, and Treatment

The data of low prevalence are also corroborated by the intense decrease in the mortality rate, as well as in cases of hospitalization due to schistosomiasis, which occurred in the last decades Fig. 3. The hospitalization rate due to schistosomiasis was 2.5 % per 100,000 inhabitants in 1988 and 0.08 % in 2013. The mortality rate decreased from 0.5 % in 1987 to 0.2 % in 2012.

In the parasite life cycle prepostural phase, the drug of choice is oxamniquine. After egg laying, praziquantel is the recommended drug (Coelho et al. 2009). The first clinical trial using praziquantel (the drug of choice) for *S. mansoni* infection was made in Brazil, by Katz et al. (1979). The recommended dose is 50 mg/kg for adults and 60 mg/kg for children (up to 15-year old), single dose and oral route. Brazilian researchers demonstrated that the specific clinical treatment prevents the appearance of hepatosplenic form, even if the patient is reinfected (Kloetzel 1963, 1967; Bina 1977). This finding led the World Health Organization to indicate morbidity control by means of specific clinical treatment, as a measure for the control of schistosomiasis in endemic areas (WHO 1985).

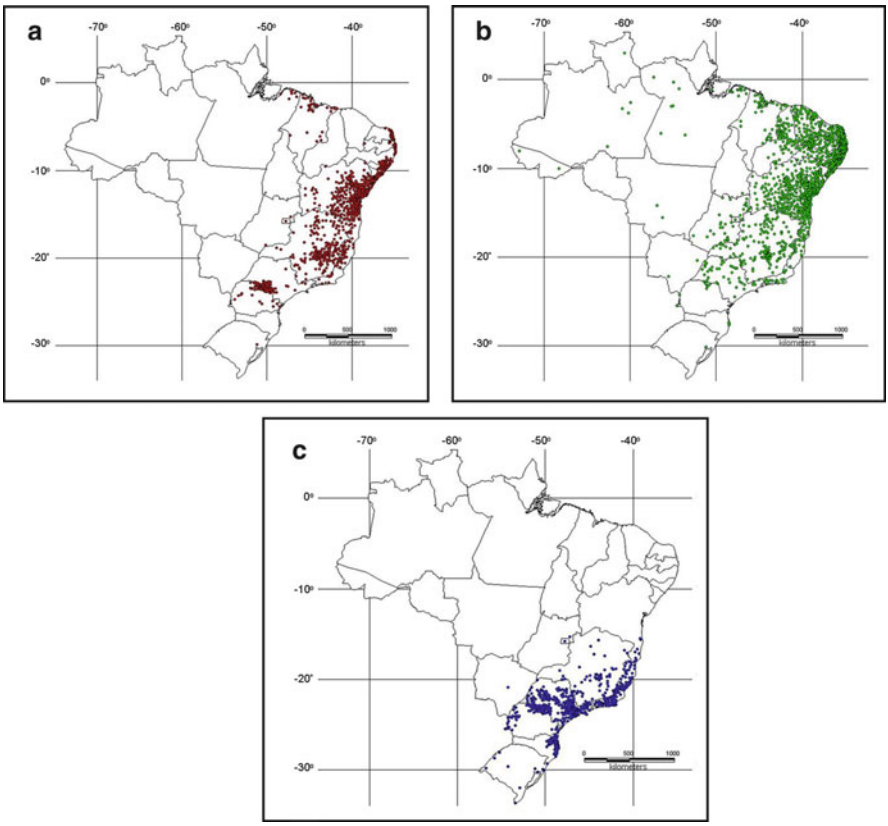

Fig. 4 Distribution of *B. glabrata* (**a**), *B. straminea* (**b**), *and B. tenagophila* (**c**) in Brazil (*Source* Carvalho et al. 2008)

2.4 Intermediate Hosts

Wladimir Lobato Paraense (1914–2012), the most important Brazilian malacologist and one of the best in the world, made the first map on the distribution of Schistosomiasis intermediate hosts in Brazil (Paraense 1970). Paraense is responsible for clarifying the classification and distribution of snail species in America and for the description of new snail species.

The data presented here are a summary of the Paraense publications, of Secretaria de Vigilância de Saúde do Ministério da Saúde do Brasil, and of the Laboratory of Intestinal Helminthosis, Research Center René Rachou/FIOCRUZ. Detailed information can be found at the review made by Carvalho et al. (2008). The three species, intermediate hosts of *S. mansoni* in Brazil, belong to the genus *Biomphalaria*: *B. glabrata, B. straminea,* and *B. tenagophila* (Fig. 4).

In recent decades, several malacological studies using molecular techniques have been carried out in Brazil in order to improve the knowledge on the genetic

variability of *Biomphalaria* spp. For example Knight et al. (1991) showed that Southern blot analysis using ribosomal gene probes may be useful for the molecular differentiation of *B. glabrata* from other intermediate hosts. Other works also showed the interest in using the RLFP analysis of the internal transcribed spacer region of the rRNA gene for the identification of several species of *Biomphalaria* (Caldeira et al. 1998, 2000; Vidigal et al. 1998).

B. glabrata
The most important intermediate host is *B. glabrata*. It is axiomatically affirmed that where *B. glabrata* is present, schistosomiasis exists. This species has been observed in 16 states and in 806 municipalities from southeastern to the south region (Carvalho et al. 2008) (Fig. 4a). Graeff-Teixeira et al. (1999) described a new schistosomiasis focus at Esteio, at the Metropolitan Area of Porto Alegre, Capital of Rio Grande do Sul, maintained by *B. glabrata*. This is a serious problem since this area is near to Argentina, Paraguay, and Uruguay where schistosomiasis is absent.

B. straminea
This snail is the second one in importance as schistosomiasis intermediate host, with the largest distribution being present in 24 states and 1,325 municipalities including the Federal District (Brasília) (Carvalho et al. 2008) (Fig. 4b). *B. straminea* is the best adapted snail for all climate and ecological conditions (Paraense 1970, 1986).

B. tenagophila
This species has a more limited distribution, starting in the south of Bahia up to Rio Grande do Sul, including Brasília, Goiás, and Mato Grosso do Sul, in a total of 10 states and 63 municipalities (Carvalho et al. 2008) (Fig. 4c).

Two new species very similar to *B. tenagophila* were described: *B. occidentalis* (Paraense 1981) and *B. guaiabensis* (Paraense 1984). Both are resistant to schistosomiasis infection. Another species, *B. amazonica,* from the Amazon region was described and showed susceptibility to infection with miracidiae from northeastern or Minas Gerais regions (Corrêa and Paraense 1971).

2.5 Nonhuman Vertebrate Hosts

In Brazil, the first findings of natural rodent infection were made by Amorim (1953) in the state of Alagoas and Barbosa et al. (1953) in Pernambuco. A larger survey was made in two cities of the State of Minas Gerais. At Jaboticatubas city, only *Didelphis paraguayensis* and *Nectomys squamipes aquaticus* were found naturally infected, with 2.5 and 57.5 % prevalences, respectively. In Belo Horizonte five species were found: *Rattus norvegicus, Oryzomis mattogrossae, Zygodomys lasiurus, Cavia aperea aperea,* and *D. paraguayensis* (Vianna Martins

et al. 1955). Infected wild rodents and marsupials were also captured in Bahia, Sergipe, Rio de Janeiro, São Paulo, and Paraná (Vianna Martins 1958).

In the wild rodent *Nectomys squamipes*, captured in Baldim, Minas Gerais, the *S. mansoni* strain (N) behaved similarly to the human strain (LE), and *Nectomys* is a good host for *S. mansoni*. The complete life cycle of *S. mansoni* could be achieved under seminatural conditions, using the system *Nectomys—B. glabrata—Nectomys* (Antunes et al. 1973). Similar results were also obtained with *Holochilus braziliensis* (Carvalho et al. 1976). Naturally infected rodents, captured in Belo Horizonte, Baldim, and Lapa Vermelha, State of Minas Gerais, and studied under experimental conditions, showed that *R. novergicus, Nectomys squamipes aquaticus, Zygodontomys lasirus, Orysomis subflavus, Oryzomis nigripes eliurus* and *Calomys expulsus* can be considered good *S. mansoni* hosts and may have some influence on the epidemiological chain (Borda 1972).

Holochilus, Zygodontomys, and *Nectomys* have been found in São Paulo (Rodrigues and Ferreira 1969; Dias (1972) similarly to that recorded for other Brazilian States (Bastos et al. 1978; Kawazoe and Pinto 1983). Studies on eco-epidemiology conducted in open areas prepared for these experiments seem to indicate that under special conditions, that is, when there is high population density of wild rodents, especially *Nectomys* and/or *Holochilus,* and when *B. glabrata* is the intermediate host, it is possible that the parasite's life cycle can exist without the presence of man (Dias 1976; Kawazoe and Pinto 1983).

In the State of Maranhão, *Holochilus brasiliensis nanus* was the only wild rodent captured throughout 1 year. At every month, infected animals were captured harboring a great number of *S. mansoni* worms and eggs (Veiga-Borgeaud et al. 1986). At Sumidouro area, in the State of Rio de Janeiro, *Nectomys squamipes* and *Akondon arviculoides* were found naturally infected. A strain isolated from one of those infected *Nectomys* was able to infect 75 % of *B. glabrata* and 100 % of albino *Mus musculus* under laboratory conditions (Rodrigues-Silva et al. 1992; D'Andrea et al. 2000; Gentile et al. 2006).

Cattle have been found infected with *S. mansoni* in Brazil (Barbosa et al. 1962; Piva and Barros 1966). Coelho et al. (1979) showed a prevalence of 3 % in cattle in an endemic area in Minas Gerais. The wild and domestic animals as reservoirs of *S. mansoni* in Brazil were recently reviewed (Modena et al. 2008).

The role of wild rodents and bovines, in the epidemiology of schistosomiasis at the endemic areas in Brazil, has not been proved. In fact, infected humans are essential for the maintenance of schistosomiasis. However, considering that the prevalence of schistosomiasis is sharply decreasing, it is possible that wild and domestic animals as reservoirs of *S. mansoni* could increase in importance.

2.6 Control

The first attempt for the control of schistosomiasis in Brazil was made by Jansen, when in the 1940s he began studying this subject in Catende, Pernambuco. In that

urban community where about 7,000 people lived, the positivity rate for schistosomiasis was initially 53 %, and *B. straminea* was found infected in several foci. The approach for control was multiple: applying calcium hydroxide as moluscicide; treatment of the human population with different antimony salts; construction of public latrines, washing tanks, and sand filter in the water reservoirs of the community; and construction of urban and rural septic tanks and health education. Two years later, the prevalence rate decreased to 12 % (Jansen 1946). Sette (1953) carried out a reevaluation in the area, where more than 3,500 people had been treated from 1943 to 1947. When schistosome-induced lesions—detected by means of histological examination performed at liver fragments obtained by viscerothomy—were compared, from 1937 to 1941 and from 1942 to 1945, the percentage was from 16.5 % to 11.5 %, and when only "cirrhosis" was considered, the frequency was 32.6 and 11.1 %, respectively. At that time, cirrhosis and hepatic fibrosis were not differentiated. The differentiation was made only in the 1960s, especially due to the work of Luigi Bogliolo, carried out at the School of Medicine, Federal University of Minas Gerais (Bogliolo 1958, 1959). Kloetzel treated a group of 112 children infected by *S. mansoni* using antimonial salt, in Gameleira, Pernambuco. Evaluation performed 6–11 months and 4 years posttreatment revealed that schistosomiasis positivity was reduced to 43 and 55 %, respectively, and to 83 % at the last evaluation. Before treatment, 23 children presented splenomegaly. At the end of the evaluation (4 years post-treatment), the spleen growth diminished in 10 cases, increased in 2, and disappeared in 11 other ones. None of the 60 children who presented intestinal and/or hepatointestinal form at the beginning of the study developed splenomegaly (Kloetzel 1963). These results led the author to conclude that 7–10-year-old children, who presented more than 500 eggs per gram, should be treated, even at risk of reinfection (Kloetzel 1967). Bina treated a group of 115 children with hycanthone, keeping another group without treatment as control, in Caatinga do Moura, Bahia. He observed that 2 to 5 years post-treatment, although all children were practically reinfected, none of them developed the hepatosplenic form, whereas in the control group 35 new cases were detected (Bina 1977). These data clearly demonstrated that it is possible to control morbidity, when children are treated, since treatment prevents the emergence of the hepatosplenic form. Many other studies were conducted in Brazil, aiming at controlling this endemia in the States of Pernambuco, Bahia, Minas Gerais, and Rio de Janeiro (Paulini et al. 1972; Prata 1976; Katz 1980; Barbosa et al. 2008)

In 1975, the Ministry of Health Almeida Machado (1977) designed and initiated the Special Program of Schistosomiasis Control—"Programa Especial de Controle da Esquistossomose" (PECE). The strategy of PECE would be (1) elimination (90 %) of miracidiae using chemotherapy (oxamniquine); (2) density reduction of snails for limited periods, to less than 1 % of the preexisting density; (3) coordination of these two activities in time and space; (4) sanitary improvements in each rural housing, latrine, shower, and laundry sink; (5) supply of drinking water and construction of public sets of fountain, latrine, shower, and collective laundry; and (6) health education. At the end of the program, it privileged the diagnosis and treatment, with very few measures for sanitation. The criterion for treatment from 1975 to 1980 in areas with prevalence superior to 20 % was mass treatment for people over 2 years old;

with prevalence between 5 and 20 %, only individuals 5–35 years old were treated, and with prevalence less than 5 %, only the positive ones were treated. After that, there were some changes of criteria used for the treatment of the population, and mass treatment was administered only when the prevalence in 7–14-year-old children was more than 50 %; when the positivity detected was 25–50 %, a selective treatment (children) was administered; and when it was less than 25 % only the positive ones were treated. Later, the family members residing in the same household were also treated. Since the end of the 1990s, praziquantel was the substitute for oxamniquine as the drug of choice, mainly due to the high cost of oxamniquine

In the last few years in Brazil, the treatment in mass scale is administered when the prevalence in children is higher than 25 %.

Although the "Schistosomiasis Control Program (PECE)" was not evaluated in all its extension, some works demonstrated that the hospitalization rate, prevalence and mortality due to schistosomiasis decreased significantly in endemic areas (Costa et al. 1996; Katz 1980; Coura and Amaral 2004; Barbosa et al. 2008) (Figs. 2 and 3).

Currently, it is estimated that more than 15 million Brazilian people have been treated in the northeast and in Minas Gerais, which are the most important endemic regions for schistosomiasis in Brazil, in the last 30 years. In 2005, an evaluation was performed in an endemic area in Minas Gerais, which has been followed up since 1974. The initial population was of 1,500 with a schistosomiasis prevalence of 70 %. Between 1981 and 1992, five treatments were administered in patients excreting *S. mansoni* eggs in stools. At the same time, more than 95 % of the houses got drinking water supply and sewage. The results showed a marked reduction of the prevalence from 70 to 1.7 % and of hepatosplenic forms from 7 to 1.3 % (Sarvel et al. 2011). Barbosa et al. (1971) in Potezinha, Pernambuco, showed for the first time that it is possible to control this parasitosis by the construction of water supply and sewage.

The significant prevalence reduction must be ascribed not only to the treatment of millions of people, but mainly to the great increase of housing water supply and sewage. As seen in Fig. 5, in 2010, more than 85 % of the housings in Brazil had water supply and about 55 % got sewage. If this action persists, perhaps in 10 or 20 years, schistosomiasis can be eliminated from the country, that is, to be no more a disease of Public Health importance.

3 Schistosomiasis in the Caribbean Islands

The Caribbean region commonly named as Antilles is composed of the Lucayan Archipelago, the West Indies, and a chain of islands surrounding the Caribbean Sea and composed of more than 700 islands, islets, reefs, and cays. The Caribbean islands are divided into the Greater Antilles on the north (Cuba, the Cayman Islands, Hispaniola (containing the Dominican Republic and Haiti), Puerto Rico, and Jamaica), and the Lesser Antilles on the south and east (Saint Kitts, Antigua and Barbuda, Montserrat, Guadeloupe, Dominica, Martinique, St. Lucia, Saint Vincent and the Grenadines, Barbados, Grenada, and Trinidad and Tobago) (Fig. 6).

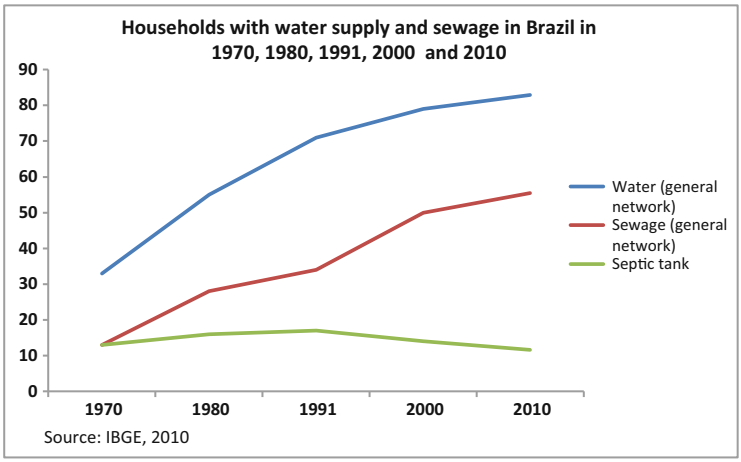

Fig. 5 Household with water supply and sewage in Brazil, 1970, 1980, 1991, 2000, and 2010

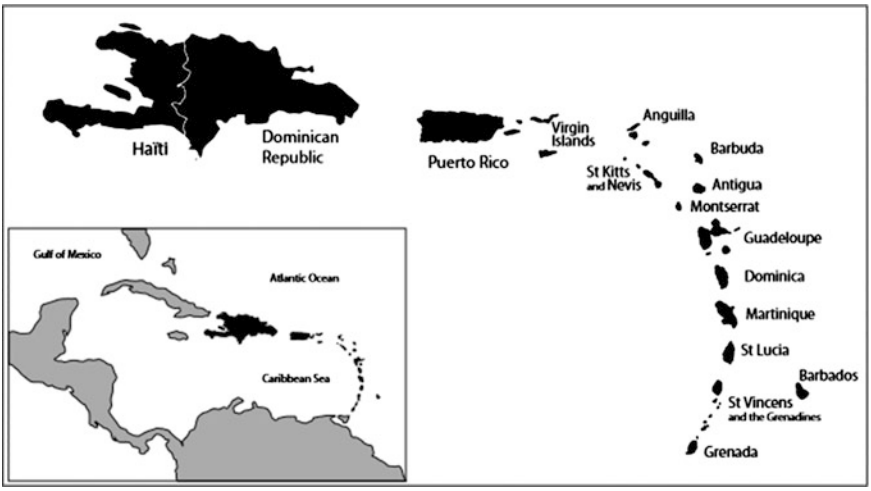

Fig. 6 Map of the Caribbean area

Historically, it is from the stool of a patient who had previously lived in Saint Kitts and Antigua that lateral-spined schistosome eggs were identified for the first time by Sir Patrick Manson (Seamen's Hospital in Greenwich) in 1902 and distinguished from *S. haematobium* with terminal-spined eggs in the urines. This new schistosome species was later described as *Schistosoma mansoni* by Luigi Sambon of the London School of Tropical Medicine in 1907 in honor of P. Manson.

The distribution of human intestinal schistosomiasis in this Caribbean region and its transmission was conditioned to the presence of freshwater habitats (rivers, pools, canals, reservoirs, and swamps) housing populations of the unique

intermediate snail host species *Biomphalaria glabrata*. Dominican Republic, Puerto Rico, St. Kitts, Antigua and Barbuda, Montserrat, Guadeloupe, Martinique, and St. Lucia were the main endemic areas of schistosomiasis *mansoni* (Doumenge et al. 1987). In spite of *B. glabrata* is present in Haiti and Dominica, no autochthonous infections with *S. mansoni* have been reported in these two islands.

For most of these countries, intestinal schistosomiasis was first diagnosed between the beginning and the half of the twentieth century. The disease appears very irregularly distributed throughout the islands, according to the geography, the freshwater environments, the agricultural activities, the population density, and the socioeconomic level of the areas (Doumenge et al. 1987). In Puerto Rico and St. Lucia, the large-scale irrigation system for sugarcane has played an important role as favorable habitat for the snail hosts and the spread of the disease (Jobin 1980). In Guadeloupe, the mean prevalence detected by stool examination was very much higher in the valleys of the mountainous volcanic part of the Basse Terre (49 % in Baillif) than in the lowlands of the calcareous dry part of the Grande Terre (1 % in Anse-Bertrand) (Fig. 7) (INSERM 1980). In Martinique, it was the multiple very small transmission foci constituted by water cress beds that were considered as important sites of infection for numerous families (INSERM 1979; Pointier et al. 1984). In this island, during the 1970s, *B. glabrata* was gradually replaced by another species, *Biomphalaria kuhniana*, best adapted to the irregular water courses encountered in Martinique (Guyard et al. 1982) and fortunately few compatible to the local strain of *S. mansoni*, contributing to the decline of the disease. Contrasting with all other islands, the epidemiology of the schistosomiasis in Guadeloupe was characterized by the presence of a murine reservoir host (*Rattus rattus*) heavily infected (Alarcón de Noya et al. 1997). In the mangrove swamp focus of Grande Terre, murine prevalence could reach locally 100 % and parasite intensities more than 500 worms per rat (Théron et al. 2004). All around the Grand Etang lake in a rain forest of the south of the Basse Terre island, the rats were able to maintain alone the life cycle of the parasite in the absence of human infection. Adaptative genetic variations were demonstrated between murine and human schistosome populations (Théron 1984). While the cercariae from the human parasite showed the typical emergence pattern with a middle-day peak shedding time adapted to the water contact period of these populations, cercariae of the murine schistosome showed a late shedding pattern with a crepuscular emergence peak adapted to the nocturnal activities of the rodent.

Human schistosomiasis was an important health problem for all of these islands particularly between 1950 and 1980. Numerous stool or serological surveys showed that human prevalence higher than 70 % were common in several parts of these islands (Doumenge et al. 1987). Puerto Rico initiated in 1953 the first control program by the Puerto Rico Health Department, using limited chemotherapy and snail control by environmental, biological, and chemical means (Negro-Aponte and Jobin 1979) (Fig. 8). At the same time, extensive programs of water supply, health education, and free latrine distribution were implanted across the island (Hillyer 2005). The St. Lucia Research and Control project was developed between the years 1965 and 1981 (Jordan 1985). If chemotherapy was an effective way to reduce the prevalence, incidence, and transmission potential of the disease, the

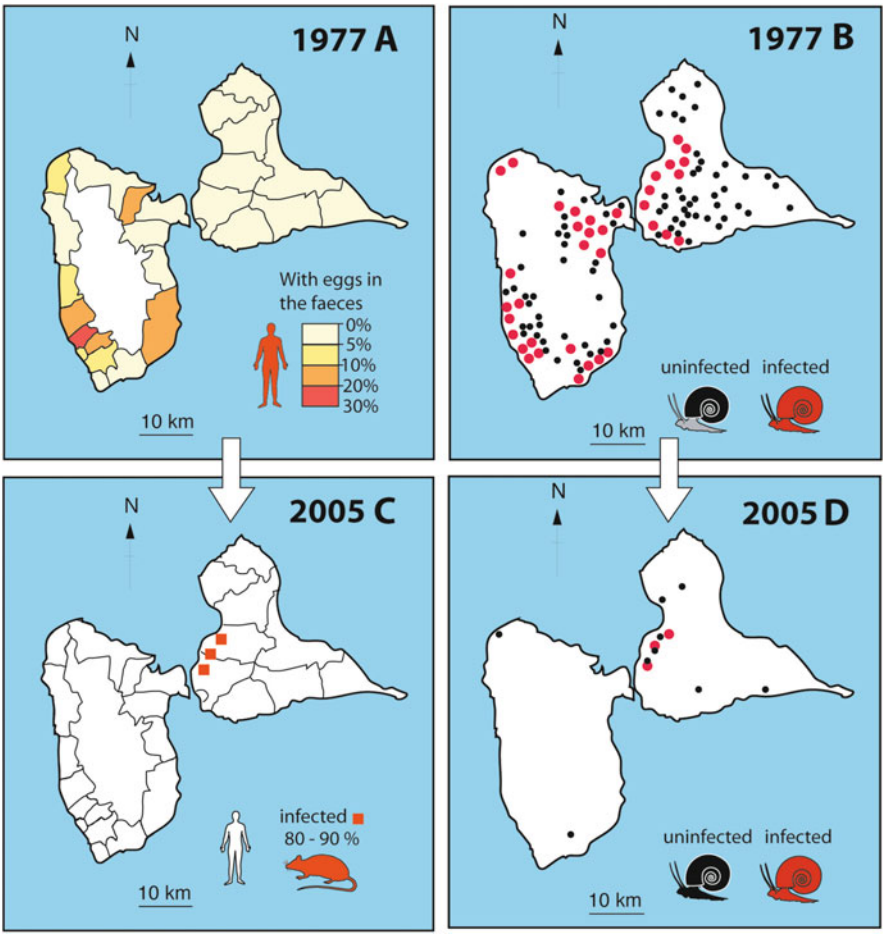

Fig. 7 Distribution and decrease of human intestinal schistosomiasis' prevalences and *Biomphalaria glabrata* snail populations in the island of Guadeloupe between 1977 and 2005

effect of snail control, the introduction of water supplies, and health education were also of importance. In Guadeloupe and Martinique, an integrated control program (chemotherapy, management of the environment, control of intermediate hosts) was initiated in 1978, and most of the transmission sites were eliminated in the1990s except the mangrove swamp foci of Guadeloupe where murine schistosomiasis was still present in 2005 (Pointier and Théron 2006).

Following the different control programs that have played an important role in the decline of the disease, other various factors have later contributed to achieve elimination (Rollinson et al. 2013). Indeed, most of these islands have experienced a rapid socioeconomic development with an improvement in housing, use of domestic water supplies and sanitation, healthcare facilities that have been essential to reduce infection level, and preventing reemergence of schistosomiasis. On another side, ecological changes, unassisted invasions of new competitor snail

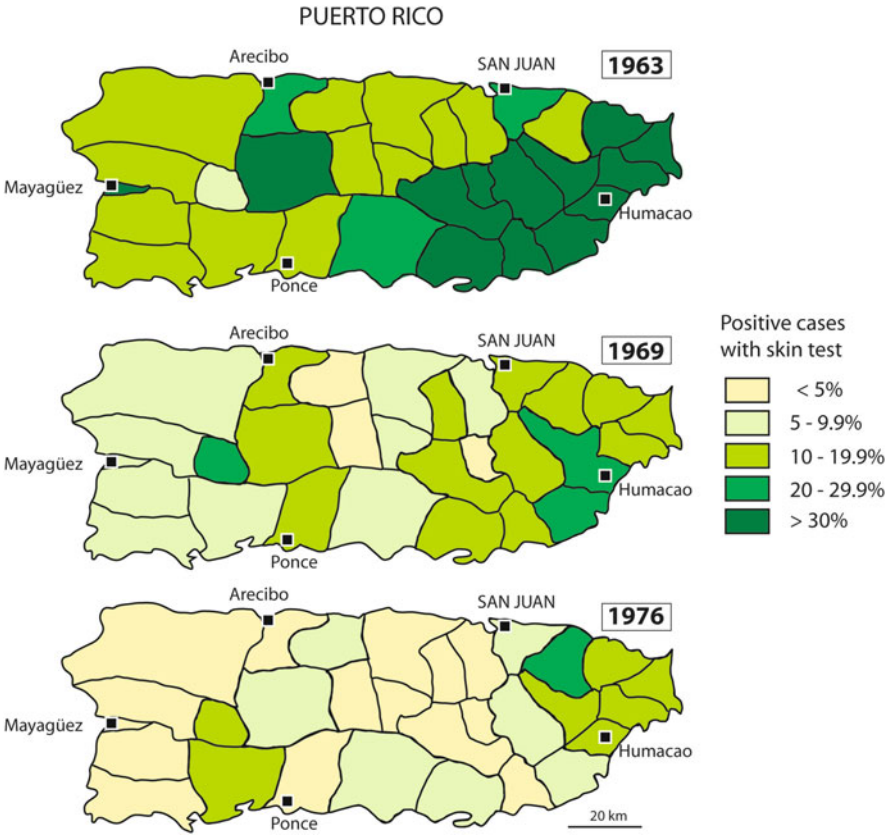

Fig. 8 Distribution and decrease of intestinal schistosomiasis between 1963 and 1976, as determined by intradermal test in 5th grade children in Puerto Rico

species, management of the environment, modification of fresh water milieu, and chemical pollution contributed to the decline and disappearance of snail host populations (Pointier et al. 2011).

All the Caribbean islands are now areas of no or very low transmission since the incidence of schistosomiasis has been dramatically reduced, making it possible for the disease to be eliminated (Schneider et al. 2011; Rollinson et al. 2013). St. Lucia seems to be the only country that has recently reported schistosomiasis infections. In 2010, a school-based study (550 children in three villages) revealed four active infections (prevalence, 0.6 %) (Kurup and Hunjan 2010). All recent trends suggest that human schistosomiasis is disappearing from Antigua, Dominican Republic, Martinique, Guadeloupe, Monserrat, and Puerto Rico. However, these countries require updating evaluation in order to verify if interruption of transmission has been achieved (WHO 2013). Vigilance remains always necessary to avoid the reemergence of the disease as recently observed in southern Europe where autochthonous transmission of the urinary schistosomiasis occurred in the Mediterranean French island of Corsica in 2012 and 2013 (Berry et al. 2014).

Fig. 9 Distribution of schistosomiasis in Suriname

4 Schistosomiasis in Suriname

Schistosomiasis mansoni is still present in Suriname, with an estimated general prevalence of 0.89 % in a country with a population of 529,000 persons. This prevalence varies between different areas and age groups. Highest prevalence is related to some occupational activities (fishing and agriculture) and to certain ethnic groups, Javanese and Hindustani, who live in rural areas of all the districts of the coastal plain (PAHO 2010; Rebollo 2010) (Fig. 9). The only available information about schistosomiasis in Suriname has been provided by a document elaborated by PAHO (2010), which is transcribed as follows: "The endemic areas comprise the territory from Commewijne district in the east to the settlement of Wagenigen in the

west. It is thought that the establishment of an irrigation scheme for rice cultivation in Wagenigen introduced schistosomiasis transmission to the west of the coastal plain. The most recent data on schistosomiasis are from surveys conducted by the Ministry of Health in Commewijne and Saramacca districts in 1997 and 1998. The overall prevalence of infection in the samples taken was 3.1 % in Commewijne and 4.7 % in Saramacca district. In none of the communities surveyed was the prevalence of infection higher than 9 %. In Saramacca district, prevalence of infection was highest in those over 39 years of age, although 17 cases in children under 15 years, including 2 cases in under 5 s, were found. In Meerzorg, Commewijne district, prevalence of infection was highest among those over 19 years of age although 12 children below this age were infected. Studies conducted in the 1990s showed that schistosomiasis was a major cause of morbidity and mortality, with hematemesis, and pulmonary hypertension being the major consequences of infection. Two districts not previously reported as endemic for schistosomiasis—Nickerie (West) and Brokopondo should be surveyed in order to confirm the autochthonous transmission" (PAHO 2010).

5 Schistosomiasis in Venezuela

In Venezuela, a country of a surface area of 912,000 km^2, transmission persists in two distinct areas, the north central coastal region of the country (Valencia lake basin) covering an area of approximately 13,000 km^2, where 15,299,729 inhabitants live, representing 52.9 % of the population, with six major cities and a total of 27 populations above 50,000 persons. There is a secondary focus in a small rural area in the Andean region (Chabasquen basin) (Fig. 10). Schistosomiasis in Venezuela was initially discovered in Caracas by Vicente Raúl Soto (Soto 1906) in a patient at the Vargas Hospital in 26th October, 1905. The initial epidemiological studies using parasitological methods revealed a general prevalence of 14.6 % between 1943 and 1960 in the Northern Central region (Balzan 1988). A vertical control program of the Ministry of Health started in 1943. It was based on snail elimination with chemical moluscicides, improving housing, extensive programs of water supply and sewage, health education, and latrine construction. These measures, together with other factors such as pollution of rivers in major cities where the prevalence of transmission was high such as Caracas, Guarenas, Guatire, Cua, Charallave, Santa Teresa del Tuy, La Victoria, Maracay and Valencia, make parasitological prevalence of 14.6 % (Scott 1942; Balzan 1988; Alarcón de Noya et al. 2006) decreased to 0.7 % in 2012 (DGSSA-MPPS 2012; (Fig. 11).

Recent data provided by the Ministry of Health suggest that there is a progressive increase on the transmission, coincident with a decade of progressive diminution of epidemiological surveillance and control activities. The estimated average prevalence for the decade 2002–2011 was 0.93 % by Kato-Katz and 6.76 % by COPT (DGSSA 2012).

Fig. 10 Map of endemic areas in Venezuela

In relation to the parasite burden, field investigations between 2002 and 2010 in the endemic area using the Kato-Katz technique (Katz et al. 1972) have found that 74 % eliminates less than 100 eggs per gram of feces (egf) (light infection), 27.6 % between 100 and 400 egf (moderate infection), and none (0 %) eliminated more than 400 egf. In concordance with that data, the majority of the population exhibited moderate clinical form as follows: Asymptomatic 48.6 %, hepatointestinal 48.6 %,

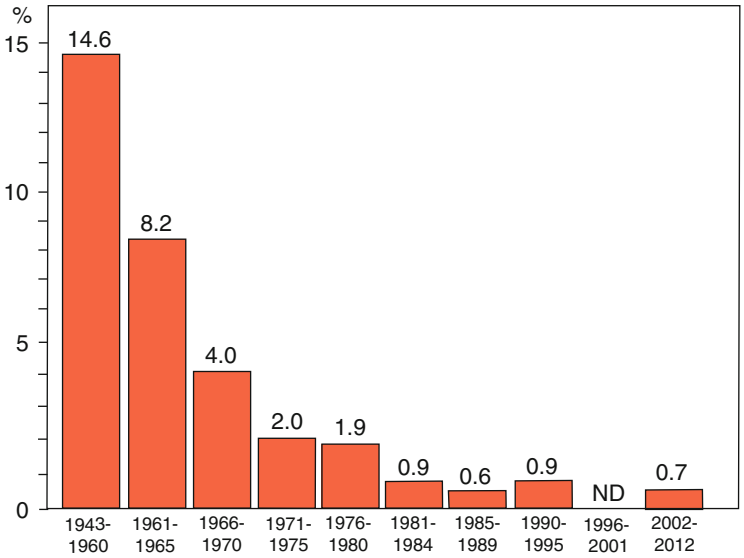

Fig. 11 Prevalence of schistosomiasis in Venezuela 1943–2012 (*ND* No Data, From Balzan (1988) and Dirección General Sectorial de Salud Ambiental, Ministerio del Poder Popular para la Salud, Venezuela, 2012)

and hepatosplenic only 2.8 % (Sección de Biohelmintiasis, IMT-UCV 2011, unpublished data). Nevertheless, since the mid-1990s, the control program was reduced, decreasing notably the epidemiological surveillance on the human population, as well as on the rivers and water bodies and its mollusk fauna. In contrast, important achievements were reached in sanitation: the increase of domestic water supply from 80 to 85 %, as well as the availability of sewage from 42 to 91 % in Venezuela, between 1970 and 2011 (INE 2011).

Currently, Venezuela is still considered an area of low transmission of schistosomiasis based on the limited epidemiological data provided by the Minister of Health, but it is susceptible to be eliminated from its territory if it is recovered the strategy of an integrated and sustained program of control. The true epidemiological situation of schistosomiasis in Venezuela is not known: When studies are done in rural populations, relatively low prevalence is achieved. However, the Ministry of Health does not know the actual percentage of infected people who are mobilized by thousands during weekends and holidays to the rivers and water bodies in the endemic area, due to the ease of movement of the inhabitants from large populations' neighbors, propitiated by the availability of vehicles and motorcycles and the low cost of gasoline.

6 The Snail Hosts of Schistosomiasis in the Caribbean

Biomphalaria is the single genus belonging to the Planorbidae family involved in the transmission of schistosomiasis in America (PAHO 1968). The correct identification of the species acting as intermediate hosts for the parasite and the ecology of the snail hosts are a key aspect for understanding snail–schistosome relationships, as well as for building control programs of the disease.

6.1 Taxonomical Aspects

Shell characters can be used to distinguish groups of planorbids, but are of limited use for separating closely allied species because of wide ecophenotypic variation. The anatomy of reproductive tracts (e.g., shape and size of penial complex) is more informative, but still not fully diagnostic. Reproductive isolation has unfortunately been little used for clarifying species' boundaries and that some species of *Biomphalaria* mainly reproduce through self-fertilization certainly sets a practical limit to such investigation. Molecular phylogenies have also been developed in the last decade and clarified the relationships among most extant species.

In the Caribbean area, including Greater and Lesser Antilles, Venezuela, and Suriname, the main snail host responsible for schistosome transmission is *Biomphalaria glabrata* (PAHO 1968). Its morphology, including shell, radula, and anatomical characters of its soft parts, has been extensively studied and details are given in Paraense and Deslandes (1955). More recently, molecular markers helped to shed some light on the phylogeny of *Biomphalaria glabrata*. Two phylogenetic analyses, both using nuclear and mitochondrial markers, have addressed this question (Mavárez et al. 2002; De Jong et al. 2003), the first focusing more on the northern part of the distribution (Venezuela and the Lesser Antilles), and the second considering samples mainly from Brazil. These studies indicated that *B. glabrata* is structured into five, rather deeply separated, main clades. Snails from the Greater Antilles form a clade perhaps basal to other clades. As these clades are partially reproductively isolated from one another, *B. glabrata* might well be a species complex (Jarne et al. 2011).

Two other species have been found sometimes infected in the field: (1) *B. kuhniana* (under the name of *B. straminea*) in Venezuela (Balzán, personal communication) and Martinique (Paraense, personal communication; Pointier 2015) and (2) *B. prona* in Venezuela (Balzán personal communication; Pointier 2015). However, the epidemiological importance of these two species is presently negligible in this area, in spite of the wide distribution in some countries as Venezuela (Fig. 12)

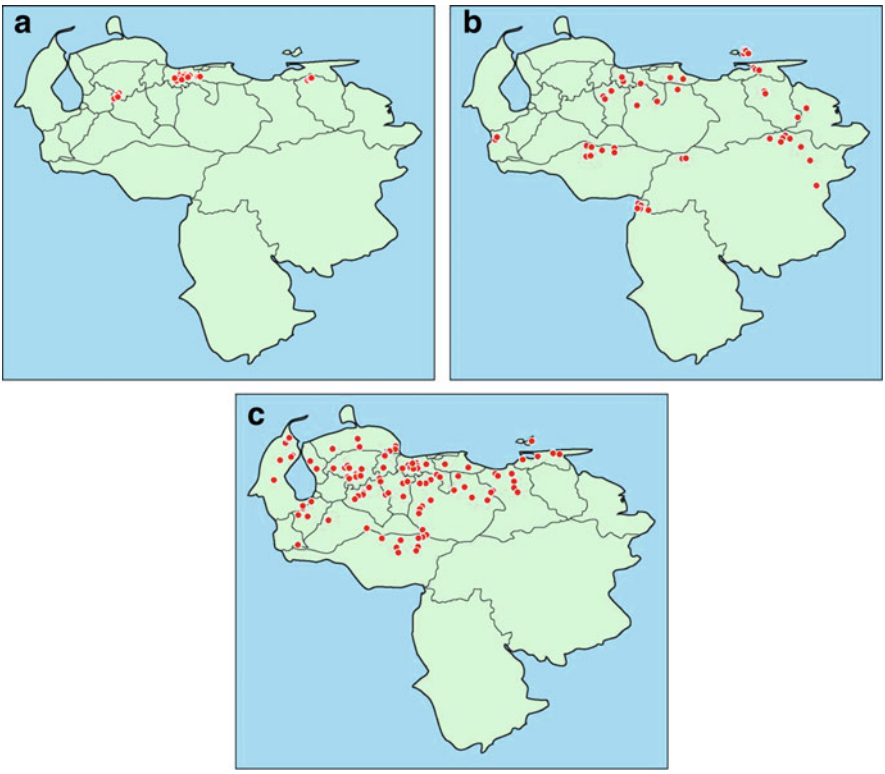

Fig. 12 Distribution of *B. glabrata* (**a**), B. *kuhniana* (**b**), *and B. prona* (**c**) in Venezuela (*Source*: Pointier & Noya, unpublished data)

6.2 Ecological Aspects and Control Measures

Biomphalaria glabrata has a very wide range extending from the Greater Antilles (Dominican Republic and Haïti) to the Southern part of Brazil (Fig. 13). In the Greater and Lesser Antilles, this species was reported from Haïti, Dominican Republic, Puerto Rico, St Marteen, St Kitts, Antigua, Montserrat, Guadeloupe, Dominica, and Martinique (PAHO 1968; Pointier 1974; Prentice 1980). However, in the last few decades, *B. glabrata* populations have strongly diminished and even disappeared following the improvement of control measures (chemical, physical, and biological control programs), the economical development, and the invasion of exotic mollusks (see Fig. 13).

Long-term studies carried out in the Caribbean area have demonstrated that two main species belonging to the Ampullariidae (*Marisa cornuarietis*) and Thiaridae (*Melanoides tuberculata*) families have succeeded in eliminating or reducing populations of the snail hosts of schistosomes, especially *B. glabrata* in several different habitats in St. Lucia, Martinique, Guadeloupe, and Venezuela (Pointier

Fig. 13 Distribution of *Biomphalaria glabrata* in America

et al. 2011). However, their efficiency is context dependent. Ampullarids and thiarids are good competitors in relatively stable habitats only when long-term resource exploitation rather than colonization is the limiting factor. At the same time, unassisted invasions by these species and by other fresh water snails, including numerous pulmonates, were detected in the 1950s, followed by rapid spread in the following decades to most Neotropical areas. These invasions were largely

responsible for the general decline of *B. glabrata* in islands such as Martinique and Guadeloupe, replicating at a larger scale the results of biological control programs. No extinctions of local snail species occurred following the invasion of exotic snails, except for *B. glabrata* in Martinique (Pointier and Théron 2006). Thus, biological invasions could qualify as efficient *unintentional biological control* agents. However, the downside of biological invasions is that snail hosts can be invasive and establish new sites of parasite transmission in formerly parasite-free areas.

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Chagas Disease

Anis Rassi Jr, Anis Rassi, and Jose Antonio Marin-Neto

Contents

Abstract In 1909, the Brazilian physician Carlos Chagas described a new pathogen—*Trypanosoma cruzi*—and an entirely new disease to the scientific community that was subsequently shown to cause serious cardiac and gastrointestinal problems. Far from being a rare nosological entity, Chagas disease was later found to affect millions of people across Latin America. The analysis of South American mummies in paleoparasitological studies indicated, however, that Chagas disease affected humans at least 9,000 years ago. Within a few years, Carlos Chagas and some of his close collaborators—including Gaspar Vianna, Belisário Penna, Eurico Villela, and Ezequiel Dias—described the main anatomopathological and clinical aspects of the disease in its acute and chronic phases. Despite the undeniable success and singularity of these preliminary investigations, Chagas disease was neglected by the medical and scientific community for long periods of the twentieth

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_3

century. The diagnosis, clinical manifestations, and prognosis, as well as the significant gaps in the understanding of the pathogenesis of cardiovascular involvement, and in the management of the disease, will be discussed in this chapter.

Keywords Chagas disease • Carlos Chagas • Brazil • Latin America • South America • Cardiomyopathy • Vector-borne • *Trypanosoma cruzi*

1 Introduction

Despite a substantial reduction in the number of *Trypanosoma cruzi* (*T. cruzi*)-infected individuals worldwide, from 16–18 million in the 1990s to an estimated 8–10 million currently (based mainly upon the success of blood bank and vector control programs), Chagas disease still represents the third largest tropical disease burden, after malaria and schistosomiasis. Most infections occur through vector-borne transmission by triatomine insects in endemic areas but can also occur through blood transfusion, from mother to infant, by ingestion of food or liquid contaminated with *T. cruzi*, and more rarely by organ transplantation and accidents among laboratory personnel who work with live parasites (Rassi et al. 2010a).

Initially, the disease was confined to socially underdeveloped rural areas in almost all countries of South and Central America and Mexico. But, because of the migration of infected individuals from endemic countries, Chagas disease has become a public health problem in nonendemic regions, including the USA, Spain (and other European countries), Japan, and Australia (Schmunis 2007). These countries have growing concerns about transmission through blood transfusion, solid organ donation, and transplacental routes. As a result, the implementation of diagnostic methods and guidelines for management of Chagas disease was intensified in countries outside Latin America, with the aim of recognizing the disease and preventing its transmission (Bern et al. 2007; Gascón et al. 2007).

2 Mechanisms of Transmission

Vectorial transmission is still the most common route of infection by *T. cruzi* in human beings and occurs when the hematophagous insect feeds by sucking blood from the host. The insect defecates on the host, and the parasites in the feces enter the blood stream through the bite wound or through intact mucous membranes near the site of the bite.

Transmission through blood transfusion is the second most common route and is probably underestimated because of under-reporting in medical settings (Wendel and Dias 1992). It is also a likely route of transmission in most countries where

Chagas disease is not endemic because of the increasing number of infected Latin American migrants who donate blood without serological screening for *T. cruzi* (Wendel 2010).

Vertical transmission via the transplacental route has been estimated to vary between 1 % in Brazil and 7 % in some regions of Bolivia and Paraguay, depending on factors such as the parasite strain, the immune state of the mother, and the diagnostic technique itself. (World Health Organization 2002) According to a recent metaanalysis of 51 studies, the overall risk of congenital infection in infants born to infected mothers was 4.7 %. Countries where *T. cruzi* is endemic had a higher rate of congenital transmission compared with nonendemic countries (5.0 % vs. 2.7 %) (Howard et al. 2014).

With the eradication of the main vector (*Triatoma infestans*) in parts of Latin America and the institution of mandatory blood donor screening for Chagas disease, the oral route is now recognized to be a major if not the most common form of transmission in some countries, such as Brazil (Shikanai-Yasuda and Carvalho 2012). Because oral transmission is unpredictable, its prevention is not feasible. The only way to control this form of transmission is gradually increasing the population's education and healthcare levels. Because the parasite load is usually high and the mucosa of the digestive tract is very permeable to the infectious agent, mortality during the acute phase is higher in cases of oral transmission (Rassi et al. 2010a; Pereira et al. 2009).

Transplantation of organs from infected patients into uninfected recipients is a less frequent route of transmission and occurs mainly in nonendemic countries. They are caused by the use of organs from donors of endemic countries, without performing the specific serological tests (Wallace et al. 2013). Moreover, not infrequently, these donors are holders of dual citizenship, which may hinder the identification of high-risk transplantations.

Accidents in laboratories are one of the less frequent routes of transmission. Training and compliance with basic and universally accepted workplace principles are essential for the prevention of infection transmission in environments where professionals work directly with individuals or materials potentially contaminated with *T. cruzi*.

3 Pathogenesis

Organ damage during the acute phase occurs as a result of high-grade parasitemia, intense direct tissue parasitism, and the immunoinflammatory response to the parasite. Affected sites typically include the heart, gastrointestinal tract, and central nervous system.

Histopathology demonstrates intense parasitism in virtually every organic system, with prominent inflammatory changes in the vicinity of ruptured infected cells (Laranja et al. 1956; Marin-Neto et al. 2007). Myocarditis is intense and diffuse

with myocyte necrosis, interstitial edema, vascular dilation, and mononuclear and polymorphonuclear infiltration.

The intensity of the autonomic neuronal depopulation and nerve degeneration that occurs in esophageal and colon tissues during the acute phase is a key factor favoring the appearance of digestive organ involvement in the chronic phase (Köberle 1968; Meneghelli 1985). Direct involvement of smooth muscle may also be a contributory factor.

The pathogenic mechanisms responsible for the development of cardiac lesions during the chronic phase are still not completely understood. Chagas heart disease (CHD) is an acquired inflammatory cardiomyopathy characterized by a progressive derangement of the cardiac conduction system and impairment of myocardial contractile function, and a chronic fibrosing myocarditis (varying from focal or multifocal to diffuse) (Rossi 1991). Numerous mechanisms have been suggested to explain the pathogenesis of CHD (Marin-Neto et al. 2007). A consensus is now emerging that parasite persistence and the parasite-driven immune response play a pivotal role (Tarleton 2003a; Kierszenbaum 2007; Bonney and Engman 2008). In contrast, whether one or more of the autoimmune events described in experimental models and human cases of Chagas disease can contribute to, or aggravate this pathology, has been more controversial and difficult to validate (Tarleton 2003a, b). The evidence supporting this viewpoint can be summarized as follows: (1) in recent years, more powerful and sensitive methods of parasite detection, such as immunohistochemistry and polymerase chain reaction (PCR), have demonstrated a higher frequency of *T. cruzi* antigens and parasite DNA in chronic lesions; also, a significant correlation between parasite persistence and tissue inflammation has been clearly documented; therefore, the supposed absence of parasites at or near sites of disease (the mainstay of the autoimmune theory) probably reflects the use of insensitive histological techniques in the past few decades; (Tarleton and Zhang 1999) (2) interventions that lessen the parasite burden, such as etiological treatment with benznidazole or nifurtimox, reduce clinical disease in humans (Viotti et al. 2006; Fabbro et al. 2007) and experimental animals (Andrade et al. 1991; Garcia et al. 2005), in contrast to immunosuppressive treatments and situations that clearly increase *T. cruzi* parasitemia (Rassi et al. 1997), and usually aggravate the inflammatory response; (Sartori et al. 2007) (3) reinfection or continued exposure (due to continued residence in areas of active transmission) seems to increase parasite load and disease severity in experimental models and in human cases; (Bustamante et al. 2002; Storino et al. 2002) (4) although antiself responses are encountered in *T. cruzi* infection, the nature of antiself antibodies in experimental and human chronic Chagas disease is heterophilic, with a poor correlation with heart lesions (i.e., there is no direct and definitive evidence that the immune reactions against the mimicked autoantigens are actually pathogenic) (Tarleton 2003a); and (5) data supporting the direct involvement of either molecular mimicry or polyclonal activation in the pathogenesis of myocardial lesions ascribed to *T. cruzi* infection are sparse and inconclusive.

The release of intracellular replicated trypanosomes followed by parasite-driven myocyte necrosis and inflammation not only contributes decisively to pathogenesis but may also trigger additional mechanisms of cardiac damage (Bonney and Engman 2008). Several coronary microvascular abnormalities, including increased platelet activity, microthrombi, microvascular spasm, and endothelial dysfunction, have been reported in animal models (Rossi 1990) and in some studies in humans (Marin-Neto et al. 1992; Simões et al. 2000). These phenomena could be explained by vascular endothelial cell damage caused either by *T. cruzi* or immune effector cells directly or could result from the underlying inflammatory process (Rossi 1990). Abnormal reactivity to vasodilating and vasoconstricting stimuli has also been reported in the epicardial coronary arteries of chagasic patients (Torres et al. 1995). It is possible that such derangements contribute to the exacerbation of myocardial cell damage and fibrosis and participate in the genesis of ischemic-like symptoms, electrocardiographic changes, and perfusion defects described in chagasic patients with angiographically normal coronary arteries (Marin-Neto et al. 1992).

Intense neuronal depopulation has been demonstrated in several independent pathologic studies since the early 1920s (Chagas and Vilella 1922). In the 1950s, studies using standardized methods of counting intramural neurons showed a strikingly diminished number of cardiac ganglion cells in chagasic hearts. Because the intramural cardiac ganglia are mostly parasympathetic, a neurogenic ("parasympathicopriva") hypothesis was postulated (Köberle 1959). According to this theory, a long-lasting autonomic imbalance leads to a catecholamine-induced cardiomyopathy characterized by myocardial hypertrophy and cardiac dilation, whereas myocardial inflammation is not considered to be an important element for cardiac damage. Consistent with anatomic parasympathetic denervation, abnormal autonomic cardiac regulation has been shown in many functional investigations, preceding the development of ventricular dysfunction (Ribeiro et al. 2001). Because of the dysautonomia, chagasic patients are deprived of the tonic inhibitory action normally exerted by the parasympathetic system on the sinus node and they also lack the vagally mediated mechanism to respond to transient changes in blood pressure or venous return by using quick-onset bradycardia or tachycardia (Amorim and Marin-Neto 1995). However, several conceptual obstacles have challenged the relevance of the neurogenic theory (Marin-Neto et al. 2007). These include the subtleness and variability of the intensity of cardiac denervation in CHD patients and the lack of correlation between parasympathetic denervation and the extent of myocardial dysfunction. Moreover, sympathetic denervation has also been shown at the sinus node level and in myocardial regions during the early stages of disease (Simões et al. 2000; Marin-Neto et al. 1980).

Nevertheless, neurogenic disturbances may play a contributing role in the complications of the chronic phase of Chagas disease by triggering malignant arrhythmia and sudden death and by disturbing the coronary microcirculation control (Matturri 1996). A schematic overview of the pathogenesis of chronic CHD is shown in Fig. 1.

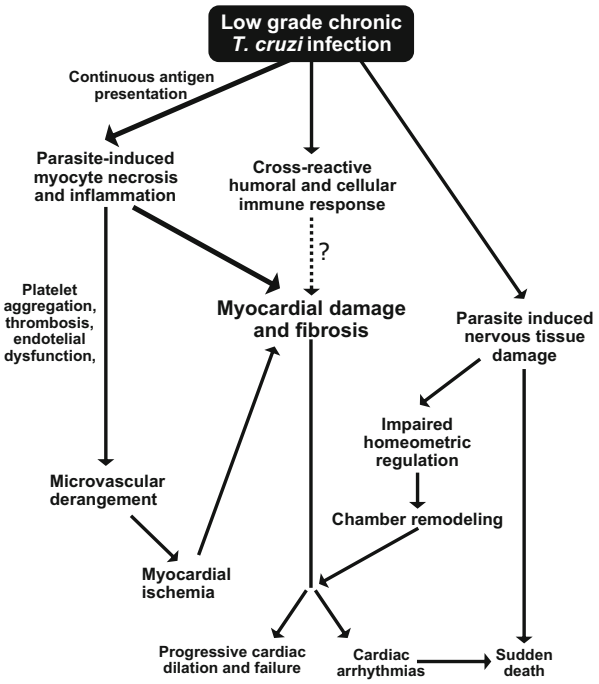

Fig. 1 Schematic view of main pathogenetic mechanisms in chronic CHD (Modified from Marin-Neto et al. 2007)

4 Phases and Forms of Chagas Disease

Human Chagas disease has a variable clinical presentation (Rassi et al. 2010a, b). *T. cruzi* infection is followed by a short acute phase, characterized by high-grade parasitemia that can usually be detected easily by direct blood examination. Despite this, the acute phase is not recognized in most cases because of the scarcity or absence of clinical manifestations. In symptomatic infected individuals, the main signs are prolonged fever, enlarged lymph nodes, hepatomegaly, splenomegaly, subcutaneous edema, signs of portal of entry of the parasite (inoculation chagoma or Romaña's sign), and, in severe cases, myocarditis or meningoencephalitis, or both. These manifestations usually disappear in 60 days, even if the infection is not treated with an antitrypanosomal drug. Then, the disease enters the chronic phase, generally starting with the indeterminate form—a long and asymptomatic or latent stage of the infection. While most patients infected with *T. cruzi* will remain in the indeterminate form forever, about 40–50 % of them, 10–30 years after infection, will develop lesions on different organs, mainly the heart, the digestive system, or both—leading to the cardiac, digestive, and cardio-digestive forms of chronic disease (Rassi et al. 2010a, b).

4.1 Acute Phase

The acute phase of vector-borne Chagas disease occurs mainly in the first or second decades of life. Clinical signs appear 8–10 days after the parasite penetrates the host. (Rassi et al. 2000a; Rassi and Rassi Junior 2013) In transfusion-transmitted Chagas disease, this period may be longer (20–40 days).

4.1.1 Portal of Entry

Romaña sign is the most typical sign of the parasite's portal of entry. It is characterized by a painless swelling of one or both eyelids of one eye (Fig. 2a, b). The eyelids show a bluish color, and conjunctival congestion and hypertrophy of the satellite lymph nodes (usually preauricular) frequently occur. Edema may spread to half of the face; sometimes dacryoadenitis and diminished conjunctival secretion are observed (Rassi et al. 2000a; Rassi and Rassi Junior 2013).

Chagoma is a sign of entry through the skin and is usually found on uncovered areas of the body. The painless and solid maculonodular erythematous lesion is surrounded by swelling and is sometimes ulcerated and is accompanied by increased volume of satellite lymph nodes (Fig. 2c, d).

4.1.2 Clinical Manifestations and Findings of Laboratory Tests

Fever is constant and is frequently accompanied by malaise, asthenia, anorexia, and headache. In children, temperature is usually higher—continuously or intermittently—and can increase further during the afternoon.

Most patients have slightly or moderately enlarged lymph nodes, either in isolation or contiguously; the nodes have a smooth surface and are painless, hard

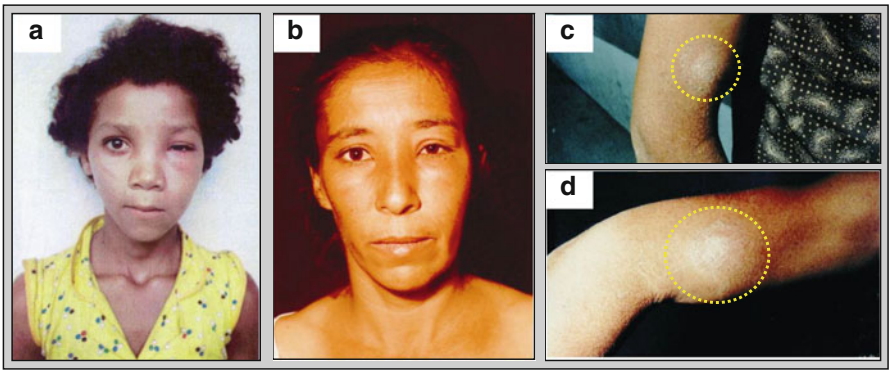

Fig. 2 Signals of portal of entry (**a**) and (**b**): Romaña signal; (**c**) and (**d**): chagoma in the arm (*circle*)

and nonadherent, and not fistulous. Hepatomegaly and splenomegaly are also common. The mechanism leading to edema is unknown. It can be generalized or restricted to the face and lower limbs and is seen most often in children. Meningoencephalitis and myocarditis (sometimes with associated pericarditis and pericardial effusion) are the most severe neurological and cardiological manifestations. Patients can develop mild-to-moderate leucocytosis, along with lymphocytosis (atypical lymphocytes), plasmocytosis, and relative neutropenia. Eosinophilia can occur as the disease evolves. Patients will have a slightly increased erythrocyte sedimentation rate and raised C-reactive protein. Plasma protein electrophoresis usually shows hypoalbuminemia and increased levels of α2 and γ globulins. When meningoencephalitis is present, the spinal fluid shows hypercellularity with lymphocytosis, a low glucose concentration, and a slightly increased protein concentration. It is possible to find trypomastigote forms of *T. cruzi* after centrifugation and specific staining (Rassi et al. 2000a; Rassi and Rassi Junior 2013).

4.1.3 ECG, Radiology, and Echocardiography Findings

Alterations in ECG and chest radiology are not common during the acute phase, but they might become more evident when these tests are repeated. A disproportional increase in heart rate can occur during recovery, when fever is no longer present. This finding was well described by Carlos Chagas (Chagas and Vilella 1922), who also noticed that disturbance of the cardiac rhythm was rare in the acute phase, but very common in the chronic phase. The most common ECG alterations during the acute phase are sinus tachycardia, low QRS voltage, primary ST-T changes, prolonged electrical systole, and first-degree atrioventricular block. The chest radiograph might show variable degrees of global cardiomegaly (Rassi et al. 2000a; Rassi and Rassi Junior 2013).

Because most cases of Chagas disease were reported before echocardiography became available, there is little information about its performance during the acute phase. However, in a recent study of 108 patients (Pinto et al. 2008), echocardiography showed that the main abnormalities are variable degrees of pericardial effusion, mitral or tricuspid valve regurgitation, and left ventricular wall thickening, often with more than one abnormality in the same patient.

4.1.4 Diagnosis

Diagnosis is based on identifying the parasite in peripheral blood, via a wet smear or after staining (thick smear), or via concentration methods (Strout, microhematocrit). Parasite identification by these methods is generally possible only during the initial weeks of the disease.

Other methods for diagnosis are biopsy of a suspected chagoma, a lymph node, or skeletal muscle; xenodiagnosis with an early examination of the triatomine bugs (5–10 days after the blood meal); and a positive serological test for IgM anti-*T. cruzi*

antibodies: conventional enzyme-linked immunosorbent assay (ELISA), ELISA with recombinant antigens, or an indirect immunofluorescence antibody test. However, assays for anti-*T. cruzi* IgM have not been standardized and are not commercially available. Hemoculture is another sensitive technique during the acute phase, but is also not widely available, and requires 2–4 weeks to show replication. More recently, detection of *T. cruzi* genetic material by the polymerase chain reaction (PCR) provided the most sensitive tool to diagnose early congenital Chagas disease and to screen for acute *T. cruzi* infection in the recipient of an infected organ (Bern et al. 2009; Chin-Hong et al. 2011). In addition, PCR assays usually show positive results days to weeks before circulating trypomastigotes are detectable on peripheral blood smears (Schijman et al. 2000). Despite these advantages, the technical complexity of PCR-based assays limits their use primarily to research settings, with minimal clinical utilization.

4.1.5 Clinical Evolution

Mortality in the acute phase used to be around 5 % of all symptomatic patients, often caused by meningoencephalitis or myocarditis. However, the use of antitrypanosomal drugs has probably reduced this percentage. Spontaneous cure, although very rare, can occur (Zeledón et al. 1988; Francolino et al. 2003; Dias et al. 2008).

Symptomatic signs of the acute phase usually disappear in 60 days, even if the infection is not treated with a trypanocidal drug. The natural evolution of the acute phase in about 90–95 % of infected individuals is to pseudo-cure, when all clinical symptoms and signs disappear spontaneously. Direct progression from the acute phase to the clinical form of chronic Chagas disease has been reported in a few patients (5–10 %) (Rassi et al. 2000a).

4.2 Chronic Phase

The chronic phase begins 2–3 months after initial infection, when the clinical signs (if any) of the acute phase disappear and parasitemia falls to undetectable levels.

4.2.1 Diagnosis

Diagnosis is made by conventional serological tests, such as indirect hemagglutination, indirect immunofluorescence, and ELISA, all of which have high sensitivity and acceptable specificity. According to the World Health Organization (WHO Control of Chagas disease 2002), diagnosis should be based on a positive result from at least two of these tests. The complement fixation reaction (Guerreiro-Machado) is no longer used because it is very complex and no more sensitive or

specific than the other tests. Xenodiagnosis, a procedure that allows the feeding of laboratory-raised triatomine bugs (known to be infection-free) to the blood of patients suspected of having Chagas disease, and that examines the bug feces after several weeks for the intermediate stages of *T. cruzi*, can be used to identify the parasite in blood, using the classic method (four boxes with ten triatomines in each, placed at the arms of the patients). Another option is the artificial method, where 20 ml of heparinized blood is collected from the patient and offered aseptically to bugs through a membrane (condom) at approximately 35–37 °C (dos Santos et al. 1995). The artificial xenodiagnosis has several advantages: it is more comfortable for the patient, avoids skin reactions to the triatomine bites, and has equal or superior sensitivity. Alternatively, hemoculture, which involves a specialized liquid culture medium, can also be used to identify the parasite. Accuracy of these techniques increases when the test is done twice or more. Nevertheless, xenodiagnosis and hemoculture are tedious to perform, require a long time to process and obtain the results, are not available commercially, and yield a sensitivity of only 50 % in the best of hands. Because of that, these methods are being viewed increasingly as historical techniques with a limited role in the diagnosis of chronic Chagas disease. In case of individuals with dubious results on serology, PCR could be used instead because it is faster and has better sensitivity than the indirect parasitological methods.

4.2.2 Indeterminate and Determinate Forms

Carlos Chagas divided individuals with chronic disease into two large groups: those without clinical signs and abnormalities in routine tests (the indeterminate form) and those with symptoms or other abnormalities, or both, in one or more tests (the determinate form) (Chagas 1916). In most cases, the chronic phase presents as the indeterminate form, which may evolve to the cardiac, digestive, or cardio-digestive forms after years or decades. This classification was simple and, since no sophisticated or expensive tests were needed, it could be used in most endemic regions.

Indeterminate Form

Definition

The concept of the indeterminate form was not based on histological findings, but on the fact that visceral lesions could not be detected by clinical examination and routine tests in a substantial proportion of patients in the chronic phase. During the first meeting of applied research in Chagas disease (Araxá, Brazil), experts agreed a consensus definition of the indeterminate form, which was published in 1985 (First Annual Meeting of Applied Research in Chagas' Disease 1984). Patients had to meet all the following criteria: positive serological or parasitological tests; absence

of signs and symptoms of disease; normal 12-lead ECG findings; and normal radiology findings for the chest, esophagus, and colon.

This strict definition is useful to categorize patients in epidemiological surveys. In cross-sectional studies in endemic areas, at least half the patients with chronic Chagas disease have the indeterminate form. These patients have a favorable prognosis, low morbidity, and the same mortality as the general population, and they are capable of doing any type of activity (Forichon 1975; Maguire et al. 1987; Manzullo and Chuit 1999; González et al. 2012). In fact, most individuals with chronic disease are actively working and do not know they are infected. A serious and frequent error in medical literature is assuming that Chagas disease has three phases—acute, indeterminate, and chronic—instead of recognizing indeterminate as one of the forms of the chronic phase. By definition, the chronic phase follows the acute phase of a disorder. Patients with the indeterminate form have been infected with *T. cruzi* for a long time and the disease is no longer acute, so the disease is in the chronic phase.

Test Findings

Some patients with the indeterminate form have structural or functional abnormalities when they are fully assessed by highly sensitive tests—for example, ergometry, 24-h Holter monitoring, vectocardiography, echocardiography, radioisotopic techniques, cardiac magnetic resonance imaging, hemodynamic and invasive angiographic study, electrophysiology, endomyocardial biopsies, autonomic tests, and esophageal and colonic manometric studies (Barreto and Arteaga-Fernandez 1986; Marin-Neto et al. 1998; Almeida-Filho et al. 2002; Dantas et al. 1999). But these abnormalities are often subtle and isolated, can occasionally be found also in healthy individuals, and do not lead to a reduced life expectancy. Notably, in most studies of highly sensitive tests in patients with chronic Chagas disease, contrast media was not used to examine the esophagus and colon; this is usually because asymptomatic individuals will not agree to have these tests. So, some of these patients could have had the digestive, not the indeterminate, form of the disease.

Few pathological studies have focused on individuals with the indeterminate form. Findings of a necropsy study of patients who died from accidental causes showed mild myocarditis, with scattered small foci of interstitial infiltration by lymphocytes, macrophages, and plasma cells (Lopes et al. 1981). The reduced number of cardiac neurons and myenteric plexuses is insufficient to produce clinical manifestations. Intact parasites are rarely seen, but PCR can be used to show *T. cruzi* DNA in the samples of myocardium, even in the absence of local inflammation (Jones et al. 1993). Whether these lesions represent sequelae of the acute phase, or result from equilibrium between the parasite and host, or are associated with cumulative progression to diffuse myocardial damage is not yet known.

Clinical Evolution

Although patients with the indeterminate form (including those with any abnormality on highly sensitive tests) have a good prognosis, epidemiological studies in endemic areas have shown that, in 1–3 % of them each year, the disease evolves from the indeterminate to the determinate form. (Dias 1989; Storino et al. 1994; Sabino et al. 2013) Whether the structural or functional abnormalities are a reliable early marker of disease progression or an innocent bystander is not known. Follow-up of patients with the indeterminate form should include reviewing their clinical symptoms and signs, a physical examination, and a 12-lead ECG tracing every year (Rassi et al. 2010a).

Cardiac Form

The cardiac form is the most serious and frequent manifestation of chronic Chagas disease. It develops in 20–30 % of individuals and presents as three major syndromes that may coexist in the same patient: arrhythmia, heart failure, and thromboembolism (systemic and pulmonary) (Rassi et al. 1992, 2000b, 2010a). Clinical presentation varies widely according to the extent of myocardial damage.

Arrhythmia

Arrhythmias are very common and each patient often has more than one type. They cause palpitations, presyncope, syncope, and Stokes–Adams syndrome; sometimes arrhythmias are asymptomatic. Frequent, complex, ventricular premature beats, including couplets and runs of nonsustained ventricular tachycardia, are a common finding on 24-h Holter monitoring or stress testing. They correlate with the severity of ventricular dysfunction, but can also occur in patients with quite well-preserved ventricular function. Nonsustained ventricular tachycardia occurs in about 40 % of patients with mild wall motion abnormalities and in virtually all patients with heart failure, which is higher than in other cardiomyopathies (Rassi Júnior et al. 1995). Sustained ventricular tachycardia is also a hallmark of the disease. This life-threatening arrhythmia can be reproduced during programmed ventricular stimulation in about 85 % of patients, and is caused by a reentry circuit (subepicardial in about 40 % of the cases), which is usually located at the inferior–lateral or posterior–lateral wall of the left ventricle (Sosa et al. 1998; d'Avila et al. 2002).

Heart Failure

Heart failure is often a late sign of the cardiac form of Chagas disease. It is usually biventricular with a predominance of right-sided failure at advanced stages (peripheral edema, hepatomegaly, and ascites are more prominent than pulmonary congestion is). Nocturnal paroxysmal dyspnea, cardiac asthma, and acute pulmonary edema are rare. Gallop rhythm is infrequent. Once the patient has cardiomegaly, a

systolic murmur of functional mitral and/or tricuspid regurgitation can be heard. Isolated left-sided heart failure can be seen in the early stages of cardiac decompensation (Rassi et al. 2000b; Marin-Neto et al. 2010). Heart failure caused by Chagas disease is associated with higher mortality than is heart failure from other causes (Freitas et al. 2005).

Thromboembolism

Systemic and pulmonary embolisms arising from mural thrombi in the cardiac chambers are quite common. (Oliveira et al. 1983) Clinically, brain is by far the most common site of embolisms (followed by limbs and lungs) but, at necropsy, embolisms are more common in the lungs, kidneys, and spleen. Chagas disease is an independent risk factor for stroke in endemic areas (Carod-Artal et al. 2005).

ECG, Radiology, and Echocardiography Findings

The most common and important ECG alterations are ventricular premature beats (monomorphic or polymorphic, isolated or in pairs), complete right bundle branch block, left anterior hemiblock, primary ST-T changes, Q waves, different degrees of atrioventricular block, signs of sinus node dysfunction (sinus bradycardia, sinoatrial block, and sinus arrest), atrial fibrillation, and nonsustained or sustained ventricular tachycardia. All these alterations may be isolated or associated. A frequent association is the complete right bundle branch block and left anterior hemiblock and, when this occurs in an endemic area, it strongly suggests the cardiac form of chronic disease (Fig. 3).

On radiology, the size of the heart is generally normal in the initial phase of cardiomyopathy and even when important ECG changes are present. The heart can be slightly, moderately, or severely enlarged in all chambers. In nearly half the cases with heart failure, the signs of pulmonary congestion are poor or even absent.

The echodopplercardiogram may be abnormal, even in patients with normal ECG and chest radiography results. Echocardiography shows wall motion abnormalities in two main areas of the left ventricle: the apex and the posterior–inferior wall. The most common findings are apical aneurysms (with or without thrombi; Fig. 4) and akinesia or hypokinesia of the posterior wall of the left ventricle (with preservation of the ventricular septum).

Ambulatory ECG monitoring, using the 24-h Holter system, is excellent for investigating patients with the cardiac form. (Rassi and Perini 1979; Rassi et al. 1985, 1990). It can identify complex ventricular arrhythmias, transitory arrhythmias, and the association of tachyarrhythmias with bradyarrhythmias. It can also assess antiarrhythmic therapy and whether an artificial pacemaker is working properly. In some cases, an event recorder or Holter is used to monitor ECG activity for several days, not just 24 h.

Exercise testing assesses the patient's functional capacity, the chronotropic response, the influence of exercise in provoking arrhythmias, the blood pressure response, and can verify the effectiveness of antiarrhythmic drugs.

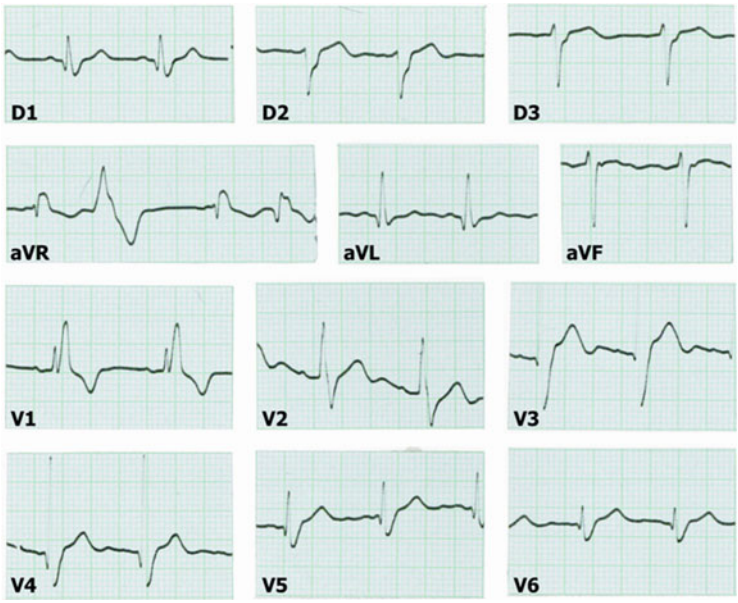

Fig. 3 ECG of a patient with Chagas heart disease showing the 3 most typical alterations: right bundle branch block, left anterior hemiblock and ventricular extrasystole

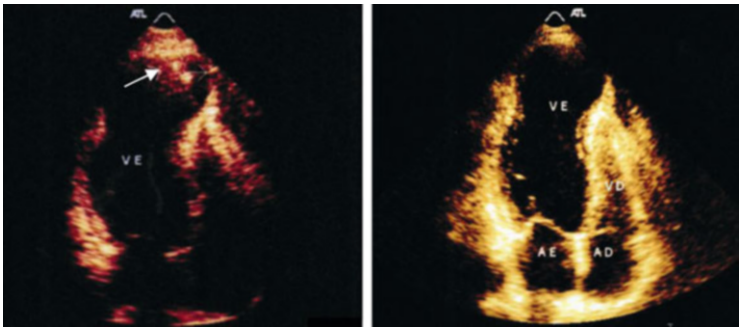

Fig. 4 Two-dimensional echocardiogram showing left ventricular apical aneurysm with (*arrow*) and without thrombus

Intracardiac electrophysiology assesses the sinus node function, may identify the location of atrioventricular and intraventricular blocks precisely, and is useful to investigate whether ventricular tachyarrhythmias can be induced, as well as their place of origin. This technique is of great value for assessing presyncope and syncope of unknown origin, the need for an artificial pacemaker, and alternative or additional treatment of sustained ventricular tachycardia (e.g., transcatheter ablation added to amiodarone or ICD). Because of its invasive nature, it should be done only in selected patients after all other noninvasive methods have been tried, such as 24-h Holter monitoring and exercise testing.

Clinical Evolution

Since Carlos Chagas' initial description, it is apparent that some patients have conduction defects or mild segmental wall motion abnormalities, or both; some develop severe symptoms of heart failure, thromboembolic phenomena, and multiple disturbances of rhythm; and others die suddenly and unexpectedly in the absence of previous cardiac symptoms. Sudden death is the main cause of death, accounting for nearly two-thirds of all deaths, followed by refractory heart failure (25–30 %) and thromboembolism (Rassi et al. 2001). It is usually associated with ventricular tachycardia and fibrillation or, more rarely, with asystole due to complete atrioventricular block or sinus node dysfunction.

Prognosis

Improved evaluation of prognostic factors in CHD has helped clinicians to identify patients' risk of death and choose appropriate treatment. Some of us used a rigorous multivariate analysis to develop a risk score for predicting mortality in 424 outpatients in Brazil; (Rassi et al. 2006) the score has been validated in two external cohorts (Rassi et al. 2006; Rocha and Ribeiro 2006). We tested several demographic, clinical, and noninvasive variables: six were independent predictors of mortality and we assigned them points according to the strength of their statistical association with the outcome. From adding the points to provide the risk score, patients could be classified into low, intermediate, and high-risk groups (Fig. 5).

Subsequently, two systematic reviews (Rassi et al. 2007a, 2009) integrated the results from all previous studies of multivariable regression models of prognosis

A

Risk Factor	Points
NYHA class III or IV	5
Cardiomegaly (chest x-ray)	5
Segmental or global WMA (2D echo)	3
Non sustained ventricular tachycardia (24h Holter)	3
Low QRS voltage (ECG)	2
Male sex	2

Total Points	Total Mortality		Risk
	5 years	10 years	
0 – 6	2%	10%	Low
7 – 11	18%	44%	Intermediate
12 – 20	63%	84%	High

Fig. 5 Prognostic factors in Chagas heart disease (A) Rassi score for prediction of total mortality *echo* echocardiogram; *NYHA* New York Heart Association; *WMA* wall motion abnormality.

Table 1 Stratification of risk of death associated with Chagas heart disease and recommended therapy

Risk of death	Risk factor			Recommended treatment
	NYHA class III/IV	LV systolic dysfunction (echo) and/or cardiomegaly (chest X-ray)	Nonsustained VT (24-h Holter)	
Very high	Present[a]	Present	Present	ACE inhibitor, espironolactone, amiodarone, diuretics, digitalis, betablocker[b], cardiac transplant[c], ICD?
High	Absent	Present	Present	ACE inhibitor, amiodarone diuretic[c], betablocker[b], ICD?
Intermediate Intermediate	Absent Absent	Present Absent	Absent Present	ACE inhibitor, betablocker, diuretic[c] Antiparasitic drug Antiparasitic treatment, amiodarone[c]
Low	Absent	Absent	Absent	Antiparasitic drug

ACE angiotensin-converting enzyme, *echo* echocardiogram, *ICD* implantable cardioverter-defibrillator, *LV* left ventricular, *NYHA* New York Heart Association, *VT* ventricular tachycardia
[a]Nearly 100 % of patients with Chagas heart disease in NYHA class III or IV also have LV systolic dysfunction on echo and nonsustained VT on 24-h Holter monitoring
[b]if clinically tolerated
[c]for selected patients

that analyzed a clearly defined outcome (all-cause mortality, sudden cardiac death, or cardiovascular death). According to these reviews, the strongest and most consistent predictors of mortality are New York Heart Association (NYHA) functional class III or IV, cardiomegaly on chest radiography, impaired left ventricular systolic function on echocardiogram or contrast cineventriculography, and nonsustained ventricular tachycardia on 24-h Holter monitoring. On the basis of these findings, Table 1 sets out a risk-stratification model for mortality that can help clinicians identify the best treatment for patients with the cardiac form.

Treatment

For the most part, the principles that guide the symptomatic treatment of the cardiac form are the same as those established for heart disease of other causes. Patients with symptomatic bradyarrhythmias, or those at a high risk of complete atrioventricular block, should be given a pacemaker. The electrode should be placed in the subtricuspid zone (Korman and Jatene 1977), avoiding the apex of the right ventricle, which may be thin, fibrotic, and contain a thrombus.

In patients given a pacemaker, 24-h Holter monitoring or exercise testing, or both, should be used to check for ventricular arrhythmias (Rassi Júnior et al. 1995).

Ventricular arrhythmias are mainly treated with amiodarone; sotalol and β blockers are second choice drugs. Propafenone and mexiletine were used in the past in some patients because of their antiectopic activity. Quinidine, procainamide, and disopiramide do not have adequate antiarrhythmic activity, but intravenous procainamide is highly effective for the treatment of paroxysmal ventricular tachycardia. Monomorphic sustained ventricular tachycardia might also respond to percutaneous endocardial or epicardial ablation, using catheter-delivered radiofrequency, in selected patients with an arrhythmia that can be mapped. The use of implantable cardioverter-defibrillators is hampered by the lack of controlled data to establish precise indications and efficacy (Rassi 2007), as well as by socioeconomic limitations.

When cardiac failure is present, it may be necessary to use higher doses of diuretics; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, espironolactone, digoxin, and β blockers, are also commonly used (Rassi et al. 2000b, 2010a; Marin-Neto et al. 2010). Some individuals—such as those with intractable cardiac failure following optimized treatment—need a heart transplant. In this situation, the patient should be sequentially and frequently monitored for reactivation after surgery. There are no data to indicate that prior antiparasitic treatment or post-transplant prophylaxis decreases the risk of reactivation; however, post-transplant prophylaxis has been administered in some heart transplant centers in Latin America. Palliative procedures, such as dynamic cardiomyoplasty and partial left ventriculectomy, are contraindicated because of unsatisfactory results. Cardiac resynchronization is another form of treatment for heart failure and is mostly for patients with left bundle branch block. However, remarkably few data support its use in patients with right bundle branch block, which is much more common in patients with Chagas disease. Transplantation of bone marrow cells for treatment of Chagas heart failure was recently assessed in a multicenter randomized controlled trial sponsored by the Brazilian Health Ministry, but failed to show any improvement in left ventricular function or quality of life when compared to placebo (Ribeiro Dos Santos et al. 2012).

Because of the high occurrence of thromboembolic phenomena in CHD patients, oral anticoagulants are recommended for patients with atrial fibrillation, previous embolic episodes, and apical aneurysm with a thrombus. If poor social and economic factors limit the use of anticoagulant therapy, aspirin is a reasonable alternative.

Digestive Form

The digestive form is seen almost exclusively south of the Amazon basin (mainly in Brazil, Argentina, Chile, and Bolivia) and is rare in northern South America, Central America, and Mexico. This geographic distribution is probably due to differences in parasite strains. Gastrointestinal dysfunction (mainly megaesophagus, megacolon, or both) develops in about 10–15 % of chronically infected patients (Rassi et al. 2010a, b). The megaesophagus causes dysphagia, regurgitation, and esophageal pain. Other less frequent symptoms are hiccups,

pyrosis, and hypersalivation accompanied by parotid hypertrophy. Malnutrition occurs with the progression of the disease. Radiologic examination is essential to confirm the diagnosis and the stage of disease from the morphofunctional characteristics of the esophagus (de Rezende 1982). The most common symptoms of megacolon are constipation, meteorism, dyskinesia, and, less often, abdominal colicky pain. Constipation can be absent in 25–30 % of individuals who have radiologic dilatation of the colon. On physical examination, an increase in the abdominal volume is observed. Because the distal colon is the most affected segment, the distended sigmoid occupies a large part of the abdominal cavity and can be localized by palpation and percussion outside its normal topography. Prolonged retention of feces in the distal colon leads to the formation of fecaloma, which can be diagnosed by simple abdominal palpation as an elastic tumor that can be molded by pressure. Rectal examination will detect a fecaloma at the rectal ampulla (Rassi et al. 2010b). Most cases of megacolon are associated with megaesophagus.

Other segments and organs of the digestive system may be compromised in Chagas disease, causing functional and morphologic alterations that can be detected by different investigative methods, but with a much lower prevalence and impact than the lesions involving the esophagus and colon (Rassi et al. 2010b).

The treatment of megaesophagus consists of balloon dilation of the lower esophageal sphincter. Those who fail to respond to repeated balloon dilation may require surgical treatment. Nifedipine and nitrates reduce lower esophageal sphincter pressure and can be used before meals in some cases as a palliative measure. Patients in the early stages of colonic dysfunction can be managed with a high-fiber diet and occasional laxatives and enemas. Several surgical procedures have been used to treat advanced chagasic megacolon, and all of them include resection of the sigmoid as well as removal of part of the rectum.

Cardiodigestive Form

The cardiodigestive form is a combination of heart disease with megaesophagus or megacolon, or both. In most countries, the development of megaesophagus usually precedes heart and colon disease, but the exact prevalence of the cardiodigestive form is not known because few appropriate studies have been done.

5 Etiological Treatment

At present, only two drugs are available for the etiological treatment of Chagas disease: benznidazole and nifurtimox. Both compounds were developed in the early 1970s, and the fact that no proven effective drug was identified since then shows that Chagas disease has been neglected by the scientific community, the government, and pharmaceutical companies.

Benznidazole and nifurtimox are active against both the intracellular amastigote and, more intensely, against the circulating trypomastigote form. (Rodriques Coura and de Castro 2002) They were initially tested empirically in patients in the acute phase of infection and resulted in clinical remission and parasitological and serological cure in up to 80 % patients (Rassi et al. 2000a). In face of this evidence, and despite the lack of more robust studies, there is a virtually universal consensus on the need for etiological treatment among all patients diagnosed with the acute phase of Chagas disease, irrespective of the mechanism of transmission (Andrade et al. 2011). This indication is also unanimously accepted for children and adolescents (up to 12 or up to 18 years of age, depending on the guideline), and when the infection is reactivated in patients in the chronic phase of disease, usually under clinical conditions of natural or iatrogenic immunosuppression (Bern et al. 2007; Andrade et al. 2011).

In contrast, the use of antitrypanosomal drugs in adults with the chronic phase of Chagas disease was discredited and contested for many years (Andrade et al. 2011; Brener 1984). This unjustifiable position was largely the result of the misconception that the main pathogenic mechanism of Chagas disease was autoimmunity, although this concept had been previously challenged (Kierszenbaum 1986). The personal experience of physicians who observe essentially the more advanced stages of the disease also contributed to this erroneous opinion. In fact, in this situation, etiological treatment is not expected to accrue any benefit.

There is now mounting evidence that parasite persistence represents the essential mechanism of development of direct or immune-mediated inflammatory tissue damage, causing myocardial cell necrosis and intense reactive and reparative fibrosis (Marin-Neto et al. 2007; Tarleton and Zhang 1999). As a corollary, it is natural to speculate that antitrypanosomal therapy in the nonadvanced clinical stage of the disease can favorably modify its natural evolution. The underlying hypothesis for this concept is that the eradication of *T. cruzi*, or even the decrease in parasite load, results in the mitigation and/or delay in the progression of chronic Chagas myocarditis. This basic concept, as already mentioned above, reflects the idea that autoimmunity (without the parasite's presence in the tissues) is not the decisive mechanism of the pathogenesis of CHD.

Thus, etiological treatment should usually be offered to most patients with the indeterminate form of the disease, and those with the digestive form (to prevent cardiac, not the gastrointestinal progression) (Rassi et al. 2010a; Marin-Neto et al. 2010). In some countries in South America, this indication is a public health policy. In the USA, it is also a firm recommendation based on a systematic review of literature led by researchers of the Centers for Disease Control and Prevention (CDC) and collaborators in Latin America (Bern et al. 2007). This position is supported by a systematic review and metaanalysis of the few randomized studies conducted with asymptomatic infected patients—mostly with the indeterminate form—which concluded that etiological treatment (particularly with benznidazole) improves the host–parasite relationship, with negative xenodiagnosis and with serological proof of the decrease in circulating anti-*T. cruzi* antibodies (Villar et al. 2002a, b). The two most conclusive studies included in this metaanalysis

were done in children and showed negative seroconversion and a cure rate of approximately 60 % over a mean follow-up period of 3–4 years (Andrade et al. 1996; Sosa-Estani et al. 1998). Characteristically, children tolerate benznidazole and nifurtimox relatively better than adults.

There is also evidence from experimental models of *T. cruzi* infection that etiological treatment attenuates progression of heart disease, even if complete eradication of the parasite has not been accomplished (with only a decrease in parasite load being achieved) (Andrade et al. 1991; Garcia et al. 2005; Bahia and de Andrade 2012). More recently, studies have shown that benznidazole and nifurtimox side effects are less frequent and the drugs better tolerated than initially believed (Rassi and Luquetti 2003; Viotti et al. 2009), and that such adverse effects, including gastrointestinal and cutaneous reactions, polyneuropathy, and reversible leukopenia, are worth the risk given the potential benefits that can be achieved by relatively short-term treatment (2–3 months) (Rassi and Luquetti 2003; Viotti et al. 2009). Of note, different observational studies that tested the effects of etiologic treatment in patients with heart disease and were based on clinically relevant outcomes showed a positive effect, thus altering the natural history of the disease in a favorable manner (Viotti et al. 2006; Fabbro et al. 2007; Fragata Filho et al. 1994, 2005; Cançado 2002). Finally, a metaanalysis including the results of three randomized and six observational studies concluded that patients treated with benznidazole had a significantly lower risk of developing clinical events compared with patients who did not receive etiological treatment (odds ratio, 0.29; 95 % confidence interval, 0.16–0.53) (Pérez-Molina et al. 2009). The treatment regimen for benznidazole in children consists of 5–10 mg per kilogram of body weight per day, administered orally in two or three divided doses for 60 days. In adults, the recommended dose is 5 mg per kilogram per day. For nifurtimox, the recommended dose is 15 mg per kilogram per day orally in three divided doses for 60–90 days in children and 8–10 mg per kilogram per day in adults (Ministério da Saúde do Brasil 2005).

In summary, there is a growing trend to offer trypanocidal treatment to most patients with chronic Chagas disease. This perspective is based on the concept that, in light of the current knowledge, and while waiting for the results of BENEFIT (Marin-Neto et al. 2008, 2009) (a large randomized clinical trial designed to assess the parasitological and clinical efficacy of benznidazole in adults, 18–75 years old with chronic CHD and no advanced lesions, which is being performed in Brazil, Argentina, Colombia, Bolivia, and El Salvador), the risk of not adopting a promising therapy (with tolerable side effects) is less acceptable than the risk of not adopting what can be proved to be useless in the future (Andrade et al. 2011). In fact, even in primary healthcare setting, the indifferent attitude of doctors who do not even consider offering etiological treatment to their patients is now ethically questionable (Tarleton et al. 2007).

The implementation of effective secondary prevention measures at the population level should include the active screening of the children of infected mothers, family members, and other individuals exposed to the risk of infection in endemic

areas. In addition, the use of diagnostic opportunities should be improved in terms of universal screening in blood banks and before organ donation.

It is possible that in the near future, new anti-*T. cruzi* drugs will become available for clinical use, either alone or in combination with drugs of proven efficacy. Some examples of the promising drugs as per preclinical studies are posaconazole (de Diniz 2013), ravuconazol (Urbina et al. 2003), and fexinidazole (Bahia and de Andrade 2012).

The efficacy and safety of posaconazole and benznidazole were recently compared in adults with chronic *T. cruzi* infection in a prospective, randomized clinical trial (CHAGASAZOL) (Molina et al. 2014). Disappointingly, treatment with low-dose or high-dose posaconazole was ineffective and resulted in a significantly larger percentage of treatment failures than did treatment with benznidazole. Another phase II proof-of-concept clinical trial with a prodrug of ravuconazole, E1224 (Proof of Concept Study of E1224), was recently completed, and unpublished reports indicated that E1224 also substantially failed to achieve the endpoint markers of effectiveness shown with benznidazole. Nevertheless, a second Phase II clinical trial of posaconazole is being conducted by Merck (STOP CHAGAS) (A Study of the Use of Oral Posaconazole) in which posaconazole, oral suspension (400 mg BID), is administered for 60 days, both as monotherapy and together with benznidazole. Benznidazole monotherapy will be employed as a monitoring arm. The objective of the study is to recruit 160 adults with chronic indeterminate Chagas disease in several centers of Latin America and follow them for 360 days. STOP CHAGAS uses PCR to evaluate *T. cruzi* levels in blood as the primary endpoint. The use of itraconazole and allopurinol is not recommended because of insufficient favorable evidence or even previous negative results (Rassi et al. 2007b).

Finally, it is expected that the supply of benznidazole and nifurtimox will not be threatened by logistic problems within the industrial suppliers (Navarro et al. 2012).

6 Prevention

Since vaccines are not available and antitrypanosomal therapy has limitations, the control of *T. cruzi* transmission in endemic countries depends on the reduction of domiciliary vector populations by spraying of insecticides, improvements in housing conditions, and education of individuals at risk. These measures, coupled with serological screening of blood donors, have markedly reduced the transmission of the parasite in several endemic countries.

Acknowledgments The authors thank Katrina Phillips for her comments, careful review, and editing of the text.

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Hookworm Infection in Latin America and the Caribbean Region

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Contents

Abstract Hookworm infection, caused by the soil-transmitted helminths *Ancylostoma duodenale* and *Necator americanus*, is a highly prevalent helminthic infection in the Latin America and the Caribbean region. The relevant disease burden, mainly in children and during pregnancy, is often associated with poor conditions of living and social inequities. For this review, all publications related to hookworm infection in Latin America and the Caribbean (LAC) region were surveyed using PubMed, Google Scholar, Global Atlas of Helminth Infections (GAHI) and local sources. The broad area, latitude and altitude differences in the LAC territory cause major difficulties in the accessibility of hookworm disease burden and true prevalence. However, hookworm infection has been described in several countries from the Central through South America. Historically, hookworm surveys and treatment have been performed in the LAC region. Here, we describe

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_4

the history and origin of hookworm infection, different aspects of clinical manifestations, distribution and disease burden of infection. Moreover, approaches for control and elimination of hookworm infection are discussed.

Keywords Hookworm infection • *Necator americanus* • *Ancylostoma duodenale* • Latin America • Caribbean

1 Background

Hookworm infection is caused by blood-feeding nematodes that, as other soil-transmitted helminths, are transmitted through contaminated soil, which provides condition to the development of unembryonated eggs to the infective stage. According to the Global Burden of Disease 2010 Study (Murray and Lopez 2013), the hookworm infection still poses a considerable global disease burden with annual losses of more than 3.2 million disability-adjusted life years and particular deleterious effect in children (Hotez 1989; Hotez et al. 2004) and during pregnancy (Bundy et al. 1995). At 2003, from the worldwide estimative of 740 million people infected with hookworms, about 50 million cases (10% of infection prevalence) occur in the LAC region (de Silva et al. 2003).

The LAC region is widely known by the social inequalities where 13.7% of the population is still considered as being extremely poor (Biggs et al. 2010). Despite important advances in recent decades, LAC remains the world's most unequal region (Barreto et al. 2012). Indeed, in the LAC region approximately 48 million people live below the World Bank poverty figure of $1.25 per day, while 99 million people live on less than $2 per day (Hotez et al. 2013). The impoverished people face a considerable of social exclusion and social inequity (Holveck et al. 2007), including lack of access to safe water and health care services (Farmer 2007; Hotez et al. 2008; Soares et al. 2002). Some development indicators for the LAC region are demonstrated in Table 1.

2 The Latin America and the Caribbean Region

The Latin America and the Caribbean (LAC) region is comprised of 41 countries, all of them considered as developing countries, including Antigua and Barbuda, Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St. Kitts and Nevis, St. Lucia, St. Vicent and the Grenadines, Suriname, Uruguay and Venezuela. It also includes other territories and/or insular countries such as Anguilla, Aruba,

Table 1 World Development indicators for Latin America and Caribbean Region (LAC), 1960–2013

Indicator	1960	1970	1980	1990	2000	2010	2013
Population, total	219,689,517	286,717,397	363,252,794	444,190,971	525,299,778	595,022,397	615,332,338
Rural population (% of total population)	50.7	43.0	35.7	29.5	24.7	21.6	20.7
Urban population (% of total)	49.3	57.0	64.3	70.5	75.3	78.4	79.3
GDP per capita (current US$)	369.35	614.10	2,136.48	2,626.27	4,401.53	8,914.71	10,004.04
Life expectancy at birth, total (years)	56.2	60.3	64.6	68.3	71.6	74.2	NA
Mortality rate, infant (per 1,000 live births)	117.4	87.3	64.1	43.1	26.8	17.5	15.3

Source WorldBank, World Development Indicators, 2014. http://data.worldbank.org/indicator
NA Not available information

Bahamas, Barbados, Bonaire, Cayman Islands, Curaçao, Guadeloupe, Martinique, Montserrat, Puerto Rico, Saba, St. Barthélemy, St. Martin, Sint Eustatius, Trinidad and Tobago, Turks and Caicos Islands and Virgin Islands. About 615 million people live in the LAC region (≈8.5% of the world population) (Table 1), led by Brazil (203 million), Mexico (110 million), Colombia (47 million), Argentina (41 million), Peru and Venezuela (30 million each), as most populated countries.

3 Methodology

For this review, publications related to hookworm infection in Latin America and the Caribbean region were surveyed using PubMed, Google Scholar, Global Atlas of Helminth Infections (GAHI) and local sources, with no restriction to date or language. Published papers in English, French, Spanish and Portuguese were included in the review.

4 Etiological Agents and Life Cycle

Human hookworm infection is a soil-transmitted helminthiasis caused by blood-feeding nematodes belonging to the family Ancylostomatidae and superfamily Strongyloidea. The major characteristic of this group is the presence of the buccal capsule on adult parasites, which may present as either teeth (subfamily Ancylostomatinae) or cutting plates (subfamily Bunostominae) (Hotez and Pritchard 1995). Over 100 species have been described in this family, but only two species are considered the etiological agents of hookworm infection in the LAC region: *Ancylostoma duodenale* (Dubini 1843) and *Necator americanus* (originally described as *Uncinaria americana*) (Stiles 1902). Both hookworms have a direct life cycle (Hoagland and Schad 1978). Eggs released in the host's faeces will originate from the first two-living larval stages (L1 and L2) and, later, they will moult to free-living infective but developmentally arrested third larval stage (L3). Humans acquire infection by skin penetration (both *N. americanus* and *A. duodenale*) or ingestion (for *A. duodenale*) of third larval stage (L3). The possibility of parasitism after ingestion of *N. americanus* L3 due to invasion of the buccal epithelium has been reported (Nagahana et al. 1963).

After entering the host, the larvae resume their development in response to host-derived signals (Hawdon and Hotez 1996) and migrate through vascular or lymphatic transport to the lungs (Looss 1901). From the lung capillaries, the larvae rupture and enter the parenchyma, where they ascend the alveoli, bronchioles, bronchi and trachea. After being coughed up and swallowed, the larvae enter the gastrointestinal tract, where they molt twice and develop to the adult stage (Hotez et al. 2004). Fourth-stage larvae with provisional buccal capsule are detected in the larynx, pharynx, oesophagus and intestine. The last moult occurs in the intestine

where adult stages mature, initiating the reproduction and shedding of eggs. Intestinal blood loss in the host begins before egg production and continues for life of the parasite. Hookworms may live in the human intestine on average from 1 to 3 years for *A. duodenale* and 3–10 years for *N. americanus* (Hoagland and Schad 1978).

5 History of Hookworm Infection

Paleoparasitological evidences suggest that human hookworm infection is present in the LAC region over 7,200 years (Ferreira et al. 1987). The presence of hookworm infections in pre-Columbia America is dated from 900 BC in Peru (Allison et al. 1974) and from 7,290 to 430 years in Brazil (Ferreira et al. 1980, 1983, 1987) suggesting its introduction in the New World by transpacific (Nozais 1985; Horne 1985) or transatlantic migrations (Araújo et al. 1988). It has been considered that the center of dispension of *N. americanus* infection was the Sub-Saharan Africa and Southern Asia, while *A. duodenale* was found in natives of Northern Africa, Southern Europe and Northen Asia, including Japan (Manter 1967).

In the early twentieth century, the Rockefeller Foundation through its International Health Board provided funding, training and organisation for several tropical diseases in the LAC region, including hookworm. All efforts towards a worldwide teamwork led to the establishment and support of several Schools of Public Health, the Pan American Sanitary Bureau and the organization of the Health Section of the League of Nations (preceding the creation of World Health Organization).

At the time, colonial administrations (among them Great Britain, France, the Netherlands and Belgium) and the United States have created agencies of health in their possessions or mandated territories in order to improve sanitary and hygienic conditions. Most of other countries received support from the International Health Board for hookworm control (Fig. 1), such as Brazil, Colombia, Dominica, El Salvador, Guatemala, Honduras, Jamaica, St. Kitts and Nevis, Nicaragua, Panama, Paraguay, Porto Rico, St. Lucia and Trinidad and Tobago. Survey and treatment of several thousand people was performed under supervision of the foundation. The effective hookworm control work not only brought immediate relief to the population residing in these endemic areas but also favoured the establishment of adequate and permanent health agencies (Rockefeller Foundation Annual Report 1924).

Fig. 1 Activities of the Rockefeller Foundation at Latin America and the Caribbean Region in 1924, including hookworm control or survey (Adapted from: Rockfeller Foundation Annual Report 1924. http://www.rockefellerfoundation.org/uploads/files/bb8f4388-7a9a-444f-8c5e-c2c88fc2531d-1924.pdf)

6 Epidemiology, Distribution and Disease Burden of Hookworm Infection

According to the Pan American Health Organization (PAHO) and World Health Organization (WHO), hookworm disease is classified based on parasite burden determined by the counting of egg per gram (epg) evaluated in the stool. It is considered light infection if parasite burden is between 1 and 1,999 epg, moderate infection 2,000–3,999 epg and heavy infection above 4,000 epg (PAHO 2011; WHO 2014). The vast majority of the studies after 2000s used Kato–Katz technique to evaluate the epg, albeit its limitation for hookworm eggs is well known (Chammartin et al. 2013a). It is estimated that hookworm disease affects at least 26 countries in LAC and 8.9% of the LAC population is infected, summed up to 8.7% of the global hookworm disease burden. One of the ways to measure disease burden is through disability-adjusted life years (DALYs). Globally, hookworm infection DALYs is between 1.5 and 22.1 million, and in LAC, it is estimated between 130,500 and 1,923,000 (Hotez et al. 2008).

The broad area, latitude and altitude differences and precipitation index during the wettest quarter through LAC territory cause major difficulties in the accessibility of hookworm disease burden and differences through its area (Chammartin et al. 2013a; de Silva et al. 2003). Hookworm infection has been described in South America from southern Chile to coastal regions of Peru. Although some areas are considered high risk for hookworm infection, minor risk areas include coastal

regions of Peru and Venezuela and Southern Chile (Chammartin et al. 2013a). In the LAC region, the risk areas can be divided into unstable transmission (UT) and beyond transmission (BT) according to arid index (UT <0.2; BT <0.03), maximum land surface temperature in the hottest month (UT >36–40 °C; BT >40 °C) and mean of land surface temperature in the warmest quarter (UT 10–15 °C; BT <10 °C) (Pullan and Brooker 2012). The prevalence of hookworm infection in LAC region has considerably decreased in 2003 with 50 million of cases when compared to 1994 where an estimated 100 million people were infected with hookworms, mainly due to national control activity and social and economical development (de Silva et al. 2003) (Table 2). Brazil has the highest prevalence of the cases (65%), with an estimate of 32.3 million cases, followed by Paraguay (3.2 million) and Guatemala and Colombia (3 million each) (Hotez et al. 2008). However, the real disease burden is not clear and still needs further elucidation as some countries have more information about the prevalence of hookworm infection than others. Moreover, some epidemiological studies covered co-infections with other species of soil-transmitted helminths (STH) or other parasites, with low or no information concerning the specific prevalence of hookworm infection.

According to PAHO, heavy infections are seen in Brazil, Colombia and Ecuador (PAHO 2011). In Honduras, the prevalence of hookworm infection was 15.9% of evaluated population, where 94% presented light infection and 3.9% had heavy infection. Moreover, in this study, 44.4% of infected children had mixed infection (hookworm + *Ascaris* = 2.6% or hookworm + *Trichuris* = 19.7%) and 26% had triple infection (hookworm + *Ascaris* + *Trichuris*). Monoparasitism, which accounted for hookworm only, was prevalent in 5.4% of the cases. Higher hookworm infection rates were associated with gender (boys are 2 times more likely to be infected than girls), the absence of toilets and low awareness about the disease. Associations with access to water, annual precipitation and hot temperature were also observed (Gabrie et al. 2014; Sanchez et al. 2013, 2014).

In Argentina, while Buenos Aires was described as a hookworm-free area, in other parts of the country, the prevalence varies between 0 and 90% with high incidence areas (Socias et al. 2014). In Bolivia, it is estimated that 11.4% of the population harbour hookworms, although in 60% of the surveyed area there are no parasitisms related to hookworms. The absence of parasites in a larger area might be due to the high range of altitude seen in country once association between high altitude and low infection was observed (Chammartin et al. 2013b). Colombia showed an interesting co-infection data where 35.82% of the malaria-infected people also had hookworm infection. There was also hookworm co-infection with *Trichuris trichiura*, *Ascaris lumbricoides*, *Giardia* sp. and many species of *Entamoeba*, *Iodamoeba*, *Endolimax* and *Blastocystis*. Hookworm co-infection cases with *Trichuris trichiura* and *Ascaris lumbricoides* were 5.62% and 11.94% of the cases, respectively (Fernandez-Nino et al. 2012). A study conducted in rural village of Guatemala showed that 10% of heavily infected people excreted 68–71% of the eggs present in the community. High prevalence of hookworm was seen in people between 10 and 60 years old with the peak of epg in people between 30 and 40 years old. Additionally, hookworm co-infection with *Ascaris lumbricoides* was

associated with the youngest group evaluated (1–9 years old) while co-infection with *Trichuris trichiura* was associated with individuals with age of 1–9 years old and more than 26 years old (Anderson et al. 1993).

In Panama, the prevalence of hookworm disease was shown in 5% of the children. Although a treatment protocol had taken place, the prevalence returned to the baseline levels 3 months after treatment. Moreover, 6 months after treatment, 41% of the houses evaluated had at least one child infected. Interestingly, children with heavy parasite burden before treatment presented heavy epg after treatment and reinfection. In Panama, low household wealth index (HWI), low household density, low maternal education and reduced access to infrastructure showed positive association with high hookworm prevalence (Halpenny et al. 2013).

Paraguay government considered hookworm as an important pathogen in 1920, when 98 % of the population was infected. Interestingly, a clear separation between hookworm species according to the position relative to Paraguay river was observed where west infections were dominated by *Ancylostoma duodenale* and east infections by *Necator americanus*. High prevalence (59%) of infection was detected in indigenous populations where 60% of the infected people had less than 1,000 epg and 9% more than 3,000 epg (Labiano-Abello et al. 1999). In Peru, a study showed hookworm prevalence in 1.2% of children between 7 and 14 months old, with positive association with age. Although the mean of epg in both groups (7–9 and 12–14 months old) was considered as light infection, the maximum epg found in the 7–9-month-old group was 13,780 (Gyorkos et al. 2011). In Brazil, several trials indicated that a light infection is prevalent in the country (epg range of 50–2,900). Variables like high vegetation index and precipitation were positively correlated with high infection rates, whereas high urban population and human development index (HDI) were associated with low hookworm infection. Moreover, areas of North and inland were considered areas of high risk while South, Southeast and Northeast are areas with low risk for hookworm infection (Scholte et al. 2013; Vercruysse et al. 2011).

Table 2 Estimation of the prevalence and number of cases of hookworm disease[a]

	Population (in millions)		Prevalence of infection (%)	Estimated number of infections (in millions)				
	Total	At risk		Age group (years)				
				0–4	5–9	10–14	≥15	Total
LAC	530	346	10	1	3	5	41	50
Total	4775	3195	15	21	50	85	584	740

[a]Modified from de Silva et al. (2003)

7 Clinical Manifestations of Hookworm Infection

After L3 penetration through the skin, the first symptom is an immediate pruritic erythematous papulovesicular rash (Brooker et al. 2004; Miller 1979). The severity of skin reactions vary according to primary or reinfection (Brumpt 1952), producing since a simple erythematous papules to severe papulation, vesiculation and generalised edema of the area and enlargement of local lymph nodes (Miller 1979). Sequential signs and symptoms are related to larval migration, usually followed by cough, sore throat and fever and the presence of larvae in the lungs, which led to transient but not severe fevers recorded frequently 2–4 weeks after infection (Hodes and Keefer 1945). During migration in the respiratory tract, upper respiratory signs and symptoms including coryza, pharyngitis, laryngitis, sensation of obstruction in the throat and pain when speaking and swalling were described (Miller 1979). Epigastric pain is related to the entry of hookworm (L3 entry) into the gastrointestinal tract and its development into an adult hookworm and is associated to depressed appetite, indigestion, colicky cramping epigastric pains, nausea, vomiting, flatulence (Miller 1979) and, in extremely severe cases, peptic and duodenal ulceration and cholecystitis (Brumpt 1952; Hodes and Keefer 1945).

After establishment in the final habitat, the laceration of intestinal mucosa and submucosa by cutting the buccal apparatus of the adult worm followed by blood suction and secretion of hydrolytic enzymes (Hotez and Pritchard 1995) and anticlotting agents (Stassens et al. 1996) result in intense intestinal blood loss. The major clinical manifestations of hookworm disease are the consequences of chronic intestinal blood loss (Hotez et al. 2004), mainly related to iron-deficiency anaemia and hypoalbuminemia (Stoltzfus et al. 1997). The hypochromic microcytic anaemia and eosinophilia coincides with the appearance of adult hookworms in the intestine (Maxwell et al. 1987) and are prominent during hookworm infection. While individuals with a light hookworm burden are usually asymptomatic, moderate or heavy hookworm burden results in recurrent epigastric pain and tenderness, nausea, exertional dyspnea, pain in the lower extremities, palpitations, joint and sternal pain, headache, fatigue and impotence (Anyaeze 2003). In addition, some individuals develop an abnormal appetite for non-nutritive substances and ingest soil, clay, chalk or sand (a phenomenon known as pica). Finally, anaemia and undernutrition may affect the labour productivity and wage-earning capacity of adult individuals (Guyatt 2000), as a direct consequence of the hookworm infection.

8 Approaches to Control and Elimination

The first programme of mass control treatment to eliminate hookworm disease was conducted under supervision of the Rockefeller Foundation and occurred in the early years of the twentieth century, initially at Southern USA and further in the LAC region. This programme included not only the medical treatment but also it

Table 3 Countries surveyed for hookworm infection by Rockefeller Foundation (1914–1925) and subsequent surveys by other workers[a]

Country	Year	% Infected population
Antigua	1916–1917	15.7
	1981	3.9
Bahamas	1979	0
Belize	1979	46.8
	2004	55
Cayman Island	1917	17.0
Dominica	1924	76.0
	1981	11
Grenada	1915–1917	65.2
	1982	5.8
Guyana	1914	62.3
	2002	28.2
Jamaica	1919–1925	50.0
	1994	0
Montserrat	1925	35.4
	1994	1.1
Nevis	1924	23.4
	1982	0
St. Kitts	1924	21.2
	1991	0
St. Lucia	1915–1922	62.7
	2010	11.9–13.2
St. Vicent	1915–1918	58.2
	1992	0.9
Trinidad	1915	75
	2000	0.9
Tobago	1924	50.7

[a]Modified from Tikasingh et al. (2011)

had an important focus on education about the disease and importance of proper use of toilets. The work of Rockefeller Foundation started in the LAC region in 1914 in a conjunction action with British Government to perform surveys and hookworm control in the British Colonies in LAC. Between 1914 and 1925, the programme for control allowed the massively reduction of hookworm infection rates and was further continued by the Governments of the Commonwealth Caribbean (Table 3) (Tikasingh et al. 2011).

Drug treatment is considered a simple process as it may be performed using a single dose of benzimidazole anthelminthic drug regardless of weight or age of the patient (400 mg of albendazole or 500 mg of mebendazole). Because of the simplicity of the treatment and its relatively low cost, WHO in 2001 set a target to treat 75% of school children by 2010 to control soil-transmited helminth (STH) infections. 5–20 years of mass drug treatment would be expected to control STH.

On the other hand, despite treatment, reinfection may occur often and efficacy of the therapy usually decreases over the years. The most efficient way to prevent hookworm infection still remains on the poverty reduction, increasing the HDI, sanitation and education (Bitran et al. 2009; Hotez et al. 2004).

In Brazil, the mass drug administration, different than observed for *Ascaris* sp. infection, was not effective to control the hookworm infection due to the constant reinfection after treatment, showing that prevalence and intensity of infection were usually similar to those values observed before treatment. Additional measures such as sanitation and healthy education along with socio-economic improvement were aimed in order to obtain better and permanent results (Camillo-Coura 1974) with an impact on the prevalence of infection (Moraes et al. 2004).

Concerning the treatment, school-based deworming programmes are not expected to reduce hookworm transmission significantly due to high hookworm intensities that occur in adults (Chan et al. 1997). Moreover, single-dose mebendazole often fails to remove adult hookworms effectively from the host's gastrointestinal tract (Bennett and Guyatt 2000). For the concern of possible anthelmintic drug resistance as observed for parasitic nematode infections of ruminants (Albonico et al. 2004) and the lack (or limited availability) of new anthelmintic agents (Utzinger and Keiser 2004), efforts have been made to develop new and complementary hookworm control tools, such as vaccine (Bottazzi 2014; Hewitson and Maizels 2014; Hotez et al. 2003, 2006) with a promising impact on control of this infection not only in the LAC region but worldwide.

9 Concluding Remarks

Despite the improvement of economic and social conditions in Latin America and the Caribbean region, in part due to the improvement of social welfare adopted by some countries, the LAC region still demonstrates an exacerbated social inequality, which is directly related to the prevalence of several neglected tropical diseases, among them hookworm infection. Some countries of the LAC region, at least the most affected by hookworm infection, have experienced a considerable economic growth over the past years reflecting the immense natural resources found in the region (oil, gas, mineral deposits and agricultural commodities). The social marginalisation observed in impoverished people and also largely in indigenous people (Montenegro and Stephens 2006) still has profound impact on neglected tropical diseases in the region and demonstrates the need of political changes in the LAC countries. In the past, hookworm infection was limited in rural areas; however, Latin America and the Caribbean have become the most urbanised regions in the developing world, increasing the number of poor living in urban areas (urbanisation of poverty) and exacerbation of socio-economic segmentation (USAID 2010). While urbanisation is not necessarily followed by proper sanitation, the impact of hookworm infection remains unclear and health policies concerning the specific control of hookworm infection have been highly relegated to rural areas. Finally, control of hookworm infection still relies on the use of few available drugs

and protocols of treatment, which should be largely improved by screening and development of new drugs and additional tools such as vaccines.

Acknowledgements The authors declare that there is no conflict of interest.

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Plasmodium vivax Malaria in Latin America

Alfonso J. Rodriguez-Morales, Adrián Bolívar-Mejía, Camila Alarcón-Olave, and Lauren S. Calvo-Betancourt

Contents

Abstract Morbidity and mortality burden of malaria, particularly in children, represents a public health threat also in those countries from regions such as South East Asia and Latin America with moderate-to-low levels of transmission. Malaria mortality in these areas has been mainly attributed to *P. falciparum*, but its direct and indirect burden has not been well defined. These patterns are increasingly causing concern in some countries. Although *P. falciparum* is justifiably regarded as a greater menace because of its high mortality, widespread antimalarial drug resistance and its dominance in Africa, malaria due to *P. vivax* has also placed significant burdens on health, longevity and general prosperity of large sections of

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_5

the human population. The debilitating impact of *P. vivax* malaria remains high, unacceptable and preventable for well over one billion inhabitants of the planet. Complicated and even fatal cases of malaria due to *P. vivax* have been increasingly reported in the medical literature. In Latin America, the burden of mortality due to malaria, although decreasing, is still significant. Powerful antimalarial campaigns in the region directed mainly to *P. falciparum* achieved a significant reduction of mortality in the last century. Evidence suggests that *P. vivax* can impose a significant burden of mortality that may have resulted from its interaction with other diseases and conditions, although this is largely neglected, compared to *P. falciparum*. These and other epidemiological issues are herein discussed, focusing in Latin America.

Keywords *Plasmodium vivax* • *Plasmodium falciparum* • Latin America • Caribbean • Malaria • Severe malaria

1 Introduction

Malaria is still the most important worldwide parasitic disease in terms of morbidity and mortality. Although its burden has decreased substantially, this complex disease, currently caused in humans by five species of *Plasmodium* (*P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi*), still kills roughly 2000 people per day, most of whom are children in Africa (Rodriguez-Morales 2008; White et al. 2014; Cox-Singh et al. 2008).

Besides *P. falciparum*, the most severe etiological agent of malaria, and its burden in Africa, other forms of disease located in other regions of world would be considered neglected. This is the case of *P. vivax* in Latin America. Just to go further in that asseveration, comparing research of *P. vivax* malaria in terms of scientific article output in a major database such as Index Medicus/Medline, up to January 2015, there are 6,447 articles published, whilst this figure is 31,210 for *P. falciparum* for the same period (almost five times higher for the last one).

Plasmodium vivax has been recently considered by multiple authors as a neglected parasite (Carlton et al. 2011; de Lacerda et al. 2007; Gething et al. 2012; Kute et al. 2012a, 2013; Mendis et al. 2001; Acharya et al. 2011; Mueller et al. 2009). Even more, in the past decade, new considerations have been made on its associated severity and mortality (Gulati 2012; Picot and Bienvenu 2009; Price et al. 2007; Singh et al. 2011; Vinetz 2006). Regardless of how this parasite is pernicious, recent data (including systematic reviews) demonstrate that the infection comes with a significant burden of morbidity and associated mortality (Baird 2013; Lacerda et al. 2012b, 2011). Although severe clinical manifestations, as classified by the World Health Organization (WHO) more than a decade ago (2000), occur more often in *P. falciparum* (World Health Organization 2000), these can be also seen, in an increasingly reported and recognized way, in *P. vivax* malaria, including brain malaria, severe anaemia, severe thrombocytopenia,

miscarriage and preterm delivery during pregnancy and acute respiratory distress syndrome (Kochar et al. 2005; Rodriguez-Morales et al. 2006c). Today, these manifestations of *P. vivax* malaria should not be erroneously considered as unusual, as some case reports, even in highly *P.* vivax-endemic countries such as Indonesia, still misleadingly report it (Fitri et al. 2013; Rodríguez-Morales et al. 2014a). In addition, is important to notice that very recenlty, 2014, World Health Organization (WHO) have recognized formally in a review of severe malaria definition, the ocurrence of severe and complicated disease in *P. vivax* infection (WHO, 2014).

Despite these clinical and biological considerations, a highly relevant and public health approach for discussion of malaria due to *P. vivax*, includes to consider, similar to other neglected diseases, that affects primarily poor people lacking access to affordable health care, trapping many in a relentless cycle of poverty because of loss of adult productivity and depletion of meagre financial reserves (Carlton et al. 2011), especially in Latin America (Franco-Paredes et al. 2007). Disease occurs in poor regions and poor countries, and its presence has a strong negative correlation with economic growth in families, communities and nations (Mendis et al. 2001).

Then, any innovative approach for control of disease should consider that after all the powerful anti-malaria campaigns, many perhaps directed primarily against *P. falciparum*, come into prominence, the residual burden of malaria of *Plasmodium vivax* should be also specifically addressed (Mendis et al. 2001). There is a consensus among malaria experts that eliminating *P. vivax* will prove more technically challenging than eliminating *P. falciparum*, and that there exist fewer tools and a weaker knowledge base from which to start an effective global elimination program (Carlton et al. 2011; Mueller et al. 2009).

The social and economic burden attributable to *P. vivax* derives from the fact that in an impoverished economy each episode absorbs relatively large amounts of cash for treatment, it diverts others of the family from work to attend the sick and it leads to the loss of 5–15 days of work or schooling by the affected patient (Mendis et al. 2001).

The present chapter seeks to address the current situation of malaria due *P. vivax* in Latin America, emphasizing the problems associated with the cases produced by this species, including some insights on its epidemiology, pathogenesis and clinical manifestations, also including the discussion on its severe manifestations as well as different preventive and therapeutic strategies that have been implemented to reduce its burden, considering the interaction of diverse social, cultural, environmental and economic factors.

2 Epidemiology

Worldwide, between 2000 and 2012, estimated malaria mortality rates fell by 42 % in all age groups and by 48 % in children under 5 years of age. If the annual rate of decrease that has occurred over the past 12 years is maintained, then malaria mortality rates are projected to decrease by 52 % in all ages, and by 60 % in children under 5 years of age by 2015; this represents substantial progress towards the World Health Assembly target of reducing malaria mortality rates by 75 % by 2015 (World Health Organization 2013).

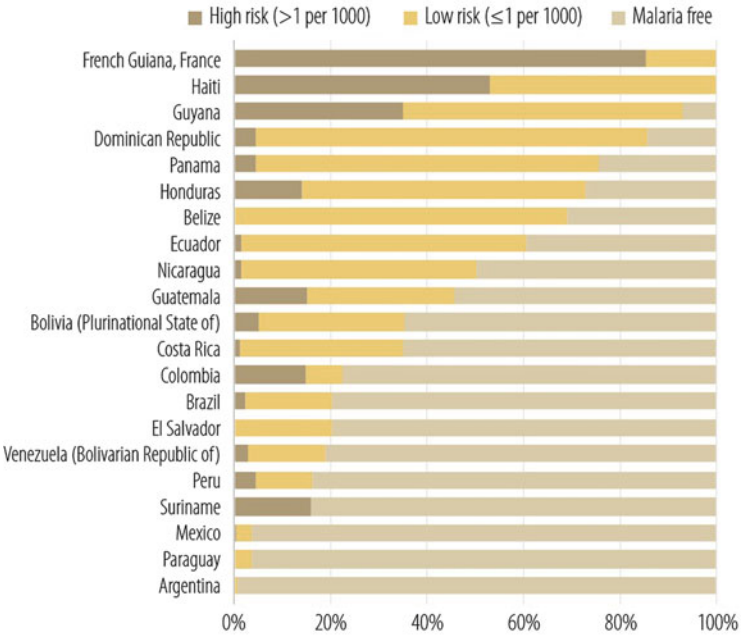

Fig. 1 Population at risk of malaria in the Americas (2012) [Reproduced from World Health Organization (2013)]

In the WHO Region of the Americas, about 120 million people in 21 countries are estimated to be at some risk for malaria, of which 25 million people are considered at high risk (Fig. 1). *P. vivax* is responsible for >80 % of malaria cases in 14 of the countries of the region (Fig. 2).

A significant achievement has been reached in the reduction of disease in the region. The number of confirmed malaria cases in the Americas has decreased by almost 58 %, from 1.1 million in 2000 to 469,000 in 2012. That residual burden of disease is mostly reported by three countries, which accounted for 76 % of cases in 2012: Brazil (52 %), Colombia (13 %) and Venezuela (1 %). Brazil and Colombia have decreased over 50 % of their burden either for *P. falciparum* or for *P. vivax* cases (Fig. 3) (World Health Organization 2013). Unfortunately, this is opposite in Venezuela, a country with a Human Development Index (HDI) of 0.748 (ranked 71° for 2012; Gross national income [GNI] per capita of US$11,475) (United Nations Development Programme 2012b; Rodríguez-Morales & Paniz-Mondolfi 2014b). During the same period (2000–2012), instead of reduction, this country reported an increase in malaria case incidence (Fig. 3). Guyana situation is similar (Fig. 3), but this country has a lower HDI (0.636, ranked 118 for 2012; GNI per capita of US$3,387) (United Nations Development Programme 2012a).

The number of cases reported in Venezuela in 2014, almost 90,000 is higher than in any year since the 1960s, after that Arnoldo Gabaldon led the campaign which achieved eradication of malaria in most of the endemic areas of the country (Gabaldon 1956; Rodríguez-Morales & Paniz-Mondolfi 2014b; Griffing

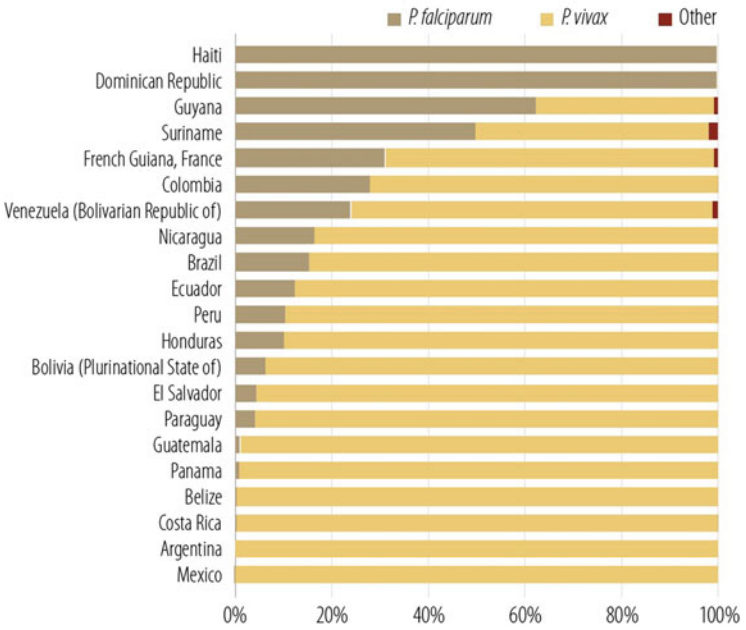

Fig. 2 Percentage of cases due to *P. falciparum* and *P. vivax* (2008–2012) [Reproduced from World Health Organization (2013)]

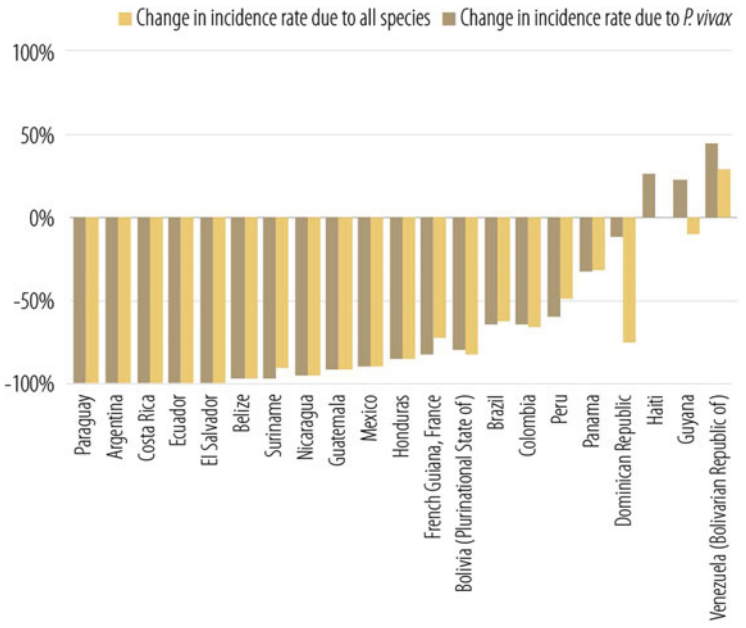

Fig. 3 Percentage change in incidence of microscopically confirmed cases (2000–2012)

et al. 2014). That number reflects a crude national rate of 297.4 cases/100,000pop (2.97 cases/1,000 pop) (but there are areas, such as Bolivar state in the southern area of the country with rates over 20 cases/1,000 pop). High incidence is concentrated in two states, Bolivar and Amazonas (Rodulfo et al. 2007; Rodríguez-Morales & Paniz-Mondolfi 2014b).

In Haiti, the number of confirmed malaria cases reported increased from 17,000 in 2000 to 25,000 in 2012 (249.8 cases/100,000 pop), but these numbers represent only a small proportion of cases that occur in the country (Raccurt et al. 2012). This may be explained by the undertaking of sufficient indoor residual spraying to cover 100 % of the population at high risk in 2012 (World Health Organization 2013).

Particularly in Venezuela, this should be further addressed by health authorities as well researchers on malaria, but this is not reflected in the recent literature from Venezuela (Rubio-Palis et al. 2013; Metzger et al. 2012), with some exceptions (Grillet et al. 2014; Zerpa et al. 2008), particularly assessing the *P. vivax* morbidity and mortality increase, especially in children (Rodriguez-Morales et al. 2008). Some authors have linked reemergence of malaria in the country to the phenomena of climate change (Delgado-Petrocelli et al. 2012). Also the study of population structures in malarial parasites has implications in control programmes and this could be part of the problems associated with surveillance, in molecular epidemiological assessments, at the final stages of malaria elimination (Chenet et al. 2012).

Regarding malaria deaths in this region, this fell from 390 in 2000 to 108 in 2012, Brazil and Colombia being responsible for 78 % of these reported deaths (World Health Organization 2013).

Even though a global progress in malaria cases control has been made in this region (Fig. 4), intensification of control efforts is needed in some parts of the region. Although, according to the World Malaria Report 2013, the mortality rate

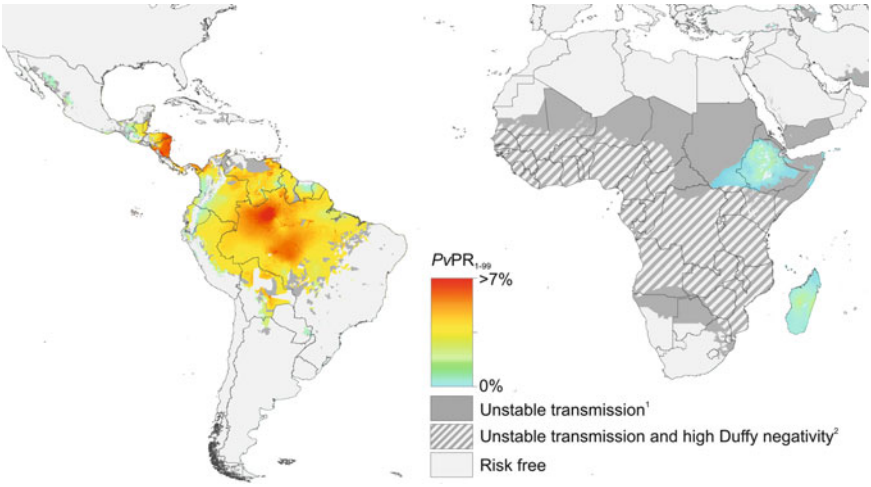

Fig. 4 Map illustrating prevalence of *Plasmodium vivax* in Latin America, 2010 [Reproduced from Gething et al. (2012)]

by malaria decreased 42 % in the whole population in the last 12 years, and it is expected to decrease another 52 % in the next 5 years, concern is brought due to the reports of severe malaria associated with *P. vivax* infection and due to the emergence of resistance to the drugs now used for the control of the disease (World Health Organization 2013).

3 Pathogenesis and Clinical Manifestations of *P. vivax* Malaria

To understand the clinical manifestations and different outcomes of *P. vivax* malaria infection, it is important to review some of the characteristics of the parasite, including a general overview of the pathogenesis of infection.

Human beings acquire the infection by the bite of female *Anopheles* mosquitoe species that inoculates microscopic sporozoites, which are the infective form in the parasite's life cycle. Once in the bloodstream, the sporozoites invade the hepatocytes and start their reproduction. It is estimated that a single sporozoite produces around 10,000–30,000 merozoites, resulting from asexual reproduction that takes around 48 h in the *P. vivax* infection ("benign" tertian malaria). The hepatocyte is invaded by merozoites which are called schizonts that bursts with the liberation of the merozoites into the blood and finally into the erythrocytes (White et al. 2014).

An intraerythrocyte parasite starts a series of changes in the red blood cells, like consumption of the cell contents and alterations in the cell membrane, which participates in the generation of anaemia which appears in both acute and chronic malaria infection. There are several hypotheses of the pathogenesis in the anaemia syndrome, being divided into two main groups (Quintero et al. 2011). The first one, the peripheral destruction of the red blood cells, happens after the invasion of the parasite into the erythrocytes, where they also multiply and finally cause the destruction of the red blood cells. Although this mechanism could explain the presence of anaemia, it is not enough to explain the low haemoglobin levels that patients develop. However, a simultaneous mechanism that could explain it has been raised. The parasite transports antigens into the infective erythrocyte that caused a deformation of the cell membrane, with the final opsonisation by antibodies, complement and macrophage activation. The second mechanism is a reduction or an alteration in the production of erythroid precursors, a theory that only partially explains it, due to the presence of inadequate production of reticulocytes and insufficient erythropoiesis (Quintero et al. 2011).

Once the humans are infected by this protozoan parasite, there are several factors that influence the clinical manifestations: the parasite, parasite–host interaction, host factors and also socio-economic conditions that seem to be related to a higher risk of developing anaemia (Quintero et al. 2011). After an incubation period of 12–14 days (White et al. 2014; Anstey et al. 2012), the host presents the prodromal period followed by fever. The prodromal period includes non-specific symptoms like headache, abdominal pain, fatigue and myalgias. It is described that after the prodromal phase, a non-fever phase occurs, followed by intermittent fever phase.

The periodic fever phase is also known as "paroxysm" that occurs after the rupture of schizont-infected red cells (Anstey et al. 2012).

Other symptoms include nausea, anorexia, headache, orthostatic hypotension, abdominal discomfort and diarrohea (Anstey et al. 2012). Another important symptom, but mostly seen in adults, is jaundice (White et al. 2014). Regarding respiratory symptoms, they have been associated with *P. vivax* malaria. Cough, dysphonia and bronchitis can occur in half of the patients with *P. vivax* malaria (Anstey et al. 2007).

A spectrum of disorders ranging from non-cardiogenic pulmonary oedema through acute lung injury to acute respiratory distress syndrome (ARDS) are well-recognized complications of *P. falciparum* infection and are associated with particularly poor outcomes, even if high dependency care is available; however, the reported cases of severe pulmonary complications in *P. vivax* malaria comprise a heterogeneous group of patients from many different parts of the world (Tan et al. 2008).

Fever and chills are cardinal symptoms in *P. vivax* malaria, particularly in children, as has been evidenced in paediatric studies in Venezuela, where these have been described in over 93 and 41 %, respectively (Rodriguez-Morales et al. 2006c).

Typically, *P. vivax* malaria has been associated with less mortality and complications compared to *P. falciparum* malaria, including anaemia in low degrees and smaller rates of mortality (Rodriguez-Morales et al. 2006d); however, these statements have been changed, due to new studies and cases that show several complications and fatal outcomes of *P. vivax* malaria (Rodriguez-Morales et al. 2006d; White et al. 2014), even showing that the trends in the number of deaths due to *P. falciparum* are decreasing and due to *P. vivax* are increasing, with a significant proportion occurring in children (Rodriguez-Morales et al. 2008).

3.1 Fever

In endemic areas, malaria is considered the first cause of fever in the population (White et al. 2014). After the prodromal symptoms, a continuous fever with daily exacerbations begins and finally there is an intermittent daily fever. The presence of parasitemia without fever in endemic areas is also reported (Anstey et al. 2012). Many potentially life-threatening infections cause fever; however, malaria remains as the most important overall cause of systemic febrile illness in tropical regions, which should be considered not only for people living in endemic areas but particularly for travellers visiting those areas (Wilson and Freedman 2007). Even more, although acute febrile illness is a key symptom of the disease, the adverse impact of *P. vivax* malaria, particularly on child health, goes beyond and could even influence child growth (Lee et al. 2012).

3.2 *Severe* P. vivax *Malaria*

Recently, *P. vivax* malaria has been associated with fatal outcomes and serious manifestations, particularly in observational studies (Anstey et al. 2012). More often, a large series reports that *P. vivax* malaria would be associated with severe and fatal disease both in adults and in children (Andrade et al. 2010; Rodriguez-Morales et al. 2008). All these case series include a variety of severe *P. vivax* malaria manifestations such as severe anaemia, respiratory distress, acute kidney injury, coma and shock (Anstey et al. 2012).

There are many risk factors that are related to severe malaria, paediatric patients have a high risk; especially children under 5 years have a greatest risk of severe *P. vivax* anaemia (Anstey et al. 2012; Rodriguez-Morales et al. 2008). Series in Indonesia have reported over 22 % of severe malaria in children (Tjitra et al. 2008). Unlike *P. falciparum* malaria, *P. vivax* malaria is generally regarded as a benign or non-fatal disease even though there have been several reports recently of severe disease and deaths associated with *P. vivax* malaria. These reports do not indicate, however, whether *P. vivax* is responsible for a significant proportion of malarial deaths. In the Indonesian series, one in 50 patients with malaria died; the risk of death was the same for patients infected with *P. falciparum*, *P. vivax* or both parasites (Tjitra et al. 2008).

Recent data from Venezuela assessing morbidity and mortality from malaria reported that among a total of 407 deaths, the most affected age group, 28.3 %, was patients under 10 years old, followed by 15.7 % in the group of 20–29 years (Rodriguez-Morales et al. 2008).

Another important risk factor that has been directly related to severe malaria and mortality is malnutrition (Berkley et al. 2009). Other co-morbidities related to fatal outcomes are HIV infection, diabetes, cirrhosis, pneumonia and congestive heart failure (Lacerda et al. 2012a).

3.2.1 Severe Anaemia

Is the typical manifestation of severe malaria (White et al. 2014), usually being normocytic and normochromic (Quintero et al. 2011) and defined as a haemoglobin (Hb) concentration less than 5 g/dl (World Health Organization 2013). This should be always directly measured, because it has been recently reported in large series of patients that the standard threefold conversion from haematocrit to haemoglobin underestimates the prevalence of anaemia and low levels of haemoglobin in children living in areas endemic not only for *Plasmodium falciparum* malaria but also for *P. vivax* malaria (Rodriguez-Morales et al. 2007b; Flores-Torres et al. 2011).

The degree and intensity of the anaemia are influenced by many factors like premorbid haemoglobin concentration, level of immunity and comorbid conditions (Anstey et al. 2012). In Venezuela, some data indicated that the frequency of

anaemia is even more frequent and severe for *P. vivax* compared to *P. falciparum*, when this occurs in *P. vivax*-predominant endemic malaria areas (Rodriguez-Morales et al. 2006d). In Latin America, anaemia generates an important burden, being the most frequent complication of severe malaria in Brazil, causing a significant increase in morbidity and mortality especially in children and in pregnant women (Costa et al. 2012).

3.2.2 Respiratory Distress

Pulmonary oedema is described as a complication of *P. vivax* malaria, with a better prognosis compared to *P. falciparum*. Pathogenesis is not well described, but it plays an important role in inflammation-mediated endothelial damage (White et al. 2014). It has been recently demonstrated that Brazilian patients with severe malaria and respiratory failure had elevated levels of inflammatory cytokines (Costa et al. 2012). Clinical respiratory failure is described to occur in 10–32 % of patients with severe anaemia and case fatality rate of 50–67 % of the patients (Andrade et al. 2010; Anstey et al. 2012). Respiratory distress and anaemia are commonly the most frequent manifestations of severe *P. vivax* infection reported worldwide (Anstey et al. 2012; Lacerda et al. 2012a; Rodriguez-Morales et al. 2006a).

3.2.3 Coma

Is considered a rare complication of severe *P. vivax* malaria, although increasing in its report. There are over 100 cases of adults and children with severe *P. vivax* infection and associated coma between 1921 and 2011. There is an association between thrombotic thrombocytopenic purpura and multiorgan dysfunction in severe malaria *P. vivax* infection and coma (Anstey et al. 2012).

3.2.4 Acute Kidney Injury

Is another important complication of severe *P. vivax* malaria commonly associated with multiorgan dysfunction, and is a risk factor for a fatal outcome (Andrade et al. 2010; Anstey et al. 2012). Four renal biopsies of four patients with severe *P. vivax*-associated acute kidney injury reported cortical necrosis and tubular necrosis (Kute et al. 2012b).

3.2.5 Thrombocytopenia

Occurs in around 24–94 % of patients with severe *P. vivax* malaria. One study in Venezuela studied the occurrence of anaemia and thrombocytopenia in a total of

78 children, finding that 58.8 % develop severe anaemia (platelets less than 60,000 cell/mm^3) (Rodriguez-Morales et al. 2006c).

3.2.6 Severe Malaria Due to *P. vivax* in Pregnancy

Effects on the Mother

Severe *P. vivax* infection is not commonly related to severe malaria in pregnant women. In the endemic areas, the most common manifestation in pregnant women is anaemia (Anstey et al. 2012). However, a majority of the studies in pregnant women have been conducted in Asia (Costa et al. 2012). In Latin America, especially in Brazil, the consequences of malaria during pregnancy have been studied, finding that *P. vivax* infection increased the risk of low birth weight, abortion and premature delivery (Campos et al. 2011; Costa et al. 2012; White et al. 2014).

Effects on the Foetus and Neonate

A reduction in birth weight is seen in around 70 % of the cases. Other complications include premature delivery and a greater infant mortality (Anstey et al. 2012).

Congenital malaria, although not frequently, has been reported. This consequence is more frequent in *P. falciparum* malaria, but also occurs in *P. vivax* infection (Orostegui-Pinilla and Rodriguez-Morales 2011). *Plasmodium vivax* infection can cause congenital malaria, having an approximate rate of 1.6 per 1,000 live births (Anstey et al. 2012; Poespoprodjo et al. 2011).

3.2.7 Other Severe Manifestations

Another manifestation includes jaundice, being most common in adults occurring in 36–57 %. Splenic rupture and bacteremia have also been reported (Anstey et al. 2012). There are also rare case reports of Acalculous cholecystitis, but only in adults (Curley et al. 2011) and a rhabdomyolysis case (Siqueira et al. 2010).

4 *Plasmodium vivax* Malaria in Brazil

Brazil is one of the most affected countries in Latin American by malaria, presenting different periods in its history of high frequency of transmission, which has led to the creation and implementation of multiple strategies in order to control this disease (Oliveira-Ferreira et al. 2010). Although Brazil is the country with high number of cases in the region, effective reduction has achieved a

significant clearance of disease, letting endemic areas mainly in the Amazon region (Fig. 4).

With a population of 198,370,000, in 2012, 2 % (4,570,000) of the inhabitants of Brazil are living in areas of high transmission (>1 case per 1,000 population), while another 18 % (35,800,000) live in an area of low transmission (0–1 cases per 1,000 population). The Amazon region represents 99.8 % of the reported cases (Fig. 1), although the *Anopheles darlingi* (main vector) is found in the 80 % of the country. It has been proposed that the predominant localization site of the disease in this region can be associated with different conditions that ultimately facilitate the transmission and limit the ability to control the disease (Oliveira-Ferreira et al. 2010; World Health Organization 2013).

Three *Plasmodium* species are responsible for the presentation of malaria in Brazil. Of these, *P. vivax* causes between 83.7 and 85 % of the cases, followed by *P. falciparum* with 15–16.3 %, *P. malariae* in the third place with only a few other cases reported.

From the 1960s decade, the Amazon region has remained one with the highest number of malaria cases in Brazil, having a similar behaviour the other neighbouring countries. At that time, population migration would be one of the main causes of the increase in cases filed; however, the implementation of measures aimed at vector control and early detection and management of the malaria cases and produces subsequently a decrease in the number of cases. However, in the late 1990s, the number of cases would have reached such alarming peak that The Brazilian National Programme for Malaria Control (NMCP for its acronym in portuguese), and the Brazilian government through the creation of a plan to intensify efforts aimed at controlling malaria (PIACM for its acronym in portuguese), managed to decrease the occurrence of malaria cases and associated morbidity and mortality, thus optimizing transmission control, which was reflected in a gradual decrease in the number of reported cases for about 4 years from 1999. However, multiple factors like an increase in the migratory movement, poor control of environmental factors, significant climate changes and the changes in agriculture and the decrease in the implementation of the measures that previously have been shown to be effective ultimately cause that in 2005 reappear an increase in the number of reported malaria cases in Brazil, a phenomenon which alerted health authorities who again stepped up efforts to prevent, control, diagnosis and early treatment of malaria cases, resulting in a new decrease in the presentation of cases since then to current date (Ferreira and Da Silva-Nunes 2010; Oliveira-Ferreira et al. 2010).

Although Brazilian malaria cases have been declining, there are some phenomena that led to still consider malaria an important public health issue. Among them are the appearance of new forms of severe clinical presentation associated with *P. vivax* infection, and the proportional increase of the disease in women and children, and worse clinical outcome of cases arising out of the Amazon region (Oliveira-Ferreira et al. 2010).

In the late 1980s, malaria cases in Brazil were practically in equal proportions to *P. vivax* and *P. falciparum*; however, with the improvements in the detection,

management approach and cases associated with P. falciparum, its participation as an etiological agent had a proportionate decrease, until only representing around the 15 % of the cases in our days, which seems to be positive because *P. falciparum* have a clinical course less favourable and are associated with a high risk of mortality (Oliveira-Ferreira et al. 2010; World Health Organization 2013). However, recently they have been reporting cases of severe malaria associated with *P. vivax* infection, a phenomenon for which there is still much to learn about and its alert was announced by WHO; even though 207 million cases of malaria occurred in the world during 2012, only 9 % have corresponded to a secondary infection with *P. vivax* (Alexandre et al. 2010; Oliveira-Ferreira et al. 2010; Raposo et al. 2013; World Health Organization 2013).

In Brazil, the reported cases with associated severe manifestations related to *P. vivax* malaria include anaemia, thrombocytopenia, pulmonary oedema, renal failure, autoimmune thrombocytopenic purpura and bleeding, dyspnoea, jaundice, liver dysfunction, vomiting and diarrohea (Alexandre et al. 2010; Lacerda et al. 2004; Oliveira-Ferreira et al. 2010; World Health Organization 2013). Although as previously mentioned, multiple studies remain to be done related to severe cases due to *P. vivax* malaria, it has been found that they are associated with the age of the patients and the presence of co-morbidities such as cardiovascular and metabolic diseases (arterial hypertension, coronary artery disease and diabetes mellitus) and poor nutritional status, these being last considered by the WHO as a determinant of great relevance (World Health Organization 2013).

Furthermore, although the total number of malaria cases has been declining, the proportion of affected women and children has been growing, increasing in prevalence from 2003 to 2008, from 34.9 to 38.6 % in women and 22–25.2 % in children (under 10 years), with factors associated with this relative increase in the presentation of cases in these two population groups not being established clearly (Oliveira-Ferreira et al. 2010).

While the Amazon region provides the highest number of malaria cases in Brazil, the course of the disease is worse in patients whose presentation is given outside that territory. As factors associated with this, it has been proposed as a less clinical suspicion by the medical group, having documented that those patients having malaria secondary fever in cities like Rio de Janeiro or in some states of Sao Paulo are initially focused as dengue cases. This is the reason why health authorities have been implementing training programs of malaria to the health professionals (Oliveira-Ferreira et al. 2010; Pedro et al. 2012).

While in Brazil malaria cases decrease continuously and the adequate control of the disease is closer to being a reality, the government has joined forces in order to ensure an adequate monitoring system that allows for complete and standardized data timely and with high quality, from which it could be easy to implement more effective measures. They actually have the SIVEP malaria database, which records all malaria cases nationwide, forming a source of information from which variables such as global coverage availability of preventive measures in the population and the opportunity in the diagnosis and treatment of detected cases can be obtained; however, not aware of the constant changes in the biology of the causative agent,

there is also promotion of new potential treatment options for malaria, due to the possibility of drug-resistant *Plasmodium* to the actual treatment options used in the national territory. For this, Brazil currently has 46 groups of highly trained researchers in the study of malaria, of which 30 are studying the chemo-resistance to therapies already available and developing new methods of drugs and 19 are studying the development of new malaria vaccines, this being a very promising scenario (Oliveira-Ferreira et al. 2010).

5 Colombia

Colombia was responsible approximately for 13 % of the total malaria cases reported in the region of the Americas during 2012 (World Health Organization 2013). Although this is a relatively low percentage of contribution in the region, it is noticeable that, while in other Latin American countries such as Peru and Ecuador, a decrease in malaria incidence has occurred during the last decade, in Colombia morbidity has remained high, with malaria cases fluctuating between 231,000 and 66,000 cases per year. During 2012, there was a rate of 1 case of *P. vivax* malaria per 1,000 habitants (World Health Organization 2013).

During 2010, a total of 117,108 diagnosed malaria cases were recorded, with Antioquia, Cordoba, Chocó, Guaviare, Vichada, Valle del Cauca and Amazon being responsible for most of the cases, with an Annual Parasitic Index (API, cases/1,000 pop) above the national average of 10.5 cases/1,000 population. The mentioned incidence reveals a 32.6 % increase in comparison to the cases reported during 2009. This increase corresponds to a seasonal epidemic transmission outbreak that coincided with a pattern of malaria transmission peak seen every 5 years period described in areas of low transmission. From the total, 70.8 % of the cases were caused by *P. vivax*, similarly to the proportion seen over the last decade where ~74 % of the cases were due to *P. vivax* (Chaparro et al. 2013). It is worthy to mention that one-third of the cases occurred in children under 15 years old; this leads to the loss of schooling days, and therefore the impoverishing cycle continues (Chaparro et al. 2013).

Complicated malaria was reported in 0.5 % of the cases caused almost equally by *P. vivax* and *P. falciparum*. Liver failure (39.2 %) and renal failure (26.8 %) were the most frequently reported complications. In a previous study done in Uraba, complicated malaria due to *P. vivax* was estimated to be 23.1 % having severe anaemia, trombocytopenia and hyperbilirubinemia as main complications (Arboleda et al. 2012). Mortality attributable to malaria in this study was 0.02 % and was produced in equal proportion by *P. vivax* (47.8 %) and *P. falciparum* (47.8 %), with most cases (69.6 %) occurring in patients aged 0–29 years, which is considered the economically active population of the country; therefore, the families of the affected patients are led to poverty as well as the whole (Chaparro et al. 2013).

Malaria also affects pregnant women in Colombia, causing increased morbidity and mortality for the mother and the child. The prevalence of gestational malaria has been estimated to be 9.1–14 % (thick smear, PCR) and is caused mainly by *P. vivax* (65 %); no congenital malaria has been observed in some series (Agudelo et al. 2013). A study done in Uraba, Antioquia, during 2004, reported 5 cases of severe neonatal *P. vivax* malaria having fever, pallor and haemoglobin levels compatible with severe neonatal anaemia as clinical manifestations; however, no one was screened for malaria, even though some of them had a history of gestational malaria and no one received adequate treatment; these cases evidence the need of improving malaria surveillance as well as systematic monitoring of infants at risk not only in this region but also in the whole Colombian territory (Pineros-Jimenez et al. 2008).

Risaralda is one of the departments with low burden of malaria; however, surveillance and periodic evaluation are required in order to improve control; a study done in this place during 2007–2009 found an incidence between 60.01 and 122.87 cases/100,000 population (annual parasitic index, API, 0.6–1.23 cases/1,000 population). *P. vivax* was responsible for 93.4 % of the cases; the mortality was 0.1 deaths/100,000 per year. The burden of malaria in this territory is explained by the climatic and social conditions of the region, where cases are focalized on more than 70 % in one single municipality in the north area of the department (Pueblo Rico). Therefore, reinforcement in control activities needs to be done (Rodríguez-Morales et al. 2012).

Colombia remains with significantly greater transmission when compared to other Latin American countries; however, it is still considered unstable with endemic–epidemic patterns and focal variables in different eco-epidemiological regions. This higher transmission may be explained by climatic, geographic and epidemiological conditions present in Colombia which are suitable for malaria transmission. Also population migration, illegal agriculture and mining appear to be growing as well as the presence of both legal military corps and insurgent troops contributes to the transmission (Chaparro et al. 2013).

However, transmission has decreased from ~200,000 cases/year to ~61,000 cases in 2012 (Chaparro et al. 2013), thanks to the control strategies implemented by the Colombian National Malaria Control Program in cooperation with the US National Institute of Health. Besides, a project sponsored by the Global Fund for AIDS, tuberculosis and malaria between 2005 and 2010 has significantly contributed to a decline in malaria transmission, particularly in bordering departments such as Nariño in the south-western region of Colombia.

Nowadays, a new Global Fund project is being conducted in the five departments that contribute >80 % of malaria cases in Colombia: Cordoba, Antioquia, Chocó, Valle del Cauca and Cauca. These strategies are likely to force malaria incidence downwards in the following years (Chaparro et al. 2013), and achieve a 75 % decrease in case incidence by 2015 (World Health Organization 2013).

6 Venezuela

In Venezuela, the proportion of malaria cases due to *P. vivax* has decreased from 80 % in 2000 to approximately 70 % in 2012, in which approximately 1.3–1.4 cases per 1,000 population were reported during this year (World Health Organization 2013). However, the total incidence of malaria during 2014 was almost 90,000 cases, evidencing an increase in the incidence when compared to 2000 (World Health Organization 2013; Rodríguez-Morales & Paniz-Mondolfi 2014b). Control activities are inefficient and some malaria states programs are in fact no longer effectively working, for malaria, as well for other vector-borne diseases, such as dengue and chikungunya (Rodríguez-Morales & Paniz-Mondolfi 2014b; Rodríguez-Morales & Paniz-Mondolfi 2015).

There are three regions of malaria transmission in Venezuela: the meridian region constituted by the states of Bolivar and Amazonas; the oriental region represented by the states of Sucre, Delta Amacuro and Monagas and the Western region that covers the states of Barinas, Portuguesa, Tachira, Mérida and Apure (Rodriguez-Morales et al. 2006b).

The burden of disease associated with malaria infection is mainly focused in just three of these states: Bolivar, Amazonas and Sucre; first two are border states with Brazil, where more than 90 % of the 276,928 cases registered in Venezuela during 1995–2004 occurred, *P. vivax* being responsible for the 85.5 % of the cases occurred during 2004 (Rodriguez-Morales et al. 2008, 2006a). During this studied period, 407 patients died from malaria in Venezuela [case fatality rate (CFR) of 1.47 % period range from 0.8 to 3.1], being *P. vivax* responsible for only 7.37 % (30) of the deaths (Rodriguez-Morales et al. 2008) with almost one-third of deaths occurring in children under 10 years old. In 2005, 45,328 cases (86.8 % *P. vivax* and 12.4 % *P. falciparum*) were reported, 84 % of them occurring just in two states, Bolivar (69 %) and Amazonas (15 %) (Rodriguez-Morales et al. 2007a). These territories constitute the source of infection and spread of *Plasmodium* species within Venezuela (Rodriguez-Morales et al. 2006b).

Historically, population movement has contributed to the spread of malaria by importation of *Plasmodium* species and subsequent local transmission by local mosquitoes; this phenomenon was responsible for 3.8 % of the malaria cases presented during 1987–1998, *P. vivax* being responsible for 91 % of them (Rodriguez-Morales et al. 2006b).

The global index of recurrence due to *P. vivax* infection has been estimated to be 27.7 % in a study done in the state of Sucre, in which recurrence occurred in 13 of 47 patients, mostly before day 80 (Barrera et al. 1999). All these patients presented with no complicated malaria due to *P. vivax* and received the curative malaria treatment contemplated by WHO (chloroquine 25 mg/kg administrated in 3 days, and primaquine 0.25 mg/kg/day during 14 days). In other South American countries, studies made in non-endemic areas reported a recurrence global index between 6.5 and 24.5 % in Brazil, and 1.5 % in Colombia.

Clinical burden of *P. vivax* malaria is often manifested with fever, chills, headache (Rodriguez-Morales et al. 2006b, 2008) and mild haematological

abnormalities: anaemia and thrombocytopenia (Rodriguez-Morales et al. 2006b, 2008). The burden of anaemia due to P. vivax has been estimated to be 96 % in a study conducted during 2002 (Rodriguez-Morales et al. 2006d). Severe manifestations have also been described associated with *P. vivax* infections such as cerebral malaria, renal failure, circulatory collapse, acute respiratory distress syndrome with respiratory failure, jaundice, haemoglobinurea, abnormal bleeding, ARDS and severe anaemia and thrombocytopenia (Rodriguez-Morales et al. 2008). During pregnancy, malaria has been associated not only with maternal anaemia and low birth weight (Rodriguez-Morales et al. 2006e) but also with miscarriages or premature deliveries, as evidenced in a series of 12 pregnant women in which 2 of them presented miscarriage and 3 of them presented preterm delivery (Rodriguez-Morales et al. 2006e).

Regarding policies and control strategies, insecticide-treated mosquito net and long-lasting insecticidal net are distributed free of charge to all age groups since 2005, and indoor residual spraying is also recommended. Diagnostic test are free of charge since 1936 for all ages in the public sector. Artemisinin-based combination therapy is free for all ages in public sector since 2004 and primaquine is used for radical treatment of *P. vivax*, however G6PD test is not a requirement before treatment with primaquine, which may lead to cases of haemolysis (World Health Organization 2013).

Besides the mentioned strategies, education of people on malaria and the presence of health facilities, where treatment is readily available at affordable cost, close to villages, should be done, as occurred in the past by the Regional Offices of Malariology as important strategies that would reduce malaria morbidity and mortality significantly (Rodriguez-Morales et al. 2006c), which currently could be expected to reach over 60,000 cases in the next few years (2013–2014), if no significant interventions on transmission are done by the health authorities.

7 Peru

In Peru, malaria is a serious problem due to the increase in incidence and its extension to other regions, focusing mainly in the north coast and the Amazon. Between the years 1993 and 1999 there were more than 100,000 cases annually reported, and during 2000 a decrease in the number of cases was evidenced; however, during 2002 an increase of 28 % occurred; in the year 2004, 67,963 cases were notified (Rosas-Aguirre et al. 2010). Since 2008, a progressive decrease in the number of cases has been observed; however, in 2012 an increase occurred again reporting 31,701 malaria cases, evidencing that despite the efforts done by the government, malaria remains an important health problem in this country, particularly in the northern regions. Nevertheless, in 2015 a 75 % decrease in malaria case incidence is predicted to be achieved (World Health Organization 2013). *P. vivax* during the last 5 years has been responsible for more than 80 % of all the malaria cases, in 2012 being responsible for 87.3 % of the notified cases. In 2004, a study conducted in Trujillo, Peru, determined a familiar history of malaria in the last year

(OR = 4.62; 95 % CI 1.90–11.26), the presence of wetlands at 100 m or less from the house (OR = 4.61; 95 % CI 2.15–9.89) or the presence of an artesian wells (OR = 10.93; 95 % CI 3.45–34.58) as risk factors for having *P. vivax* malaria.

As there is a high proportion of malaria cases due to *P. vivax*, the emergence of chloroquine (CQ)-resistant *P. vivax* represents a serious health problem. In the Amazon region of Peru, two confirmed cases of CQ-resistant *P. vivax* have been reported, occurring in of 7- and 13-year-old residents of a relatively circumscribed area, 10–20 km to the west of the city of Iquitos. This situation is of obvious concern to the Peruvian Ministry of Health. However, no changes have been made in national malaria treatment policy since CQ continues to cure blood stage *P. vivax* parasitemia in the great majority of patients (Ruebush et al. 2003), but further studies should be done.

8 Conclusions

The novel strategies for malaria control introduced in some countries in South America, such as Suriname, have led to a significant decrease in the national malaria burden (Hiwat et al. 2012). Ecuador is another good example, with highly significant reductions in incidence over the last decade, with no cases in some extensive, before endemic, areas of northern region of the country (Cifuentes et al. 2013).

The challenge is to further reduce malaria using the available strategies as appropriate in the affected areas and populations (Hiwat et al. 2012). Elimination of *P. vivax* malaria in Latin America will require a thorough understanding of transmission dynamics and a dedicated investment in key effective interventions (Hiwat et al. 2012).

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Leishmaniasis in the Americas

Julio Vladimir Cruz-Chan, Jesus Valenzuela, and Eric Dumonteil

Contents

Abstract Leishmaniasis is a neglected tropical disease caused by kinetoplastid protozoan parasites belonging to the *Leishmania* genus. Infection causes a wide diversity of clinical manifestations, ranging in severity from asymptomatic infections, self-healing cutaneous lesions (cutaneous leishmaniasis (CL)), mucocutaneous lesions (mucocutaneous leishmaniasis (MCL)), diffuse leishmaniasis, and visceral leishmaniasis (VL) which can be lethal when untreated. *Leishmania* parasites are transmitted to vertebrate hosts through the bite of female sandflies of the genus *Lutzomyia* in the New World. We review here some of the key aspects of leishmaniasis in Latin America and highlight some of the specificities of the disease in the American continent. The diversity of vector and parasite species poses

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_6

additional challenges compared to the situation in the Old World. Indeed, this diversity implies that most tools for disease surveillance and control, including diagnostics, vector control interventions, therapeutic treatments, and vaccines, need to be adapted to ensure their efficacy. Further research is thus needed to optimize leishmaniasis control and surveillance in the Americas.

Keywords *Leishmania* • Sand fly • *Lutzomyia* • Visceral leishmaniasis • Cutaneous leishmaniasis • New world

1 Introduction

Leishmaniasis is a neglected tropical disease caused by kinetoplastid protozoan parasites belonging to the *Leishmania* genus, which includes at least 35 species of which 20 are considered pathogenic to humans (Fraga et al. 2013; WHO 2010). Infection with *Leishmania* parasites causes a wide diversity of clinical manifestations, ranging in severity from asymptomatic infections, self-healing cutaneous lesions (cutaneous leishmaniasis (CL)), mucocutaneous lesions (mucocutaneous leishmaniasis (MCL)), diffuse leishmaniasis, and visceral leishmaniasis (VL) which can be lethal when untreated (WHO 2010). Leishmaniasis has a global geographic distribution in 98 countries, affecting about 12 million people worldwide, with a yearly incidence estimated at 0.2–0.4 million cases of VL and 0.7–1.2 million of CL (Alvar et al. 2012; Pigott et al. 2014). It is thus considered as one of the most important public health problem in these endemic countries.

CL is the most frequent clinical form of the disease, representing 75 % of leishmaniasis total cases, and 75 % of its global incidence is distributed in Colombia, Brazil, Peru, Costa Rica, Iran, Syria, Afghanistan, Algeria, Ethiopia, and Sudan (Pigott et al. 2014). CL is responsible for 2,356,000 Disability Adjusted Lost Years (DALYs) in men, and 946,000 in women (Murray et al. 2005). On the other hand, 90 % of all VL cases are reported in Brazil, Ethiopia, Sudan, South Sudan, India, and Bangladesh (Pigott et al. 2014).

Leishmania parasites are transmitted to vertebrate hosts through the bite of female sandflies of the genus *Phlebotomus* and *Lutzomyia* in the Old and New World, respectively. About 70 sand fly species from nearly 900 existing species have been incriminated in *Leishmania* transmission (Ready 2013). Several domestic and wild mammals are involved as host reservoirs, including dogs, sloths, anteaters, raccoons, and opossums, as well as some small rodent species (WHO 2010).

Given the diversity of parasite, vector, and host species, the epidemiology of leishmaniasis is complex, with urban and rural transmission cycles involving different species often in the same geographical area (Pigott et al. 2014, Ready, 2013; Shaw 2002; Lainson 2010). We review here some of the key aspects of leishmaniasis in Latin America and highlight some of the specificities of the disease in the American continent.

2 Epidemiology of Leishmaniasis in the Americas

Leishmaniasis is widely present in the Americas, and particularly relevant in the tropical and subtropical regions of the continent, ranging from the southern US and Mexico to northern Argentina and Chile. There were a total of 66,941 cases of CL/year reported in recent years in the American region, which, accounting for underreporting, corresponds to an estimated incidence of 187,000–307,800 cases of CL/year (Alvar et al. 2012). Similarly, 3,662 cases of VL/year have been reported in the region, corresponding to an estimated incidence of 4,500–6,800 cases of VL/year (Alvar et al. 2012). Thus, the American continent accounts for around 25–30 % of global CL and 1.5–2 % of global VL cases and burden.

The incidence of the disease is rather heterogeneous, with some countries showing a high incidence while others do not report cases (Fig. 1). Countries with the highest incidence are Brazil, Peru, and Colombia, while Canada and the United States do not present autochthonous cases.

Leishmaniasis has been extensively studied in Brazil over the past years, due to its very high incidence. Over 90 % of VL cases of the American continent occur in Brazil and 85 % of these cases are distributed in the northeast of the country (Harhay et al. 2011). Only in the Maranhao state, an epidemiological survey in children showed a prevalence of over 19 % of infection by *Leishmania infantum chagasi* (Nascimento Mdo et al. 2005). Similarly, in the other northeastern states of Piauí and Bahía, the affected population was around 14–16 % (Werneck et al. 2002; Felipe et al. 2011). In the Amazon rainforest in the state of Ceará, a prevalence of 4.6 % of VL was reported in children <11 years old, while in the state of Pará, a prevalence of 3.4 % was measured in a cohort study of 946 individuals living in endemic areas (Evans et al. 1992). Due to the high prevalence and incidence of VL in the country, Brazil has established a VL Control and Surveillance Program, in which all suspected and confirmed cases must be reported (de Araujo et al. 2012). CL is also very frequent, with an estimated yearly incidence of 26,000 cases (Fig. 1).

In Colombia, both visceral and dermatropic clinical forms have been described, but cutaneous leishmaniasis is largely predominant in 99 % of total cases. There is an estimated incidence of over 17,000 CL cases/year. *Leishmania (Viannia) panamensis* is responsible for 54–80 % of cases in northern and southwestern Colombia. On the other hand, *L. (Viannia) braziliensis* is distributed in most of the country and is responsible for 10–30 % of CL cases. About 1–5 % of additional leishmaniasis cases are caused by *L. (Leishmania) mexicana* and *L. (Viannia) guyanensis* (Martinez et al. 2010). Peru also has a high incidence of CL, reaching about 6,500 estimated cases/year (Llanos-Cuentas et al. 2008) and the disease is present in over 70 % of the country.

Bolivia, Ecuador, Venezuela, and Central American countries show intermediate incidence rates (Fig. 1). Bolivia presents a predominance of CL, and only 10 cases of VL have been reported in the period of 1983–2006. In contrast, the incidence of CL was estimated in 2006 at 32.7/100,000 habitants (Garcia

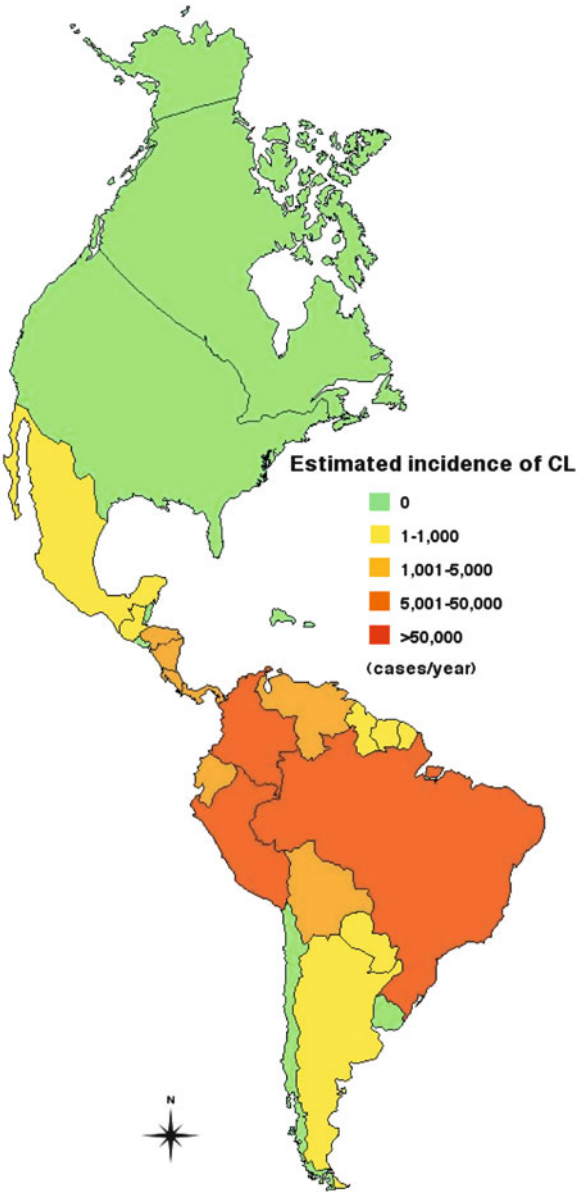

Fig. 1 Estimated incidence of CL in the Americas [Data were taken from Alvar et al. (2012)]

et al. 2009). Importantly, 90 % of cases were reported from only three of Bolivia's nine departments. The main causal agents involved were *L. (V.) braziliensis*, *L. (V.) amazonensis,* and *L. (V.) lainsoni*, with up to 85 % of total cases (Garcia et al. 2009).

In Ecuador, there is an estimated incidence of 3,000–4,500 cases of leishmaniasis per year, with CL found in most of the country, while MCL is rather restricted to the Amazon region (Calvopina et al. 2013).

VL is endemic in Venezuela, with an estimated yearly incidence of 0.2/100,000 people from 1995 to 2000, according to the National Registry of Leishmaniasis data (Feliciangeli et al. 2005; Convit et al. 2003; Zerpa et al. 2002). The main causative agent is *L. infantum chagasi*. The estimated incidence of CL is about 2,500 cases/year (Fig. 1).

Limited information is available for Central American countries. Cases have been described in patients from Guatemala and Belize, who present chronic ulcerative lesions characteristic of CL caused by *L. (L.) mexicana* (Blaylock and Wortmann 2012; Vinetz and Soong 2007; Demers et al. 2013). Panama seems to present the highest incidence, reporting up to 100 new cases/100,000 inhabitants per year, although incidence may still be underestimated (Miranda et al. 2009).

In spite of limited information, a significant incidence is also reported in the countries of Argentina, Paraguay, Guatemala, Mexico, Guyana, French Guiana and Suriname. In Mexico, both visceral and cutaneous leishmaniasis are present, mainly in the southern part of the country, but some cases have also been detected in northern states such as Sinaloa and Durango (Salazar-Mejia et al. 2010; Perez-Vega et al. 2009). Leishmaniasis is endemic in 22 of 31 Mexican states, but most cases have been found in the states of Veracruz, Tabasco, Chiapas, and in the Yucatan peninsula. Since 1995, only around 900 cases of both CL and VL have been reported per year (Bottazzi et al. 2011), but the epidemiology of the disease is poorly understood and controversial (Sanchez-Garcia et al. 2010; Andrade-Narvaez et al. 1990). VL is mostly present in the state of Chiapas, with 89 cases reported from the period of 1990–2006 (Pastor-Santiago et al. 2012).

In French Guiana, 100–350 CL cases/year have been reported in the past years, and the incidence appears to be significantly increasing, possibly in association with the development of ecotourism and mining in endemic forested areas (Rotureau 2006; Rotureau et al. 2007).

Uruguay, Chile, El Salvador, and Belize do not report any cases but are likely to have some disease present. For example, some sporadic cases have been described in Belize (Vinetz and Soong 2007), but the magnitude of *Leishmania* transmission to humans remains unknown. In the USA, canine leishmaniasis has been reported in several kennels, starting from an initial outbreak in 1999 in New York (Petersen and Barr 2009; Petersen 2009a), but there does not seem to have autochthonous human cases. The mechanisms of transmission of canine leishmaniasis in the USA remain largely unknown, although congenital transmission has been incriminated (Petersen 2009b; Boggiatto et al. 2011).

3 Clinical Forms and *Leishmania* Species

In Latin America, the clinical forms of leishmaniasis include CL and VL as mentioned above, but also disseminated, atypical cutaneous and mucocutaneous leishmaniasis. This diversity of clinical forms of the disease is strongly associated with the diversity of *Leishmania* parasite species. Indeed, while leishmaniasis is caused by only five species of *Leishmania* in the old world (*L. aethiopica,*

Table 1 Main *Leishmania* species and their common clinical manifestations

Genus	Subgenus	Species	Clinical manifestations
Leishmania	*(Leishmania)*	***donovani***	VL
		infantum	VL
		infantum chagasi	VL
		major	CL
		tropica	CL
		aethiopica	CL
		mexicana	CL (VL[a])
		amazonensis	CL, ADCL
	(Viannia)[b]	***braziliensis***	CL, MCL
		guyanensis	CL, MCL
		panamensis	CL, MCL
		naiffi	CL
		peruviana	CL
		colombiensis	CL
		shawi	CL

[a]Mostly in immunocompromized patients. Bold fonts indicate species for which the genome sequence is available
[b]The *Viannia* subgenus is exclusively present in the Americas

L. donovani, L. infantum, L. major, and *L. tropica*), a key characteristic of the American continent is the presence of a much greater diversity of parasite species, which include both the *Leishmania* and *Viannia* subgenus (Table 1). Species from the *Viannia* subgenus are endemic only in the new world. This diversity of species has important implications for disease epidemiology, control, and patient care. Indeed, it complicates vector control as well as diagnosis and treatment of patients in the Americas.

The species status of *L. chagasi* has been debated for many years, but recent molecular studies provided very strong evidence indicating that it should be considered as a subspecies of *L. infantum*, hence denominated *L. infantum chagasi*. Phylogeographic analysis indeed suggests a recent introduction of *L. infantum chagasi* in the new world, potentially from infected dogs brought to the Americas from Europe around 500 years ago during colonization (Marcili et al. 2014). This introduction was associated with a major bottleneck signature in *L. infantum chagasi* in the New World and a dramatic 1,000-fold reduction in the genetic diversity of this subspecies compared to *L. (L.) infantum* in the Old World.

CL can result from the infection with most of the species, including *L. (L.) mexicana, L. (L.) venezuelensis, L. (L.) amazonensis* as well as *L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis, L. (V.) shawi, L. (V.) naiffi, L. (V.) lainsoni, L. (V.) lindenbergui,* and *L. (V.) peruviana* (Shaw 2002; WHO 2010). Localized cutaneous lesions are usually characterized by a unique or a few round-to-oval well-delimited ulcerated lesions with elevated borders, which can persist for months or even years, leaving a scar which can have severe social implications according to its severity (Banuls et al. 1999, 2011; Guimaraes et al. 2009). There are important geographic variations in the frequency of the different *Leishmania* species found. For example, *L. (L.) mexicana* is the most frequent species present in southern

Mexico. In Panama, the most frequent species is *L. (V.) panamensis* while other species such as *L. (V.) amazonensis*, *L. (V.) colombiensis, and L. (L.) mexicana* are less frequent (Miranda et al. 2009). In Peru, *L. (V.) peruviana, L. (V.) guyanensis,* and *L. (V.) braziliensis* are the most frequent species infecting humans, although *L. (V.) guyanensis* is also present in the Andean region. The identification of *Leishmania* species is important for the diagnosis and treatment, as treatment failure with pentavalent antimonials can be very frequent, particularly in infections with *L. (V.) peruviana* and *L. (V.) braziliensis* (Llanos-Cuentas et al. 2008; Adaui et al. 2011). *Leishmania* species identification can be achieved using monoclonal antibodies, but these methods have now largely been replaced by PCR-based molecular approaches based on a variety of molecular targets (Tsukayama et al. 2009, 2013; Valencia et al. 2012; Fraga et al. 2012).

Atypical manifestations of cutaneous leishmaniasis have been reported in Bahia, Brazil, where 1,396 cases between 2005 and 2006 were studied and 1.3 % patients without other morbidities resulted with vegetative, verrucous, crusted, and lupoid lesions. *L. (V.) braziliensis* was isolated and responsible for atypical leishmaniasis in 8 of these patients (Guimaraes et al. 2009). In Costa Rica and Nicaragua, some patients infected with *L. infantum chagasi* also showed atypical cutaneous cases (Convit et al. 2005).

Disseminated leishmaniasis appears as multiple pleomorphic lesions in at least two separated parts of the body and it is characterized by limited T cell responses to *Leishmania* antigens and a high number of phagocytized parasites within macrophages (Turetz et al. 2002). Disseminated leishmaniasis is rather rare, as it occurred in 1.9 % of 2,206 cutaneous leishmaniasis cases reported from 1992 to 1998, and patients showed an initial and isolated ulcer lesion, which developed into >10 up to hundreds of acneiform, nodular, papular, and ulcerated lesions over the following days. The principal causal agent of disseminated leishmaniasis is *L. (V.) braziliensis* (Turetz et al. 2002) and it has been observed mainly in northeastern Brazil, but some cases have been reported in other countries where this species is present (Table 1).

More than a clinical form, the mucocutaneous or mucosal leishmaniasis is the involvement of the mouth, pharynx, and larynx following the extension of cutaneous lesions. MCL is characterized by early nose block and bleeding. Patients can show a septal perforation after days or months postinfection, nose skin can be thickened and hyperemic, with deformation of the nasal pyramid. Metastasis can occur in mucosal tissues of the mouth and the upper respiratory tract, resulting in severe mutilation and difficulties for feeding or breathing (WHO 2010; Lessa et al. 2012). Also known as "espundia," mucosal leishmaniasis occurs in 3 % of CL cases in Bahia, Brazil. In the Amazon region of Brazil, mucosal leishmaniasis cases are often caused by *L. (V.) braziliensis* in 2/3 of the cases, while *L. (V.) guyanensis* is responsible for 1/3 of the cases (Guerra et al. 2011). Mucosal leishmaniasis has also been reported in Bolivia and Peru (WHO 2010; Lessa et al. 2012).

The visceral form (VL) is exclusive of *L. infantum* infection in the new world and its subspecies *L. infantum chagasi*. It is characterized by liver and spleen

involvement, and it is often fatal if not treated. The main symptoms associated with an unfavorable prognosis of VL include jaundice, thrombocytopenia, hemorrhage, diarrhea, severe neutropenia, and dyspnea, and the associated factors are HIV co-infection, age <5 and age >40–50 years, and bacterial infections (Belo et al. 2013). Tubuloglomerular dysfunction and renal inflammation have also been observed in some VL patients, suggesting that renal damage may also be part of the clinical evolution of VL (Silva Junior et al. 2014). Although Brazilian government efforts are directed toward early diagnosis and treatment, the fatality rate reported for VL was estimated to be 7 %, and in Belo Horizonte, Mina Gerais, it reached 12.6 % during the years 2002–2009 (de Araujo et al. 2012). HIV co-infection is also a growing concern, as it leads to a much more severe VL outcome (van Griensven et al. 2014; Lindoso et al. 2014). Other species such as *L. (L.) mexicana* can also cause VL, particularly in patients with low immune status (Ramos-Santos et al. 2000).

Following the sequencing of *L. (L.) major* genome in 2005 (Ivens et al. 2005), the complete genomes of 17 additional *Leishmania* species and strains are now available, including for *L. (L.) donovani, L. (L.) infantum, L. (L.) mexicana, L. tarentolae, L. (V.) panamensis,* and *L. (V.) braziliensis*. It is expected that these sequences and databases will allow a large variety of studies to further understand the pathogenesis and biology associated with the different species of *Leishmania* (Table 1).

4 Sand Fly Vectors of *Leishmania* Parasites in the Americas

A large diversity of sand fly vectors is present in the Americas, and they have adapted to a variety of habitats throughout the continent. Most species are associated with sylvatic habitats, but some have adapted to peridomestic habitats as well. Figure 2 summarizes the major sand fly species that have been incriminated as vectors of *Leishmania* in the Americas.

In contrast to the rather good knowledge of vectors in the Old World, much less is known about *Leishmania* vectors in the New World. For example, while a few vector species have been established for the transmission of *L. (L.) mexicana*, *L. (L.) infantum*, *L. (V.) braziliensis*, *L. (V.) guyanensis,* and *L. (L.) amazonensis*, the sandfly species associated with *L. peruviana*, *L. panamensis*, *L. shawi*, *L. Lainsoni*, *L. colombiensis*, *L. naiffi,* and *L. venezuelensis* transmission are still not clearly established (Ready 2013). A number of sand fly species are suspected vectors, but many await confirmation.

As can be seen, *Lu. longipalpis* is the most widespread and predominant vector of *Leishmania* (Fig. 2). It is considered the main vector for *L. infantum* in Brazil, where it has been able to adapt to the peridomestic habitat, possibly in association with environmental changes (Lainson and Rangel 2005). *Lu. Longipalpis* is also

Fig. 2 Diversity of sand fly vectors of *Leishmania* in the Americas. Only demonstrated vectors are indicated. Bold fonts indicate the most epidemiologically relevant species. Additional species of sandflies are also suspected to contribute to *Leishmania* transmission but are not indicated

present in Bolivia, Colombia, Venezuela, various parts of Central America, and to a lesser extent in Mexico. In some instances, such as in Panama, *Lu. longipalplis* has been found but no case of VL has been reported (Miranda et al. 2009). *L. infantum* infection rate can be up to 19 % for *Lu. Longipalpis,* but other sand fly species such as *Nyssomiya intermedia* and *Ny. Whitmani* also present high *L. infantum* infection

rates in Brazil (Saraiva et al. 2010), and *Lu. pseudolongipalpis* has also been proposed as a vector for *L. infantum* (Feliciangeli et al. 2005).

Important vector species for dermotropic *Leishmania* parasites include *Lu. ovallesi*, which is widely distributed in Guatemala, Belize, Panama, Colombia, and Venezuela (Fig. 2). It presents anthropophilic habits and shows high susceptibility to parasite infection, and it is considered the main vector of *L. (V.) braziliensis* in Venezuela (Nieves et al. 2012). *Lu. olmeca* and *Lu. cruciata* are the principal vectors of *L. (L.) mexicana* in Mexico and America Central (Pech-May et al. 2010). *Lu. panamensis*, *Lu. trapidoi*, *Lu. ylephileptor*, *Lu. gomezi,* and *Lu. sanguinaria* are incriminated in *L. panamensis* transmission. In the USA, *Lu. shannoni* and *Lu. vexator* are present, but seem to participate only in zoonotic transmission cycles.

This extensive diversity of sand fly species involved in parasite transmission to humans in the Americas has important implications. First it makes vector control very challenging, given the diversity of ecological niches and habitats implicated for the different sand fly species. Second, it also complicates the study of the role of sand fly saliva in Leishmania pathogenesis. Indeed, following pioneering studies with *L. (L.) major* and *Phlebotomus papatasii*, an Old World vector (Belkaid et al. 1998; Kamhawi et al. 2000), it is now clearly established that while the primary role of salivary proteins is to facilitate sand fly blood feeding, an important secondary property is to modulate the host immune response and the outcome of *Leishmania* infection (Kamhawi et al. 2000, 2014). Protection against *Leishmania* may be obtained following exposure with specific sand fly salivary proteins, and these have thus been proposed as a vaccine component against *Leishmania* parasites. In the Americas, most studies have focused on *Lu. longipalpis*, given its epidemiological relevance (Kamhawi et al. 2014), and some studies have highlighted some level of antigenic variability in key salivary proteins such as maxadilan (Milleron et al. 2004). The immune response to salivary proteins may also be used as a biological marker of exposure to sand fly bites in epidemiological studies (Souza et al. 2010). However, much less is known about the repertoire of salivary proteins from other species and their biological properties, although recent studies are beginning to unravel some information on the saliva of a variety of sand fly species, including *Lu. intermedia* (Weinkopff et al. 2014) and *Lu. ovallesi* (Nieves et al. 2012).

5 Reservoir Hosts of *Leishmania* in the Americas

A reservoir host is considered to be responsible for the long-term maintenance of circulating *Leishmania* parasites. Humans are rather considered to be incidental hosts, who may in some cases be involved in parasite transmission, but are not considered essential to complete transmission cycles.

In southern Texas *Neotoma micropus* is one of the most common rodent species which is associated with cactus vegetation where *Lu. anthophora* is present, and at least 9 % of the rodents are found positive to *L. (L.) mexicana* (Ashford 1996). In

Mexico, small rodents such as *Ototylomys phyllotis* and *Peromyscus yucatanicus* have been incriminated as reservoirs for *L. (L.) mexicana* parasites (Van Wynsberghe et al. 2009). Sloths and anteaters have been reported to be infected with *L. (V.) guyanensis* and *L. (V.) panamensis*, and may serve as reservoirs for these species, as well as opposums for *L. (V.) guyanensis*, *L. (L.) infantum,* and *L. (V.) peruviana*; and raccoons may serve as reservoirs for *L. (V.) panamensis* parasites (WHO 2010).

However, domestic dogs (*Canis familiaris*) are considered the most important domestic reservoir of *Leishmania* parasites in most of its geographic distribution, including the Americas. Dogs have been found infected with *L. infantum*, *L. tropica*, *L. major*, *L. (L.) mexicana,* and *L. (V.) braziliensis* (Ashford 1996). Canine infection with *Leishmania* spp., as in humans, can thus lead to VL or CL clinical forms, although many animals may remain asymptomatic as well. In peridomestic transmission cycles, dogs play a major role in attracting sandflies around human dwellings as demonstrated in southern Brazil, where the presence of infected dogs increases the risk of human infection 4.39 times (CI: 1.37–13.45) (Membrive et al. 2012). *L. infantum chagasi* infection rates can be very high in dogs, reaching nearly 50 % in Maranhao, or even 67 % in Sao Luis, Brazil (Felipe et al. 2011). While it is clearly established that dogs are the main reservoirs of *L. infantum chagasi* in many regions (Moreno and Alvar 2002; Baneth et al. 2008), their role in the transmission of cutaneous *Leishmania* species is not well understood. The observation of long-lasting skin ulcer lesions and a high susceptibility of dogs from Argentina suggests that they could act as reservoirs for other *Leishmania* parasites species (Padilla et al. 2002; Cruz-Chan et al. 2014). This has important implications for the definition of epidemiological control measures of this important reservoir. Indeed, the massive euthanasia of infected dogs in Brazil has been strongly discussed and has had a questionable efficacy to reduce infection rate in humans (Moreira et al. 2004; Grimaldi et al. 2012). Thus, alternative control strategies, including dog vaccination still need to be considered (Otranto and Dantas-Torres 2013; Palatnik-de-Sousa 2012). A few canine vaccines against VL are available in some countries, such as Brazil, and while they are highly immunogenic, their protective potential is still debated (Fernandes et al. 2014; Wylie et al. 2014). Further evaluation of these vaccines, as well as their improvement, is thus needed for an optimal control of canine leishmaniasis, and as for a human vaccine, these need to take into account the diversity of *Leishmania* species circulating in the region.

6 Concluding Remarks

Leishmaniasis remains a significant neglected disease in the Americas, with a rather high incidence in many regions and countries. Importantly, the diversity of vector and parasite species poses additional challenges compared to the situation in the Old World where leishmaniasis is also highly endemic. Indeed, this diversity

implies that most tools for disease surveillance and control, including diagnostics, vector control interventions, therapeutic treatments, and vaccines, need to be adapted to the species involved to ensure their efficacy. Further research is thus needed to optimize leishmaniasis control and surveillance in the Americas.

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Fascioliasis

S. Mas-Coma, M.A. Valero, and M.D. Bargues

Contents

Abstract Fascioliasis in Latin America is caused by *Fasciola hepatica*. Animal fascioliasis is distributed throughout. Human infection occurs in many countries, mainly Cuba, Mexico, and all Andean countries. Peru is the country where more people are affected, mainly in altitude areas. The Northern Altiplano, in Bolivia and Peru, is the area with higher prevalence and intensities in humans. Children and females are the most affected. Cattle and sheep are the main reservoirs throughout. Pigs and donkeys play an additional reservoir role in human endemic areas. Snail vectors belong to the *Galba/Fossaria* group of lymnaeids, excepting *Pseudosuccinea columella*. Human fascioliasis in Latin America includes hypoendemic, mesoendemic, and hyperendemic situations, human epidemics in both human and nonhuman endemic areas, and other areas with authochthonous

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_7

isolated cases and imported cases. The altiplanic and valley patterns at high altitude and the Caribbean insular pattern are the most important transmission patterns. Different freshwater and terrestrial vegetables, local traditional beverages, and water drinking have been reported as human infection sources. Pathology and clinical manifestations in Latin America do not differ from the main pictures known elsewhere, including from no symptoms up to death. Diagnosis mainly relies on stool and serological techniques. Triclabendazole is of choice for human treatment, although resistance to this drug has already been reported in South America, including even a human endemic area. The large WHO control initiative is based on the costless availability of triclabendazole. Successful pilot action in Bolivia and Peru furnished the base for the present mass treatments of children.

Keywords Human fascioliasis • *Fasciola hepatica* • Latin America • Livestock • Animal reservoirs • Lymnaeid snail vectors • Geographical distribution • Transmission patterns • Epidemiological situations • Disease burden • Human infection sources • Pathology and major manifestations • Diagnosis • Treatment • Control

1 Introduction

This food-borne trematodiasis is a great veterinary problem of worldwide distribution. In the last two decades, many surveys have also shown it to be an important public health problem as well (Chen and Mott 1990; Mas-Coma et al. 1999a, 2009a), including estimations of 2,4 million, up to 17 million people, or even higher depending on the hitherto unknown situations in mainly Asia and Africa (Mas-Coma 2004). Many human fascioliasis endemic areas have already been described and the number of human case reports is increasing in many countries of the five continents, comprising mainly developing countries (Mas-Coma 2005; Mas-Coma et al. 2005, 2009a, 2014a), but also developed countries (Arjona et al. 1995).

Moreover, studies on pathogenicity have demonstrated that this disease may be highly pathogenic in humans throughout its long biliary chronic phase, and not only in its invasive acute phase as hitherto considered (Valero et al. 2003, 2006a, 2008), including impressive clinical pictures, high pathogenicity, many sequelae, and a higher mortality rate than the one usually noted (Mas-Coma et al. 2014b). Research on immunity aspects has also shown that fasciolid flukes downregulate the host's immune response during both the early phase of infection (Brady et al. 1999) and the chronic phase (Girones et al. 2007). A consequence of liver fluke infection is the suppression of immune responses directed against concurrent pathogenic infections. The synergistic capacity of fasciolids in coinfection with other pathogenic agents is well known, immunological responses to pathogen antigens being

markedly suppressed and concomitant infection being exacerbated following fascioliasis infection (Esteban et al. 1999, 2002, 2003; Gonzalez et al. 2011; Zumaquero-Ríos et al. 2013).

Additionally, results of recent research showing that human fascioliasis is pronouncedly influenced by climate change and global change add concern on the present situation of this disease in many endemic areas (Mas-Coma et al. 2009b; Afshan et al. 2014).

Such a worrying global scenario underlies the decision to consider fascioliasis an important human parasitic disease henceforth (Mas-Coma et al. 1999b) and include it as a food-borne trematode disease priority within the agenda of the World Health Organization (WHO 2013).

2 The Causal Agent: Systematics, Phenotype, and Genotype

This parasitic disease is caused by two digenean trematodes, *Fasciola hepatica* of worldwide distribution and *F. gigantica* restricted to given regions of Africa and Asia. In the Americas, only *F. hepatica* is present. Two other species of Fasciola were described in the Americas some time ago, namely *F. californica* from the lymnaeid *L. bulimoides* in California and adult experimentally obtained in the rabbit, and *F. halli* found in the liver of cattle and sheep in Texas and Louisiana, transmitted by the lymnaeid *L. bulimoid*es and experimental adults obtained in sheep, although both fasciolids were later synonymized with *F. hepatica* (Mas-Coma et al. 2009a).

Adult worms have a leaf-shaped body, with a broadly pointed posterior end. The two suckers are relatively small and located close to one another in a cone-like anterior extension of the body. The pharynx is well visible. The intestinal caeca are long, reaching the posterior end of the body and presenting a large number of lateral branches. The two branched testes are located in a longitudinal tandem, within the second and third fourth of the body. The cirrus pouch, containing a protrusible spined cirrus, is prominent, preacetabular, and opening in a postbifurcal genital pore. The branched ovary is pretesticular and dextral. The vitellaria extend bilaterally up to the hindbody. The short uterus is located between the ovary and the caecal bifurcation.

The adult stage of *F. hepatica* has a maximum length of 29.0 mm and a maximum width of 14.1 mm (Fig. 1) (Periago et al. 2006), although its morphometric characteristics vary according to the different definitive host species (Valero et al. 2001). Two phenotypic patterns could be distinguished in *F. hepatica* adult size in Andean endemic areas: the valley pattern (Cajamarca and Mantaro, Peru) and the altiplanic pattern (Northern Altiplano, Bolivia). Results showed that the Andean valley population presented a phenotypic homogeneity with European standard populations. The Altiplano population showed a large size range with a pronouncedly lower minimum size indicating that uterus gravidity is reached at a

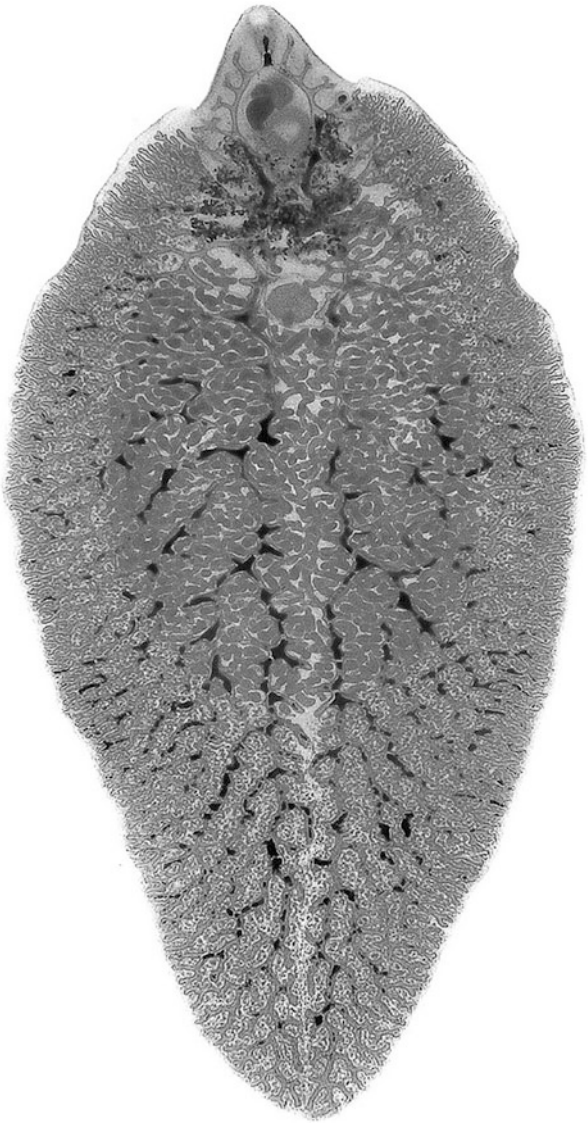

Fig. 1 Adult stage of *Fasciola hepatica* found in a biliary canal of cattle. Note marked shoulders and leaf-shaped body (original S. Mas-Coma)

size lower than in valley populations. The results of this study demonstrated that there is no apparent relationship between the shape of fasciolid adults with regard to the difference in altitude or geographical origin and that allometry-free shape appears as a more stable trait than size in fasciolid species (Valero et al. 2012a).

The eggs of *F. hepatica* are operculated, ovoid, yellow, and nonembryonated when laid (Fig. 2). Their measurements also vary depending on the definitive host species. They are 100.6–162.2/65.9–104.6 μm in humans and 73.8–156.8/58.1–98.1 μm in animals (Valero et al. 2009).

Fig. 2 Egg of *Fasciola hepatica* found in stools of a human patient. Note that fasciolid eggs are still unembryonated when laid and shed with feces (original S. Mas-Coma)

In a wide multicountry genotyping study in different continents, within the nuclear ribosomal DNA (rDNA) operon of *F. hepatica*, the 432-bp-long ITS-1 appeared to be fully uniform (only one haplotype FhITS1-A distributed everywhere), whereas up to four haplotypes of the 364-bp-long sequence of the ITS-2 could be distinguished (FhITS2-1 to 4), of which FhITS2-1 and FhITS2-2 have been found in Latin America: FhITS2-H1 in Peru, Argentina, Chile, Bolivia, Venezuela, Ecuador, México, and Uruguay and FhITS2-H2 in Peru, Argentina, Bolivia, Mexico, and Uruguay (Mas-Coma et al. 2009a).

In the mitochondrial DNA (mtDNA) of *F. hepatica*, a total of 69 different haplotypes of the 1533-bp-long *cox*1-coding gene (Fh*cox*1-1 to 69) and 23 different haplotypes in the corresponding 510-aa-long aminoacid COX1 protein (FhCOX1-1 to 23) were found in this worldwide study. Of the 23 COX1 protein haplotypes, one is the most abundant and present in all countries studied, whereas several countries such as Argentina, Bolivia, Peru, and Mexico present exclusive haplotypes not detected in any of the other countries studied. In the same mitochondrial genome, a total of 51 different haplotypes of the 903-bp-long *nad*1 coding gene (Fh*nad*1-1 to

51) and 15 different haplotypes in the corresponding 300-aa-long aminoacid NAD1 protein (FhNAD1-1 to 15) were found in the same study. Of the 15 NAD1 protein haplotypes, five were exclusive for Argentina, two for Bolivia, two for Peru, one for Mexico, and another for Europe (Spain and Poland). The other haplotypes were shared by different countries (Mas-Coma et al. 2009a).

3 Parasites Life Cycle and Disease Transmission

The two-host life cycle of *F. hepatica* follows a transmission pattern which takes about 14–23 weeks and comprises four phases (Mas-Coma and Bargues 1997; Mas-Coma et al. 2003):

(a) The definitive host harbors the fluke adult stage in the large biliary passages and gallbladder, eggs reaching the external milieu by way of bile and intestine; the definitive host is infected by the ingestion of metacercariae; metacercariae excyst in the small intestine within an hour after ingestion, penetrate the host's intestine wall, and appear in the abdominal cavity by about 2 h after ingestion; most reach the liver within 6 days after excystment; in the liver, they migrate for 5–6 weeks, preferentially feeding directly on liver tissues; they eventually penetrate into the bile ducts where they become sexually mature; the prepatent period (from the ingestion of metacercariae to the first appearance of the first eggs in the feces) is about 2 months (6–13 weeks) in sheep and cattle, varies according to the host, and also depends on the number of the adult flukes in the liver (Valero et al. 2006b); in man, a period of at least 3–4 months is necessary for the flukes to attain sexual maturity; several studies show that the life span of the parasite in sheep can be as long as 11 years and 9–12 months in cattle; different estimations suggest a life span of the adult fluke in man of between 9 and 13.5 years

(b) The transit between definitive mammal host and intermediate snail host includes the long resistance phase of the egg and the short active phase of miracidium; eggs shed with the mammal feces will only continue their development if they reach freshwater of appropriate physicochemical characteristics; if the climatic conditions are suitable (15-25 ° C), the miracidia develop and hatch in about 9–21 days; if conditions are unfavorable, they may not mature but may remain viable for several months; the miracidium hatches under light stimulation and swims rapidly until it contacts an appropriate aquatic or amphibious snail host

(c) The development at intermediate host level includes miracidium penetration into the snail, sporocyst, redial generations, production of cercariae, and shedding of the latter into water; up to four redial generations have been found, although 3 generations are usually produced after a monomiracidial infection; the redial generations follow the same developmental pattern in different lymnaeid species; the complex development of redial generations has

been recently described (Rondelaud et al. 2009); cercariae develop within 6–7 weeks at 20–25 ° C; at lower temperatures the development is delayed; the prepatent period is dependent on temperature, with higher temperatures reducing the period (15 ° C: 56–86 days; 20 ° C: 48–51 days; 25 ° C: 38 days)

(d) The transit between intermediate snail host and definitive mammal host includes the short swimming phase of cercaria and the long resistance phase of metacercaria until its ingestion by the definitive host; the shedding process takes place between 9° and 26 ° C, independent of light or darkness; cercariae swim for a short time (1 h) until contacting a solid support, mostly leaves of water plants above or below the water line; they then lose their tails and quickly encyst, changing into metacercariae; metacercarial cysts become infective within 24 h after encystment

The development of this trematode is thus very dependent on the environmental characteristics according to the nature of phases B and D, which take place fully in the external freshwater milieu, and phase C, which develops completely within a freshwater snail, in its turn also very dependent on the environment. That is why this disease is pronouncedly influenced by climate change (Mas-Coma et al. 2009b). Additionally, it is markedly influenceable by human activities at phase A, which explains its relationships with human behavior (e.g., eating traditions, livestock management) and also anthropogenic modifications of the environment as a component of global change (e.g., artificial irrigation for agriculture, animal export/import) (Afshan et al. 2014). Despite these restrictions, *F. hepatica* has succeeded in expanding from the Near East original geographical area up to actually colonizing the five continents, including the Americas where it was introduced by the Spanish conquistadores 500 years ago (Mas-Coma et al. 2001, 2009a). At present, fascioliasis by *F. hepatica* is the vector-borne parasitic disease presenting the widest latitudinal, longitudinal, and altitudinal distribution known (Mas-Coma et al. 2003).

4 The Animal Reservoirs

Adult fasciolid worms parasitize ruminants, mainly sheep, goats, and cattle, and many other herbivorous domestic and wild mammals, including horses, donkeys, mules, and also Old and New World camelids. Buffalo, deer, wild sheep, domestic and wild pig, various marsupials, rabbit, hare, and nutria are also susceptible hosts (Mas-Coma and Bargues 1997; Mas-Coma et al. 2009a).

In Latin America, cattle and sheep are the main reservoir hosts in the human endemic areas (Mas-Coma et al. 1999c), followed by donkeys and pigs (Mas-Coma et al. 1997; Valero et al. 2001). The capacity of donkeys and pigs to contribute to the transmission and spread of the disease in these areas has proven to be similar to that of cattle and sheep (Mas-Coma et al. 1997; Valero and Mas-Coma 2000).

The Andean camelids, llama, alpaca, guanaco, and vicuña, are very susceptible to *F. hepatica*. Liver fluke infection induces a high pathogenicity in these autochthonous mammals, giving rise to serious economic losses in their husbandry (Timoteo et al. 2005).

5 The Snail Vectors

Freshwater snails of the family Lymnaeidae (Gastropoda) act as intermediate hosts or vectors of fasciolid flukes. Although livestock species play an important reservoir role, transmission studies have shown that the metacercarial infective stage from different origins, such as sheep, cattle, pig, and donkey, represents similar infectivity sources (Valero and Mas-Coma 2000; Valero et al. 2001). On the contrary, the specificity of fasciolid species regarding concrete lymnaeid species (Bargues et al. 2001) represents a crucial factor in establishing not only the geographical distribution of the disease in both animals and humans but also prevalences and intensities due to more or less appropriate ecological characteristics (population dynamics, anthropophylic characteristics, type of water bodies, etc.) of the different lymnaeid intermediate host or vector species. That is why different lymnaeid species appear linked to different transmission patterns and epidemiological scenarios of this very heterogeneous disease in humans (Mas-Coma 2005; Mas-Coma et al. 2009a). The continental differences in lymnaeid faunas also explain that in the Americas fascioliasis is only caused by *F. hepatica*, due to the absence of lymnaeids of the genus *Radix* which act as transmitters of *F. gigantica* (Bargues et al. 2001). Similarly, as in other vector-borne diseases, this relationship supports the use of lymnaeids as biomarkers of the disease at both local and large scales and can thus be useful for the validation of mathematical modeling and remote sensing—geographical information system (RS-GIS) tools for the control of the disease (Fuentes et al. 1999, 2001).

At lymnaeid species level, the problems are found mainly because of the interspecific morphological and anatomic uniformity numerous species show, usually giving serious difficulties in specimen classification, sometimes even impeding it (Bargues et al. 2007a, 2011a; Bargues and Mas-Coma 2005). Moreover, intraspecific variation of shell shape is particularly well marked within lymnaeids depending on environmental conditions. Thus, there are many specimen classification problems, mainly related to species of the "stagnicoline" group, the "radix" group, and the "fossarine" or "*Galba/Fossaria*" group (Bargues et al. 2011a). Fortunately, there are sequence markers in both the nuclear rDNA and the mtDNA which allow today for the appropriate specimen classification (Bargues et al. 2001, 2011a; Bargues and Mas-Coma 2005).

In the Americas, except the only species of the genus *Pseudosuccinea*, *P. columella*, all lymnaeid species involved in the transmission of *F. hepatica* belong to the *Galba/Fossaria* group, a fact that makes specimen classification by simple malacological tools pronouncedly difficult. In northern and central America, as well

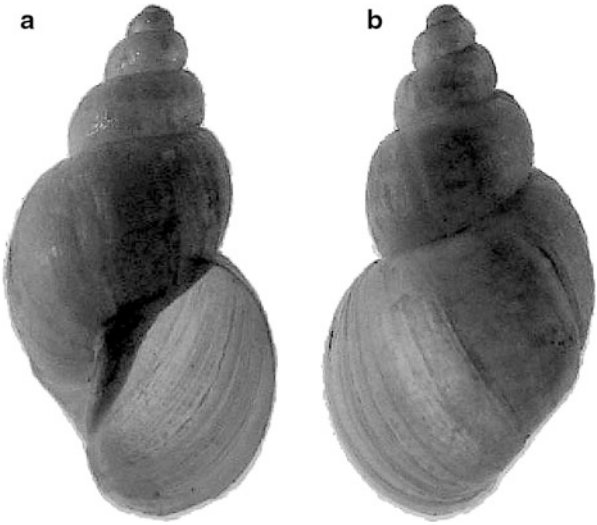

Fig. 3 Specimen of *Galba truncatula*, the main lymnaeid snail vector responsible for human infection in endemic areas of the Andean countries: (**a**) ventral view; (**b**) dorsal view (original S. Mas-Coma)

as in the Caribbean islands and lowlands of northern Venezuela, the lymnaeid vector species are *Lymnaea cubensis* and *P. columella*, and secondarily *L. humilis* and *L. bulimoides* in northern mainland territories of the USA and Mexico (Bargues et al. 1997, 2011a, b).

In South America, the main species related to endemic areas of altitude in the Andean region are *Galba truncatula*, *L. neotropica*, *L. cubensis*, and *L. cousini* in northern countries such as Venezuela, Colombia, Ecuador, and Peru (Bargues et al. 2007a, 2011a, b, c, 2012a). In the human endemic high altitude area of the Northern Altiplano of both Bolivia and Peru, only *G. truncatula* is involved (Fig. 3) (Mas-Coma et al. 2001). In Brazil, the transmission is mainly assured by *P. columella*, and in the Southern Cone countries of Uruguay, Chile, and Argentina, the latter species appears accompanied by the species *G. truncatula*, *L. neotropica*, *L. viator* (= *L. viatrix*), and *L. diaphana* as the main vectors (Bargues et al. 2007a, b, 2012b; Mera y Sierra et al. 2009; Artigas et al. 2011).

6 Epidemiology

Traditionally, the epidemiological characteristics of animal fascioliasis were extrapolated to human fascioliasis. However, in the last two decades, numerous field studies have demonstrated that this was a misunderstading and that human fascioliasis only shows common features with animal fascioliasis at a basic level (Mas-Coma 2005; Mas-Coma et al. 2009a).

6.1 Geographical Distribution

Whereas animal fascioliasis shows an almost worldwide distribution, human infection appears more geographically focused, including human endemic areas in the Near East, Southeast Asia, Western Europe, Northeastern Africa, and Latin America. This does not mean, however, that patients infected by *Fasciola* have been diagnosed in many other countries outside of these hotspot areas (Mas-Coma et al. 2005, 2009a, 2014a).

In Latin America, human infection appears mainly in altitude areas of the Andean region. In the Bolivian Altiplano, human prevalences were of up to 72 % and 100 % in coprological and serological surveys, respectively (Hillyer et al. 1992; Bjorland et al. 1995; Esteban et al. 1997a, b, 1999; Mas-Coma et al. 1999c), and intensities reached up to more than 8000 eggs per gram (epg) in children, both higher in females than in males (Fig. 4) (Mas-Coma et al. 2009a). Similar situations, although with lower intensities, have been described in other altitude areas of Peru, such as in Puno (Esteban et al. 2002), Mantaro valley (Raymundo et al. 2004), and Cajamarca (Gonzalez et al. 2011). Human infection has also been described in altitude areas of Ecuador (Trueba et al. 2000), Colombia (see review in Bargues et al. 2011c), Venezuela (see review in Bargues et al. 2011b), and recently also in Argentina (Carnevale et al. 2013). A few human endemic areas have also been described in lowland areas in countries of the Southern Cone, such as Argentina (Mera y Sierra et al. 2011) and Chile (Apt et al. 1993; Artigas et al. 2011).

Very recently, a human fascioliasis endemic area has been described for the first time in North America. Children proved to be infected in the state of Puebla, at a mean altitude of 1,840 m. Fascioliasis prevalences indicate this area to be mesoendemic, with isolated hyperendemic foci, a situation which adds concern

Fig. 4 Recreational and washing activities of the people in a fascioliasis transmission focus of the Northern Bolivian Altiplano, the endemic area with higher prevalences and intensities known in humans (original S. Mas-Coma)

about possible human fascioliasis underestimation in other areas of Mexico (Zumaquero-Ríos et al. 2013).

In the Caribbean region, human fascioliasis mainly poses problems in Cuba, where the first human case was already diagnosed in the first half of the last century (Kouri et al. 1938), many outbreaks have been reported (Esteban et al. 1998) since the first one (Arenas et al. 1948), losses in livestock husbandry due to fascioliasis are very high (Brito Alberto et al. 2010), and patients are continuously diagnosed (Millan et al. 2000; Diaz Fernandez et al. 2011), even in high numbers (Gonzales Santana et al. 2013). Unfortunately, appropriate field surveys are still lacking (Rojas et al. 2009) and hence the real situation in the different parts of the island remains unknown. Puerto Rico may still be considered a human infection risky area after the epidemiological situation in the past (Hillyer 1981), and Haiti has recently proved to be also affected by this disease at human level nowadays (Agnamey et al. 2012), although human infection was already detected in Haiti some time ago (Clay and Straight 1961).

6.2 Transmission Patterns

Human infection by the liver fluke shows a marked heterogeneity of different epidemiological situations and transmission patterns throughout the world. Thus, well-known situations and patterns of fascioliasis may not always explain the disease characteristics in a given area. In other terms, when dealing with an endemic zone not previously studied, the above-noted known situations and patterns of human infection must always be taken into account merely as the starting base. Only once epidemiology and transmission characteristics of the new area are sufficiently assessed, may appropriate control measures be designed for the endemic area in question.

In Latin America, the following human fascioliasis transmission patterns have been highlighted among the different ones which have been described throughout (Mas-Coma 2005; Mas-Coma et al. 2009a):

1. A very high altitude pattern related to only *F. hepatica* transmitted by imported *G. truncatula* in Andean countries following transmission from seasonal to permanent; at very high altitude, experimental studies have demonstrated that fascioliasis transmission becomes enhanced mainly due to:

   (a) A longer cercarial shedding period
   (b) A higher metacercarial production per snail, and
   (c) A longer survival of the lymnaeid vectors (Mas-Coma et al. 2001).

   Within this category, two subpatterns may be distinguished according to physiographic and seasonal characteristics:

   (i) The altiplanic pattern, with transmission throughout the whole year due to high evapotranspiration rates and the consequent restriction of lymnaeids to

permanent water bodies, e.g., in the Northern Bolivian Altiplano (Fig. 4) and the Puno Altiplano (Mas-Coma et al. 1999c; Esteban et al. 2002)

(ii) The valley pattern, with seasonality and prevalences and intensities related to altitude, higher human infection rates correlating an altitude increase (Gonzalez et al. 2011); examples of such human endemic areas are the valleys of Cajamarca and Mantaro (Valero et al. 2012a); other *Galba*/*Fossaria* vector species appear accompanying *G. truncatula* in these areas (Bargues et al. 2012a)

2. A Caribbean insular pattern, with reduced but repeated outbreaks in human hypoendemic areas and lymnaeid species (*L. cubensis*, *P. columella*) other than the main vector species being involved in the transmission, e.g., the Pinar del Rio Province and other areas in Cuba

Studies are at present under way to assess whether other human fascioliasis transmission patterns may be defined according to more recent descriptions of additional human endemic areas.

6.3 Epidemiological Situations and Disease Burdens

This trematodiasis presents a very wide spectrum of transmission and epidemiological patterns In human hypo- to hyperendemic areas. These are related to the large diversity of environments, including different human endemic/epidemic situations, different human demographies, races, diets, habits, traditions, and religions, different domestic and wild mammal reservoir species, different lymnaeid transmitting species, zones in both the Northern and Southern hemispheres, altitudes from −27 m up to 4,200 m, hot and cold weathers, seasonal and yearly constant temperatures, scarce to pronounced annual rainfall, low and high mean annual potential evapotranspiration, and from lack of dry period to lack of wet period through different dryness/humidity rates. From the landscape point of view, these areas include from altiplanos to valleys, from islands to mainlands, from natural to artificial irrigations, from lakes to lagoons, from large rivers to small streams, and from permanent to temporal water bodies (Mas-Coma et al. 2003).

The only classification of epidemiological situations hitherto proposed (Mas-Coma et al. 1999a) still appears to be fully valid and useful.

In Latin America, human fascoliasis shows all of these epidemiological situations depending on countries and areas. Authochthonous, isolated, nonconstant cases are typical in Colombia, Brazil, Uruguay, and most of Argentina (e.g., Bargues et al. 2011c; Mera y Sierra et al. 2011), and imported cases from one country to another have been reported several times. Examples of hyperendemic situations are those in the Northern Bolivian Altiplano (Hillyer et al. 1992; Bjorland et al. 1995; Esteban et al. 1999; Mas-Coma et al. 1999c), rural altitude areas throughout the Andean chain of Peru (Esteban et al. 2002; Raymundo et al. 2004; Gonzalez et al. 2011), and an area in central Chile (Apt et al. 1993; Artigas et al.

2011). A mesoendemic situation has recently been described in Mexico, even including a short number of hyperendemic foci (Zumaquero-Ríos et al. 2013). Areas described in Ecuador and Venezuela fit a hypoendemic situation's characteristics (Trueba et al. 2000; Bargues et al. 2011b).

Epidemics in nonhuman endemic but animal endemic areas, including familiar outbreaks involving only a few subjects, have been reported several times from Argentina (Mera y Sierra et al. 2011). A situation of relatively large epidemics involving many subjects in human endemic areas is the one typically reported from Cuba (Esteban et al. 1998).

6.4 Human Infection Sources

The infectivity of metacercariae is dependent upon storage time. In experimental assays, it proved to be lower when metacercariae are older: the maximum longevity was 31 and 48 weeks using doses of 20 and 150 metacercariae per host, respectively, although in the latter case only a very low percentage was viable. Moreover, metacercarial viability and infectivity did not show differences between isolates from different reservoir species, demonstrating that flukes from secondary reservoirs as pigs and donkeys involve the same potential risk as those from the main ones sheep and cattle (Valero and Mas-Coma 2000).

The ingestion of infective metacercariae by humans may occur by different ways. Several infection sources have been distinguished in studies performed in the last two decades (Mas-Coma 2004): (1) ingestion of freshwater wild plants (important in animal endemic areas); (2) ingestion of freshwater cultivated plants, mainly watercress; (3) ingestion of terrestrial wild plants, including even those collected in dry habitats but which were submerged in water a few weeks or months before; (4) ingestion of terrestrial cultivated plants needing frequent irrigation; (5) drinking of contaminated water; (6) ingestion of dishes and soups made with contaminated water; (7) washing of kitchen utensils or other objects with contaminated water; and (8) ingestion of raw liver infected with migrating metacercariae which may keep the capacity to restart migration.

Cultural traditions prove to be highly important in given endemic areas. Experimental studies performed with plant-made foods showed the role they may play in human infection (Ashrafi et al. 2006).

In the Northern Bolivian Altiplano, a study was performed on the presence of metacercariae in semi-aquatic plants collected from a swamp in an endemic locality. According to the fluke number obtained in guinea pigs experimentally infected with 100 g of plant, the plants could be classified into seven risk levels: Compositae: 56,3; *Eleocharis* sp.: 50,9; *Senicio* sp.: 12,0; *Vallisneria* sp.: 10,3; *Scirpus* sp.: 3,3; Ranunculaceae: 2,6; and Liliaceae: 0. In this high human endemic area, reports suggest that human infection is related to traditional consumption of uncooked aquatic plants, including:

– matara: *Juncus andicola* (Juncaceae);
– totorilla = "kosko-oskosko": *Juncus ebracteatus* (Juncaceae);
– watercress = berros = "okororo": *Mimulus glabratus* and *Nasturtium officinale* (Scrophulariaceae);
– brown algae = cochaguyo = "llayta": *Nostoc* sp. (Cianofitas);
– and others still undetermined (Mas-Coma et al. 1995).

The typical plant of the Lake Titicaca, *Schoenoplectus californicus* ssp. *tatora*, known as totora or "chullu" (Cyperaceae), had been also involved in the transmission, but subsequent analyses showing that the roots of this plant produce molluscicidal secretions enabled to rule out its participation (Mas-Coma et al. 1999c).

In Mexican children, an association between fascioliasis and the habit of eating raw vegetables was identified, including from more to less risk as follows: watercress and radish with pronouncedly higher relative risk than lettuce, corncob, spinach, alfalfa juice, and broccoli. The link of fascioliasis risk with the consumption of raw vegetables other than watercress should be highlighted, as it suggests contamination when washing terrestrial vegetables with untreated water and/or in plant cultures using natural water for irrigation (Zumaquero-Ríos et al. 2013). In Peru, patients mentioned having eaten watercress (45.6 %), lettuce (31.6 %), alfalfa (10.5 %), or spinach (5.3 %), drinking natural water from small streams (10.5 %), or emollients (warm beverages made from various plants, chiefly alfalfa and watercress, and supposed to be good for liver diseases) (5.3 %), among others (Blancas et al. 2004).

Water is often cited as a human infection source. In the Bolivian Altiplano, 13 % of the metacercariae of all isolates are floating (Bargues et al. 1996). This becomes very important owing to the very high number of cercariae-shedding lymnaeids which may be found: 31.6 % prevalence in lymnaeids from the endemic locality of Tambillo, where up to 7 metacercariae were found in only half a liter of water from the small river crossing this locality (Mas-Coma 2004). The importance of fascioliasis transmission through water is supported by many indirect results. There are significant positive associations between liver fluke infection and infection by other waterborne parasites, such as *Giardia intestinalis* in both Bolivia and Peru (Esteban et al. 1997a, 2002). Moreover, in many human hyperendemic areas of the Americas, people do not have a history of eating watercress (Hillyer and Apt 1997), and in zones as the Asillo irrigation area of the Peruvian Altiplano, inhabitants do not consume freshwater plants (Esteban et al. 2002).

7 Pathology and Major Manifestations

In human fascioliasis, four clinical periods may be distinguished (Chen and Mott 1990; Mas-Coma and Bargues 1997; Mas-Coma et al. 1999b, 2000). The incubation period includes from the ingestion of metacercariae to the appearance of the first symptoms. In man, this period has not been accurately determined (only "a

few" days, 6 weeks, 2–3 months, or even more). The invasive or acute period comprises fluke migration up to the bile ducts. The latent period includes maturation of the parasites and starting of oviposition. This period can last for months or years and the proportion of asymptomatic subjects in this phase is unknown, being often discovered during family screening after a patient is diagnosed (Arjona et al. 1995). Patients may have prominent eosinophilia suggestive of infection, gastrointestinal complaints, or one or more relapses of the acute symptoms. Finally, the biliary, chronic, or obstructive period may develop after months to years of infection. Of these four periods, the second and fourth are the most important, because patients are in one or the other of these two periods almost always when diagnosed.

In the invasive or acute period, symptoms are due mainly to mechanical destruction of liver tissue and abdominal peritoneum by the migrating larvae causing localized or generalized toxic and allergic reactions lasting 2–4 months. The major symptoms of this phase include fever, abdominal pain usually in the right hypochondrium or below the xyphoid, gastrointestinal disturbances such as loss of appetite, abdominal flatulence, nausea, and diarrhea, respiratory symptoms such as cough, dyspnea, hemoptysis, and chest pain, and also urticaria.

In the biliary or chronic period, adult flukes cause inflammation, hyperplasia of the epithelium, and thickening and dilatation of the bile duct and gallbladder walls. The resulting cholangitis and cholecystitis, combined with the large body of the flukes, are sufficient to cause obstruction. This phase includes biliary colic, epigastric pain, fatty food intolerance, nausea, jaundice, pruritus, and right upper-quadrant abdominal tenderness, among others. Lithiasis of the bile duct or the gallbladder is frequent, whereas cirrhosis does not appear to be so (Marcos et al. 2009). The bile duct and the gallbladder may contain blood mixed with bile (hemobilia), blood clots, and fibrinous plugs. Symptomatology in children from human endemic areas of Peru includes abdominal pain localized in the epigastrium, the Murphy symptom, and jaundice as the most frequent clinical biliary characteristics, the rest of the symptoms being nonspecific (Marcos et al. 2002).

The very long life span of fasciolid flukes in humans, of up to 13.5 years (Mas-Coma & Bargues 1997), underlies many problems regarding complications and sequelae in long-term chronicity. The most common clinical complications listed in the literature are biliary obstruction, cholecystitis, recurrent cholangitis, liver abscesses, and subcapsular hemorrhages (Arjona et al. 1995). Bleeding, multiple extrahepatic venous thrombosis, pancreatitis, and biliary colics have also been reported. Anemia, lithiasis, and bacteriobilia have recently proven to be additional important complications in the chronic period (Valero et al. 2003, 2006a, 2008). In human endemic areas of developing countries, coinfections with other protozoan and helminth parasites may add more complications to the patients, mainly due to the immunesuppression induced by the liver fluke infection.

Hepatic lesions may appear persistent many years after a successful treatment which allowed for short-term normalization of symptoms and laboratory values (Rondelaud et al. 2006). Clinical recovery is much faster than radiological clearance (Kabaalioglu et al. 2007).

In human hyperendemic zones with depauperated socioeconomic status, unhygienic conditions, and high child morbidity and mortality as the Bolivian Altiplano (Mas-Coma et al. 1995), studies are needed to ascertain whether fasciolosis may be related to death, above all in very young children and on the new light about immunesupression, coinfections, and complications.

Ectopic fascioliasis comprises clinical pictures caused by fasciolids in locations of the human body different from the liver. Flukes may deviate during migration, enter other organs and cause ectopic fascioliasis. In almost all patients, the causal agent is an immature juvenile, but a reduced number of ectopic cases caused by mature flukes shedding eggs have also been reported (Mas-Coma et al. 2014b). In humans, the most frequent ectopic lesions are in the gastrointestinal tract. Other such lesions are in abdominal wall, pancreas, spleen, subcutaneous tissue, heart, blood vessels, the lung and pleural cavity, skeletal muscle, appendix, and epididymis (Mas-Coma and Bargues, 1997; Mas-Coma et al. 2014b). Pathological effects of ectopic lesions are due to the migratory tracks causing tissue damage with inflammation and fibrosis.

A recent wide analysis has shown that neurofascioliasis or intracranial infection by *Fasciola* and ophthalmofascioliasis or direct affection of the eye by migrating flukes may be rare, although not sporadic as previously believed. However, manifestations including a very wide range of neurological symptoms, signs, and syndromes, together with meningeal, psychiatric, or neuropsychic manifestations, and ocular disorders caused at distance by flukes infecting the liver may be frequent but underestimated due to misdiagnosis, mainly in low-income regions. The impressive clinical pictures should be highlighted. They include from hemiplegia and paraplegia to disturbances and difficulties of walking capacity, speech disorders, convulsions, epilepsia and coma, amnesia, or visual hallucinations and permanent blindness, only to mention a few, plus the clinical complexity of the puzzling poymorphisms, the disconcerting multifocality of the manifestations, and their changes along the evolution of the disease in a same patient, as well as differences between the clinical pictures shown by different patients. Moreover, these studies emphasize postreatment sequelae and mortality in neurological patients and the need to consider neurological fascioliasis when estimating the global burden of this disease (Mas-Coma et al. 2014b).

8 Diagnosis

In a developed country, blood eosinophilia and the ingestion of watercress or any other suggestive freshwater plant in anamnesis are extremely useful in guiding towards a fascioliasis diagnosis. Unfortunately, these two aspects are usually not helpful in human endemic areas of developing countries, where eosinophilia may be also caused by other helminth infections and local food traditions including the ingestion of many uncooked plants may mask liver fluke infection (Mas-Coma et al. 2014b).

Abnormal laboratory findings concern leucocytosis, eosinophilia, anemia, erythrocyte sedimentation rate, hepatic functions, and serum immnunoglobulin levels (Chen and Mott 1990; Mas-Coma et al. 1999b, 2000). Several suggestive clinical presentation aspects may be useful, mainly in human endemic areas where physicians are aware about liver fluke infection risk in humans. However, verification needs the use of at least one among the direct parasitological techniques or indirect immunological tests (Mas-Coma et al. 2014a). Other noninvasive diagnostic techniques presently available may be additionally helpful. Noninvasive diagnostic techniques which can be used for human diagnosis are radiology, radioisotope scanning, ultrasound, computed tomography, and magnetic resonance (Esteban et al. 1998; Hillyer 1999).

Finding and identification of fasciolid eggs in fecal samples, duodenal contents, or bile continue to be the most appropriate diagnostic strategy for both detection of infection and estimation of intensity. This is even in spite of the recognized lower sensitivity of egg detection in fecal samples and its uselessness for the diagnosis of patients in the acute period, as well as the lack of an accurate relationship between egg counts per g of feces and the fluke burden (Valero et al. 2006b, 2009). Techniques ranging from a simple direct smear to different concentration methods may be used. Egg concentration has been achieved by flotation and sedimentation techniques. The sedimentation techniques appear to be more accurate and sensitive than flotation techniques (Esteban et al. 1998; Mas-Coma et al. 2014a).

Egg counting is crucial in the moment of deciding the appropriate treatment dose. The 400-epg threshold has been proposed for identifying high intensity infections. To avoid the risk of colic, a repeated, timely spaciated middose is recommended to patients shedding more than 400 eggs (WHO 2007; Valero et al. 2012b). The second half of the regimen is administered 24 h later, once the absence of secondary effects is verified. The Kato–Katz technique appears to be appropriate because of its simplicity, very low cost, and reproducibility (Mas-Coma et al. 1999b). Its low sensitivity may be solved by repeated application. Quantitative coprological analyses also become important in epidemiological surveys as well as postreatment monitoring (Mas-Coma et al. 2014a).

Fasciolid worms and eggs may be also found elsewhere by means of other invasive techniques: obtaining duodenal fluid, duodenal, and biliary aspirates; surgery (laparotomy, cholecystectomy, and sphincterotomy); and histological examination of liver and/or other organ biopsy materials (Mas-Coma et al. 1999b).

Many serological, intradermal, and stool antigen detection tests have been developed. Immunological techniques present the advantages of being applicable during all periods of the disease, but fundamentally during the invasive or acute period, as well as other situations in which coprological techniques may present problems. However, immunological techniques offer other types of problems related mainly to sensibility and specificity. Efforts have been concentrated in obtaining purified excretory/secretory antigens and/or recombinant molecules to improve serological tests, owing to the problems of the parasitological diagnosis because of (1) the delay in its usefulness in the acute period (coprological examination positive only after 3–4 months postinfection), (2) intermitent egg output

dynamics, (3) very low or even the absence of egg shedding in cases of only one or a few fluke adults and old, chronic infections, (4) ectopic infections, (5) "false" fascioliasis related to eggs in transit after ingestion of infected liver from domestic animals, or (6) flukes unable to attain maturity in human subjects in nonhuman endemic areas (Mas-Coma et al. 2014a).

Cysteine proteinases offer highly sensitive and specific markers for human fascioliasis serodiagnosis for *F. hepatica* (O'Neill et al. 1999; Strauss et al. 1999; Mezo et al. 2004; Espinoza et al. 2007). *Fasciola hepatica* recombinant cysteine proteinases produced in yeast (O'Neill et al. 1999) or in *Escherichia coli* (Carnevale et al. 2001) have been used in ELISA methods for human infection diagnosis.

In Bolivia and Peru, the MM3 coproantigen-detection test allowed for high sensitivity and specificity, fast large mass screening capacity, detection in the chronic period, early detection of treatment failure or reinfection in post-treated subjects, and usefulness for surveillance programs. However, this technique falls short when evaluating the fluke burden on its own (Valero et al. 2012b). The use of a new preservative/diluent CoproGuard™, developed for the preservation of *Fasciola* coproantigens, proved to enhance coproantigen extraction and the antigenicity throughout the complete observation period (Ubeira et al. 2009).

In a wide assay in different epidemiological situations, the commercialized DRG *Fasciola hepatica* IgG (human) ELISA proved to be highly sensitive and specific, with a high negative predictive value but a low positive predictive value. No correlation with egg output was observed. This test may be used both as an individual serodiagnostic test when backed up by a compatible clinical history together with a second diagnostic technique for other cross-reactive helminth infections and in future large-scale epidemiological studies (Valero et al. 2012c).

A useful step forward for human diagnosis is the development of a new lateral flow test (SeroFluke) (Martinez-Sernandez et al. 2011). In comparison with an ELISA test (MM3-SERO), the SeroFluke test showed maximal specificity and sensitivity and the advantage of being applicable to both serum and whole blood samples. Its simplicity allows it to be used in major hospitals as well as in endemic/hyperendemic regions.

9 Treatment

Drugs such as emetine and the better tolerated dehydroemetine were used widely in the past and still continue to be used today, given intramuscularly or subcutaneously at doses of 1–10 mg/kg a day for 10 days. However, the use of emetine was progressively abandoned due to their toxic side effects involving heart, liver, and digestive tract (Mas-Coma et al. 2014b). Chloroquine improved the symptoms when applied in the acute phase. Bithionol was proposed as the drug of choice for fascioliasis treatment during the last three decades of the last century. It was usually applied at a dose of 30–50 mg/kg daily, divided into 3 oral doses on alternate days for 20–30 days. Occasionally, the patients required a second course to obtain a

complete cure. The side effects were usually mild (Chen and Mott 1990; Esteban et al. 1998).

With regard to praziquantel, fasciolids are the only trematodes that have practically no response to this drug. Metronidazole and albendazole and sporadically also mebendazole have been also applied for human fascioliasis treatment with more or less success.

Triclabendazole (Egaten®) has become the drug of choice for human fascioliasis at present (Savioli et al. 1999). This drug is better adsorbed if administered after meals (Lecaillon et al. 1998). The recommended dosage is two separate regimens of 10 mg/kg. A cure rate of 79.2 % when first used and 100 % after a second round of therapy was found in Chile (Apt et al. 1995), and 79.4 % and 93.9 %, respectively, in Egypt (El-Morshedy et al. 1999). Triclabendazole appears to keep its efficiency at standard regimes in human endemic areas after years (Talaie et al. 2004), although the need for a third dose has been reported in Cuba (Millan et al. 2000).

However, the risk of appearance of resistance to triclabendazole cannot be forgotten. Triclabendazole resistance was first described in Australia, later in European countries such as Ireland, Scotland, the Netherlands, and Spain (see review in Mas-Coma et al. 2007). Very recently it has also been found in southern Brazil (Oliveira et al. 2008) and Argentina (Olaechea et al. 2011). Up to that moment, triclabendazole resistance only concerned livestock in animal endemic areas, but unfortunately it has very recently been also described (Ortiz et al. 2013) in a human highly endemic area such as Cajamarca, Peru.

Nitazoxanide may be an alternative to triclabendazole, at least for the chronic stage of fascioliasis and for patients with low burdens, mainly in those countries where Egaten® is still not registered but nitazoxanide is since several years. Nitazoxanide had demonstrated its efficacy against human fascioliasis in a few trials, in Egypt (Rossignol et al. 1998; Kabil et al. 2000) and Peru (Favennec et al. 2003). Its long 7-day treatment course may nevertheless become a problem. However, its usefulness for the treatment of human cases not responding to triclabendazole (Gargala et al. 2005) is of important additional value. A good nitazoxanide efficacy has recently been reported when applied to liver fluke-infected children in Mexico (Zumaquero-Ríos et al. 2013). However, differences in fasciolid susceptibility to nitazoxanide may exist depending on geographical strains. Thus, a triclabendazole-resistant *F. hepatica*-infected patient not responding to nitazoxanide treatment has recently been reported in the Netherlands (Winkelhagen et al. 2012), and no response to nitazoxanide treatment was reported in 24 cases of liver fluke infection in Esmeralda, Camagüey, Cuba (Del Risco et al. 2001).

10 Control and Elimination

The prevention of human infection may be achieved by strict control of the human infection sources in each place, mainly with regard to watercress and other metacercariae-carrying aquatic plants for human consumption, especially in

endemic zones. Commercial growing of watercress should be carried out under completely controlled conditions, without access for snails and ruminants. Potassium permanganate, which had been suggested to be the most effective preventive tool for killing metacercariae attached to leaves and vegetables used in salads, has been unfortunately shown to have no effect on metacercarial viability, even at very high doses of 300 mg/l, 600 mg/l, and 1,200 mg/l (Ashrafi et al. 2006).

Human infection risk shall not be restricted to only ingestion of freshwater vegetables, as always mentioned. The aforementioned different human infection sources may be considered, mainly in high human endemic areas. Drinking of natural freshwater should be avoided in human endemic areas. Moreover, the possibility of human infection in urban areas should also be taken into account. Thanks to transport of vegetables (both aquatic and terrestrial) from rural endemic zones to cities, plants carrying metacercariae can be sold in noncontrolled city markets giving rise to urban infection (Mas-Coma 2004).

Education should always be included within general control measures to be applied in human fascioliasis endemic areas, mainly with regard to the need to let know inhabitants about the human infection sources. The community should be appropriately informed about the disease, its transmission, and its danger.

The availability of a very effective drug against fascioliasis as triclabendazole prompted the WHO to launch a decisive step forward within its worldwide initiative against human fascioliasis (WHO 2007, 2008). This initiative includes action in human fascioliasis endemic areas presenting different epidemiological situations and transmission patterns (Mas-Coma 2005; Mas-Coma et al. 2009a). Pilot schemes were designed to assess the best control strategies according to different epidemiological situations and transmission patterns in the way to decrease morbidity, mainly in children. Bolivia and Peru were the two countries selected for priority intervention due to the very large public health problem posed by this disease. The Northern Bolivian Altiplano was chosen as an example of the Altiplanic pattern, while the Cajamarca valley was chosen as an example of the valley pattern. The respective pilot interventions in the two Andean human endemic areas demonstrated the absence of serious side effects in triclabendazole treatments of schoolchildren (Villegas et al. 2012), which subsequently allowed for the launching of mass treatments of mainly children in these two Andean countries. Many other countries are nowadays receiving yearly triclabendazole donations through WHO for the treatment of their patients.

Regarding veterinary control, previous epidemiological studies may provide for general recommendations on the appropriate time for treatment with effective drugs to achieve economic control and better information from the livestock farming community. Forecasts of outbreaks may be made based on climatological data and epidemiological models. Recommendations for control measures should be made on a preventive rather than a curative basis, and all measures have to be considered from the point of view of the economy and assessment of local topographical and meteorological conditions. The efficiency of fascioliasis control depends on the correct and integrated application of (1) reduction of the parasite load of the animal hosts and pasture contamination by regular strategic use of drugs (preventive

treatment in appropriate year periods according to different regions); (2) reduction of the number of snails by physical, chemical, and biological means; and (3) reduction of the risks of infection through correct farm management practices (rotational system through fluke-infected and fluke-free paddocks, combined with effective treatment) (Mas-Coma and Bargues 1997).

Lymnaeid snail vector control has unfortunately not received the attention from public health officials required to definitively eliminate transmission (Chen and Mott 1990). Intensive agricultural methods must be applied to reduce suitable snail habitats. Besides physical methods, there are available control strategies which consist of the use of chemical molluscicides, natural molluscicides of plant origin, biological control (including predators, competitors, the decoy effect and related phenomena, parasitic castration, interspecific trematode antagonism, and pathogens), genetic manipulation, and engineering control. However, the practical application of chemical methods in the control of snails is of doubtful value, and requires labor and equipment, and regular yearly strategic molluscicide applications. Moreover, the application of molluscicides in the fight against vector species of the *Galba/Fossaria* group becomes very difficult and sometimes unaffordable when the snails inhabit small temporary waterbodies from rainfall. The ecological requirements of *P. columella* may, however, be more appropriate for molluscicidal application.

Acknowledgments Reviews of fascioliasis funded by Projects SAF2010-20805 of the Ministry of Economy and Competitiveness, Madrid, Spain; ISCIII-RETIC RD12/0018/0013, Red de Investigación de Centros de Enfermedades Tropicales—RICET, of the Program of Redes Temáticas de Investigación Cooperativa RETICS/FEDER, Ministry of Health and Consumption, Madrid, Spain; and PROMETEO/2012/042, of the Program of Ayudas para Grupos de Investigación de Excelencia, Generalitat Valenciana, Valencia, Spain. Joint coordination research activities with endemic countries of Latin America also carried out within the "Worldwide initiative of WHO against human fascioliasis" (WHO Headquarters Geneva), and Project No. RLA5049 of the International Atomic Energy Agency (Animal Production and Health Section, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Department of Nuclear Sciences and Applications, IAEA Headquarters Vienna, Austria).

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A Roadmap Followed: The Path Towards the Elimination of Onchocerciasis in Latin America

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_8

Abstract Onchocerciasis, a chronic, debilitating, poverty-promoting parasitic disease, is one of the five most common of the officially designated neglected tropical diseases. It has been found in 13 discrete foci distributed among six countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela) in Latin America (LA). Onchocerciasis was brought to the Americas through the slave trade in the sixteenth century, was transmitted to the indigenous American population once introduced, and was then spread through migration. Since its discovery in LA, numerous efforts have been put forth to understand the epidemiology of the disease to control and eventually eliminate the disease. The establishment of public–private partnerships and the development of community wide mass distribution programs of Mectizan® (ivermectin, donated by Merck, Sharpe, and Dohme) have resulted in dramatic progress against onchocerciasis in all of the endemic foci of LA. Transmission has been interrupted in 11 of 13 foci in LA, including all foci in Colombia, Ecuador, Guatemala, and Mexico as well as in two of the three foci in Venezuela. Transmission remains active only in the two foci straddling the border between Brazil and Venezuela. This area is inhabited by the Yanomami tribe indigenous to the Amazonian forest, and evidence suggests that transmission has been suppressed in some Yanomami communities. Interruption of transmission in these Amazonian foci, the last active foci in LA, will require intensified efforts and cross-border collaboration, but once successful, will culminate in the complete elimination of this scourge from the Americas.

Keywords Onchocerciasis • River blindness • Latin America • Caribbean • *Onchocerca volvulus* • Ivermectin • Diethylcarbamazine • Elimination

1 Introduction

The global network for Neglected Tropical Diseases (NTD) is a group of 13 parasitic and bacterial infections that affect over 1.4 billion people, most of whom live an income of less than $1.25 per day (Liese et al. 2010). The diseases included in this definition are ascariasis, Buruli ulcer, dengue, dracunculiasis, human African trypanosomiasis, hookworm, leishmaniasis, leprosy, lymphatic filariasis, schistosomiasis, trachoma, trichuriasis, and onchocerciasis. Among these, lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, trachoma, and

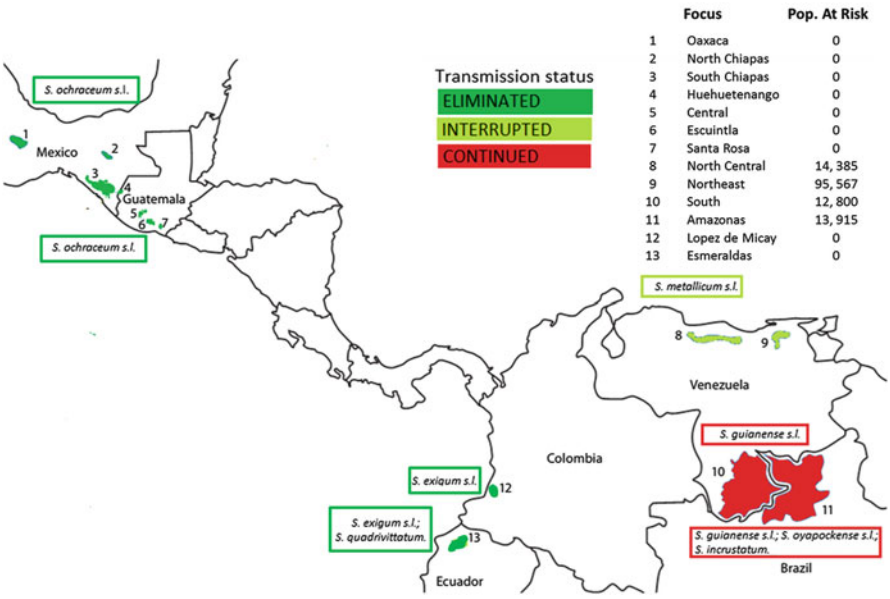

Fig. 1 Distribution of human onchocerciasis endemic areas, current status of transmission in Latin America, and vector species discussed in the text. The current population at risk is also presented per each focus in the *inset box* [All data were provided by the Onchocerciasis Programs (Mexico, Guatemala, Ecuador, Colombia, Venezuela, and Brazil) in coordination with the Onchocerciasis Elimination Program for the Americas (OEPA)]

onchocerciasis are the five most common neglected diseases (Gyapong et al. 2010). NTDs represent a major public health problem for most developing countries. Several factors including social stigma, prejudice, marginalization, the extreme poverty of suffering populations, and low mortality contribute to the classification of these diseases as neglected (Liese et al. 2010). Their prevalence in isolated geographical and environmental conditions outside the developed world and lack of attention paid to them by the pharmaceutical industry have further diminished the profile of these NTDs in the global health arena (WHO 2006).

Human onchocerciasis (river blindness) can be found in 13 isolated regional foci distributed among six countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela) in Latin America (LA; Fig. 1) (WER 2013). Onchocerciasis is caused by infection with the filarial nematode *Onchocerca volvulus*, which is transmitted by the bites of black flies of *Simulium* species which breed in fast-flowing rivers. The adult worms inside humans reproduce within fibrous tissue (nodules), where the fertile adult females produce millions of microfilariae that move through the skin or enter the eye, causing the symptomatology associated with the dermal and ocular manifestations of the disease.

Onchocerciasis is addressed in the resolution entitled "Elimination of Neglected Diseases and Other Infections Related to Poverty" written in 2009 during the 49th Meeting of the Directing Council of the Pan American Health Organization

(PAHO). This resolution encouraged the engagement of PAHO's affiliate States to eliminate or reduce the neglected diseases and other infections related to poverty for which tools exist to levels where these diseases will no longer be considered as public health problems in Latin America and the Caribbean by 2015. This chapter reviews the approaches and strategies followed for the control and elimination of onchocerciasis in LA, in keeping with the spirit of PAHO's resolution.

2 The Arrival of Onchocerciasis to the Americas

The phylogenetic analysis of *O. volvulus* parasites revealed a relationship between African Old World and American New World parasites which supported the hypothesis that onchocerciasis is an imported infection (Zimmerman et al. 1994). These studies suggested that *O. volvulus* parasites arrived in the Americas (Central and South America) through the West African slave trade. Slaves carrying the infection by the parasites then were transmitted to the indigenous American population by the local black fly species (Gustavsen et al. 2011). The infection was spread further through migration of infected individuals within the colonies, including migrant workers working on coffee plantations (Rodríguez-Pérez et al. 2007; Gustavsen et al. 2011). Despite having been an infection introduced from Africa, onchocerciasis was first described in 1915 by Rodolfo Robles in Guatemala (Robles 1919). Since it was first discovered, numerous efforts have been undertaken to understand the epidemiology of the disease, with the eventual goal of controlling and eventually eliminating the disease.

3 The Burden of the Disease

Onchocerciasis represents an important public health problem predominantly in Africa. It is ranked among the top five causes of visual impairment overall and as the second leading cause of infectious blindness, following only trachoma (Etya'ale 2008; Hotez et al. 2008). Onchocerciasis is in the twelfth place in health impact among the neglected tropical diseases that afflict LA (Hotez et al. 2008). According to the classification system of the World Health Organization (WHO), which is based on emergence, control, and drug availability, onchocerciasis is in category three, indicating that there is a control strategy which has been demonstrated to be effective, there is a plan for their elimination, and the burden of the disease is decreasing (Lindoso and Lindoso 2009). Despite encouraging control achievements in some areas of West Africa, onchocerciasis is still particularly prevalent in Africa, where more than 99 % of all cases occur; current estimations indicate that around 123 million persons are at risk for infection in 38 endemic countries, at least 25.7 million are infected, and 1 million are blind or have severe visual impairment in Africa (Centers for Disease and Prevention 2013). In contrast, no new cases of impaired vision attributable to onchocerciasis have been reported in LA since 1995

(PAHO/WHO 2013). In the Americas, only 379,234 persons were considered at risk for infection with *O. volvulus* as of 2013 (WER 2013). Currently, only 136,667 persons at risk are the reports from (OEPA 2015).

4 The Parasite and the Vector

Genotypic and phenotypic variation plays an important role in the ecology of transmission of onchocerciasis in LA (Shelley 1991). Most importantly, *O. volvulus* is transmitted by several different species of black fly in LA (Fig. 1), which differ greatly in their ability to transmit the parasite, or their vectorial capacity. One of the most important variables in the different vectorial capacities of the various *Simulium* species that transmit the parasite is their vector competence or their intrinsic ability to support the development of the parasite to the infectious stage. Vector competence is dramatically influenced by the presence or absence of an anatomical structure known as the cibarial armature (Duke 1970; Reid 1994; Basanez et al. 2000). Vector competence in species with a cibarial armature is constantly low because the "teeth" of the armature frequently cause damage to the microfilarie ingested during blood feeding, preventing their development to the infective L3 larvae on the fly. In contrast, species without this structure have a higher vector competence, because the microfilariae arrive in the midgut undamaged, and are able to more efficiently develop to the infectious L3 stage. The number of parasites taken up during a blood meal also influences the vector competence of these species, because increased numbers of parasites increase the probability that some may pass the armature undamaged, thereby resulting in an increased probability of successful transmission. *O. volvulus* in the Northern part of the Americas (e.g., Guatemala and Mexico) is primarily transmitted by *S. ochraceum* s.l. which is a species with armed cibarium and therefore a relatively inefficient vector. In contrast, *S. exiguum* s.l. and *S. guianense* s.l. species found in Ecuador, Colombia, Venezuela, and Brazil lack an armature and as a result are extremely competent vectors rivaling the African vector *S. damnosum s.l.* in this respect (Convit et al. 2013).

In addition to vector competence, vectorial capacity is determined by a number of other factors, including vector density, host preference, extrinsic incubation period, and the daily survival probability of an infected fly (Basáñez et al. 1996; Basáñez and Ricardez-Esquinca 2001). These additional factors influence the overall role that a given species will play in the overall transmission of the parasite. For example, if a given species has a high vector competence, but man–fly contact is low because of low biting rates, due to either a small vector population size or a prediction of the species for zoophily, the efficiency of the vector for transmission will be reduced. Conversely, if a species has low competence but if man–fly contact is high because of high biting rates, the efficiency of the vector for transmission will be increased. In onchocerciasis, vector capacity is usually measured by the Annual Transmission Potential (ATP), a theoretical number of infective larvae a resident is exposed to in 1 year (Basáñez et al. 2002).

5 The Pathogenic Process and Clinical Diagnosis of Onchocerciasis

The clinical presentation of onchocerciasis includes acute and chronic forms (Udall 2007). Onchocerciasis in its acute forms presents clinically as a diffuse papular dermatitis, associated with intense pruritus. The chronic manifestations of the disease also involve different grades of cutaneous manifestations such as pruritic lichenification an asymptomatic depigmentation of the skin known as the "leopard skin" pattern. However, some patients suffering from chronic disease have also a papular disease similar to an acute papular eruption. TH-1- and TH-2-based immune responses are associated with the acute and chronic cutaneous forms, respectively (Timmann et al. 2003). The "onchocercomata," i.e., a subdermal nodule, is another frequently seen manifestation. The location of these subdermal nodules changes according to the geographic origin of the patient. In Africa, onchocercomata are often found located at the bony prominences of the torso and hips, whereas in South America, the infection typically produces nodules on the head and shoulders (Udall 2007). Furthermore, the skin manifestations as well as the ocular symptoms are in part caused by retinal and retinoic acids that are stored in tissues after the death of microfilariae (Mawson and WaKabongo 2002). Moreover, a strong eosinophilic response is elicited due to the contact with the products resulting from parasite metabolism (Pearlman et al. 1999). On the other hand, the ocular pathology has been linked to an immunological response to *Wolbachia* antigens released when microfilariae suffer the natural decrease of its fitness over time (Brattig 2004).

6 Diagnostic Tests for Onchocerciasis

The gold standard for the onchocerciasis diagnosis historically has been microscopic examination of skin biopsies from the iliac crests (African patients) and/or from the shoulders (Guatemalan–Mexican patients) and/or from the lower part of the body in individuals of the Amazonian focus (Vivas-Martínez et al. 2007) for microfilariae (WHO 1987). This method depends on the intensity and prevalence of the infection in the communities. Thus, while a suitable indicator for evaluating prevalence in untreated areas, the skin sinp is an insensitive test when applied to areas in which control is ongoing, and the prevalence of patent infections is quite low. As a result, more sensitive tests, including skin-snip PCR and ELISA assays, to monitor for the presence of antibodies to the parasite are replacing the skin snip in monitoring the progress towards elimination in areas subject to successful control programs (Boatin et al. 1998, 2002).

In LA, the onchocerciasis elimination programs have been employing an ELISA-based serologic antibody test to monitor for the presence of antibodies to a 16 kDa antigen present in the parasite, known as the Ov16 ELISA. This method

has a disadvantage that it cannot distinguish present from past infection, or even exposure to the parasite. Despite these limitations, the Ov16 ELISA has become the test of choice for assessing the advances of the Mectizan® program in LA (Rodríguez-Pérez et al. 2011). In employing the Ov16 ELISA, screens are restricted to children under the age of 10, thus providing a more accurate measure of host–parasite contact in the control period, and limiting the confounding effects of the prolonged antibody response on the assessment of transmission intensity.

A conventional PCR assay targeting an *Onchocerca*-specific tandem repeat has been widely adopted as the most sensitive way to detect the presence of parasites by the programs in LA. This assay detects all life cycle stages of the parasite and can be employed to detecting parasite DNA in both the human and black fly vector hosts of the parasite. In Ecuador, pool screen PCR assays using the O-150 PCR were performed to monitor the infection levels in the vector populations (Guevara et al. 2003). Extensive entomological studies employing the O-150 PCR were also performed in Mexico (Rodríguez-Pérez et al. 2004, 2006a). The O-150 PCR is being employed as a reliable approach to estimate parasite transmission levels in some foci of Africa and the six affected countries of LA (Adjami et al. 2004; Rodríguez-Pérez et al. 2006b, 2008a, b, 2010a, b; Lindblade et al. 2007; Marchon-Silva et al. 2007; Vieira et al. 2007).

The O-150 PCR, when employed to screen pools for vectors, has been recommended by OEPA as the key metric for monitoring transmission interruption in the posttreatment surveillance (PTS) phase of the elimination programs in LA (Rodríguez-Pérez et al. 2011). In the PTS phase, large numbers of black flies need to be screened to confirm that transmission has not recurred. Recent advances in technology have been reported that will facilitate this process. First, oligonucleotide magnetic based techniques have been developed for the specific purification of DNA sequences containing the O-150 repeat (Gopal et al. 2012). This method has allowed the number of flies that may be included on a single pool to be increased fourfold over that possible using conventional DNA purification methods. In addition, novel traps for LA vector black flies have recently been developed that should permit the replacement of human landing collections to collect the necessary number of flies to certify transmission suppression and eventually interrupting and elimination (Rodriguez-Perez et al. 2013a). These advances will also aid in continued entomological surveillance of the vector populations after elimination has been regionally declared.

7 Control and Treatment of Onchocerciasis

The control and treatment of onchocerciasis historically has involved targeting both the vector and infected human populations. In Africa, the first large scale onchocerciasis control program, the Onchocerciasis Control Programme in West Africa (OCP), relied almost entirely upon vector control, based on aerial larviciding of breeding sites on the rivers. In some areas of LA, successful vector control

campaigns using the larvicide Temephos have been realized, including the San Vicente Pacaya area in Guatemala (Ochoa et al. 1997). In general, however, in LA vector control campaigns have been difficult to implement due to the limited access imposed by the geographical localization of the foci and elevated operational costs (Shelley 1991; Vivas-Martínez et al. 2007).

In LA, surgical and chemotherapeutic procedures have been the major methods employed in the treatment of the infected individuals (Rodríguez-Pérez et al. 2011). Control through surgical nodulectomy provides beneficial effects to the infected people by reducing the microfilarial loads, decreasing the amount of microfilaria entering the eye, and diminishing the skin pathology. However, the efficacy of this procedure differs as a function of onchocerciasis prevalence. For instance, nodulectomy had a positive effect in reducing the intensity of infection in hypoendemic areas. This result was also observed in hyperendemic areas, but the effect was short lived, with new nodules developing rapidly (Guderian 1988).

Before the 1990s, the only choice of treatment to onchocerciasis was the potent microfilaricidal drug diethylcarbamazine (DEC). DEC produced numerous, frequent, and serious side effects such as headache, musculoskeletal pains, fever, tachycardia, hypotension, vertigo, and optic nerve damage, making it unsuitable for mass chemotherapy campaigns (Greene 1990; Rodríguez-Pérez and Rodríguez-López 1994). Currently, this drug is no longer used for the treatment of onchocerciasis. The advent of ivermectin in the 1990s, which rapidly proved to be a safer microfilaricidal drug than DEC, drastically improved the prospects for onchocerciasis control (Lara-Ramirez et al. 2013). Ivermectin is a semisynthetic product, derived of the macrocyclic lactones synthesized by the actinomycete *Streptomyces avermectilis* (Omura and Crump 2004). The drug acts by blocking postsynaptic, glutamate-gated chloride ion channels, paralyzing the nematode. The standard dose for onchocerciasis is 150 μg/kg weight taken quarterly, per annum, or twice a year (Kamgno et al. 2004; Rodríguez-Pérez et al. 2008b). Initially, children under 5 years of age, or less than 15 kg body weight or 90 cm height were not eligible for treatment. However, since 2004, ivermectin has been approved for use in children once they are 5 years old (Rodríguez-Pérez et al. 2011). Pregnant women, breast-feeding mothers within 1 week of delivery and persons with neurological disorders or severe intercurrent disease are still excluded from treatment with ivermectin.

The adverse effects of ivermectin depend on microfilarial loads (Keiser et al. 2002). At concentrations of more than 20–50 microfilariae per mg of skin, the adverse effects appear within 1–2 days of treatment, which can include pruritus, urticaria, dermatitis, fever, urticaria, myalgia, oedematous swelling of the limbs and face, or postural hypotension (Keiser et al. 2002; Taylor et al. 2010). Release of *Wolbachia* endosymbiotic bacterial products from dying microfilariae induces innate immune responses that are thought to contribute to these symptoms (Cross et al. 2001). The modality of treatment based on long-scale-repeated administration of ivermectin to the infected individuals and the population at risk is more effective than a short scheme of treatment.

8 Epidemiological Models for Aid the Control of Onchocerciasis

Several mathematical models have been developed to simulate onchocerciasis transmission in specific endemic zones of African and LA (Plaisier et al. 1990; Davies 1993; Basanez and Boussinesq 1999; Basáñez and Ricardez-Esquinca 2001; Winnen et al. 2002; Filipe et al. 2005). These methods mainly take into account the life cycle of the parasite, the type of treatment, the phenotypic characteristics of the vector, the microfilarial load in the skin, and the biting rate of the vectors. These mathematical models have been applied to explore the epidemiological consequences and the effects of treatment and control interventions on the parasite population dynamics. For example, the computer simulation model for onchocerciasis in the Americas (SIMON-a), designed to emulate the transmission dynamics of onchocerciasis in LA under different regimes of ivermectin distribution, showed that a few members of a community will continue to be infected at a low parasite level at the termination of the treatment regime. These members include the 2–3 % people who are not eligible for treatment, implying that they will continue to be infected (and theoretically infective to vectors) for up to 10 years, the average estimated life span of the adult worms (Bradley et al. 2005). Hence, the infected individuals will probably remain infectious for the vector population, raising the possibility that the transmission may continue at a low level for some period once the treatment is halted (Dadzie et al. 2003). Therefore, these simulation results have provided important strategic suggestions for the control programs in the posttreatment era.

9 Programs to Combat Onchocerciasis

The Onchocerciasis Control Programme (OCP) was the first internationally coordinated initiative addressing a neglected tropical disease. It was launched in 1974, with cosponsorship by WHO, the World Bank, UNDP, and the Food and Agriculture Organization (Benton et al. 2002). Its primary objectives were to eliminate the blinding form of the disease as a public health problem and to open up large areas of prime agricultural land, areas that were precluded for agricultural use due to the high probability of developing ocular onchocerciasis for those attempting to reside there. The OCP covered parts of 11 West African countries and primarily employed a strategy of aerial larvicide spraying of the breeding sites of the larvae of *Simulium* (the immature state of the black fly). In the latter stages of the program, when Mectizan became available, this strategic plan was broadened to include Mectizan distribution. The OCP ended its operations in 2002, having successfully met its goal of eliminating blinding onchocerciasis as a public health problem from large parts of West Africa, as a result freeing up 250 000 km^2 of arable land for agricultural use.

The African Programme for Onchocerciasis Control (APOC), launched in 1992, is similar to the structure of OCP (Remme 1995). Its primary objective is control of the disease (Liese et al. 2010), using a strategy of community-directed mass treatment with Mectizan. In 1995, APOC expanded the area of onchocerciasis control to the remaining 19 endemic countries throughout Africa. Initially, the APOC strategy was thought to be capable on only controlling the disease and not eliminating the infection. However, recent studies have suggested that mass distribution of Mectizan (ivermectin) to afflicted communities may be effective in achieving local elimination of the parasite (Diawara et al. 2009; Traore et al. 2012). These findings have resulted in a shift in the international community from a strategic focus on control of river blindness towards the goal of elimination, both in Africa and in LA.

The Onchocerciasis Elimination Program of the Americas (OEPA), a multinational, multiagency coalition between national governments, Merck (MSD Donation Program), PAHO, the US CDC, the Carter Center, the Bill & Melinda Gates Foundation, Lions Club International, and others, was established in 1992 (Sauerbrey 2008). Like APOC, OEPA relies upon community wide mass treatment with Mectizan as its primary tool to eliminate onchocerciasis. OEPA provides programmatic and technical review services to the member countries; however, the main responsibility for implementation lies with national control programs of the participating countries themselves (Blanks et al. 1998; Sauerbrey 2008). OEPA's goal is to eliminate the disease in the Americas through a community-directed treatment with ivermectin. The OEPA strategy is to support national programs in the six endemic countries to provide twice-yearly (or quarterly if needed) mass drug administration (MDA) of ivermectin to $\geq$85 % of the eligible population at risk (WER 2013). A total of 11,069,285 treatments with ivermectin had been administrated under the OEPA umbrella to the eligible populations in 13 endemic foci of LA from 1993 to 2012 (Centers for Disease and Prevention2013). Due to the success of the program, most LA countries have successfully interrupted transmission and have suspended the use of ivermectin as a result. Thus, only 23,378 endemic individuals were treated with ivermectin in the whole region in 2013 (Centers for Disease and Prevention 2013). OEPA has now succeeded in ending onchocerciasis-induced ocular morbidity (defined as $<$1 % prevalence in endemic areas of microfilaria in the anterior segment of the eye) in the Americas (WER 2006) and will likely end its operations when the elimination of onchocerciasis from LA is announced by PAHO/WHO.

10 Summary and Conclusions

Since it's founding in the early-1990s, OPEA has been remarkably successful in its efforts to eliminate onchocerciasis from LA. In the 1990s, the program faced a daunting situation where millions of individuals residing in multiple foci in six countries were at risk. OEPA has reduced this to a population of less than 20,000

individuals residing in a remote focus spanning the border of Venezuela and Brazil. Elimination of onchocerciasis from Colombia and Ecuador has been verified by WHO. Mexico has applied in 2014 and it is expected that Guatemala will be applying to WHO for verification in 2015 as well.

The success of OEPA provides a strategic model for eventual elimination of onchocerciasis from Africa, although the scale of the problem in Africa is much greater that that faced by OEPA in LA in the early-1990s. OEPA's strategy was predicated upon developing a complete understanding of the extent of the problem, initially identifying every community in which onchocerciasis was endemic. OEPA instituted an aggressive program of semiannual treatment of all endemic communities, regardless of the level of endemicity, and increased this to quarterly treatments in some recalcitrant areas. The program maintained high levels of coverage of the eligible population for every treatment round through multiple rounds of treatment. Finally, OEPA maintained flexibility in their use of diagnostic tools to monitor the progress towards elimination and in finally certifying elimination of transmission of onchocerciasis. This process involved dropping certain diagnostic criteria that proved to lack the specificity necessary to measure prevalence at low levels (e.g., ocular morbidity criteria) and the aggressive application of methods that were applicable to low prevalence situations (e.g., the Ov16 ELISA in children and O-150 PCR screening of large numbers of vector black flies). It is likely that a similar operational strategy of emphasizing frequent mass treatments with Mectizan with consistent high coverage rates, together with the application of appropriate diagnostic techniques to monitor the success of the problem and identify problem areas warranting additional attention, will prove to be successful in eliminating onchocerciasis from much of Africa.

11 Epidemiological Policies for the Control of Onchocerciasis

A framework of epidemiological policies has been employed to aid in the control of onchocerciasis. Mapping, monitoring, and surveillance constitute this framework (Baker et al. 2010). The first of three procedures is the mapping of disease prevalence and distributions, which is crucial for any control efforts. Detailed mapping information is needed to allow planning for implementation of control measures. In this context, APOC developed the rapid epidemiological mapping of onchocerciasis (REMO) risk assessment instrument (Noma et al. 2002), on the basis of the proximity of probable *Simulium* breeding sites, to identify priority areas for mass distribution of ivermectin. Then a subsample of communities in areas identified as high risk by REMO is screened with the rapid epidemiological assessment (REA) method to estimate onchocercal nodule prevalence (Noma et al. 2002). The REA consists in performing skin snips on a sample of individuals in the community. If none of the persons examined had positive snips, the community is classified as

negative. However, if worms are identified in biopsies, the community is classified (according to the number of people who test positive) as hypoendemic (prevalence of mf infection < 20 %), mesoendemic (prevalence ≥ 20 % but lower than 60 %), or hyperendemic (prevalence ≥ 60 %). The prevalence is also needed to identify what age groups should be targeted for treatment and the frequency of treatment. Once the essential information needed for each village or community, and further stratification of communities by prevalence, has been obtained through mapping, the intervention program can be implemented.

Monitoring aims to assess program progress. Monitoring procedures include routine monitoring of indicators and periodic or one-time evaluations. The programs of Africa and LA employ the treatment coverage as a one key indicator to monitor the program results (APOC/WHO 1998; OEPA 2015). In addition, various methods for quantifying coverage through household visits have been used. Moreover, assessment of sentinel sites every 4–5 years to evaluate the current stage of transmission, through effects on eye and skin lesions, clinical examinations, and entomological studies, is also used (WHO 1987, 1995).

Posttreatment surveillance is defined as surveillance after intervention activities end and is therefore a key component of the elimination programs for onchocerciasis. In 2001, WHO published a document entitled "Certification of elimination of human onchocerciasis: criteria and procedures," which established the different phases to be followed by a country to achieve verification of elimination of onchocerciasis (WHO 2001). Each phase is associated with an aspect of parasite transmission resulting in four phases. Phase 1 is the stage where the transmission is active and is demonstrated by the presence of *O. volvulus* infective larvae (L3 stage) in the vector population, mf in the skin, parasite nodules, and positive serology in the population and especially in children <5 years old. This phase involves ivermectin treatment until transmission is suppressed. Phase 2 is the stage when the transmission is suppressed, demonstrated by negative results of the above indicators. Suppression is maintained through treatment of the mean reproductive lifespan of the adult female. Phase 3 is the stage when transmission is interrupted, which is demonstrated by specific epidemiological indicators including (1) prevalence of < 1 % of *O. volvulus* mf in the cornea and/ or anterior chamber of the eye, (2) an infectivity rate (L3 infection in heads) by PCR of $< 1/1{,}000$ (0.1 %) in parous flies or $<1/2{,}000$ (0.05 %) in all flies, assuming a 50 % parous rate, (3) an ATP or seasonal transmission potential (STP) of under 20; and (4) a reduction of new infections to an incidence rate of less than one new case per 1,000 individuals (<0.1 %) defined as lack of specific Ov-16 antibodies to *O. volvulus* in children less than 10 years of age. In this phase, suspension of treatment is suggested and a 3-year period posttreatment surveillance is begun to monitor for transmission recrudescence. Phase 4 takes place after the 3 years of posttreatment surveillance, once the surveillance parameters confirm no recrudescence of disease. Onchocerciasis is then declared eliminated by WHO after the country requests evaluation; however, long-term surveillance should continue.

12 The Geographical Distribution and Current Epidemiology Situation of the Disease in LA

Onchocerciasis in LA currently exhibits a severely geographically circumscribed endemicity. This is a result of the ecology of the infection in LA, coupled with the effect of the intensive public health interventions to eliminate the disease. Onchocerciasis was historically endemic in six countries in 13 isolated foci (Figure 1).

12.1 Brazil

There is a single focus of onchocerciasis in the Amazon region of Brazil located among the Yanomami population. The first record of the disease in Brazil was reported in 1967. Later studies in the 1970s defined the limits of the focus in an area occupied by Amerindians (the Yanomámi tribe) (Shelley 2002). This is a region which is contiguous with the endemic focus found in Southern Venezuela. The affected region is remote and mountainous, densely forested, and the migratory Yanomami tribe freely move across the border into Venezuela. Brazil's focus is divided according to its endemicity level. At present, there are 22 endemic organizational areas (seven hyperendemic, nine mesoendemic, and six hypoendemic) called "polos bases", where there are 13,915 people at risk of infection. The most recent assessments suggest that Brazil is near to suppressing onchocerciasis transmission in its part of the shared endemic Yanomami area (Centers for Disease and Prevention 2013).

12.2 Colombia

There was a single focus of onchocerciasis in Colombia located in the town López de Micay. The first confirmed case of onchocerciasis in Colombia was in 1965; later epidemiologic studies identified nine communities near the headwaters of the Micay River with infected people, designated the López de Micay focus (Corredor et al. 1998). The López de Micay focus was a mesoendemic focus with a total of 1,366 people considered at risk of infection. Colombia initiated an intensive program of 6-monthly ivermectin MDA in 1996 (WER 2013), providing 20 rounds of MDA coverage to least 85 % of the eligible population before it interrupted transmission in 2007, and halted MDA in 2008 (Centers for Disease and Prevention 2013). Colombia successfully completed posttreatment surveillance (PTS) in 2010 and applied to WHO for verification of elimination of onchocerciasis in 2012 (Centers for Disease and Prevention 2013). Recently, the elimination of onchocerciasis from Colombia was announced (Burki 2013); this news positioned Colombia as the first country in the world that has achieved onchocerciasis elimination.

12.3 Ecuador

Ecuador has a single focus of onchocerciasis located in the Esmeraldas region. The first case of onchocerciasis in Ecuador was recognized in 1980 (Carbajal and Zerega 1980). Subsequent epidemiological studies defined the geographic location of the focus as the Santiago River Basin (formed by the merger of 3 main rivers: Río Cayapas, Río Onzoles, and Río Santiago). This focus included 119 populations with different grades of endemicity (42 hyperendemic, 23 mesoendemic, and 54 hypoendemic), representing 25,863 at risk for infection. Epidemiological and entomological surveys confirmed that transmission of *O. volvulus* was interrupted in 2009, and treatments were stopped as a result. A posttreatment follow-up survey (PTS) in 2012 revealed no evidence for transmission recrudescence. Recently, the elimination of onchocerciasis from Ecuador was also announced (OEPA 2015) becoming the second nation after Colombia to request verification of elimination.

12.4 Guatemala

Guatemala was the first place in the Americas where onchocerciasis was detected (Robles 1919). There were four recognized foci in Guatemala (Santa Rosa, Escuintla-Guatemala, Huehuetenango, and the Central Endemic Zone of Guatemala [Departments of Suchitepéquez, Solol, and Chimaltenango]) (González et al. 2009). The four foci included a total of 518 endemic communities (42 hyperendemic, 15 mesoendemic, and 461 hypoendemic). The four foci of Guatemala include the highest number of persons at risk for onchocerciasis in the Americas (231,467). In 2006 and 2007, respectively, Guatemala's Santa Rosa and Escuintla foci were the first in the region to report interruption of transmission (Lindblade et al. 2007; González et al. 2009), followed by the Huehuetenango focus in 2008 (Cruz-Ortiz et al. 2012). Recently, these three foci (Santa Rosa, Escuintla-Guatemala, and Huehuetenango) have completed the PTS phase, and the results have supported the conclusion that transmission has been eliminated (PAHO/WHO 2013). The hyperendemic central endemic focus stopped ivermectin treatment at the beginning of 2012 and has completed the PTS phase, the country of Guatemala will be applying for WHO verification of elimination, a process that is estimated to commence in 2015 (Centers for Disease and Prevention 2013).

12.5 Mexico

There are three endemic foci of onchocerciasis in Mexico, all of which are found in mountainous areas of Southeast México (Martin-Tellaeche et al. 1998). Two are in the state of Chiapas (Northern and Southern foci) and one is in the state of Oaxaca

(Rodríguez-Pérez et al. 2010a, b; Rodriguez-Perez et al. 2013b). These three foci encompass 670 endemic communities (39 hyperendemic, 220 mesoendemic, and 411 hypoendemic). The three foci include 169,869 persons at risk for onchocerciasis, the second highest country total in the Americas after Guatemala. Northern Chiapas eliminated the transmission in 2010 and Oaxaca in 2011 (OEPA 2015). Transmission was also interrupted in the Southern Chiapas focus in 2011 (Rodriguez-Perez et al. 2013b). The PTS surveys concluded that there has been no recrudescence of transmission during the PTS period, thus, Mexico applied for WHO verification in 2014 (PAHO/WHO 2013; OEPA 2015).

12.6 Venezuela

There are two different endemic regions in Venezuela. The North-central (Arends et al. 1954) and Northeast (Potenza et al. 1948) foci together make up the Northern endemic area. These two foci are located in the coastal mountains ("Cordillera de la Costa"). The third focus, the southern Amazonian focus, is restricted to the rainforest of the Upper Orinoco River region and, as mentioned above is contiguous with the Brazilian focus. The North-central, Northeast, and Southern foci in Venezuela contain 122,752 persons at risk for onchocerciasis, the third highest national total in the Americas. The transmission was interrupted in the North-central and Northeast foci in 2010 and 2012, respectively (Convit et al. 2013). In those foci, the population under PTS is approximately 109,952 people. In the Southern focus, suspect areas exist where transmission may still be active and within which endemic communities may remain to be identified. Such unidentified endemic communities represent the major obstacle to achieving regional elimination of onchocerciasis (Centers for Disease and Prevention 2013).

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Leprosy in Latin America and the Caribbean: Burden of Disease and Approaches for Elimination

Carlos Franco-Paredes, Anna Hare, and Carlos del Rio

Contents

Abstract Leprosy is a highly treatable chronic bacterial NTD with multidrug therapy (MDT), which has a high cure rate. Early initiation of treatment in leprosy is important for limiting transmission and disability. Proper treatment decreases bacterial burden and thus likely decreases transmissibility considerably, though the degree of transmission risk reduction remains unknown due to lack of exact knowledge of transmission mode and mechanism. In order to eliminate leprosy in the Americas or elsewhere, concerted efforts need to target the stigma and discrimination legacy of this disease. Furthermore, monitoring, treatment, and rehabilitation of those who have important disability among new cases and among those individuals who have completed treatment will remain a challenge, even if the elimination goals are achieved. Finally, the statistics presented in this chapter and

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DOI 10.1007/978-3-7091-1422-3_9

reported from WHO/PAHO do not capture the burden of disease associated with long-term disability even after completing MDT, as well as the potential occurrence of late leprosy reactions among many individuals classified as microbiologically cured. Setting realistic goals for elimination of leprosy in Latin America and other regions is crucial.

Keywords Leprosy • Multibacillary • Paucibacillary • Dapsone • Rifampin • *Mycobacterium leprae* • Latin America • Elimination • Control

1 Introduction

Leprosy is a chronic bacterial infection caused by the bacillus *Mycobacterium leprae* (Walker and Lockwood 2007; White and Franco-Paredes 2015). Approximately, 5 % of individuals are susceptible to become infected and develop clinical manifestations of this infection (Scollard et al. 2006). This bacterial pathogen has a tropism to infect keratinocytes and histiocytes on the skin and Schwann cells of the peripheral nerves (White and Franco-Paredes 2015; Scollard et al. 2015; Franco-Paredes et al. 2009; Polycarpou et al. 2013). The histopathologic hallmark of leprosy is perineural inflammation, and this localization reflects a vascular route of entry of the bacilli into nerves (Scollard et al. 2015). Once *M. leprae* enters into Schwann cells, it leads to axonal atrophy and dysfunction and segmental demyelination (Scollard et al. 2015). This affinity may also favor its spread by acting as a Trojan horse carrying the bacilli to other organs by dedifferentiated Schwann cells (White and Franco-Paredes 2015).

The predilection of *M. leprae* to infect Schwann cells is responsible for many of the clinical manifestations of the disease (Walker and Lockwood 2007; Scollard et al. 2015). Leprosy can be viewed as two distinct disease processes (Scollard et al. 2006). First, it is a peripheral neuropathy caused by the perineural inflammation associated with nerve injury. Second, this infection can elicit a broad range of exuberant cellular immune responses that exacerbate nerve damage including partial or complete loss of touch, temperature, proprioception, and vibratory sensations. Depending on the degree of affection, disability and deformity may ensue, impairing the quality of life of affected individuals and thus considered within the Neglected Tropical Diseases (NTD) (White and Franco-Paredes 2015). The organs primarily affected include the skin, mucous membranes, eyes, upper respiratory tract, and peripheral nerves (Walker and Lockwood 2007; Scollard et al. 2006). Leprosy can be diagnosed clinically by identifying characteristic skin lesions with anesthesia or hypoesthesia and palpating thickened peripheral nerves (Franco-Paredes et al. 2009). Confirmation of diagnosis can be accomplished by the presence of granulomatous inflammation in skin and nerve biopsy specimens or through the detection of acid-fast bacilli in slit skin smears (Walker and Lockwood

Table 1 Ridley–Jopling and World Health Organization classifications of leprosy and risk of leprosy reactions

WHO	Paucibacillary		Multibacillary		
Ridley–Jopling[a]	TT	BT	BB	BL[b]	LL
Type 1 reaction	No	Yes	Yes	Yes	No
Type 2 reaction	No	No	No	Yes	Yes

WHO classification is used for operational field purposes, and it is based on a number of skin lesions and previously also included the bacillary index

[a]Ridley–Jopling classification (RJ) is an immunopathological and clinical classification and includes in its most simplified form five clinical phenotypes: Tuberculoid (TT); Borderline tuberculoid (BT); Borderline borderline (BB); Borderline lepromatous (BL); and Lepromatous (LL)

[b]Patients with BL can develop type 1 and/or type 2 reactions

2007; Franco-Paredes et al. 2009). Without treatment, nerve damage can continue and become profound, leaving a person vulnerable to tissue damage and infection and subsequent limb loss or blindness from corneal scarring associated with lagophtalmos (Franco-Paredes et al. 2009). The range of clinical phenotypes has been defined by several classification systems, based primarily on histopathologic findings, immunological patterns, and prevalence of bacilli on biopsy (White and Franco-Paredes 2015; Scollard et al. 2006; Franco-Paredes et al. 2009) (Table 1).

2 Leprosy Is a Neglected Tropical Disease

M. leprae is an obligate, intracellular bacillus discovered in 1872 by Armauer Hansen (Scollard et al. 2006). Much has been learned about this bacterial pathogen over the last few decades (White and Franco-Paredes 2015). Leprosy is a highly treatable chronic bacterial NTD with multidrug therapy (MDT), which has a cure rate of about 98 % (Lockwood et al. 2014). Early initiation of treatment in leprosy is important for limiting transmission and disability. Proper treatment decreases bacterial burden and thus likely decreases transmissibility considerably, though the degree of transmission risk reduction remains unknown due to lack of exact knowledge of transmission mode and mechanism. Thus early diagnosis to decrease the amount of time cases remain undiagnosed and untreated is key to limiting transmission, particularly given the long latent period before symptoms are recognized. Further, early treatment can prevent the nerve damage that eventually results in disability. Developing technology to diagnose and treat leprosy has taken over a century, and there is much still to learn about this disease. The first effective treatment was not discovered until 1949 with dapsone. The use of this antibacterial drug spreads quickly throughout the globe, and the first evidence of drug resistance was detected in the 1970s. In 1982, the WHO recommended a combination of treatment medications (MDT). This combination of medication, namely rifampicin and dapsone with the addition of clofazimine in multibacillary disease, continues to

be effective today for treatment of the disease (Walker and Lockwood 2007). Treatment depends on the bacterial burden in patients, which makes proper diagnosis imperative. Multibacilliary forms of the disease require a more extensive treatment than the paucibacillary types (Franco-Paredes et al. 2009).

These attributes make leprosy a tempting target for control and potentially elimination given the fact that the associated disability can be significantly limited or precluded with early diagnosis and treatment. Therefore, early diagnosis and treatment of all patients is the mainstay of the elimination approach that will hopefully translate into a transmission-lowering strategy (Smith et al. 2014). However, there continues to be a plethora of impediments to reduce the tremendous medical and social impact of leprosy. From a biological standpoint, inability to cultivate these bacteria in the laboratory has slowed our understanding of the disease and the development of treatment and vaccines, which in turn has hindered our ability to control this NTD (Scollard et al. 2006). Relevant epidemiologic factors that have limited our ability to decrease the impact of leprosy include the following:

(a) The incubation period can be as long as 30 years, but typically ranges around 2–5 years limiting our ability to establish targeted preemptive strategies (White and Franco-Paredes 2015; Scollard et al. 2006; Lockwood et al. 2014). The consequent delay in its recognition and thus in its diagnosis allows time for potential transmission prior to treatment and for significant nerve damage to occur.
(b) Further complicating control efforts, the mode of acquiring this infection remains uncertain but it is likely that respiratory droplets of patients suffering from lepromatous forms of leprosy with elevated bacillary loads are responsible for some transmission. This gap in knowledge impairs our ability to both assess the need for prophylaxis and develop effective prophylaxis to prevent transmission among close contacts.
(c) Once the diagnosis of leprosy is made, further support can be given in the form of education on self-care, which has been shown to be a determinant of the extent of disability (Ault 2011; World Health Organization 2014). However, early treatment initiation depends on early diagnosis and barriers to early diagnosis, poor access to health care, and stigma remain.
(d) Finally, effective antibacterial therapy is not enough to prevent the long-term complications of nerve injury in many cases, particularly among those who present with important nerve injury at the time of leprosy diagnosis (more than 60 % of cases) (Lockwood et al. 2014). Immune-mediated reactions may also occur even years after completing effective MDT further exacerbating nerve damage. Additionally, patients need education and follow-up monitoring to prevent damage to hands, feet, and eyes.

In summary, despite significant improvements in leprosy treatment and outlook for patients since the introduction of MDT three decades ago, global incidence remains high and patients often have long-term complications associated with the disease (Ault 2011; World Health Organization 2014; Noto and Nunzi 2008; Dogra

et al. 2013). Although worldwide prevalence of the disease has significantly decreased, leprosy is still not a completely understood illness, and often the statistics do not capture the disability and dysfunction that persists even after completing adequate MDT (White and Franco-Paredes 2015; Franco-Paredes et al. 2009).

3 Epidemiology and Burden of Disease of Leprosy in the Americas

Even though there are efforts toward elimination over two decades and some progress in that direction, leprosy continues to pose a public health threat in many countries, including some countries in the Americas. The reasons for the persistence of leprosy remain difficult to define concretely, but many characteristics of the disease and our current level of knowledge contribute to making elimination goals difficult to define and therefore to attain (Lockwood et al. 2014).

In 1991, the World Health Assembly established a goal to eliminate leprosy as a public health problem by the year 2000. The elimination goal was set to decrease prevalence below 1 case per 10,000 people. This goal was successfully achieved at a global level through an expansion of diagnostic services and treatment availability with the help of local governments and NGOs. However, in many countries and regions, prevalence of leprosy and new case detection rate remained high. In 2000, the World Health Organization (WHO) established the WHO Strategic Plan for Leprosy Elimination 2000–2005, focused on elimination at a national level, followed in 2005 by the Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities 2006–2010, and, currently, the "Final Push" strategy for elimination (Lockwood et al. 2014; Smith et al. 2014). In 1985, the prevalence of the disease was 5.2 million cases with cases occurring in 122 countries. By 2005, the global prevalence of the disease had decreased to between 200,000 and 300,000 and the number of countries involved continues to shrink. Nonetheless, and since 2005, there continues to be around 230000 new cases diagnosed every year mainly in India, Brazil, Indonesia, and in other 40 countries. In recent years, further prevalence reduction seems more difficult to attain with many areas leveling out (Smith et al. 2014; World Health Organization 2014). Sadly, at a global level the rate of *grade 2 disability* remains the same in 2013 as to rate of 2010 (World Health Organization 2014).

In the Americas region, leprosy remains a public health problem in many countries. In 2013, the Americas represented approximately 15 % of the global burden of leprosy (World Health Organization 2014). Yet some important achievements have occurred in this region: in the decade between 2003 and 2013, detection of new cases has decreased from 52,435 to 33,084 corresponding to a 37 % decline. In 2013, there were 33,084 new cases identified corresponding to an incidence rate of 5.3 per 100,000 (Table 2) (World Health Organization 2014). The recent

Table 2 Registered prevalence and incidence (newly detected) cases of leprosy in the Americas 2013

Country	Registered prevalence	New cases detected
Anguilla	NR	NR
Antigua and Barbuda	NR	NR
Argentina	538	309
Aruba	NR	NR
Bahamas	NR	NR
Barbados	NR	NR
Belize	0	0
Bermuda	NR	NR
Bolivia	NR	NR
Brazil	28,485	31,044
British Virgin Islands	NR	NR
Canada	NR	NR
Cayman Islands	NR	NR
Chile	0	0
Colombia	584	430
Costa Rica	74	26
Cuba	253	232
Dominica	NR	NR
Dominican Republic	344	128
Ecuador	NR	NR
Falkland Islands	NR	NR
French Guiana	NR	NR
Greenland	NR	NR
Grenada	2	1
Guadeloupe	NR	NR
Guatemala	4	1
Guyana	50	20
Haiti	NR	NR
Honduras	4	4
Jamaica	NR	NR
Martinique	NR	NR
Mexico	451	172
Montserrat	NR	NR
Netherland Antilles	NR	NR
Nicaragua	15	21
Panama	8	3
Paraguay	509	407
Peru	38	27
Puerto Rico	NR	NR
El Salvador	4	1
Saint Kitts and Nevis	NR	NR

(continued)

Table 2 (continued)

Country	Registered prevalence	New cases detected
Saint Lucia	4	2
St Pierre & Miquelon	NR	NR
Saint Vincent and Grenadines	NR	NR
Suriname	30	25
Trinidad and Tobago	62	38
Turks and Caicos	NR	NR
U.S. Virgin Islands	0	0
Uruguay	5	5
U.S.A.	289	188
Venezuela	NR	NR
Total	31,753	33,084

Source Modified from World Health Organization (2014)
NR No report available

decrease suggests that aggressive treatment roll-out and attention to decrease prevalence may be having an effect on incidence, as expected, though it has been slower to manifest. However, a major caveat of these data is that there is probably an underreporting of cases in countries such as Bolivia, Ecuador, Venezuela, and Haiti. On a regional level, Brazil continues to host the highest prevalence outside of India with 94 % of the reported cases. Leprosy remains a public health concern among 24 of 35 countries of the Americas with a higher prevalence (over 200 cases annually) among Argentina, Colombia, Cuba, Mexico, Paraguay, and Venezuela. Mexico, Venezuela, and Paraguay have an increased in the prevalence rate over the past 4 years for unclear reasons (Table 2) (White and Franco-Paredes 2015). Another important consideration is the important number of new cases of leprosy with *grade 2 disability* (2168—6.6 %) reflecting low awareness in the community about leprosy and sub-optimal capacity of health systems to detect the disease.

Some geographic foci of high incidence and prevalence continue to be primarily isolated hard-to-reach communities, such as NE Brazil, Argentina, Bolivia, Dominican Republic, Venezuela, and Paraguay. Communities that are isolated either geographically, such as very rural communities or work camps in the Amazon, or economically, such as in those living in slums and favelas, often have poor healthcare access and the highest disease burden. Migration, common in NE Brazil and other areas where people migrate to find work, additionally plays a role in inhibiting access to care for diagnosis and treatment initiation and adherence (Ault 2011). This confluence of risk factors in communities where access to healthcare and MDT is limited allows the persistence of disease in some communities.

The provision of MDT is a free program in LAC through the Pan American Health Organization (PAHO) and donated by Novartis laboratories. Since adopting Resolution CD49.R19 on October 2, 2009 by PAHO's member states, leprosy was included as one of the NTD for which the goal of elimination at first subnational level was defined by the year 2015. Many of these successes have been achieved

through a strategy that has included expanding access to early diagnosis by integrating leprosy services into primary health activities and school-based mass deworming campaigns.

While all countries in the region had reached the national goal of leprosy elimination (<1 case per 10,000 inhabitants) except for Brazil, patient completion of MDT is not always enough to reflect the long-term neurologic sequelae and dysfunction that occurs among those with severe nerve involvement.

4 Elimination/Control Approaches in the Americas

Nowadays, the challenge of antileprosy efforts is that since 2005 the prevalence and incidence of the disease has plateaued at around 200,000 cases yearly (Lockwood et al. 2014; Smith et al. 2014). This implies ongoing transmission in the affected communities. The enhanced global strategy for further reducing disease burden due to leprosy has the target of reducing new cases with visible deformities or grade 2 disabilities to 35 % of the rate in 2010. As mentioned above, this rate has not declined from 2010 to the end of 2013. Therefore, further efforts are needed to achieve the stated goals (Lockwood et al. 2014).

The principles of eradication of an infectious disease rely on four factors: biologic feasibility, adequate public health infrastructure, funding, and sustained political and societal will (Dowdle and Cochi 2011; Hopkins 2013; Tarantola and Foster 2011). Global decisions on disease eradication require consideration of prioritization and costs in order to achieve the most appropriate, cost-beneficial, and equitable outcome of disease control (Dowdle and Cochi 2011; Hopkins 2013). In addition, other conditions need to be met such as a disease with a straightforward diagnosis, low transmissibility, and ability to distinguish between current and past infection (Lockwood et al. 2014; Tarantola and Foster 2011). There is also limited availability of diagnostic tools for early diagnosis of the disease (White and Franco-Paredes 2015). Based on all these premises, today, and realistically, leprosy elimination seems a distant possibility.

Some of the key interventions that may likely foster reaching the elimination goal include rigorous tracing of contacts to cases with leprosy and case detection campaigns to target individuals (household contacts of lepromatous cases) and populations at risk. The potential introduction of chemoprophylactic regimens or vaccines, which could effectively protect healthy individuals, is needed to prevent further leprosy transmission (World Health Organization 2014). Postexposure prophylaxis with one dose of rifampin may reduce detection rates of new patients by about 50–60 % (Smith et al. 2014). It is estimated that 95 % of the population is naturally immune to the disease (Scollard et al. 2006). The Bacillus Calmette–Guérin (BCG) vaccine widely used for protection against tuberculosis does provide some moderate protection against leprosy, with estimates ranging from 2 to 90 % (Scollard et al. 2006). Unfortunately, a second dose of BCG in school age children

(1999–2006) (BCG-REVAC) in Brazil (Manaus) did not confer protection against leprosy among household contacts (Cunha et al. 2008).

5 Conclusions

In order to eliminate leprosy in the Americas or elsewhere, concerted efforts need to target the stigma and discrimination legacy of this disease. Furthermore, monitoring, treatment, and rehabilitation of those who have important disability among new cases and among those individuals who have completed treatment will remain a challenge, even if the elimination goals are achieved. Finally, the statistics presented in this chapter and reported from WHO/PAHO do not capture the burden of disease associated with long-term disability even after completing MDT, as well as the potential occurrence of late immune complications (i.e., leprosy reactions) among many individuals classified as microbiologically cured. Setting realistic goals for elimination of leprosy is crucial (Lockwood et al. 2014). A major advance in this directing is the selection of a new indicator of *Grade 2 disability* among newly detected cases as a rate per million population. A reduction in this indicator will indicate earlier identification of cases that will likely limit further transmission, and also importantly, of decreased chances of long-term disability.

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Carrion's Disease 2015

Ciro Maguiña and Eduardo Gotuzzo

Contents

Abstract Infection due to *Bartonella bacilliformis* remains a major public health challenge in the South American countries of Peru and Ecuador. Despite multiple control efforts, major outbreaks continue to occur in these areas. Currently, there is no preventive vaccine, and thus early diagnosis and prompt treatment of cases remain the

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_10

cornerstone of control and prevention. Although it is not possible to eradicate the *Lutzomyia* vector, epidemiological and entomological surveillance can be achieved concomitantly with vector control, including physical and chemical control to reduce the adult population. Better control of this disease requires further clinical and epidemiological studies to better understand the ecology of this Neglected Tropical Disease.

Keywords *Bartonella bacilliformis* • Bartonellosis • Oroya fever • Peru • Ecuador • Latin America • Control

1 Introduction

On a global scale, in the last 30 years, new diseases have started to emerge and others have reemerged. Among them is the group of diseases caused by the genus Bartonella, which includes 26 species, 11 of which can cause diseases in humans (Walker 2002; Walker 2006).

Bartonella bacilliformis was the first of the species described in 1905 as the causal pathogen for Carrion's Disease, which during its acute phase produces "La Oroya Fever" and in its chronic phase the Peruvian wart. Other important Bartonella species include *Bartonella quintana* (1914), causal pathogen of the Trench Fever and Bacillar angiomatosis in immunocompromised patients infected with HIV; *B. henselae* and *B. clarrigdgeiae*, which cause Cat Scratch Disease; and *B. elizabethae,* which causes endocarditis and neuroretinits (Relman 1990). Finally, *Bartonella rochaliame*, recently discovered (2007) in an American tourist visiting Peru who presented with fever, enlarged spleen, and bacteremia; initially the patient was thought to have the acute phase of Carrion's Disease, but after appropriate genotyping studies a new *Bartonella* species was identified (Blazes 2013; Spach 2014; Seas 2012).

In 2013, a new strain of the *Bartonella ancashi* was discovered; this had been thoroughly investigated since 2003, using solid and modern molecular biology and genotyping assays carried out by renowned national and international investigators (Mullins 2013). This enabled the finding to be published in prestigious international journals such as in the Emerging Infectious Diseases Journal (July 2013) and Journal of Clinical Microbiology (August 2013). This new species is a new candidate that first needs to be ratified by experts and then has to be further studied in order to get a better understanding of its bacteriology, epidemiology, and clinical correlate as has been the process followed by many different pathogens (Mullins 2013; Blazes 2013; Eremeeva 2007).

Carrion's Disease or Peruvian wart was historically described in Peru, Ecuador, and Colombia; that is why in many scientific publications it was considered as an exotic disease in Tropical Medicine, but starting in 1993, with the discovery of other *Bartonella* species in other countries, it is now considered as one of the main emerging infectious disease (Walker 2006).

1.1 History of Carrion's Disease

Monolith of the Huaylas culture (400 AD) with evidence of the eruptive phase of Carrion's disease. Courtesy of Dr. Ciro Maguiña Vargas' collection

The first described Bartonella, *Bartonella bacilliformis*, has caused multiple clinical syndromes throughout history; one of them is the eruptive form known as the Peruvian wart; this form has been described since precolumbian times and evidence of that can be found in different representations (art work in ceramic and stone), as shown in the image above. In 1886, Dr. David Matto wrote that before the start of the construction of the railroad from Lima to La Oroya, Hospitals in Lima had many soldiers that escorted the extracted silver from La Oroya to Lima, who upon arriving to Lima presented high fevers and anemia so severe that they "turned white and died with no blood (Walker 2006; Arrese 1992)." Beginning in 1870, once the construction of the railroad started at 3,800 m above sea level, many construction workers came down with an unknown disease characterized by fever, severe pallor, and finally death. Of the 21,000 construction workers that labored during the 30-year period it took to complete the railroad, 7,000 of them died. That is why it received its name "La Oroya Fever," one of the greatest public health tragedies caused by a vector-borne infectious pathogen. This epidemic fueled and motivated physicians and medical students alike to investigate this severe and unknown disease (Maguiña 2008). In 1855, Daniel Alcides Carrión, a medical student from the San Fernando School of Medicine born in Cerro de Pasco, inoculated himself with a sample from a male patient stricken by the Peruvian wart (Maguiña 2002). Three weeks later, he presented fever, vomit, malaise, severe paleness, and finally died on October 5th (Peruvian Medicine Day). With his selfless sacrifice, the link was established between the acute anemic phase, known as "La Oroya Fever," and the chronic phase, Peruvian wart; that is why he is considered a hero and martyr of Peruvian Medicine. One year after his death, the Society "Union Fernandina" proposed to pay tribute to his memory by renaming the Peruvian wart and "La Oroya Fever" as Carrion's Disease (Bass 1997; Walker 2002).

Photo of Daniel Alcides Carrion 1885

Dr. Alberto Barton, a Peruvian physician, discovered the bacteria that caused "La Oroya Fever," which he gave the name of "endoglobular bodies," nowadays known as the *Bartonella bacilliformis*. In 1913, Towsend discovered the vector in charge of the transmission of the disease, which he named *Phlebotomus* (today known as *Lutzomyia verrucarum*), the female being the one that produces the disease. In 1926, Pedro Weiss studied the immunity of the disease. Antibiotics were first used in 1945 with the administration of Penicillin. Because of the coexistence of typhi and nontyphi strains of *Salmonella* during the acute febrile state, Cuadra and Colichón successfully used Cloramphenicol (CAF) to treat the disease (Maguiña 1997). We have been studying Carrion's Disease since the 1970s and alongside other researchers have determined that many old concepts of the disease (old paradigms) have changed thanks to new investigation and so we present this updated review (Maguiña 2003; Sanchez 2012).

2 Etiology

The *Bartonellas* are members of the alfa proteobacteria, which also include the genus *Ricketssia, Ehrlichia, Brucella, and Agrobacterium tumefaciens*. The causal agent of the Bartonellosis (Carrion's Disease) is the *Bartonella bacilliformis* first discovered in 1905 by Alberto Barton. This is a gram-negative bacteria, facultative intracellular pathogen, aerobic, and quite small measuring 0.2–0.5 um wide and 2–3 um long, it is pleomorphic (cocci and rods), and it has flagella on one pole (between 2 and 16) which provide great motility (Koehler 1992; Koehler 1994; Llanos 1996). The flagella have a wavelength of 800 nm, and the flagellar filaments are composed of 42-kDa polypeptides. Newer molecular biology assays have detected 24 antigens, with the 11, 18, 26, 36, 48, 65, and 75 kDa polipeptides being the most specific (Relman 1990; Maguiña 2003). Proteins such as flagellin, iaIBb, deformin, and

RhoA have also been detected and are allowing researchers to understand the molecular mechanisms of erythrocyte invasion by *Bartonella bacilliformis* (Regnery 1992; Relman 1990).

This bacterium can be recovered from the blood of all patients during the acute phase. Cultures are performed in semisolid medium that contains hemoglobin, different types of semisolid agar, and rabbit or potato serum, at temperatures of 25–28 °C requiring around 5–8 weeks for their development. Colonies tend to be small, clear, with no color change in a different medium and no hemolysis in agar. Birtles showed six genetic variants in different epidemics in Peru, which could explain the differences in mortality and affected individuals between these episodes.

3 Epidemiology

Classically, the disease existed in the interandean valleys, narrow and deep with poor vegetation, located between 500 and 2,800 m above sea level in Ecuador, Colombia (Nariño), and in Ancash, Lima, Cajamarca, Amazonas, and Piura, provinces of Peru. Newer studies carried in 1993 revealed that the disease was also present in newer areas of the Peruvian highland forests (Amazonas, Cuzco, and Cajamarca) and at higher altitudes: 500–3,200 m above sea level (Ancash). In recent years, outbreaks of the acute febrile phase were reported in different geographical areas like Jaen, San Ignacio, including the Sacred Valley of the Incas and the rainforest region of Quillabamba in Cuzco. This is mainly due to changes stemming from global climate change (Maguiña 2013).

In order for this disease to exist, certain climate and ecological conditions have to be present, which allow for the existence of the vector and the reservoir. The vector responsible for the transmission of *Bartonella bacilliformis* is the female of the genus *Lutzomyia spp*.; the main vector in Peru is *Lutzomyia verrucarum*, located between parallels 5° and 13°13′ south latitude, unique to subxerophytic environments—like western valleys and some Peruvian interandean valleys (Chamberlain 2002; Cáceres 1995; Cáceres 1997). In Colombia, *Lutzomyia colombiana* has been determined to spread the disease. Other new species like *Lutzomyia maranonensis* and *Lutzomyia robusta* have adapted to tropical environments like Amazonas, Cajamarca, and Ecuador. *Lutzomyia peruensis*, one of the mosquitoes also responsible of the transmission of cutaneous Leishmaniasis, was found to be the responsible vector in the epidemic in Cuzco in 1998 (Burstein 2007; Caceres 1993). In 2004, the worst outbreak of Carrion's Disease in the last four decades happened in Peru, with more than 11,000 cases between acute and chronic phases of the disease. These were contained in the following years and have started to trend downward, such as in 2010, 225 cases were reported, and in 2011, 209 cases were reported with a slight increase in 2012 reaching 455 cases. For many years it was thought that the reservoir had to be some animal found in endemic areas, but newer studies started in 2000 have found that the main reservoir are patients with the chronic phase of the disease. So far, no other reservoirs besides humans have been identified. Climatic

phenomena, such as "el Niño," have been associated with a significant increase in the risk for Carrion's Disease.

4 Clinical Presentation

Historically, three typical clinical phases were described for Carrion's Disease: Acute hematic phase ("La Oroya Fever"), In-between phase (Odriozola phase), and chronic or eruptive phase known as the Peruvian wart (Ministerio de Salud del Perú 2007).

Newer studies in the last 40 years have modified this old concept and we now point out that the clinical spectrum caused by *Bartonella bacilliformis* varies greatly, from a subclinical illness, to a moderately acute febrile illness, and to a severe acute illness with high mortality. Likewise, there is a large group of patients who present with the acute febrile phase but never go on to develop the chronic eruptive phase while others present with eruptive lesions but never present with the initial acute phase. The acute febrile hematologic phase lasts between 2 and 4 weeks and most of the patients treated recover while some may die, with less than 5 % developing bleeding skin lesions weeks to months after the initial phase. Lately, relapses during the acute phase and recurrences during the chronic phase have been reported (Maguiña 2001).

After Daniel Alcides Carrion's death, the incubation period was thought to be 21 days, but given that Carrion's experiment did not follow the traditional transmission, field studies have found an average incubation period of 61 days (ranging from 10 to 210 days). After this time, nonspecific signs appear such as malaise, fever, hyporexia, headache, myalgias, somnolence, paleness, jaundice, etc. During this initial phase, the clinical picture is indistinguishable from any generalized infectious process like malaria, typhoid fever, acute brucellosis, viral hepatitis, yellow fever, dengue, leptospirosis, or hematologic malignancies. As the disease progresses, a number of infectious complications appear that could potentially lead to multiple organ dysfunction. Pregnant patients can develop a series of complications like abortion, stillbirth, premature delivery, maternal death, and even transplacental infection of the newborn (Maguiña 2009).

In the 1950s, many investigators found that during the acute febrile phase a number of complications appeared, especially related to infection with *Salmonellas spp. (dublín, anatum, cholerae- suis, typhymurium*) typhi and nontyphi, Amebiasis, Malaria, etc. In recent studies, we found that aside from the classic association with Salmonellas, other complications may occur such as the reactivation of Toxoplasmosis, Tuberculosis, Disseminated Histoplasmosis, S. aureus sepsis, *Enterobacter spp., Shigella dysenteriae*, *Pseudomona aeruginosa, Acinetobacter,* Pneumocystosis, *P. vivax* Malaria, and Leptospirosis, among others (Pachas 2007). Among noninfectious complications, the most important ones are cardiovascular complications (CHF, myocarditis, endocarditis, acute pulmonary edema, pericardial effusion, and diastolic dysfunction) and neurologic complications (psychomotor agitation, seizures, meningeal irritation, and coma) associated with

greater mortality. Sever cases with multiple organ dysfunction have also been described. During pregnancy, in the acute febrile phase, many severe complications can happen in the fetus and the mother like abortion, stillbirth, premature delivery, neonatal death, and maternal death; this highlights the importance of adequate and timely management of pregnant patients. We will describe the main neurologic, cardiovascular, and gastrointestinal complications and multiple organ dysfunction (Maguiña 1997; Maguiña 2001).

4.1 Neurologic Complications

It is one of the most common complications during the acute phase. Ricketts reported a frequency of 27 % of neurologic complications; Lastres found neurologic symptoms that ranged from headache, decreased level of consciousness, photophobia, vertigo, amblyopia, amaurosis, and coma. In our 68 patient series during the acute phase, we found somnolence, abnormal fundoscopic exam, bilateral Babinsky sign, seizures, coma, meningeal irritation, irritability, delirium, disorientation, cranial hypertension, tremor at rest, asterixis, hemiparesis, and cerebellar crisis. Upon examination of cerebrospinal fluid (CSF) from 14 patients, only one had gram-negative cocobacilli and another one isolated Bartonella bacilliformis from the sample. Historically, Bartonella bacilliformis has only been isolated from the CSF three times: by Monge in 1932, Solano in 1988 and Maguiña in 1993. Much of the symptoms during the acute phase have been attributed to severe hypoxia secondary to severe anemia, but because of the presence of cerebral edema among other findings, it has been hypothesized that Bartonella bacilliformis could have a direct effect on the CNS (Llanos 1996; Maguiña 2013).

Regarding the ophthalmologic complications, we conducted a descriptive study, where we included adult patients admitted to the Hospital Nacional Cayetano Heredia (HNCH) with the acute phase of Carrion's Disease from 1991 to 2007 and had a fundoscopic exam performed. We ended up with 29 patients, 22 (76 %) males. The average age was 25.9 years (SD = 14), 23 (79 %) patients came from or had traveled to an endemic area recently. The average time of the disease was 18 days (SD = 7.7). The symptoms they presented on entry were fever (100 %), malaise (100 %), headache (97 %), weight loss (93 %), and paleness (86 %); 6 (21 %) patients presented altered vision. All of them presented some degree of anemia, with severe anemia accounting for 17 (59 %) cases. 11 (38 %) patients presented some fundoscopic anomaly, with hemorrhagic and exudative retinopathy present in 4 (37 %), blunting of the papillae in 3 (27 %), exudative retinopathy in 2 (18 %), hemorrhagic retinopathy in 1 (9 %), and pale retina in 1 (9 %) patient. One of the patients who presented with hemorrhagic and exudative retinopathy had severe vision loss on the left eye. The rest of the cases had a favorable outcome. None of our patients died, and it was concluded that nonsevere acute phases may present with multiple alterations that require further investigation (Maguiña 2013).

A study performed by Breña in Lima in 32 children with acute phase reported finding some complication in 78 % of patients, infectious complications accounting

for 25 % of these and noninfectious complications 22 %. From the infectious complications, the most frequent were respiratory infections (25 %), typhoid fever, and salmonellosis (19 %). From the noninfectious, cardiovascular complications were most frequent (pericardial effusion being the most frequent) and neurobartonellosis, autoimmune hemolytic anemia secondary to cryoglobulins, and postinfectious glomerulonephritis (these last two complications suggesting immunologic phenomenon associated to Bartonelosis infection) (Maguiña 2013; Walker 2006).

4.2 Cardiovascular Component

Odriozola first described the cardiovascular component in Carrion's Disease in his 1898 book La Maladie de Carrón, where he describes an anemic murmur, pericardial effusion, and cardiomegaly in autopsies performed. Hurtado refers to an "anemic anoxia," tachycardia, palpitations, hypotension, and functional murmurs. Cuadra reported the findings of pericardial effusion and pleuresis. Pérez Araníbar found hypotension with a wide pulse pressure, anemic murmur secondary to anemia, high and pointy T waves on the ECG (secondary to hyperkalemia), and tachycardia secondary to fever; however, he describes low frequencies for heart failure and does not mention pericardial effusion (Maguiña 2013; Maguiña 2001). Peralta described a case with pericardial effusion, cardiomegaly, heart failure, and anasarca. Breña, in 2005, in 32 pediatric cases reported tachycardia in 75 %, tachypnea in 63 % and multifocal systolic murmur in 53 %. Among the reported noninfectious complications, he reported pericardial effusions in 19 %, heart failure in 13 %, myocarditis in 9 %, cardiogenic shock in 6 %, cardiac tamponade in 3 %, and one case (3 %) with infectious endocarditis of a native patient from Ancash, with a coronary right-ventricle fistula, the first reported case in national and international literature (Maguiña 2000; Maguiña 2001).

In a recent observational study, in 20 years of experience at the Hospital Nacional Cayetano Heredia (1987–2007), 68 acute phase patients were studied, 52 males and 16 females; median age was 25.7 years. None had previous cardiovascular disease. Main clinical findings included fever (99 %), hepatomegaly (79 %), jaundice (74 %), tachycardia (74 %), tachypnea (71 %), systolic murmur (68 %), dyspnea (62 %), hepato–jugular reflex (19 %), and jugular vein distention (15 %). 64 chest x-rays showed: 44 % cardiomegaly, 20 % pulmonary congestion, and 16 % pleural effusion (Maguiña 2009). Ecochardiogram of 42 patients showed 31 (74 %) patients with some anomaly. Pericardial effusion was the most frequent alteration 16 (38 %), 10 (63 %) of these had minor effusion. Other findings included minor dilation of the left atrium and left ventricle in 8 (19 %) and 7 (17 %) patients, respectively, tricuspid regurgitation in 4 (9.5 %) cases, pulmonary hypertension in 4 (9.5 %) other cases, and signs of cardiac tamponade in 4 (9.5 %) cases. Left ventricular function was preserved in 39 (93 %) cases, with a mean ejection fraction of 63 % and a median 65 % (ranging 18–86 %). 36 patients developed cardiovascular complications: heart failure was found in 92 %, pericardial effusion in 44 %,

acute pulmonary edema in 36 %, cardiogenic shock in 17 %, cardiac tamponade in 11 %, and myocarditis in 11 %. 5 (7 %) were pregnant; all of them developed cardiovascular complications and one of them died. 2 (40 %) had a stillbirth and 1 (20 %) an incomplete abortion. The first patient had a gestational age of 16 weeks and developed acute pulmonary edema, cardiac tamponade, stillbirth, multiorgan failure, cardiogenic shock, and died afterward. The other two patients had a good outcome to their pregnancies. One of them arrived to the ER with 36 weeks of gestational age and had a c-section performed because of acute fetal distress; the newborn was healthy. The other patient was discharged at 18 weeks of gestational age without any obstetric complications during her admission. Overall mortality accounted for 6 (8.8 %) patients, 5 (83 %) of which presented some cardiovascular complication. Ecochardiography was performed only on 62 % of the patients because it was available at the Hospital since 1991, which could bias our findings. Most of them had a normal ejection fraction (97 %) with a preserved ventricular function. One new finding was the minor dilation of the left atrium and ventricle in 93 % of cases, with a mean ejection fraction of 63 % and a median of 65 %. These findings are interesting if we consider that dilation of the left atrium by itself reflects an increase in pressure at the end of the diastole in the left ventricle and could therefore indicate diastolic or systolic dysfunction. Dilation of the left ventricle reflects an increase in the volume at the end of the diastole and could be associated with an increase in cardiac output (Maguiña 2013).

We can coalesce these findings together as a diastolic dysfunction with a preserved ejection fraction and with pulmonary edema that can't be explained by the pericardial effusion alone and hence requires the coexistence of a high output heart failure secondary to anemia (worsened in pregnancy) to explain all of the cardiovascular findings. On the other hand, the small percentage of patients with systolic dysfunction were mainly due to myocardial alteration, probably related to myocarditis, but must also consider as a transitory cause of systolic dysfunction the myocardial alteration secondary to interleukins (TNF and other inflammatory cytokines tend to be elevated in Carrion's Disease).

The three main cardiovascular complications were heart failure, pericardial effusion, and acute pulmonary edema. On admission, however, heart failure was more prevalent while pericardial effusion was only present in only half of the patients and only 30 % of the cases of pulmonary edema. On the other hand, during the course of their hospital stay patients developed cardiogenic shock (6 cases), myocarditis (4 cases) 70 % of all cases of pulmonary edema, 50 % of pericardial effusions, and 75 % of cardiac tamponade cases; all of these complications carry a high mortality risk and must be properly followed. When comparing patients with cardiovascular complications and patients with no cardiovascular complications, we find that the first group had a greater rate of infectious complications which required ICU management and longer hospital stays (Maguiña 2013; Maguiña 2008). Many received chloramphenicol alone or in association with other antibiotics; on the other hand, use of ciprofloxacin reduced many infectious and cardiovascular complications.

4.3 Gastrointestinal Complications

In a study performed in 2001, we point out that the most frequent gastrointestinal symptoms were abdominal pain, hepatomegaly, altered hepatic function tests, enlarged spleen, dark urine, vomiting, jaundice, diarrhea, and constipation. Hinojosa, in 1977, reported 76 cases of patients with Carrion's Disease with the most important GI symptoms being diarrhea, abdominal pain, vomiting, anorexia, and constipation; relevant clinical findings being enlarged spleen, jaundice and ascites. Another study in the Hospital Regional del Cusco with 26 acute phase cases reported nausea, vomiting, hepatomegaly, enlarged spleen, and jaundice. Three of these patients after having negative blood cultures with *Bartonella bacilliformis* in blood continued with fever, jaundice, hepatomegaly, and altered hepatic function tests (Maguiña 2008a).

4.4 Multiple Organ Dysfunction Syndrome

The first study reporting this complication was done in the Hospital of Huaraz by Lopez de Guimaraes. From a total of 30 cases of severe Carrion's Disease, 9 patients (30 %) met the criteria for this complication. The most frequent complications were neurobartonelosis, cardiac tamponade, kidney failure, adult respiratory distress syndrome (ARDS), thrombocytopenic purpura, and acute respiratory distress. Abnormal lab tests were elevated erythrocyte sedimentation rate (ESR) and positive C reactive protein (CRP). Lethality was 55.9 % (4/9). It is believed that this presentation may be related to a immunologic disregulation as a final phase of a systemic inflammatory response syndrome (SIRS). In a study conducted by our group in admitted patients in Lima, factors related to bad prognosis during the acute phase were anasarca, petechiae, and altered mental status. On the other hand, Montoya et al. during the 1998 outbreak in Cusco found that the factors associated with higher mortality were age older than 45 years, history of alcoholism, shock upon admission, cardiogenic acute pulmonary edema, acute pericarditis seizures, coma, and acute kidney failure (Walker 2006).

During pregnancy, several complications have been described in patients during the acute phase such as abortion, stillbirth, neonatal death, and maternal death. In the last study in 2008, we had two cases with acute pericardial effusion, one of them requiring surgical drainage with pericardiac window. Both had positive outcomes with viable fetuses. Montoya in Cusco reported 25 % rate of complications in pregnant women, whereas and Lopez de Guimares in Huaraz reported a 48 % rate of complications and 4 % of stillbirth (Maguiña 2013).

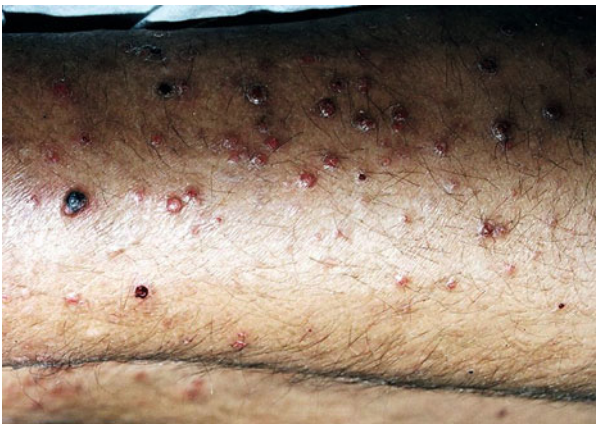
4.5 Mortality

In the preantibiotic era, mortality rate was high. In 1932, Kikuth estimated rates between 75 and 95 %, Jaramillo (1939) and Patino (1940) estimated the mortality of the outbreak in Colombia to be around 40 %. Hurtado, Pons, and Merino in 1938 reported a mortality rate of 48 % (16/33). Jimenez Franco in 1938 reported 24 deaths, 8 from tuberculosis, 6 from paratyphoids, 3 from dysentery, 2 from pneumonia, 2 from typhoid fever, 2 from paludism, 1 from cysticercosis, and 1 from pure bartonellosis. In 1940, Alzamora Castro reported 80 % lethality (25/31); from 25 deceased people, 12 were from complications from salmonellosis. Aldana in 1949 reports 24.6 % of deaths (60/243), the causes being 7 from Salmonella enteritidis meritidis and the other causes, pneumonia, tuberculosis, amebiasis, and meningitis. Cuadra in 1954, out of 38 patients studied with acute bartonelosis, showed infectious complications exclusively by salmonellas in 14 patients, 9 of them were cured and 5 died. In the autopsy of the deceased, he found tuberculosis, pleurisy, and pericarditis with effusion. With the use of antibiotics and other measures like blood transfusions, lethality went significantly down. In later studies, such as the one by Hinostrosa in 1977 in Ancash, he reported that from 21 patients in the acute phase admitted, 9 had complications and 3 died from milliary tuberculosis. Other study from Espinoza in 1987 studied retrospectively 39 patients admitted to the Children's Hospital didn't find complications due to salmonella but showed predominance of respiratory infections (7/17) with 3 deceased. Tokeshi in 1987 described 11 patients from "Hipolito Unanue" Hospital, during their acute phase of the disease; 2 of them were pregnant and one of them had a stillbirth complicated with consumption coagulopathy; the curse of the other one was complicated with typhoid fever and premature birth; overall there were no deaths. In 1993, Cesias reported in Huari (Ancash) 14.8 % (4/27) of deaths, while Huatuco in San Ignacio (Cajamarca) reported 7.7 % (336/461) of deaths. In 1997, Marroquin and Cabanilas reported a rate of 15 % (2/13) of deaths in an outbreak in Cachachi, Cajabamba (personal communication) (Ministerio de Salud del Perú 2007).

The acute hematic phase lasts between 2 and 4 weeks and most of the patients who receive treatment experience full recovery, some of them die, and 5 % develop, after some weeks or months, eruptive bleeding lesions as part of the second phase, the eruptive phase; however, lately recurrence of the acute hematic phase has been reported.

Finally, it is remarkable that in the last report of HNCH in 2008, the mortality rate was 0 % in comparison to other studies with mortality rates between 6 and 9 %. The decrease in mortality may be related to the changes in antibiotic schemes and the management of complications in a reference center such as the Department of Infectious Diseases and Tropical Medicine of HNCH and the Tropical Medicine Institute Alexander Von Humboldt. However, it is important to mention that a patient deceased in 2005 was not included in the database since death occurred less than 24 h after admission in the trauma shock unit at the emergency room of HNCH.

4.6 Eruptive Phase: Peruvian Wart



Patient with Peruvian wart (small lesions on different stages)

The eruptive phase, also classically known as "peruvian wart," generally presents in endemic zones, affecting mainly children and teenagers without them having the classic features of the acute hematic phase. The eruptive lesions are usually located in the upper and lower limbs as well as the face. Without treatment, they last between 3 and 6 months and do not leave scars (see illustrations 6, 9) (Maguiña 1997; Maguiña 2002). Typically, three kinds of lesions have been described: the milliary lesions, which consist of papules smaller than 3 mm, globulous, bright red, sometimes pruriginous, and usually numerous. The second kind is denominated mular, it is formed by nodular tumors bigger than 5 mm of diameter, erythematous, sessile, and eroded. The third kind of lesions are the deep nodules, skin colored without skin alteration also denominated subdermic or nodular type. The Peruvian Wart is considered a vascular hyperplasia. The milliary wart is located in the papillary and middle dermis and the nodular wart may extend down to the hypodermis. The initial histologic reaction is characterized by endothelial, monocyte, and macrophage proliferation. The number of mitotic cells is variable; in some cases, they are numerous and are associated with cellular atypic with a histologic image similar to a malignant neoformation. Kosek and Recavaren have developed an immunohistochemical technique specific for *B. baciliformis* in skin lesions (Maguiña 1997).

Mortality during this phase is exceptional. We have also described lesions in oral and nasal mucosa as well as conjunctiva; we have not seen visceral wart lesions. Most patients, once treated with antibiotics, do not have scars at all. In a prospective study since 1989, we reported recurrence of the eruptive lesions in native people as well as people from nonendemic zones. The differential diagnosis should include hemangioma, pyogenic granuloma, chickenpox, molluscum contagiosum, bacillary angiomatosis, Kaposi sacroma, malignant sarcoma, juvenile melanoma or Spitz tumor, fibrosarcoma, histioid leprosy, malignant lymphoma, urticaria, nodular prurigo, psoriasis, liquen, etc (Maguiña 2013).

The acute phase may have a lethality up to 90 % if left untreated; on the other hand, when appropriate and prompt treatment is given, mortality rate goes down to 9 %. In our studies, we found bad prognosis factors during the acute phase such as anasarca, petechiae, and altered mental status. On the other hand, Montoya, during the 1998 outbreak in Cusco found that the factors associated with higher mortality were age older than 45 years, history of alcoholism, shock upon admission, anasarca, hospital-acquired pneumonia, acute cardiogenic pulmonary edema, acute pericarditis, seizures, coma, and acute kidney failure (Maguiña 2001).

The initial histologic reaction is characterized by endothelial, monocyte, and macrophage proliferation. . Lymphocytes, masticates, and plasma cells are found in few occasions. The progression is characterized by a softening phase and a final stage of reabsorption: the superficial warts do not leave scars. The clinical diagnosis during this stage is done by the characteristics of the lesions and is confirmed by conventional anatomopathology studies that allow distinguishing the histologic characteristics of the Peruvian Wart and the Warthin-Starry silver stain that shows the Bartonellas scattered in wart nodules (Maguiña 2013).

We have also described lesions in the oral and nasal mucosa as well as the conjuntiva. No visceral warts have been observed. Most of the patients, after being treated with antibiotics don't have scars; in a prospective study started in 1980 we reported a recurrence of lesions in both native and nonendemic patients.

The differential diagnosis should include hemangioma, pyogenic granuloma, chickenpox, molluscum contagiosum, bacillary angiomatosis, Kaposi sarcoma, malignant sarcoma, juvenile melanoma or Spitz tumor, fibrosarcoma, histioid leprosy, malignant lymphoma, urticaria, nodular prurigo, psoriasis, liquen, etc. The mortality caused by Peruvian wart is exceptional (Maguiña 2009).

5 Diagnosis

Anemia is evident and it becomes severe in few days; it is hemolytic and has been typified as macrocytic and hypocromic. Most patients present with important leukocytosis with left shift, although leukopenia can also be present. There is also an important rise of reticulocytes and normoblasts.

In many complicated patients, a moderate increase of transaminases and bilirubin, both direct and indirect, was evidenced. Thrombocytopenia is less frequent, and it is associated with a consumption coagulopathy (DIC) or secondary sepsis. Bone marrow exam during the hematic acute phase shows reactive hyperplasia of all three series, predominantly the erythroid and megakaryocytic series. In most cases, coagulation tests, thromboplastin time, prothrombin time, and fibrinogen are within normal ranges.

The best technique for bacteriologic diagnostics during the acute phase is by blood smear with Giemsa or Wright strain, which show red blood cells with parasites inside, in their bacillary form during the first stages of infection and later in the coccoid form (Henríquez 2002). Up until a few years ago, this technique was believed to be 100 % diagnostic in all cases; however, new studies have

revealed some limitations for the diagnostic; Ellis found that in Cuzco, the sensitivity of the smear was 36 % and specificity was between 91 and 96 %. We have evidence of false positives for *B. bacilliformis* in smears that were stained with old stains that precipitated toxic granulations; Howell Jolly and Papenheimer bodies may also be confused with parasites.

Knoblock et al. found specific antigens for Immunoblot and immunoprecipitation tests. Although this test has high sensibility and specificity rates, it is very expensive and the use on a daily basis is very limited. By using a sonicated diagnostic immunoblot, Mallqui et al. detected that this test is 70 % sensitive in the acute phase of Bartonelosis and 94 % sensitive in chronic stages of the disease. Cross-link reactions with *Clamidia psitacci* 5 %, *Coxiella burnettii* 14 %, and *Brucella* 34 % have also been presented; therefore a positive result may not be as useful in endemic areas of the aforementioned diseases (Huarcaya 2000; Huarcaya 2004; Huarcaya 2011). The Indirect Immunofluorescense test (IIF) has been used for many years to detect several diseases because it only requires a small amount of antigen present. This test is a cheap serologic analysis for the detection of antibodies against *B. bacilliformis* with a sensitivity of 93 % during the chronic stage and 82 % during the acute phase in patients with confirmed positive blood smear or cultures. The positive predictive value for this test is 89 % in endemic areas and 45 % in areas that present outbreaks. PCR for the detection of *B. bacilliformis* has poor sensibility (47 %) but good specificity (98 %) (Henríquez 2002).

Among all serologic methods, Western blot has high sensibility and specificity in many endemic areas, both in the acute and chronic phases with 97 % positive rate in confirmed cases by skin biopsy; it is also very useful in further follow-up.

In order to have a better explanation of the pathogenesis and physiopathology of Carrion's disease, in 1926 Dr. Pedro Weiss was the first to show that during the acute hematic phase there was a state of "anergy" responsible for several secondary complications. He also showed that during the eruptive phase there was a "hiperergy." Subsequently, Dr. Contreras showed that there is no humoral immunodeficiency nor a specific anergy state. In 1980, Dr. Patrucco described in patients during the acute phase of Carrion's disease a quantitative alteration in the cellular immunologic system by detecting a reduction in the number of T CD4+ lymphocyte series, which returned to normal values after 2–4 weeks; however, during the chronic phase, this alteration was not significant. In 2006, in conjunction with researches from the Tropical Medicine Institute "Alexander Von Humboldt" at UPCH (Huarcaya, Palmira Ventosilla, and Ivan Best), in order to determine the immunologic alterations that occur in patients affected by the acute febrile phase and the wart phase of Carrion's disease, we measured for the first time proinflammatory cytokines (specific for a Th1 response) and anti-inflammatory cytokines (specific for a Th2 response), as well as the count of T CD4+ and T CD8+ lymphocytes by flow cytometry. In the acute phase, we found in some patients a low count of CD4+ and CD8+ lymphocytes as well as a significant increase of interferon gamma (IFN) and interleukin 10 (IL-10) (Huarcaya 2011). A possible explanation of this would be the "immune paralysis" induced by IL-10, as it happens in other cases of sepsis due to gram-negative bacteria. On the other

hand, in the wart phase, there was no decrease of CD4+ but similarly patients had increased levels of IL-10.

For Peruvian Wart disease, serologic tests are also a diagnostic aid; however, histopathology is still the best method to confirm the suspicious cases. In the skin biopsy, it is possible to see several histopathologic alterations. The initial histologic reaction is characterized by endothelial cell, monocyte, and macrophage proliferation with very few lymphocytes, masticates, and plasma cells. The number of mitotic cells is variable; in some cases, they may be numerous and are associated with atypic cells giving a histologic image similar to a malignant neoformation, and there may also be capillary neovascularization.

The evolution of the disease is characterized by a softening phase and a reabsorption final stage. The Warthin–Starry stain shows scattered bacteria which generally do not accumulate unlike other Bartonellas that originate from the bacillary angiomatosis. Electronic microscopy shows B. bacilliformis initially located in the fibrillary interstitium of the warts and posteriorly it is engulfed and destroyed by the verrucoma cells. Bartonella bacilliformis may also be cultured and isolated from skin biopsy samples.

6 Therapeutics

In vitro studies have shown that the antibiotics penicillin, amoxicillin, cephalosporins, tetracycline, fluoroquinolones, macrolides, rifampin, and chloramphenicol have good inhibition levels, ceftriaxone being the best of all of them. This was determined by Minimum Inhibitory Concentration (MIC) studies. On the other hand, the antibiotics vancomycin, aminoglycosides, clindamycin, and imipenem require higher doses for inhibition and are therefore not good choices for *Bartonella bacilliformis* (Walker 2002).

Historically, due to the infectious complications that may present during the acute phase—especially those caused by typhi and nontyphi Salmonellas—experts in Peru used chloramphenicol (CAF) as the drug of choice. The dose of CAF is 50 mg/kg/day until fever disappears and then the dose is reduced to 25 mg/kg/day until an overall 10-day course is completed. In our experience with CAF, some patients had poor response to treatment. In the last years we have used, with great success, ciprofloxacin, which has showed lower mortality and lower complication rate. The dose for adults (weighing more than 50 kg) is 500 mg administered orally every 12 h for 14 days. In children older than 14 (and weighing more than 45 kg), the dose is 250 mg administered orally every 12 h for 14 days. During pregnancy and children younger than 14 years (and weight less than 45 kg), amoxicillin plus clavulanic acid is used (Burstein 2007).

For severe neurologic complications (coma, delirium), we gave dexamethasone, 4 mg every 8 h intravenously, for 3–4 days. For patients with severe anemia and cerebral hypoxia we use red blood cell package transfusions. In those who present

with severe pericardial effusion, we recommend drainage and creation of a pericardial window (Spach 2014).

During the eruptive phase, streptomycin was used in the past, but since it was administered intramuscularly, there was low patient adherence. For this reason, we started using rifampin (RFP) at 10 mg/kg/day given orally for 14–21 days. Currently, the drug of choice during the wart phase (eruptive phase) is azithromycin in all patients, at 10 mg/kg/day given orally for 10–14 days. Second line therapy drugs are ciprofloxacin, erythromycin, or rifampin (Tarazona 2006).

7 Control

This historical disease is still a Public Health problem in Peru and Ecuador. Despite multiple control campaigns, in 2004, the major outbreak of the last decades occurred, with more than 11,000 cases. Up to now there is no vaccine that prevents the disease, nor studies regarding prophylactic use of antibiotics; therefore, early diagnosis and prompt treatment of cases detected is one of the main prevention and control measures because they act on the host (Maguiña 2008a). Although it is not possible to eradicate the vector, epidemiological and entomological surveillance can be done, as well as controlling Lutzomyia by integral vector control, which includes physical and chemical control to reduce adult population. Individuals who visit the endemic areas (tourists and workers) should avoid disease-transmitting mosquito bites by using mosquito nets, long sleeve shirts, and long pants (Tarazona 2006; Villaseca 1999). They should also avoid outdoor activities during the periods of activity of Lutzomyias, that is to say, from 5 in the afternoon on, and refraining from camping or sleeping in abandoned houses or sleeping in potential mosquito-breeding or resting places such as caves, trees, animal farms, etc.

Better control of this disease requires further and deeper clinical, epidemiological, therapeutic, and immunologic studies, especially those referring to disease control.

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Dengue in Latin America: A Persistent and Growing Public Health Challenge

Hugo Lopez-Gatell, Mauricio Hernandez-Avila, Juan E. Hernández Avila, and Celia M. Alpuche-Aranda

Contents

Abstract Over the last 50 years, dengue has been a growing public health challenge. Half of the World's population lives in areas of risk; Latin America and the Caribbean (LAC) are not exceptions. *Aedes aegypti*, the main vector of dengue in the Americas, is widely spread, and autochthonous transmission of dengue virus (DENV) has been documented in all American countries except for Chile and Uruguay. In 2013, the largest epidemic of dengue in the history of the Americas accounted for a total of 2.3 million reported cases, 37,898 of them severe, including 1,318 deaths.

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_11

Despite different and enormous efforts, prevention and control programs have not been effective enough to halt dengue in the LAC region. Difficulties to implement and accomplish successful dengue control programs lie in diverse realms. Some of these relate to the biology of DENV: other to social and environmental factors favoring vector density and other to health systems, like the appropriate entomology or epidemiologic surveillance systems and access to medical services to detect and confirm clinical cases. Implementing multisectoral approaches of vector control has been particularly challenging. Complex dynamics of all such determinants, within and between countries, lead to the continuous increase of dengue incidence in the region, resulting in major health and economic burden.

In this chapter we summarize the epidemiology of dengue in LAC, compare it to that in other regions, and discuss existing evidence supporting the urgent need for developing and implementing integrated multisectoral strategies to effectively control dengue in this region.

Keywords *Aedes aegypti* • *Aedes albopictus* • Dengue • Dengue fever • Fever • Dengue hemorrhagic fever • Shock • Dengue serotype

Abbreviations

CFR	Case fatality rate
CI	Confidence interval
DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DF	Dengue fever
DSS	Dengue shock syndrome
LAC	Latin America and the Caribbean
PAHO	Pan American Health Organization
WHO	World Health Organization

1 Virus, Vector, and Disease

Dengue virus (DENV) is a single-stranded RNA Flavivirus that exists as four closely related but antigenically different serotypes (DENV 1–4). Besides the genome, the main components of the virus are a capsid, membrane envelope glycoproteins, and seven nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. These nonstructural proteins are related to viral replication and pathogenesis (Halstead 2008; World Health Organization 2009; Guzman and Harris 2015).

Phylogenetic analyses, based on partial or complete genomic sequences, have defined several DENV genotypes and allowed better understanding of genetic diversity, mechanisms of pathogenesis, transmission dynamics, and epidemic potential of the different DENV strains. For instance, some genotypes of DENV 2 and DENV 3 from the Americas are known to be less virulent than Asian genotypes of the same serotype (Holmes and Twiddy 2003; Weaver and Vasilakis 2009; Halstead 2007). Despite such differences, all serotypes and genotypes of DENV can produce epidemics and are associated with similar syndromes in humans, including severe clinical presentations (Halstead 2007; Messina et al. 2014; Costa et al. 2012; Ramirez et al. 2010). However, complex virus–vector–human interactions, transmission patterns in varying environments, and accumulation of human susceptibility underscore the need to continue investigating to further understand dengue epidemic dynamics, and to inform the design and implementation of more effective control strategies (Halstead 2008; Carrington and Simmons 2014; Tapia-Conyer et al. 2012; Tapia-Conyer et al. 2009; San Martin 2014b).

Although mosquitoes of both *Aedes aegypti* and *Aedes albopictus* species are competent vectors of DENV, *A. aegypti* is the main vector in the Americas (World Health Organization 2012). After it was imported from Africa or Asia many years ago, through travel and commerce (Holmes and Twiddy 2003; Halstead 2008; Brathwaite Dick et al. 2012), the *Aedes* genus has expanded its global span over the last 50 years, reaching all continents except the Antarctica. Spread of *Aedes* in America has been followed by a 30-fold increase in the incidence of dengue disease in the region, including large urban outbreaks (Halstead 2008; Tapia-Conyer et al. 2009; World Health Organization 2009; Gomez-Dantes et al. 2011; World Health Organization 2012).

Aedes mosquitos are endophilic; thus they feed on human blood and mostly breed in water containers of diverse sizes and types, in and around homes. Factors favoring vector breeding are common in most Latin American countries (Quintero et al. 2014; Halstead 2008; World Health Organization 2009). *Aedes* has high vectorial capacity, is well adapted to urban environments, and is mostly active during daylight hours (Halstead 2008). Increasing urbanization and climate change have been identified as the main drivers of geographic expansion into wider habitats and dispersion of the dengue vectors (Morin et al. 2013; Colon-Gonzalez et al. 2013; Gubler 2011). Prolonged rainy seasons and humidity have been also implicated as major factors of vector spread into milder climates and higher altitudes, leading to increased incidence of dengue and its emergence or reemergence in previously unaffected regions over the last few decades (Halstead 2008; Jansen and Beebe 2010; Lambrechts et al. 2011; Colon-Gonzalez et al. 2013).

Some authors have argued against climate change as a prominent determinant of dengue dispersion by pointing that increased urbanization, population growth, and the use of open containers for storing domestic water have promoted proliferation of *Aedes* within the immediate environment of humans, as has been documented in some dry areas in Australia (Jansen and Beebe 2010; Morin et al. 2013). Nonetheless, such demographic trends and behaviors may, in turn, be partially stimulated by

climate change (Alirol et al. 2011; Gubler 2011; Morin et al. 2013; Kyle and Harris 2008).

The clinical spectrum of dengue disease ranges from asymptomatic infection to dengue fever (DF), severe hemorrhagic fever (DHF), and shock (DSS). Dengue disease, either mild or severe, resembles other infectious diseases presenting as febrile exanthema: yellow fever, chikungunya, leptospirosis, and rickettsial infections, among many others. DHF characterizes by fever, bleeding diathesis, and plasma leakage; a small proportion of cases can also progress to DSS with increased probability of fatal outcomes, but the crude estimated case fatality rate (CFR) for dengue fever is usually much lower than 1 % in most countries (World Health Organization 2009; Halstead 2008, 2007; Huy et al. 2013).

The risk of DHF increases with sequential infections by different DENV serotypes (Guzman and Harris 2015; Halstead 2012; Wahala and Silva 2011; Guzman et al. 1990; Whitehorn and Simmons 2011). Some evidence suggests that hemorrhagic risk grows larger after exposure to the second serotype of DENV than it does after further heterotypic infections beyond the second (Gibbons et al. 2007). Nonetheless, viral genetics and specific serotype infection sequences may also play a role in the pathogenesis of DHF (OhAinle et al. 2011).

An intricate network of cellular, tissular, and systemic processes links dengue immune response to its pathogenesis (Halstead 2007; Lai et al. 2008; Halstead et al. 2010; Whitehorn and Simmons 2011; Wahala and Silva 2011; Halstead 2012; Guzman and Harris 2015). Severity of infection relates to viral biology (Holmes and Twiddy 2003; Guzman and Harris 2015), host factors (Loke et al. 2001; Perez et al. 2010; Xavier-Carvalho et al. 2013; Guzman and Harris 2015), or a combination of both along with specific features of the immune response to subsequent dengue infections (Guzman and Harris 2015; Halstead 2012; Whitehorn and Simmons 2011; Wahala and Silva 2011).

Primary dengue infection induces neutralizing antibodies and results in lifelong protection against subsequent infections with the homologous serotype, but only transitory protection to heterologous serotypes (Halstead 2007; Whitehorn and Simmons 2011). Induction of strong cross-reactive non-neutralizing antibodies can enhance disease during infection by DENV of a different serotype, favoring the entry of virions into monocytes, macrophages, and immature and mature dendritic cells. Such enhancement of viral replication results in high viremia and elevated concentrations of pro-inflammatory and immunomodulatory cytokines (Halstead et al. 2010; Whitehorn and Simmons 2011; Guzman and Harris 2015).

Modeling studies have suggested that population immunity to each DENV serotype is shaped even at small geographic scales, such that spaciotemporal dependence in homotypic individual immunity occurs within large neighborhoods in dense urban settings (Salje et al. 2012; Rodriguez-Barraquer et al. 2014). Deeper understanding of the immunological response to dengue at individual and population levels is crucial to enlighten dengue vaccine development, estimate disease risk, and predict transmission dynamics across populations (Rodriguez-Barraquer et al. 2013).

Laboratory diagnosis of dengue includes virus isolation, serology, and detection by molecular testing (Guzman and Harris 2015; Guzman et al. 2010). The sensitivity of each test highly depends on the timing of clinical sample collection after the onset of fever. No specific antiviral treatment exists so clinical case management is mainly supportive. Early recognition of severe disease by monitoring hemorrhagic and shock development is paramount to reduce fatality in severe cases (Guzman et al. 2010; World Health Organization 2009).

Since 1975, the World Health Organization (WHO) has convened expert committees for drafting various technical guidelines on standard practices for laboratory diagnostics and clinical management. These guidelines, updated in 1986 and 1997, were used to classify dengue disease in three mutually exclusive sets: DF, DHF, and DSS. Such discrete classification aimed to help healthcare workers identify severe cases of disease (World Health Organization 1986). Over time, using these guidelines around the world evidenced the challenges of differentiating clinical expressions of intermediate level of severity and led to confusion regarding appropriate conduct in triage, treatment, and reporting. Most countries adapted the guidelines to their own needs (Rigau-Pérez 2006; Alexander et al. 2011).

WHO responded by revisiting the Guidelines trying to overcome these classification issues and its consequences on both clinical care and public health. A new version, published in 2009, reorganized signs and symptoms attributed to dengue in three levels of assumed incremental severity: Dengue, Dengue with Warning Signs, and Severe Dengue. Several countries have validated this severity-based classification and use it to guide standard medical interventions (World Health Organization 2009). Whereas some investigators deem the new classification more appropriate for preventing dengue casualties, others argue that using it may contribute to overwhelming hospitals by admitting mild cases and, therefore, potentially impair the quality of clinical case management (Srikiatkhachorn et al. 2011; Barniol et al. 2011; Lima et al. 2013; Horstick et al. 2012). Therefore, they suggest revising the 2009 WHO Case Definition to achieve more accurate identification of syndromes within the spectrum of dengue disease (Narvaez et al. 2011; Halstead 2013a).

2 Dengue Situation in the Twenty-First-Century Latin America and Caribbean

The recorded history of introduction, expansion and resultant epidemics of dengue in the LAC region goes back to seventeenth century. However the lack of etiologic confirmation and its clinical resemblance to other VBD, such as chikungunya, Yellow Fever, and other infectious diseases, make it hard to define the actual origin of dengue in the region (Brathwaite Dick et al. 2012). The initial isolation DENV occurred in 1943–1944 and the first diagnostic laboratory test was made available soon after, helping confirmation of endemic and epidemic transmission (Sabin and

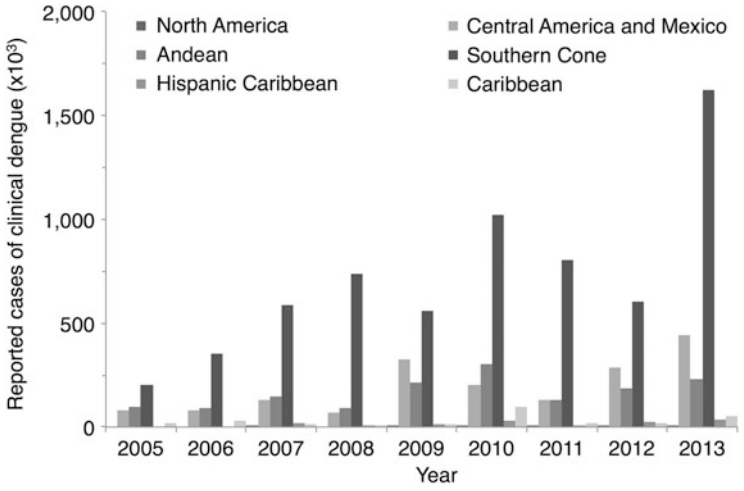

Fig. 1 Total number of cases of dengue (clinical cases) reported to Pan American Health Organization by Latin America and Caribbean Region, 2005–2013 (*Source* Adapted from number of reported cases of dengue and dengue hemorrhagic fever in the Americas, by country, years 2005–2013 (http://www.paho.org/hq/index.php?option=com_topics&view=article&id=1&Itemid=40734&lang=en) Access 10 Oct 2014)

Schlesinger 1945). As it has been recently described, the history of dengue in LAC has four distinct phases: (1) DENV introduction, from 1600 to 1946; (2) a plan for the eradication of *Aedes aegypti* from 1947 to 1970; (3) reinfestation, from 1971 to 2000; and (4) increased dispersion of *Aedes* and dengue virus circulation since 2001 (Brathwaite Dick et al. 2012).

After World War II, the Yellow Fever control campaign, jointly implemented by the Pan American Health Organization (PAHO) and countries in the region, contributed to substantial reduction of *Aedes aegypti* populations and significantly decreased dengue infections in the Americas. Unfortunately, some countries were unable to eradicate the vector before the campaign was discontinued in early 1970s. One decade later, dengue incidence was on the rise and reached pre-campaign numbers by 1995 (Brathwaite Dick et al. 2012), making clear that mosquito density is a key element of dengue transmission and vector control programs are essential to mitigate dengue and other diseases sharing the same vector.

Estimating and comparing the burden of dengue infection across countries is challenged by regional heterogeneity in access to medical care, design and performance of surveillance systems, and availability of laboratory infrastructure for etiologic confirmation, among other issues (Badurdeen et al. 2013; Beatty et al. 2010). Despite these differences, it has been evident that dengue transmission increased in almost all countries in the Americas (Tapia-Conyer et al. 2009; San Martin 2014b) (Fig. 1), and currently, only Uruguay and Continental Chile remain free of dengue transmission (PanAmerican Health Organization 2014a). Since the year 2000, outbreaks of significant magnitude been reported: (Fig. 2).

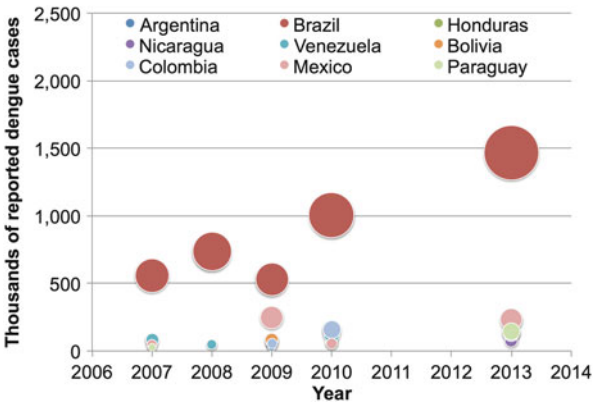

Fig. 2 Main outbreaks reported to Pan American Health Organization, 2005–2013 (Adapted from number of reported cases of dengue and dengue hemorrhagic fever in the Americas, by country, years 2005–2013 (http://www.paho.org/hq/index.php.option=com_topics&view=article&id=1&Itemid=40734&lang=en) Access 10 Oct 2014)

Several countries in LAC have reported large outbreaks (San Martin 2014a), supporting the view of progressive rise in dengue incidence due to one or several serotypes, either emerging or reintroduced: in 2000 Ecuador (DENV 2 and DENV 3) and Paraguay (DENV 1); in 2001 Peru; in 2002 (DENV 1–4) Honduras Venezuela, Colombia, and Brazil (DENV 1–4, mainly DENV–3); in 2005 Costa Rica (DENV 1 and reintroduction of DENV 2); in 2006 and 2007 Paraguay (DENV 3); in 2007–2008 Brazil (DENV 1, 2, and 3, mainly DENV 2); in 2009 Bolivia (DENV 1, 2, and 3), Argentina (DENV 1), Mexico (DENV 1 and some DENV 2), and Nicaragua (DENV 3); and in 2010 Colombia (DEV 1–4 mainly DENV 2), Venezuela, Honduras (DEV 1–4), and Brazil (DENV 1–4, mainly DENV 4). The Caribbean was the subregion most affected by outbreaks in 2010 such as in Guadeloupe with incidence of 1,289.99 × 100,000 inhabitants (DEND-1) using confirmed cases. In 2011, Brazil (DEV-1–4) and Paraguay were highly affected (DENG-1–3); in 2012, El Salvador (DENV-1–3), Nicaragua (DEV-1–3), Bolivia (DENV-2), Brazil (DENV-1–4), Mexico (DENV-1 and 2, occasional cases of DEV-3 and 4), Paraguay (DENV-2 and 4), Dominican Republic (DENV-2), and Puerto Rico (DENV-1–4); and finally in 2013, Mexico (DENV-1 and 2, occasional cases of DEV-3 and 4), Costa Rica (DENV-1–3), Nicaragua, Colombia, and Brazil (DEV-1–4), French Guiana, Puerto Rico, Dominican Republic, and Paraguay (DENV-1, 2, and 4) (PanAmerican Health Organization 2014b).

Although countries report transmission of more than one DENV serotype per year, the relative caseload associated with each one is inconsistently assessed because some of these serotypes are more prevalent than others even within the same country, the rate of dispersion varies among serotypes, or their transmission and predominance is confined to specific areas within countries, perhaps alternating along successive years (Dirección General de Epidemiologia and Secretaría de Salud 2014; Dantes et al. 2014; Tumioto et al. 2014; Vázquez-Pichardo et al. 2011; Gutierrez et al. 2011) (Fig. 4).

The largest epidemic cycle of dengue in the history of the Americas was reported in 2013, encompassing 2.3 million cases, 37,898 severe, and including 1,318 deaths

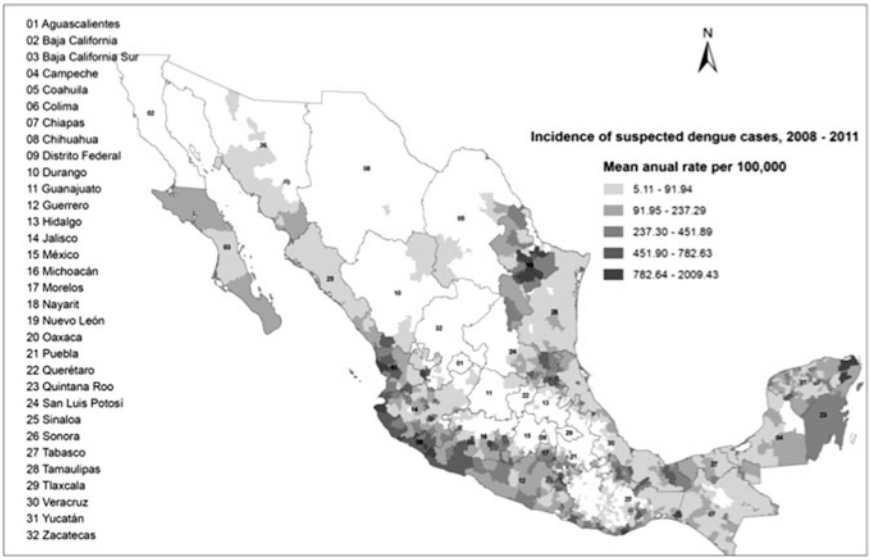

Fig. 3 Differential dengue transmission within geographic areas in Mexico, 2009–2012. Dengue cases have been reported in 30 of the 32 Mexican states. Georeferenced case reporting is an interoperative system between the National Epidemiologic Surveillance Platform and the Geographical Information System (Dengue-GIS) (*Source* Hernandez-Avila (2013))

(San Martin 2014b). The four DENV serotypes circulate in the region, with cycling periods of predominance of one or two serotypes in some countries and sustained co-circulation in others (San Martin 2014b; Nunes et al. 2014; Messina et al. 2014; Torres-Galicia 2014; Vázquez-Pichardo et al. 2011; Alvarez et al. 2006). Nonetheless, the estimated CFR of dengue has declined in the LAC, being the lowest of any WHO region (0.055 %) (PanAmerican Health Organization 2014b). Use of the 2009 dengue severity classification and efforts to train physicians on the early detection and appropriate treatment of severe dengue cases may have contributed to this outcome. Unfortunately, social and health inequalities, precarious sanitation, and water scarcity are still present in LAC and counter the potential effectiveness of dengue control programs (Tapia-Conyer et al. 2012; Gomez-Dantes et al. 2011).

In some countries such as Mexico, dengue transmission in certain geographic areas is not interrupted along the year, producing focal or regional outbreaks, some of them very large and prolonged in time, particularly in highly populated urban areas (e.g., Guadalajara, Jalisco in 2009 and Mérida, Yucatán in 2010–2011). Furthermore, the estimated incidence in municipalities or states is largely heterogeneous even within the same state region in the country (Fig. 3) (Dantes et al. 2014; Hernandez-Avila et al. 2013; Dirección General de Epidemiologia and Secretaría de Salud 2012).

In the last few decades, countries in the LAC region have strived to develop dengue surveillance systems, including expanded laboratory capacities, to better understand the local epidemiology of dengue and to shape up prevention and

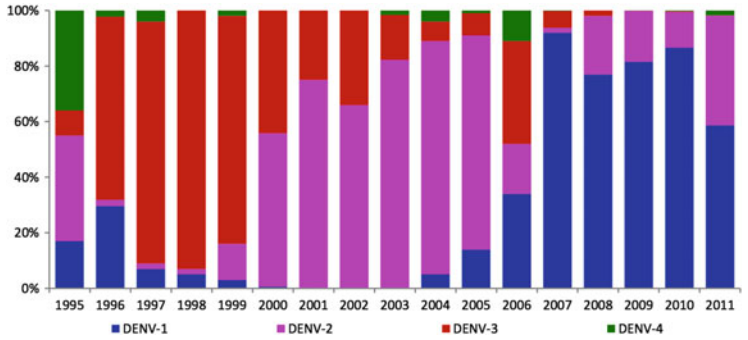

Fig. 4 Proportional distribution of dengue serotypes detected by surveillance in Mexico, 1995–2011. Dengue virological surveillance in Mexico has been conducted since 1995; however the special national dengue epidemiological surveillance system with defined proportion of virological characterization started in 2008. (*Source* Dengue Epidemiological Surveillance, 1995–2011)

control interventions. However, several challenges remain in developing effective dengue surveillance (Horstick and Morrison 2014; PanAmerican Health Organization 2014b; Messina et al. 2014; Badurdeen et al. 2013). This task has faced some challenges such as the need of well-designed and properly implemented surveillance systems, including electronic reporting to speed transference of core data.

A crucial step in establishing a sustainable capacity for prevention and control is developing, attracting, and retaining competent epidemiologist with advanced skills in quantitative data analysis and comprehensive training on interpreting primary surveillance information in context with scientific evidence (Subramanian et al. 2013). These are the professionals who can feed decision-makers with integrated knowledge on near real-time trends of dengue epidemics.

Geographic information systems and a solid laboratory network infrastructure help characterizing and confirming cases (PanAmerican Health Organization 2014b; Hernandez-Avila et al. 2013; Oliveira et al. 2013; Badurdeen et al. 2013). A successful example of these tools was established in Mexico in 2008. A web-based, geographically enabled dengue integral surveillance system (Dengue-GIS) was developed for the nation-wide collection, integration, analysis and reporting of geo-referenced epidemiologic, entomologic, and control interventions data (Hernandez-Avila et al. 2013). This system was a joint effort of the National Institute of Public Health investigators, vector control program personnel and Epidemiological surveillance programs of the Secretary of Health authorities. This system provides geographical detail evidence to plan, implement and evaluate dengue control activities (Figs. 4 and 5).

Estimating the magnitude of disease burden at local and regional scales, describing spatiotemporal trends of dengue transmission, and assessing the occurrence of severe disease are key elements of knowledge that would help better design, planning, and implementation of policies and programs aiming to prevent and control dengue (Nagao et al. 2008). Unfortunately, many surveillance systems in

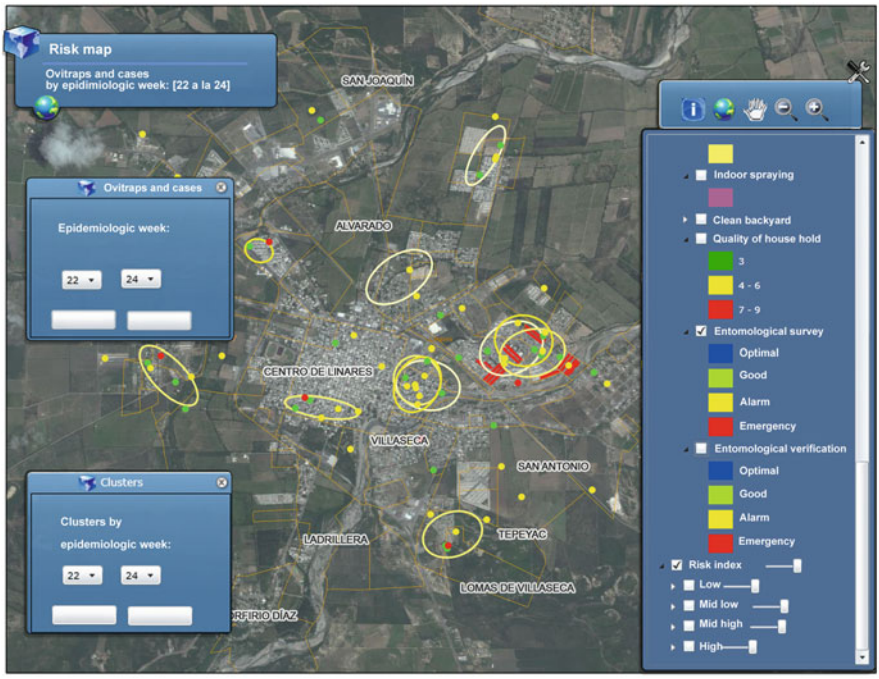

Fig. 5 National epidemiologic surveillance platform and the geographical information system (Dengue-GIS) application for dengue control program activities. Dengue-GIS screenshot describing distribution of probable cases and case clusters (high transmission areas) during the CDC weeks 22–24 2012 in Linares City, Nuevo Leon. Locations of entomological survey activities (*squares*) and dengue fever cases accumulation in space and time (*ellipses*) represent the graphical output of the cluster detection algorithm. Two areas, one very close to downtown Linares and the other to the west of the city, show three intersecting ellipses; this indicates that transmission occurred uninterrupted during the 3-week period shown. Pictures presented here were modified to translate the text presented to English; the actual Dengue-GIS is an all-Spanish language system. doi:10.1371/journal.pone.0070231.g004 (*Source* Hernandez-Avila (2013))

the region currently limit their scope to accounting the caseload and, at most, describe basic clinical characteristics of suspect or laboratory-confirmed cases. This reduced approach to surveillance is both uninformative and sensitive to wide imprecision. Overestimation of the observed number of cases ensues when sensitive case definitions—such as clinical, probable, or suspected cases—are used, which can contribute to unnecessarily overwhelming prevention and control interventions. On the other hand, less sensitive, more specific definitions—such as laboratory confirmed cases—would lead to the underestimation of disease burden and potentially stimulate dismissal from public health authorities.

Comprehensive public health risk assessment is necessary to attain better preparedness, including predictive modeling of human disease, vector dynamics, public health interventions and healthcare availability and access. Semiquantitative risk stratification helps to predict areas of high probabilities for enhanced

transmission and can guide focal interventions (PanAmerican Health Organization 2014b; Rodriguez-Barraquer et al. 2014; Badurdeen et al. 2013; Brady et al. 2012; Beatty et al. 2010).

The total annual cost of dengue in the Americas has been estimated at US$2.1 billion with a range of $1–4 billion with temporary variation (Shepard et al. 2011). In addition, the analysis of DALYs exhibits 36 % lost in Brazil, 28 % in the Andean region, and 21 % in Central America and Mexico. Another study analyzed cost in dengue ambulatory and hospitalized patients in Asia and the Americas (Suaya et al. 2009), and the average illness lasted 11.9 days for ambulatory patients and 11.0 days for hospitalized cases, 5.6 days of lost school for students, and 9.9 work days per lost work average per dengue episode. These studies did not include costs of vector control programs.

3 Dengue Control Programs

Aedes density is the main factor driving dengue transmission and vector control programs are essential to mitigate dengue disease, similar to other VBD. *Aedes Aegypti* proliferates in all kinds of toys, bottles, and devices that can hold water, which are commonly found in patios and other domiciliary environments. Thus, the successes of *Aedes* control programs are focused to eliminate vectors and to implement barriers to house colonization or to contact with humans (bednets) (Jansen and Beebe 2010; World Health Organization 2009; Ballenger-Browning and Elder 2009). Steps must be taken to sustain the elimination of mosquito habitats, such as preventing access of the vector to breeding containers, to eliminate or control vector young stages (larval), or to kill the adult vector using insecticides or biological control agents (PanAmerican Health Organization 2014b). Every step involves different determinants in dynamic complicated interactions: individual, domestic, and cultural behavior, community participation, economical and social conditions, climate and local ecology, appropriated and coordinated plan, and excellent communication at all levels. *Aedes* control methods (San Martin 2014b; World Health Organization 2009) must include environmental management to hamper with the access and breeding of the mosquitos by improving water supply and storage systems and waste management. This approach must be implemented in occupied and vacant buildings, public areas—parks, gardens, cemeteries, schools, etc.

Simultaneously, access and promotion of the use of individual and household barrier methods, including protective clothing to avoid mosquito biting, repellents, window and door screens, and bednets, are warranted. Chemical controls with larvicides or adulticides complement vector abatement (Torres-Estrada and Rodiles-Cruz Ndel 2013; Tapia-Conyer et al. 2012; World Health Organization 2009). Insecticide-treated materials (curtains and bednets) in combination with vector control methods have also been proposed as individual protection measures (Jones et al. 2014; Tapia-Conyer et al. 2012; Ballenger-Browning and Elder 2009;

Kroeger et al. 2006). A number of entomological indices have been proposed for entomologic surveillance systems and to lead the monitoring and impact evaluation of vector control programs (World Health Organization 2009; Ballenger-Browning and Elder 2009; Gomez-Dantes et al. 2011).

Most public health systems in the LAC region have relied on governmental action for guide and operate surveillance, vector control and health promotion activities, but a core quandary is how to boost community participation in a consistent partnership framework that optimizes the impact of transmission mitigation measures (Tapia-Conyer et al. 2012). The theoretical advantages of coordinated interdisciplinary and intergovernmental approaches are encouraging, but there is need to populate the repertoire of hard evidence on the return on the investment vis-à-vis vertical and fragmented public health programs (World Health Organization 2009).

Integrated programs are expensive and complex to manage, as they require accurate information to focus activities and keep track of progress. Competing agendas of partners and sponsors may challenge the political and financial sustainability of joint ventures. Therefore vector control programs are mostly driven by routine entomologic surveillance and disease-specific surveillance programs that frequently target the most immediate outcomes, such as vector density and frequency of clinical and confirmed cases in specific areas. Disperse control interventions and missing opportunities for collaboration between political authorities across national boundaries or subnational entities, such as states or municipalities, are a reminder that infectious disease recognizes no borders (PanAmerican Health Organization 2014b). Accurate surveillance, transparent data exchange, and concerted public health action are the fundamentals of effective preparedness and response against dengue and most public health challenges (World Health Organization 2008).

Since 2001, PAHO established a reference frame to develop interdisciplinary approach for dengue prevention and control. The Integrated Management Strategy for Dengue Prevention and Control (IMS-dengue), launched in 2003, presents a model of six components: epidemiology, entomology, healthcare, laboratory, social communication, and environment (San Martin and Brathwaite-Dick 2007). By the end of the first decade of twenty-first century, 19 countries in the LAC region had implemented the IMS—dengue approach (Argentina, Bolivia, Brazil Colombia, Costa Rica, Chile, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, the Dominican Republic, Uruguay, and Venezuela). Four subnational IMS—dengue plans have also been established in Central America, the Andean Sub Region, MERCOSUR, and the Caribbean.

Despite encouraging signs of progress, the LAC region has reported a progressive increasing number of dengue cases. Some of this trend needs to disentangle the effects of improved surveillance and reporting of all forms of dengue cases, not just severe dengue (PanAmerican Health Organization 2014b; San Martin 2014b). In 2010, WHO launched the Global Strategy for the Prevention and Control of Dengue 2012–2020, aiming to reduce 50 % of dengue mortality and 25 % of morbidity by 2020 (World Health Organization 2012). The Strategy stems on five technical

Table 1 Integrated management strategy for the prevention and control of dengue in the Americas (IMS-Dengue), PAHO/WHO

Components	Technical elements
• Diagnosis and case management • Integrated surveillance and outbreak preparedness • Sustainable vector control • Future vaccine implementation • Basic operational and implementation of research	• Monitoring and evaluation • Capacity building • Communication for behavioral outcomes • Advocacy and resources mobilization • Partnership, coordination, and collaboration

Source Adapted from Pan American Health Organization; State of the Art in the Prevention and Control of Dengue in the Americas, 2014

components (Table 1): (1) Diagnosis and case management; (2) Integrated surveillance and outbreak preparedness; (3) Sustainable vector control; (4) Future vaccine implementation; and (5) Basic operational and implementation research. The successful implementation of this global strategy requires integrated action, strong advocacy and effective resource mobilization, vigorous partnerships, effective coordination and collaboration, transparent communication, sustainable capacity building, and rigorous monitoring and evaluation.

In May 2014, PAHO analyzed dengue prevention and control in the Americas (PanAmerican Health Organization 2014b) by reviewing regional experiences in surveillance, detection, diagnosis, management, treatment, and prevention. Lessons learned by countries in recent years along with current scientific and operational evidence and best practices on dengue prevention and control conformed this comprehensive assessment. The Organization presented a standard set of recommendations to the regional programs for dengue control in the Americas and pointed at ways to identify research opportunities and fill gaps in the IMS-Dengue Strategy.

Experts and country representatives concluded that implementation of this strategy provided with a solid instrument for preventing and controlling dengue, which can be adapted to the needs and capacities of each country. Mexico IMS-Dengue include seven components: (1) Health promotion; (2) Social, community, intra-, and intersectoral participation; (3) Epidemiological and entomological surveillance; (4) Laboratory diagnosis by the state public health laboratory; (5) Patient care; (6) Control of health risks; and (7) Chemical vector control. Brazil pointed that decentralization of the health system allowed surveillance and vector control activities to be expanded across the country. Several countries in the Americas have implemented an outbreak control system that uses risk stratification and integrated actions to optimize the management of material and human resources in dengue prevention and control.

Dengue outbreaks are increasing in frequency and are associated with social and economic disruption and overwhelming of health services, many times with adverse political consequences due to mass media magnification. Dengue control programs

need strengthening at different levels. While financial and human resources are in the need to support program actions, it is also clear that more operational research is needed to better understand how to mobilize community participation and how to achieve effective intersectoral and multilevel government control actions. There is an urgent need to improve early disease and vector surveillance with effective risk communication and vector control activities.

4 Dengue Vaccines

Due to the continuous increase of dengue cases, the high social and economic costs associated with its health effects, and the proven difficulty to accomplish successfully control programs, developing a dengue vaccine has become a global priority. Dengue vaccine development needs some particular considerations: first, the vaccine needs to protect effectively against the four serotypes simultaneously, and second, the vaccine needs to be safe and not to enhance severe disease manifestations associated with antibody-dependent enhancement associated with infection with a second serotype that may lead to severe disease manifestations, as it happens with natural dengue infections; thus a vaccine that induces protection in an early period of time might later increase the risk for enhanced disease, impact of previous immunity due to primary infections at early ages, among many others (Yauch and Shresta 2014; del Angel and Reyes-del Valle 2013; Halstead 2013b).

Several DENV vaccines are under development: live-attenuated, inactivated, recombinant subunit, viral vectored, and DNA vaccines. The most advanced studies are focused on live-attenuated developments; some of them are in phase II and III trials (Yauch and Shresta 2014; Thisyakorn and Thisyakorn 2014). Only one candidate vaccine is reaching phase III clinical trials, a live-attenuated chimeric containing dengue structural genes inserted into the infectious cDNA backbone of a yellow fever vaccine virus strain 17D (manufacture by Sanofi-Pasteur). The results of the phase 2b study of this vaccine showed good immunogenicity for all four serotypes (Sabchareon et al. 2012). However the global vaccine efficacy was 30.2 % (95 % confidence interval [CI]: 13.4–56.6) with wide differences by serotype: better for DENV 3 and 4, less for DENV 1, and no efficacy against DENV 2. In addition, the vaccine was well tolerated with no safety issues after 2 years of follow-up. The same vaccine has been evaluated in large phase III trials in Asia and Latin America.

The Asia arm of the study including 10,275 children (Capeding et al. 2014) estimated 56.6 % (95 % CI: 43.8–66.4) vaccine efficacy against confirmed dengue and, again, differences between serotypes are found with efficacy of 50 % (95 % CI: 24.6–66.8) for DENV 1, 35 % (95 % CI: −9.2–61.0) for DENV 2, 78.3 % (95 % CI: 52.9–90.8) for DENV 3, and 73.5 % (95 % CI: 54.5–87.0) for DENV 4. Vaccine efficacy against DENV 2 in this study is still significantly lower than the other serotypes and the CI is reaching no efficacy, similarly to the 2b trial.

In this study, the vaccine appears safe and well tolerated in the short term. Some other results showed that almost two-thirds of subjects in the trial were seropositive for dengue at baseline by microneutralization assay, and the proportion of seropositivity increased with age. Vaccine efficacy seems to be higher for participants who were seropositive for dengue than for those who were seronegative. The authors describe differences in DENV 2 genotypes in the vaccine components in comparison to those circulating during the trial, as a possible explanation of the lack of vaccine efficacy against this serotype. The increased efficacy observed in the phase III trial is obviously associated with more diversity of DENV serotypes circulating in different countries than the predominant DENV 2 cases detected in the 2b trial performed in only one specific area. In addition, the investigators pointed high vaccine efficacy against dengue hemorrhagic fever and clinically important reductions in severe disease and hospital admissions. These findings of vaccine efficacy on severe disease are encouraging, but we must keep in mind that the numbers for these conclusions are limited (Capeding et al. 2014).

The Latin American trial enrolled a total of 20,875 children aged 9–16 years from dengue endemic areas of Brazil, Colombia, Mexico, Honduras, and Puerto Rico (Villar et al. 2014), and the results demonstrated global vaccine efficacy of 60.8 % (95 % CI: 52.0–68.0). Differences in serotype vaccine efficacy were also found, with estimated mean values of 50.3 % (95 % CI: 29.1–65.2) for DENV 1, 42.3 % (95 % CI: 14.0–61.1) for DENV-2, 74.0 % (95 % CI: 61.9–82.4) for DENV 3, and 77.7 % (95 % CI: 60.2–88.0) for DENV 4. This study further showed differential vaccine efficacy for dengue serotypes: it is good for DENV 3 and 4, less for DENV 1, and significantly lower for DENV 2. In addition, vaccine efficacy seems to be better in the population previously immune to dengue. The vaccine was also safe and well tolerated and again vaccine efficacy seems to be higher in those children with seropositive dengue baseline status.

There is no doubt that the results of this live-attenuated chimeric dengue vaccine are good news for a first line of dengue vaccine development. Approximately 60 % global vaccine efficacy with no safety concerns after 25 months follow-up of disease enhancement is a great achievement for dengue control due to the magnitude of the disease transmission. The possibility of 50–60 % reduction of diseases, and even more on severe cases, would be very beneficial. Because dengue pathogenesis is mostly associated with subsequent infections (Thomas 2015), it will be important to define if the safety findings are sustained through longer period of time than the 25 months follow-up to date and to further characterize waning immunity. Furthermore -before its population use- more information is needed regarding the vaccine efficacy to prevent symptomatic and asymptomatic diseases and severe manifestations of disease associated with secondary infections (Guzman and Harris 2015).

However, other key issues (World Health Organization and Experts and S. A. G. O 2012) need to be considered by country public health decisions makers before introducing a dengue vaccine in the current immunization programs, either with the current available product or any with any other future development dengue vaccine program with the current available product or any other vaccine in progress

(Mahoney 2014; Douglas et al. 2013; Live Dengue Vaccines Technical Consultation Reporting et al. 2013). As previously discussed, if transmission of one predominant or combined serotypes often occurred within and among countries and some of these serotypes may last for several years, then vaccine efficacy may be different and even lower if DENV 1 and 2 are predominant. There are still gaps in further understanding specific dynamic introduction and reintroduction and timing of each or combined serotypes in specific regions.

Some studies have reported cost-effectiveness of dengue vaccination studies including transmission and a different range of clinical vaccine efficacy (Durham et al. 2013). Interestingly, the findings exhibited that it is necessary to reach 82 % of population vaccination to reach herd immunity, and with 70 % vaccine efficacy, vaccination may be cost-effective with a price up to US $534 (95 % CI: $369–1008) per vaccinated individual and cost saving up to $204 (95 % CI: $39–678). If the vaccine efficacy is only 30 %, cost-effectiveness could be achieved to a cost of $237 (95 % CI: $159–512) with savings of $93 (95 % CI: $15–368).

Further cost-effectives studies per different region may include efficacy between serotypes in addition to mathematical models to address how a partial efficacious dengue vaccine would be expected to behave in a certain period of time, in different geographic areas, even within a country (Shepard et al. 2011). In regards of implementation of dengue vaccination, on one side, there is no question that dengue is a public health priority, in terms of the magnitude of the disease burden and associated costs and prevention with vaccine is an excellent option. Vaccine prices currently not known; in a costing exercise prices for public sector were fixed at US $15 ($10–20); with these figures, it has been estimated that dengue immunization programs for Colombia and Brazil's will require an investment from public sector of US $2,400 million over 5 years.

As it happens in many of LAC, decision makers will need to analyze and prioritize use of funds for several public health problems, for example, investing in environmental improvements like water sanitation to reduce mosquito breeding sites, or strengthening vector control and surveillance systems, which may produce a greater benefit at lower cost. The vector control programs cannot be discontinued, not even think to be decreased, because the time and limit to reach dengue-vaccinated population proportion to have an impact in dengue transmission is not known. This is now more relevant when Chikungunya currently emerging in the Americas, a disease that shares vector and clinical presentation, imposes additional burden on established vector control programs (San Martin 2014b).

Furthermore, funding for a new vaccine program must carefully consider direct and indirect costs to assure the extra needs in human resources and infrastructure (World Health Organization and Experts and S. A. G. O 2012), not only for the specific new vaccine program but also for the National Vaccine Program of each country. This is a crucial step of programmatic and budgetary rationale to avoid jeopardizing global vaccine coverage already accomplished. After dengue vaccine introduction, epidemiological surveillance, including hospitalized severe cases, must be extensively improved, not only to further evaluate the global vaccination

strategy impact but also to assure possible risk for enhanced disease after longer periods than the so far good safety results of this candidate vaccine.

Other concerns related to the capacity of immunization programs to successfully introduce any new vaccine is to deliver it over the long term. This will vary from country to country. However, given the large size of the target population and number of doses required, this is certainly an important point to consider.

5 Conclusion

The persistence problems related to escalating dengue disease spread in the Latin America and Caribbean region, vector control problems, absence of specific treatment, and the status of vaccine development impose a need for further development of research in several aspects of dengue disease: stronger epidemiological and entomological surveillance systems, basic immunology and virus genetic characterization, pathogenesis, vaccine development, fill the gaps to further understand specific dynamic introduction, and reintroduction and timing of serotypes per regions using specific modeling studies, among others.

Current available data suggest caution in the introduction of dengue vaccine; although disease is recognized as a public health priority, vaccine should be introduced with appropriate safety controls and economical evaluations for LAC. More evidence-based actions and integrated commitment are required to reinforce our battle against dengue.

Author Contributions Review of the literature: CMAA and HLG. Information contribution: JHEA, MHA: Analysis and Discussion of information: CMAA, HLG, JHEA, MHA.

Conflict of Interest CMAA serves on the Independent Data and Monitoring Committee for ongoing dengue vaccine trials being conducted by Sanofi-Pasteur.

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Cysticercosis Disease Burden in Latin America

Jaime R. Torres

Contents

Abstract Cysticercosis is caused by infection with the larval form (or cysticercus) of the tapeworm *Taenia solium*. The most important clinical manifestations are caused by cysts in invading the central nervous system known as neurocysticercosis, which is associated with significant morbidity and disability in Latin America. Taeniasis and cysticercosis occur globally, with the highest rates in areas of Latin America, Asia, and sub-Saharan Africa associated with poor sanitation and free-ranging pigs with access to human feces. Control efforts in Latin America require an integration of both medical treatment of cases of taeniasis to prevent further transmission and of neurocysticercosis to decrease the burden of disease with antiparasitic drugs, steroids, and anticonvulsant therapy. Further efforts targeting interventions to improve health education of communities living in highly endemic settings combined with sanitation and poverty alleviation initiatives in Latin America may prove to have the highest impact to decrease the substantial morbidity and long-term neurologic consequences associated with this neglected tropical disease.

Keywords Latin America • Cysticercosis • Neurocysticersosis • Taeniasis

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_12

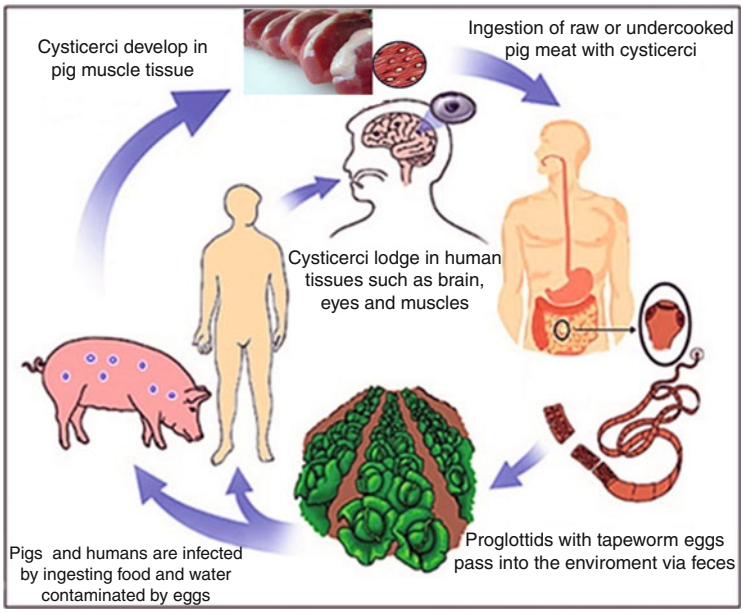

Fig. 1 *Taenia solium* life cycle (Modified from: Kraft R (2007) Am Fam Physician 75:91–96)

1 Introduction

Human cysticercosis, defined by the presence of *Taenia solium* larvae in human tissues, occurs when people ingest the parasite's eggs from food, drink, or soil contaminated by the feces of another person carrying the adult tapeworm. Thus, humans become dead-end hosts of the larval stage of the parasite and develop cysticercosis in a similar way to pigs, the natural intermediate hosts (*see the parasite's life cycle in* Fig. 1) (Kraft 2007; Garcia and Del Brutto 2000).

Ingestion of *T. solium* eggs usually occurs through fecal–oral transmission via infected food handlers with poor hygiene, or by fruit and vegetables fertilized with contaminated human waste. Thousands of infective eggs are daily detached from the distal end of the adult tapeworm and are passed with feces of *Taenia* carriers. In places where both improper disposal of human feces and poor husbandry are common, pigs get access to human feces and ingest *T. solium* eggs. Eggs mature into oncospheres and metacestodes and lodge in the striated muscles and other tissues of pigs, the natural intermediate host; there, metacestodes evolve into larvae (cysticerci). When humans ingest improperly cooked pork infected with cysticerci, larvae evaginate and adhere to the intestinal mucosa. Then, the adult worm begins to grow—forming proglottids—and the life cycle is completed when proglottids become gravid and are passed with human feces. Humans may also become intermediate hosts in the life cycle of *T. solium* after ingesting its eggs. In these cases, human cysticercosis ensues (Kraft 2007; Garcia and Del Brutto 2000). More rarely, it associates with autoinfection, which involves the retrograde transmission

of proglottids from the intestines into the stomach, with subsequent release of eggs into the human gut (Kraft 2007; Garcia and Del Brutto 2000).

People are at risk of developing cysticercosis due to poor hygiene and living conditions that allow pigs' access to human feces. The most important risk factor for the acquisition of human cysticercosis is the proximity of a tapeworm carrier. It must be stressed that the ingestion of undercooked encysted pork meat does not directly cause cysticercosis; rather, it produces an intestinal infection of the adult tapeworm and a carrier state for the eggs that, when ingested by another humans, produce the clinical syndrome of cysticercosis. Indeed, even populations who do not eat pork, such as vegetarians or certain religious groups, can develop cysticercosis (Kraft 2007; Garcia and Del Brutto 2000).

Cysticercosis is considered the most common parasitic disease of the central nervous system (CNS) worldwide, and the single most common cause of epilepsy in the developing countries, with an estimated prevalence greater than 50 million persons infected (Kraft 2007; Garcia and Del Brutto 2000; Garcia et al. 2003a). The infection is endemic in Mexico, Central and South America, as well as in parts of Africa, Asia, and India (Kraft 2007; Garcia and Del Brutto 2000; Garcia et al. 2003a; Prasad et al. 2008a). Cysticercosis is a disease of poverty and underdevelopment, which is common in communities lacking basic sanitary facilities, where pigs are allowed to meander freely, and consumption of undercooked pork is customary. It is regarded as one of the most representative neglected tropical diseases (NTD), worldwide. Moreover, cysticercosis has been designated as a "biological marker" of the social and economic development of a community (Prasad et al. 2008a; Carpio et al. 1998; Garcia and Del Brutto 2005).

Nevertheless, in endemic countries, the disease is also widely prevalent in urban, middle class areas. Migration from the countryside and the rise of urban slums might influence the changing epidemiology of cysticercosis. Of note, *T. solium* infections may also be imported by migrant workers into the developing countries causing unexpected cases of cysticercosis (Prasad et al. 2008a; Carpio et al. 1998).

Cysticerci may invade almost any organ or tissue of the human economy, including subcutaneous tissue, striated muscle, heart, liver, or other organs; however, apart from some cases of massive muscle involvement by hundreds of cysts, which may cause muscular pseudo-hypertrophy and myositis, or some sporadic cases of intraocular cysticercosis and arrhythmias related to cardiac cysts, most instances of systemic nonneurological cysticercosis are clinically irrelevant and account for less than 5 % of all cases of symptomatic disease (Garcia and Del Brutto 2005; Del Brutto 1997).

2 Neurocysticercosis

Significant relevant disease is most often related to invasion of the CNS, giving rise to the condition called neurocysticercosis (NCC). According to conservative figures, NCC causes 50,000 deaths/year and is the most common cause of acquired

epilepsy worldwide, accounting for up to 30 % of the excess fraction of epilepsy seen in the developing world (Del Brutto 2013). Furthermore, case–control studies have reported prevalence odds ratios as high as 6.9 between NCC and epilepsy (Cruz et al. 1999).

NCC is the most prevalent infection of the brain worldwide being one of the leading causes of adult-onset seizures. The disease is endemic in Latin America, India, and China (Garcia et al. 2003b; Prasad et al. 2008b). Preliminary studies suggest that it may also be endemic in sub-Saharan Africa (Pal et al. 2000).

From the clinical point of view, NCC is highly pleomorphic and there is no possibility to define a pathognomonic clinical syndrome. The proportion of persons whose infections progress to symptomatic disease is unknown. Most of the patients develop seizures as the main or sole manifestation of the disease, but this is true only for those with parenchymal brain cysticercosis, since the subarachnoid and ventricular forms of the disease often associate with focal neurological deficits or intracranial hypertension. The clinical pleomorphism of NCC is directly related to differences in the severity of infection, in the location of lesions within the CNS and the intensity of the reaction of the host immune system against the parasites.

The definitive diagnosis of NCC has to be made by a combination of methods including neuroimaging procedures, histopathological techniques, and immunological investigations, because the use of any single method may provide faulty diagnoses.

Whereas seizures are the most common manifestation of symptomatic human NCC explaining most of the disease burden, the illness may also be associated with headache, hydrocephalus, chronic meningitis, or symptoms due to a space-occupying CNS lesion. Isolated nonneurological manifestations, such as ocular or dermal cysts, account for <5 % of cases of symptomatic disease (Del Brutto 1997; Garcia et al. 2003b).

Recent meta-analysis has revealed that epilepsy is consistently associated with NCC in over one-quarter of patients residing in endemic regions, regardless of the type of epilepsy, if single epileptic seizures were included or not, and where and among whom the study was conducted. Such estimates confirm the importance of NCC infection in the etiology of epilepsy in developing countries and suggest that NCC may be associated with a very large burden in cysticercosis endemic areas where epilepsy is prevalent. Although NCC is widely recognized as a cause of late-onset epilepsy (first episode of seizure at age 20 or older), the proportion of NCC among epileptic children appears to be equally high (Ndimubanzi et al. 2010). Such estimates of the prevalence of NCC in people with epilepsy have proven accurate in communities from rural areas of endemic countries; however, since most epidemiological studies are based on a single CT-scan diagnosis, they may either over- or underestimate the actual frequency of NCC (Ndimubanzi et al. 2010).

Whereas the worldwide prevalence of NCC still remains to be known, the data on the burden of NCC associated with epilepsy are relatively well documented; hence it is customarily used to provide estimates of prevalence and incidence of NCC in endemic regions. The estimated numbers of people suffering from epilepsy due to NCC are as high as 0.45–1.35 million in Latin America, 0.31–4.6 million in

sub-Saharan Africa, 1 million in India, and 0.3–0.7 million in China (Coyle et al. 2012). Estimates of prevalence from some Latin American countries have ranged from 15 to 38 % (Coyle et al. 2012). In a community-wide screening survey from rural Peru, the prevalence of seropositive individuals was 24 % and was associated with seizures with an odds ratio of 2.1, with an additional 13 % of those with negative serology demonstrating calcifications typical of NCC on computed tomography (CT) scans, thereby giving an overall estimate of 37 % prevalence of cysticercosis (Montano et al. 2005; Abhishek et al. 2013).

Although there is no sufficient evidence at this time to accurately estimate the prevalence of NCC globally, cysticercosis certainly represents a major public health problem in many developing countries, affecting several million people by not only causing neurological morbidity but also imposing economic hardship on impoverished populations. However, there are wide variations in the prevalence rates in different regions and different socioeconomic groups in the same country (Abhishek et al. 2013).

Besides prevalence and incidence figures, estimates of the proportion of NCC-associated health outcomes (i.e., epilepsy and headaches) are dearly needed to assess the real burden of the disease. Unfortunately, these figures are often lacking because studies to measure the attribution rate of NCC require complicated and expensive well-designed studies.

3 Cysticercosis-Associated Burden of Disease and Control Strategies

The burden of disease (BoD) is a public health measure used to assess and compare the relative impact of different illnesses and injuries on populations. It quantifies health loss due to disease and injury that remains after treatment, rehabilitation, or prevention efforts of the health system and society generally.

One widely used measure of BoD is disability-adjusted life years or DALYs, which estimate years of life lost due to premature death (YLL), as well as years of healthy life lost due to disability from disease and injury (YLD). One DALY is considered the equivalent of 1 year of healthy life lost. Such standardized measures have become instrumental in guiding health policies based on more reliable and meaningful data (Murray et al. 1994; Murray and Lopez 1997).

Unfortunately, only limited data exist on the BoD associated with most NTD. Indeed, the few research initiatives that have attempted to estimate the burden of NTDs have been criticized for grossly underestimating their global impact (Hotez and Brown 2009; Hotez et al. 2008). In addition, the global burden of several zoonotic NTDs, such as cysticercosis, has never been estimated.

Well-designed epidemiological studies are badly needed to estimate the burden of NCC in many endemic countries, in order to facilitate international comparison of BoD and identify priorities for control. However, investigations aimed to assess

the burden of NCC are notoriously scanty. Two early African studies estimated the burden of cysticercosis in specific countries. A study in Cameroon using serology for the diagnosis of NCC calculated the average number of DALYs lost due to NCC-associated epilepsy as 9.0 per 1,000 person-years (95 % CR: 2.8–20.4) and the monetary burden per case amounted to 194 Euros (95 % CR: 147–253) (Praet et al. 2009). Another study conducted in one province of South Africa estimated that the monetary burden of NCC varied from US$ 632 to US$ 844 per NCC-associated epilepsy case, indicating high financial losses associated with this condition (Carabin et al. 2006).

More recently, a study performed in Mexico, incorporating two common clinical manifestations of patients with NCC, epilepsy and severe chronic headaches, provided the first estimate of DALYs associated with NCC in that country (Bhattarai et al. 2012). The total number of DALYs lost due to NCC-associated epilepsy and severe chronic headaches was estimated at 23,020 (95 % CR: 11,283–43,276) and 2,321 (95 % CR: 198–8,754), respectively, with 0.25 (95 % CR: 0.12–0.46) DALY lost per 1,000 person-years. Twenty-eight percent of DALYs lost due to NCC in Mexico was attributed to YLL and the remaining 72 % was due to YLD (Bhattarai et al. 2012).

The wide differences in BoD estimates observed between the above mentioned studies of Cameroon and Mexico (9.0 vs. 0.25 DALYs lost per 1,000 person-years, respectively) reflect some of the predicaments faced when comparing seemingly similar studies. For instance, while the data from Mexico were stratified by urban/rural areas, age groups, and gender, such stratification was not used in the Cameroon study. Besides, since the proportion of epilepsy cases attributable to NCC is lower in urban areas and the majority of the Mexican population is urban, the overall burden per person would be lower in Mexico. In addition, if most NCC-associated epilepsy patients are likely to be treated the DALYS per 1,000 person-years would be fewer, as the disability weight for treated epilepsy is much lower than that for untreated epilepsy (Carabin et al. 2006; Bhattarai et al. 2012). Similarly, the annual number of deaths attributed to NCC-associated epilepsy in a given country, a subjective figure expressing basically an experts' educated guess, will greatly influence the number of DALYs per 1,000 person-years projected and, as a consequence, the estimated disease burden.

The assessment of the global burden of NCC might be ultimately improved if a standard diagnosis for the illness, such as that developed by Del Brutto et al. (2001), could be adopted; nonetheless, to that purpose all endemic countries would require the availability of adequate diagnostic tools, as well as enough professionals with adequate clinical expertise. Moreover, attempts have been made by some researches to declare NCC an international reportable disease (Román et al. 2000). Although compulsory notification would have the benefit of providing accurate quantification of NCC prevalence in endemic areas, such proposal was indeed considered but rejected by the World Health Assembly in 2003 because it was felt that only diseases with the potential to cause large-scale international outbreaks should be included in the list of internationally notifiable diseases

[World Health Organization (WHO) 2003]. However, countries were encouraged to add this disease to their national list of notifiable diseases.

Compulsory notification of cases, in combination with autopsy reports, has proven to be a valuable resource in the study of the epidemiology of NCC, allowing for a more reliable estimation of its true prevalence in endemic regions, as shown by the experience of the municipality of Ribeiraõ Preto in Brazil, which since 1992 decided to make NCC a reportable disease (Chimelli and Lovalho 1998).

Comprehensive collaborative data would greatly improve the decision-making process regarding curative and preventive measures for a disease associated with potentially severe sequelae. In order to better establish the global burden of NCC and facilitate future systematic reviews of published or unpublished relevant experiences, standardization of NCC epidemiological and clinical diagnostic criteria, as well as compulsory notification of cases and deaths, may prove instrumental.

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Atlas of Histopathology of Selected Neglected Tropical Diseases Prevalent in Latin America and the Caribbean

Jeannette Guarner

Contents

Abstract The objective of this chapter is to present an atlas of histopathological findings of some of the major Neglected Tropical Diseases that continue to pose a substantial burden of disease in Latin America and the Caribbean.

Keywords Histopathology • Atlas • Neglected tropical diseases • Latin America • Caribbean • Leishmaniasis • Chagas disease • *Trypanosoma cruzi* • *Wolbachia* • Onchocerciasis • Leprosy • Buruli ulcer • *Mycobacterium ulcerans* • Rabies • Lymphatic filariasis • Echinococcosis

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C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_13

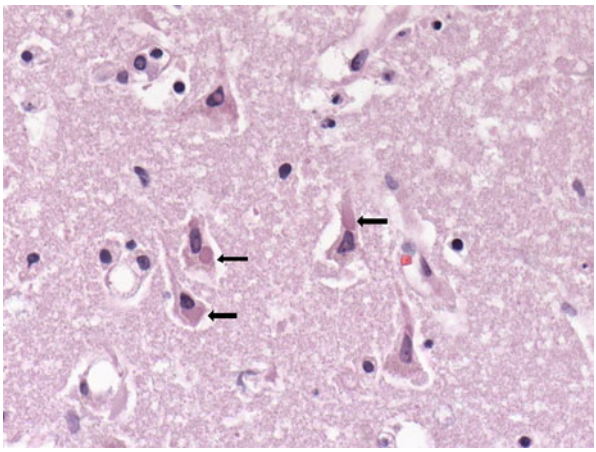

Fig. 1 Histopathological features of rabies

1 Introduction

The objective of this chapter is to present some of the cardinal histopathological manifestations of some of the major Neglected Tropical Diseases that are prevalent in Latin America and the Caribbean.

1.1 Rabies

Despite major control efforts, rabies continues to cause many cases of rabies in LAC. From a histopathology point of view, Negri bodies are the hallmark of rabies diagnosis/confirmation. These are intracytoplasmic eosinophilic inclusions that can be seen in neurons. They are classically located in the Purkinje cells of the cerebellum and the hippocampus but can be seen in many areas of the brain. In Fig. 1, multiple Negri bodies are marked with arrows.

In response to the virus, there is an intense perivascular mononuclear inflammatory response as well as glial nodules and scattered necrotic foci. This pattern is recognized by pathologists as an encephalitis and is shown in the following image where the perivascular inflammation is circled and the glial nodule is marked with an arrow (Fig. 2).

1.2 Dengue

Dengue is a major cause of morbidity and mortality in LAC. In comparison to rabies where there is an inclusion body that defines the disease, dengue does not produce a tissue cytopathic effect. The target cells of dengue virus are monocytes, macrophages, and dendritic cells which upon infection result in extensive T-cell activation and production of high amounts of cytokines. These cytokines lead to

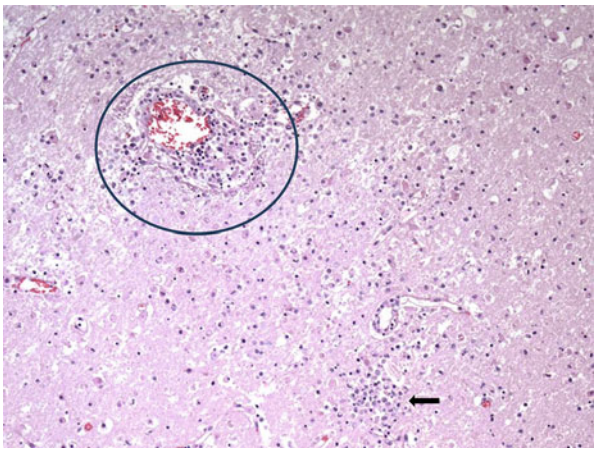

Fig. 2 Perivascular inflammation associated with glial nodules characteristic of encephalitis

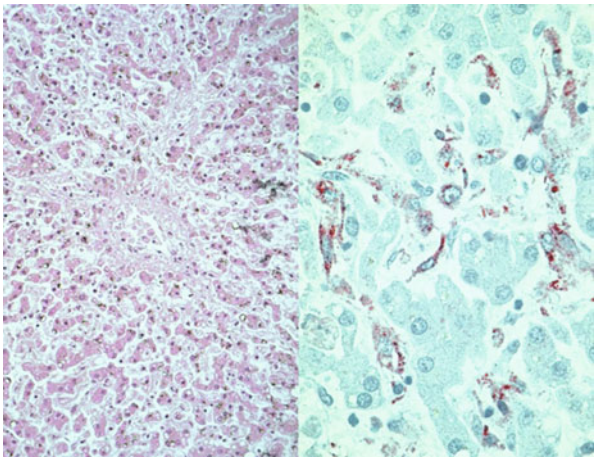

Fig. 3 Histopathological features of dengue

endothelial damage and plasma leakage (Rodenhuis-Zybert et al. 2010). Thus, on routine staining with hematoxylin and eosin, there is edema shown in the liver image on the left as hepatocytes are much more separated from one another. By using immunohistochemistry against dengue virus, the viral antigens can be observed in the Kupffer cells (liver macrophages) which are seen containing a red pigment in the image on the right (Fig. 3).

1.3 Chagas Disease

During acute disease, *Trypanosoma cruzi* can be seen in blood smears. Several features are important to recognize circulating trypomastigotes: These are extracellular parasites that have a kinetoplast at one end (black arrow), a centrally located nucleus (blue arrow), an undulating membrane, and a flagellum (red

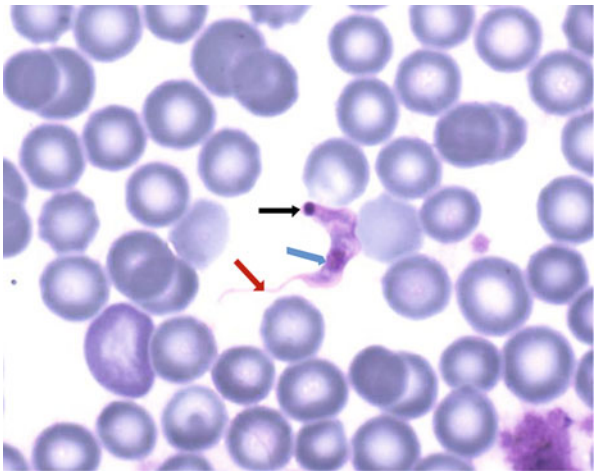

Fig. 4 *Trypanosoma cruzi* identified in a peripheral blood smear

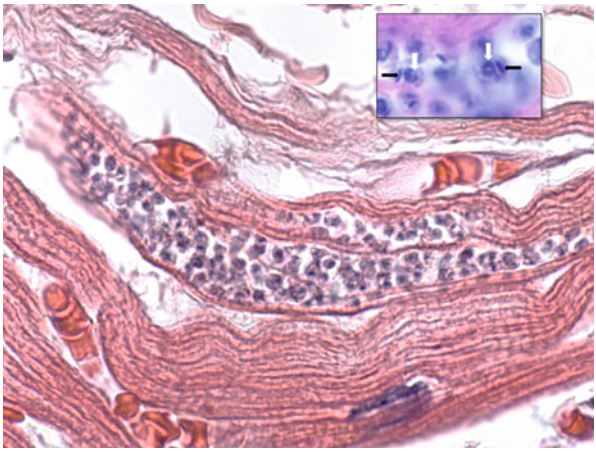

Fig. 5 Chronic *Trypanosoma cruzi* infection demonstrating tropism for muscle cells with nests of amastigotes

arrow) running along the undulating membrane that can be seen on the side of the body of the parasite (Fig. 4).

Once the acute phase is passed, the parasites have tropism for all muscle cells in the body where they form amastigotes nests image. Amastigotes are characterized by a single nucleus (white arrows) and kinetoplast (black arrows) as seen in the image insert (Fig. 5).

1.4 Leishmaniases

This protozoan has a tropism for macrophages. In skin lesions, it shows a nucleus and a kinetoplast. The arrow in the image points to an amastigote. (Image from the Centers for Disease Control and Prevention DPDx website) (Fig. 6).

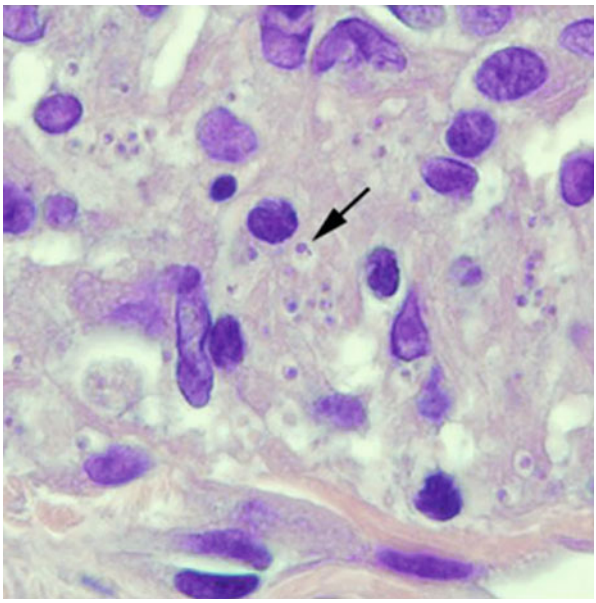

Fig. 6 Histopathological features of cutaneous leishmaniasis

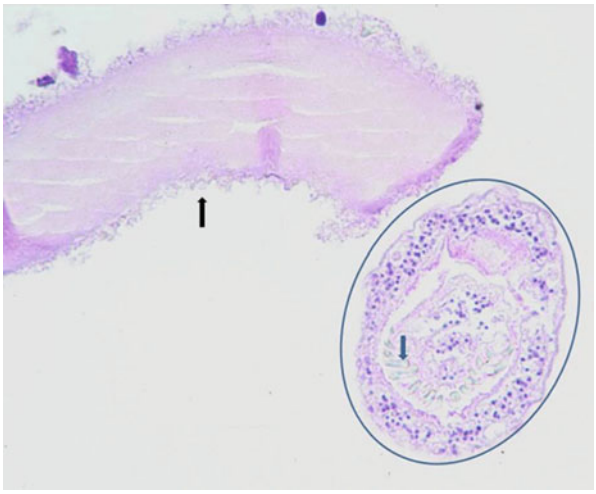

Fig. 7 Histopathological features of echinococcosis

1.5 Echinococcosis

Echinococci occur mostly in the Andean region of Latin America leading to severe morbidity. This helminthic infection produces a hydatid cyst with a thick acellular capsule (black arrow) that contains many protoscoleces (larval stages) of the helmith. In the protoscoleces (circled), refractile hooklets (blue arrow) can be noted (Fig. 7).

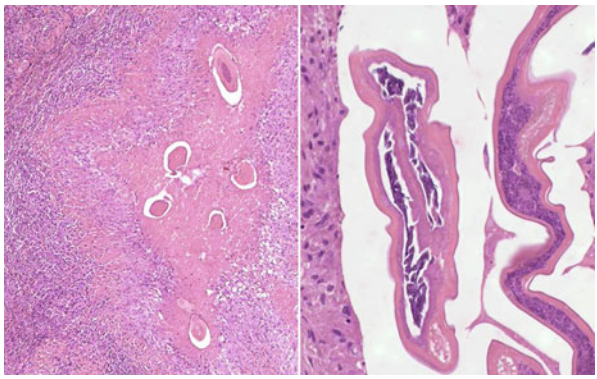

Fig. 8 Histopathological features of onchocerciasis

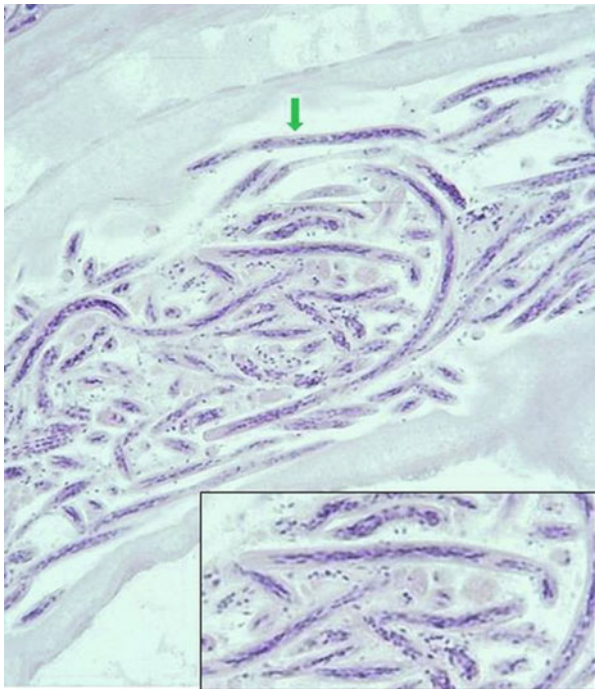

Fig. 9 Identification of viable adult female filarial parasites that continue to produce microfilaria

1.6 Onchocerciasis

The larvae of *Onchocerca volvulus* penetrate skin at the site of the blackfly bite. In the subcutaneous tissue, the filarial larvae develop into adults. The host produces a granulomatous reaction around the parasites (image on the left) giving rise to subcutaneous nodules. The parasites in these nodules may degenerate (image on the right) (Fig. 8).

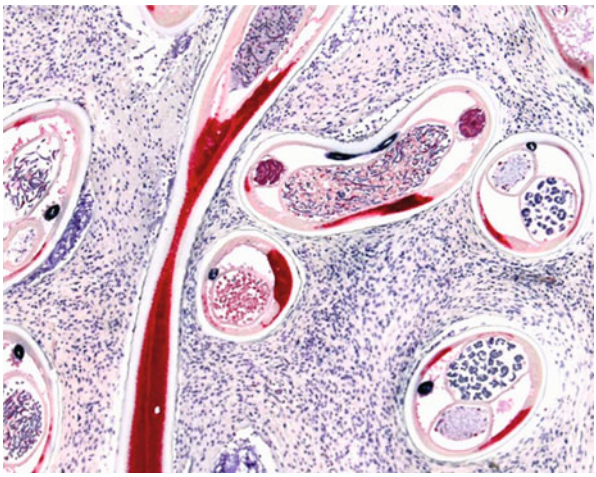

Fig. 10 Detection of *Wolbachia*, a symbiotic bacteria of filarial nematodes

Some nodules have viable adult female parasites that continue to produce microfilaria (image green arrow and insert) (Fig. 9).

Wolbachia, a symbiotic bacteria of filarial nematodes, is essential for normal development and fertility (Taylor et al. 2005). This bacteria is also thought to contribute to the inflammatory response. The image is an immunohistochemistry using an anti-*Wolbachia* antibody (staining in red). The bacteria are noted in the lateral hypodermal cord cells and embryos within the uterus (Richards-Jr et al. 2007) (Fig. 10).

1.7 Lymphatic Filariasis

The effect of filarial organisms lodging in lymphatics is lymphedema and elephantiasis. When skin biopsies are obtained from these patients, organisms are not observed; however, several changes can be observed in the skin including thickening of the epidermis (acanthosis) (image on the left blue arrow), dilated vessels (image on the right green arrows), and perivascular mononuclear inflammatory infiltrate (image on the right red arrow) (Fig. 11) (Wilson et al. 2004).

1.8 Schistosomiasis

In humans, adult *Schistosoma* worms reside in venules in various locations. Females deposit eggs in these venules and the eggs move toward the lumen of the intestine and bladder. The host produces a granulomatous reaction (circled in image on left side) and fibrosis to the eggs (image on the right) (Fig. 12). The spine of the

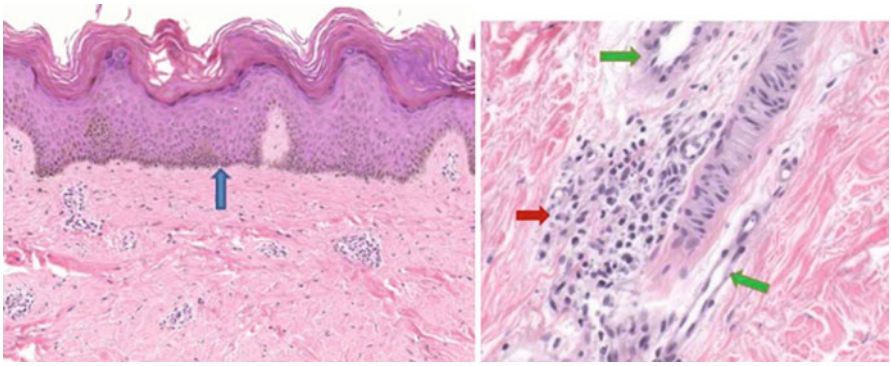

Fig. 11 Histopathological features of lymphatic filariasis

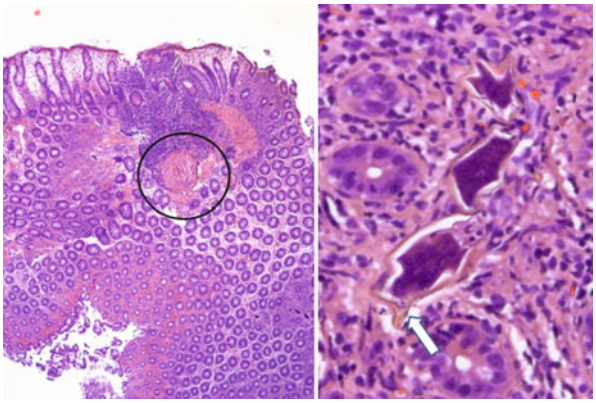

Fig. 12 Histopathological features of schistosomiasis

egg can sometimes be observed. In the image on the right, the arrow points to the lateral spine indicating this is *Schistosoma mansoni*.

1.9 Buruli Ulcer

The pathology of *Mycobacterium ulcerans* ranges from a nodule with abundant necrosis and mycobacteria in the initial stages to large ulcers (Guarner et al. 2003). While there is a nodule, the epidermis is intact although there may be some acanthosis (epidermal hyperplasia) (image on the left) and mild mononuclear inflammatory infiltrate in the superficial dermis. The deep dermis shows intense necrosis with little inflammation for the degree of necrosis present. Staining for acid-fast organisms will reveal large clumps of organisms in the necrotic material (Fig. 13).

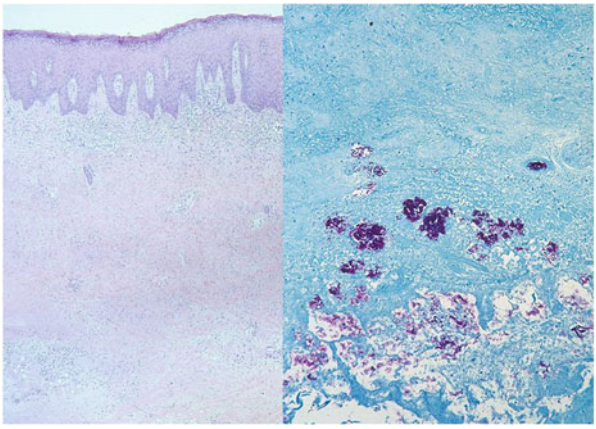

Fig. 13 Histopathological features of the initial stages of buruli ulcer

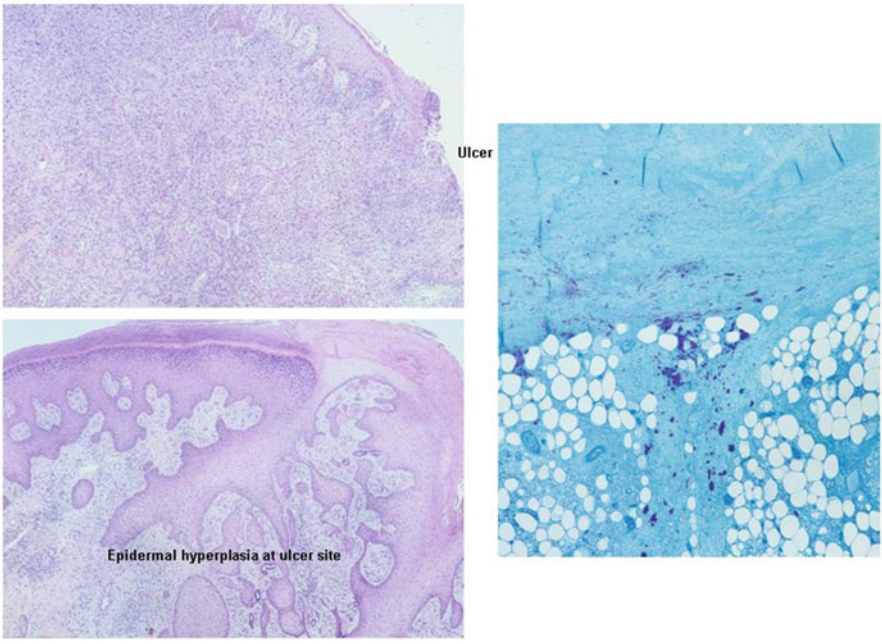

Fig. 14 Histopathological features of later stages of buruli ulcer

Once the epidermis sloughs off, the ulcer appears. The ulcer usually includes deeper tissues since these are necrotic. The epidermis can continue to show the acanthosis (upper image on left) or may become hyperplastic (lower image on left). More intense inflammatory infiltrate which includes neutrophils is noted in the dermis. The presence of acid-fast bacilli is focal, but they may be found in the subcutaneous tissues (Fig. 14).

1.10 Leprosy

Leprosy is a complex disease in which the host reaction varies significantly. Patients with multibacillary leprosy usually have abundant foamy macrophages that have acid-fast bacilli. The macrophages span the entire dermis as can be seen in the image to the left and, as the name implies, multiple acid-fast bacilli can be observed (image on the right) (Fig. 15). It is important to note that the acid-fast stain that needs to be used is a modified acid-fast stain called Fite.

Patients with paucibacillary leprosy show mononuclear inflammatory infiltrate around nerves (image from the Centers for Disease Control and Prevention public health image library, arrow pointing to nerve in the dermis) occasionally multinucleated giant cells are noted. As the name implies, there are few acid-fast bacilli which makes it difficult to pinpoint the diagnosis by histopathology (Fig. 16).

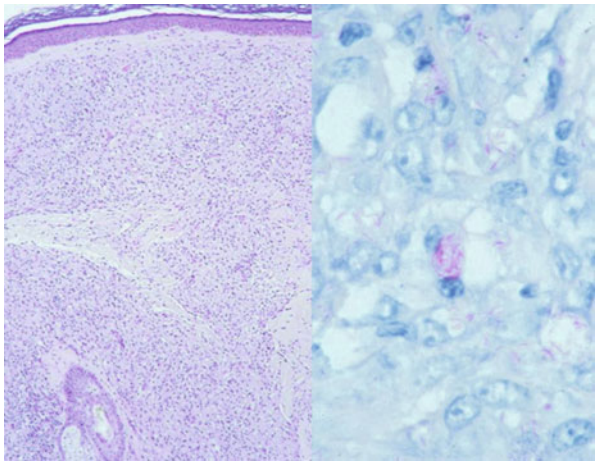

Fig. 15 Histopathological features of multibacillary leprosy

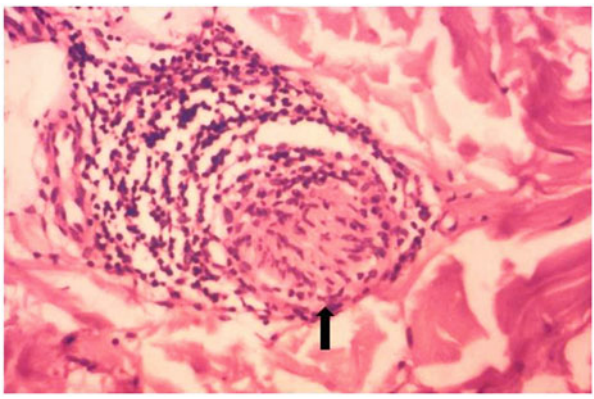

Fig. 16 Histopathological features of paucibacillary leprosy

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