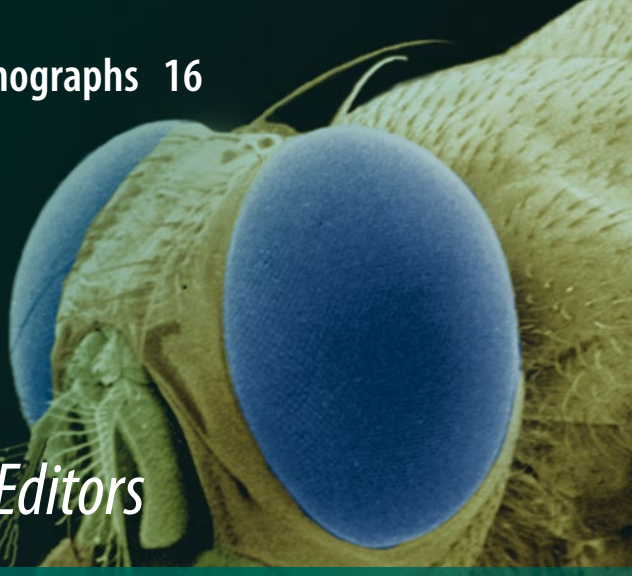
Parasitology Research Monographs 16



Heinz Mehlhorn
Jorg Heukelbach *Editors*

Infectious Tropical Diseases and One Health in Latin America

Springer

Parasitology Research Monographs

Volume 16

This book series “Parasitology Research Monographs” presents carefully refereed volumes on selected parasitological topics. Parasites have an increasing impact on animal and human health in the present times of globalization and global warming. Parasites may be agents of diseases and- often at the same time- vectors of other agents of disease such as viruses, bacteria, fungi, protozoa and/or worms. The growth in knowledge of parasitic physiology, cell structure, biotechnological and genetic approaches, ecology, therapeutic capabilities, vaccination, immunology, diagnosis, transmission pathways and many other aspects of parasitology is increasing dramatically, even in the face of the breakthroughs that have already been made. Reflecting these most recent achievements and the importance of parasites as a threat to human and animal health, the series’ broad scope concentrates on particularly hot topics emerging from the scientific community. Chapters offer compact but intense insights into the ongoing research and into the methods and technologies used to control parasites. The volumes in the series build on these topics, and the volume editors are well-known experts in their respective fields. Each volume offers 10 to 20 comprehensive reviews covering all relevant aspects of the topic in focus.

Heinz Mehlhorn • Jorg Heukelbach
Editors

Infectious Tropical Diseases and One Health in Latin America

Springer

Editors
Heinz Mehlhorn
Department of Parasitology
Heinrich Heine University
Düsseldorf, Germany

Jorg Heukelbach
Departamento de Saúde Comunitária, Faculdade de Medicina
Universidade Federal do Ceará
Fortaleza, CE, Brazil

ISSN 2192-3671 ISSN 2192-368X (electronic)
Parasitology Research Monographs
ISBN 978-3-030-99711-3 ISBN 978-3-030-99712-0 (eBook)
https://doi.org/10.1007/978-3-030-99712-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

Yellow Fever

1

Pedro Fernando da Costa Vasconcelos
and Juarez Antonio Simões Quaresma

Abstract

Yellow fever is an infectious disease caused by yellow fever virus (YFV), *Flavivirus* genus of the *Flaviviridae* family, which is endemic in South America and Africa, and periodically has caused limited outbreaks or large epidemics in the endemic regions.

Keywords

Flaviviridae · Hemorrhagic fever · Cytokines · Kupffer cells · Flavivirus

1.1 Introduction

Yellow fever is an infectious disease caused by yellow fever virus (YFV), *Flavivirus* genus of the *Flaviviridae* family, which is endemic in South America and Africa, and periodically has caused limited outbreaks or large epidemics in the endemic regions.

P. F. d. C. Vasconcelos (✉)
Department of Pathology, Pará State University, Belém, Pará, Brazil

Department of Arbovirology and Hemorrhagic Fevers, Evandro Chagas Institute, Ananindeua, Pará, Brazil
e-mail: pedro.vasconcelos@uepa.br; pedrovasconcelos@iec.gov.br

J. A. S. Quaresma
Department of Pathology, Pará State University, Belém, Pará, Brazil

Department of Arbovirology and Hemorrhagic Fevers, Evandro Chagas Institute, Ananindeua, Pará, Brazil

Tropical Medicine Nucleus, Federal University of Pará, Belém, Pará, Brazil
e-mail: Juarez@ufpa.br

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_1

YFV is one of the most prominent and ancient flaviviruses that infects humans and was originally isolated in Ghana in 1927 (Asibi strain) (Stokes et al. 1928). The virus causes yellow fever, the original viral hemorrhagic fever that mainly affects tropical areas of Africa, and due to the slave trade in the 17–1800s, the virus and its urban vector *Aedes aegypti* mosquito were introduced to the Americas, where they also became endemic/enzootic (Monath 2001).

The YFV genome is composed of a single-stranded RNA, plus sense, with near 11 Kb; the entire genome encodes a polyprotein containing ten genes, giving rise to three structural proteins, capsid (C), glycoprotein precursor of M protein (PrM)/membrane (M) protein, and envelope (E), and seven non-structural proteins (NS), named NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Rice et al. 1985). The genetic polymorphisms of YFV generated seven different genotypes, two in South America and five in Africa. The genetic differences have not been associated with differences in clinical presentation nor disease severity, but reflect the evolution of the YFV along the time and also due to the infidelity of the RNA-dependent RNA polymerase during replication of the virus in the hosts (Wang et al. 1996; Mutebi and Barrett 2002; Vasconcelos et al. 2004).

The disease caused by YFV infection, yellow fever, is the original hemorrhagic fever described all over the world and was for almost three centuries a disease that caused fear and closure of the economy and trade in countries reporting epidemics. Indeed, yellow fever was an important player in recent centuries and recognized as a major human public health disease. Even today, yellow fever is an important but preventable disease killing hundreds of non-immunized people in Africa and South America affecting 47 countries (11 in South America and 36 in Africa). The World Health Organization (WHO) estimates an annual occurrence of more than 30,000 infections and approximately 3000 deaths (Monath and Vasconcelos 2015).

1.2 The Virus

YFV was initially isolated by Stokes et al. (1928), from the blood of a febrile human. The YFV prototype, Asibi strain, was obtained in West Africa from a Ghanaian with an illness characterized by fever, headache, and muscle pains. The Asibi strain was maintained in rhesus monkeys for serial passages for many years before its initial passages in adult and later in suckling mice by Theiler (1930).

YFV, like other flaviviruses, has small spherical particles with approximately 50 nm of diameter, containing a core with nearly 30 nm. This core is covered by an envelope formed by lipids and glycoproteins. The envelope (E) glycoprotein is the principal virus antigenic determinant and responsible for the induction of immune response. This protein is also responsible for the fusion of the virus particle with the host cells enhancing the fusion and entry of the virus particle into the host cell. Two other glycoproteins are also present in the surfaces of the virus particles: the membrane (M) or pre-membrane (prM) depending on the pH of extracellular or intracellular and capsid (C) protein. They are important components of the structure of the YFV (Rice et al. 1985). These coding proteins are involved in the virus

pathogenesis and are associated with virus diversity including the emergence of different genotypes of YFV. Seven non-structural proteins have been described; although these proteins were not components of the virus archabbot, they play an important role in the gene expression and virus pathogenicity. Indeed, these non-structural (NS) proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are completely associated with YFV replication and pathogenesis (Rice et al. 1985; Chambers et al. 1990). NS5 is the major NS protein and is a replicase and RNA-dependent RNA polymerase, while NS3 is an integrase and replicase; NS1 is the first protein to be expressed during acute infection and has the capacity to fix complement. The minor NS proteins, NS2A, NS2B, NS4A, and NS4B, have multiple accessory functions that support major NS proteins (Rice et al. 1985; Chambers et al. 1990).

1.3 Epidemiology

1.3.1 Origin of YFV

Presently yellow fever is a global public health concern and endemic in sub-Saharan Africa and South America where annually sporadic cases, small outbreaks, or major epidemics are registered. According to the WHO, each year at least 100,000 cases and 30,000 deaths due to yellow fever occur all over the world, but very few cases are officially reported which is characterized by enormous underreporting of cases. Actually, 45 countries are considered endemic to YFV, 11 in South America and 34 in the sub-Saharan Africa (Jentes et al. 2011; Monath and Vasconcelos 2015; Vasconcelos and Monath 2016).

For decades the origin of the YFV was polemic since the initial reports of yellow fever were registered in the Americas; however, the close relationship of YFV with other African flaviviruses (among other Banzi, Sepik, Uganda S, and Wesselsbron viruses) was indicative of an African origin. Another important aspect of its origin is the higher diversity of YFV in Africa compared to the Americas. Indeed, in Africa five genotypes (West African I, West African II, East African, Central African, and Angola) are recognized (Mutebi and Barrett 2002), while in South America only two genotypes (South American I and South American II) are registered (Wang et al. 1996; Vasconcelos et al. 2004). The question was definitely clarified by an elegant molecular study (Bryant et al. 2007) which showed special signatures showing that YFV is definitely an African virus.

1.3.2 Cycles

YFV is maintained in jungle cycles in both regions, but the Culicidae vectors are different. In Africa several *Aedes* species are responsible for transmission in the Old World forests. *Aedes africanus* is the most important sylvatic vector in Africa, but other *Aedes* mosquitoes play a secondary role and have been associated with the

transmission cycle in Africa including *Aedes furcifer*, *Aedes luteocephalus*, and *Aedes simpsoni*, among many others. On the other side of the Atlantic Ocean, *Haemagogus janthinomys* is the most important sylvatic vector of YFV in South America, but in Southern Cone *Haemagogus leucocelaenus* is responsible for jungle transmission cycle; other mosquitoes have been incriminated as secondary vectors including *Haemagogus albomaculatus*, *Haemagogus tropicalis*, *Sabethes chloropterus*, *Sabethes soperi*, and *Sabethes cyaneus* (Vasconcelos 2003; Vasconcelos et al. 2001; Monath and Vasconcelos 2015).

On both continents the primary hosts are non-human primates (NHPs). It is clear that the NHPs are clearly implicated in the transmission cycles of the YFV as vertebrate host. Other vertebrate can be infected by YFV but without epidemiologic importance. In the Americas, the New World NHPs are largely susceptible to YFV infection and many animals die with hemorrhagic disease. The rate of lethality is variable, but in general Howler monkeys (*Alouatta* sp.) are more susceptible, while Capuchin monkeys (*Callicebus* sp.) are more resistant to YFV and lethality is lower (Vasconcelos 2003). Other genera have intermediate lethality such as marmosets (*Callithrix* sp.) and squirrel monkeys (*Saimiri* sp.). On the contrary, in Africa monkeys are resistant to YFV and do not die of yellow fever. These differences are important, and represent an advantage for surveillance of YFV in the Americas, once the monkey deaths are an important marker to intensify investigation and increase vaccination. This limits the number of cases of yellow fever in the region, while in Africa as the NHPs do not die of yellow fever, the circulation of the virus is silent and the spread becomes easier in urban settings. In addition, in Africa the intermediate cycle is the link between jungle and urban areas and facilitates the virus circulation and spread, where *Aedes aegypti* levels are high. In NHPs, the YFV is viscerotropic, and causes severe hemorrhagic diathesis and the liver is the main target organ. As the liver is responsible for the synthesis of almost all coagulation factors, the damage in the hepatic tissue is followed by hepatic insufficiency and hemorrhages, in a picture too similar to that of humans.

In urban areas in both regions transmission is by *Aedes aegypti* mosquitoes directly to humans. While in the Americas urban cycles were eliminated in the 1950s, in Africa the urban epidemics remain a threat and, almost annually, small or large urban epidemics of yellow fever are reported (Monath 2001; Jentes et al. 2011).

In Africa an intermediate cycle (or emergence cycle) is well described; it is recognized as Savannah cycle and is frequent in moist savannah regions where different *Aedes* species have been incriminated in the transmission cycle; the species are different in West and East Africa. In South America, an intermediate cycle has not been recognized, but recently YFV was isolated from pools of *Aedes albopictus* in Minas Gerais state (Lívia Martins, personal communication), and this finding calls attention to this possibility, that is, that the Asian Tiger can be the linking vector between sylvatic and urban cycles.

Infections in mosquitoes are for life and they do not present apparent tissue changes or lesions. In the NHPs, the primary hosts, the infection is apparent, and like humans they can become ill or develop asymptomatic infection. When they become sick, the disease evolution will result in death or survival. The immune

response of both the recovered NHPs and humans will be strong and protect against other secondary YFV infections due to the presence of specific antibodies and memory cells, meaning that they develop long-term protective immunity against YFV. Interestingly, although African monkeys can be infected by YFV and develop viremia, they do not develop clinical symptoms (i.e., do not show clinical signs/symptoms nor die of yellow fever). In NHPs the viremia is short and in general lasts up to 5 days (Monath and Vasconcelos 2015; Vasconcelos 2003).

1.3.3 Factors Associated with Disease Emergence

It is well known that several factors have been associated with emergence of yellow fever activity. Since old times, it was observed that some environmental variables are implicated with the increase of YFV circulation in the endemic areas of Africa and South America. It is also clear that these factors play different role in the YFV emergence. We have no intention to evaluate all of them, just the most commonly implicated in the eco-epidemiology of yellow fever and the (re)emergence of YFV in areas previously free of YFV for more than 50 years in South America and Africa. For more detailed information, we suggest to review Barrett and Monath (2003), Vasconcelos (2010), and Monath (2001) or Monath and Vasconcelos (2015).

1.3.4 The Role of Climatic Changes

In endemic countries, YFV activity is more frequently observed during rainy season and in areas with increases of temperature during the summer. This occurs because the vectors are more abundant; the reproductive period of the vectors is shorter and increases the number of adult mosquitoes, facilitating the virus infection and transmission not only to NHPs but also to susceptible (not immunized) humans. During the dry season on the contrary, there is limitation in the activity and the density of mosquitoes, which makes YFV circulation and mosquito infections difficult. Consequently, the host infections (NHPs and humans) are rarer and many times absent. Other climatic factors including El Nino have been incriminated in the YFV emergence, but more studies are necessary to confirm the role of global warming in it. It has been proposed that during dry season, animal movement looking for water can be a source of YFV spread carried out by viremic animals especially NHPs (Monath et al. 1981; Monath 2001).

Monath has shown that the epidemic in Nigeria in 1986 was caused by an increase in rainfall, prolonged rainy season, and growing of vegetation. He had also proposed that El Nino events were implicated in the emergence of yellow fever in West Africa (Monath 2001). Similarly, Vasconcelos et al. (2001) showed that the increase in the average temperature (in 2° C) associated with severe rainfall in Central Brazil was implicated in the emergence of an yellow fever epidemic in Goiás state.

1.3.5 Cutting of Forest and Mining

This is another factor for the emergence of YFV. Indeed, deforestation for several purposes especially cattle grazing, but also mining and construction of hydroelectric power plant and its dam, has been well characterized as a risk factor of yellow fever in endemic areas mainly in South America, where new colonized areas propitiate favorable conditions for virus circulation and emergence of outbreaks and/or epizootics. This has been well documented in the Brazilian Central and Amazon regions (Vasconcelos et al. 2001, 2001).

1.3.6 Animal Traffic and Human Migration

These two factors although different have more or less the same mechanism and show the movement of humans from one place (YFV endemic) to another (free of YFV) and vice versa. In Brazil, the circulation of identical YFV strains in distant areas far from one other for more than 2000 km in short times was demonstrated, and the only possibility for this to occur was the human migration of infected people to receptive areas but free of YFV or alternatively by traffic of sylvan animals particularly the viremic NHPs by traffickers (Vasconcelos et al. 2004).

1.3.7 Recent Epidemic Emergence in Africa and South America

Urban yellow fever outbreaks have been recently described in Angola, Uganda, and the Democratic Republic of Congo in 2015–2016, thereby demonstrating the constant presence of YFV in Africa (Kraemer et al. 2017). Subsequently, between December 2016 and June 2018, one of the largest yellow fever outbreaks in the last eight decades occurred in Brazil, and 2153 human cases were confirmed to be caused by YFV in Northern (Amazonas, Pará, and Tocantins States), Middle-Western (Goiás, Brasília, and Mato Grosso States), and Southeast (Espírito Santo, Rio de Janeiro, Minas Gerais, and São Paulo States) regions of Brazil. The mortality rate was 34.56% (744 fatal cases). The highest number of cases occurred in Minas Gerais (604; 28%) and São Paulo (397; 18.5%). In the same period, 2276 epizootics were confirmed in the Northern (Pará, Rondônia, Roraima, and Tocantins States), Northeast (Bahia State), Middle-Western (Brasília, Mato Grosso do Sul, and Mato Grosso States), and Southeast (Espírito Santo, Rio de Janeiro, Minas Gerais, and São Paulo States) regions of Brazil, with a predominance of *Callithrix* (26.7%) and *Alouatta* (22.5%) species of NHPs and the first report involving the genera *Aotus* spp. and *Saimiri* spp. in Brazil. Epizootics were more concentrated in the Southeast Region of Brazil with a prevalence of 38% in Espírito Santo, 27.8% in Minas Gerais, and 15.3% in São Paulo (Bonaldo et al. 2017; Brasil 2018). In Southeast Brazil, during the epidemic of 2016–2018 there was evidence of multiple transmission cycles simultaneously in different geographic areas and states (Moreira-Soto et al. 2018), while in São Paulo the velocity of YFV movement by day and week was

determined, and it was observed that corridors of circulation of infected monkeys in residual Atlantic forest were responsible for spread of the virus in the neighboring city of São Paulo (Cunha et al. 2019; Delatorre et al. 2019).

1.3.8 Pathogenesis

The pathophysiological characteristics of yellow fever virus (YFV) infection are known, in part thanks to scientific experiments carried out in PNH, hamsters, and mice and the description of fatal cases in humans (Xiao, et al. 2001; Quaresma et al. 2006). Hamsters are used in studies to look at YFV viscerotropism. In these animals the viral titer in the bloodstream rises up to 96 h after infection and then rapidly decreases to be rarely found after 120 h. Many succumb to the infection presenting a picture of fulminant hepatitis (Tesh et al. 2001).

The pathophysiology of yellow fever is characterized by vascular damage resulting in increased permeability and, consequently, in low-flow tissue hypoxia. Thus, hemodynamic stress in connection with hepatic tropism is directly linked to the lesions caused in this organ, as it has also been described that hepatocyte death in AF results preferentially from apoptotic phenomena and not from necrosis as previously found (Quaresma et al. 2005).

In primates and humans, YFV is viscerotropic causing damage to various organs such as the liver, spleen, heart, and kidneys. In the human liver, it induces hepatocellular damage characterized by eosinophilic necrosis, macrosteatosis and microsteatosis, and apoptosis. Hemorrhagic foci and small neutrophil clumps were observed around the areas of lytic necrosis. In addition, small inflammatory infiltrates are found, as described in the literature (Hudson 1928; Councilman 1981; Quaresma et al. 2005).

The swelling, which is an increase in hepatocyte volume, is seen in all areas of the lobes (Z1, Z2, and Z3), but is easily identified in Z1 and Z3 where the severity of hepatocyte involvement is less intense. Hepatocytic steatosis is found mainly in the Z2 region. In addition to the intense apoptotic component, there is a disproportion between the degree of parenchymal involvement and the scarcity of inflammatory infiltrate. Damage to hepatocytes leads to high blood levels of alanine, aminotransferase, and aspartate aminotransferase transaminases that aid in diagnosis (Tuboi et al. 2007; Vieira et al. 1983; Quaresma et al. 2005).

In an experiment with rhesus monkey, the YFV in the liver infects Kupffer cells, determining acidophilic degeneration in focal zones during the initial period of replication, with ballooning degeneration characterized by vacuoles that gather around the nucleus (Tigertt et al. 1960). In PNH, hyaline coagulation necrosis is the main lesion in the hepatocyte, presenting a mild inflammatory process, especially in areas where apoptosis is abundant (Monath 2001).

The appearance of Councilman-Rocha Lima bodies and necrosis in Z2 is a late event that appears 24–48 h before death. In cases that evolved to cure, the preservation of cell architecture and complete regeneration of the organ is maintained (Monath et al. 1981). They were also observed in *Alouatta* sp. apoptosis of

hepatocytes, hepatocyte necrosis, steatosis, and hepatic hemorrhage that showed a positive correlation with hepatocyte apoptosis indicating association with the pathogenic effect of YFV (Leal et al. 2016).

The immune responses in yellow fever aim to neutralize the virus and interfere with its intracellular replication, inducing responses aimed at eliminating infected cells. It is known that this immunological process has adverse reactions, as they cause release of cytokines that go beyond antiviral responses (Chisari and Ferrari 1995). This process involves not only CD8+ T lymphocytes, but also CD4+ T lymphocytes, macrophages, polymorphonuclear cells, and natural killer (NK) cells, as well as cytokines, chemokines, and components of the complement system (Quaresma et al. 2007).

It is important to mention that during yellow fever the anti-YFV IgM antibodies appear within a few days of disease onset and are detected for up to 3 months. As for IgG, it develops in days following the IgM response, and can be detected years later (Gibney et al. 2012). In human yellow fever infection, the lysis of infected cells can release viral particles that will be exposed to antibodies produced by B cells. B cells are easily found in portal tracts (PT); therefore, they can play an important role in the antigen processing mechanism during the immune response (Quaresma et al. 2005; Quaresma et al. 2006; Monath et al. 1981).

NK cells recognize infected cells by molecules involved with the class I major histocompatibility complex (MHC I), lysing these cells through the action of granzymes and perforins. In addition, these cells stimulate the release of interferon-gamma (IFN-γ), an antiviral cytokine that activates phagocytes and potentiates MHC expression. CD4+ T lymphocytes express IFN-γ and tumor necrosis factor-α (TNF-α) promoting an immune response of the Th1 profile, where molecules will stimulate CD8+ T cells, inducing inflammation and phagocyte activation (Quaresma et al. 2007). Several cytokines are involved in the immune response process against YFV, and these actions cannot only be limited to the liver; cytokines may also be implicated in severe vasculopathy in severe cases of the YF, dengue hemorrhagic fever, and dengue shock syndrome (Quaresma et al. 2006; Basu and Chaturvedi 2008).

The main cell of the immune response against YFV is constituted by CD4+ T lymphocytes, and to a lesser degree by CD8+ T lymphocytes. Associated with these cells, antigen-presenting cells, S100 +, CD68+ macrophages, and CD57+ NK cells are also found in the acinus areas (Quaresma et al. 2006; Quaresma et al. 2007). However, the exact role and mechanisms of action of these cells in the immunopathogenesis of yellow fever require further studies.

In the YFV-infected liver, the lack of inflammatory cells in areas of intense apoptosis can, in part, be explained by the fact that the apoptotic phenomenon does not trigger a cellular immune response, as the apoptotic bodies are phagocytosed by nearby macrophages, leading to a shortage of inflammatory infiltrate location (Quaresma et al. 2007). The expression of antigen-presenting cells, macrophages, and NK cells is greater in the Z2 region, and their activities in the characterization of the disease's evolutionary image seem to be fundamental (Quaresma et al. 2013).

In the case of **severe fatal yellow fever**, a higher density of immunostained T lymphocytes was observed in PT by the immunohistochemical method when compared to acini, since the inflow of inflammatory cells into the liver tissue is from the PT. In both acini and PT, CD4+ T cells are more frequent than CD8+ T cells. The predominance of CD4+ T lymphocyte is a common finding in other hepatotropic viral infections, which may be involved in viral destruction in the yellow fever, as in hepatitis B and C infections (Quaresma et al. 2013). Furthermore, activated macrophages release TNF-α which acts in the pathogenesis of tissue damage during yellow fever (Monath 2001). Cytotoxic CD8+ T lymphocytes, induced by the expression of class I MHC molecules, will interact with infected hepatocytes playing an important role in inducing necrosis or apoptotic cell death (Quaresma et al. 2006, 2007).

The induction of apoptotic cell death by TNF-α may be associated with the persistence of the infection in the host (Quaresma et al. 2007; Rowan et al. 2007; Brenndörfer et al. 2010). The interactions of TNF-α and IFN-γ in yellow fever have yet to be determined; however, as a characteristic of cells of a Th1 type response, it is known that T cells release these cytokines and act on the differentiation of CD8+ T lymphocytes into T cytolytic lymphocytes, in the induction of inflammation and activation of macrophages (Quaresma et al. 2007).

The intense presence of TGF-β cytokine immunostaining is a feature of yellow fever liver infection; this has an immunosuppressive and pro-apoptotic action that possibly induces an intense tissue damage observed in the yellow fever liver in fatal cases (Quaresma et al. 2006).

1.4 Clinical Presentation

The period of incubation of yellow fever ranges from three to 7 days after the infectious bite. The period of infection or viremia is characterized by prodromic symptoms and a sudden onset of high fever, malaise, and severe aches (headache, muscle, and joint pains). During this period viremia shows high levels of serum YFV titers and during this period mosquitoes can be infected (Vasconcelos 2003).

Yellow fever is a severe public health threat, that is, an infectious disease of short course and variable severity; clinically, the outcome of the classic hemorrhagic fever in general is dramatic with case fatality rates reaching 50% (Monath and Vasconcelos 2015). Nonetheless, the severe cases represent less than 20% of cases of disease and around 10% of all YFV infections. In general, the yellow fever infection can be asymptomatic and symptomatic (Monath 2001; Monath and Vasconcelos 2015). Asymptomatic infections represent around 40% of all YFV infections. The symptomatic infections can be classified according to their severity: mild, moderate, and severe. This means that the clinical pictures are completely different in terms of severity, presence of symptoms and signs, including the occurrence of the classic triad (jaundice, hemorrhage, and albuminuria), and of course the outcome. Indeed, while some patients present a light febrile illness, others will present a dramatic picture of dying with the classic disease presentation. And as

Nott has stated in the USA, and many other confirmed around the world, the variation of severity of disease in an epidemic is superb even among members of the same family or neighbors of a street or district. Globally, the case fatality rate of yellow fever is approximately 15%; however, it can reach more than 50% in severe forms. It is important to emphasize that any kind of clinical presentation will show change in viremia; only the time of viremia is longer in severe disease (Monath and Vasconcelos 2015).

1.4.1 Degrees of Yellow Fever Severity

Mild form: in general, patients present fever, headache ,and malaise for up 2–3 days. The disease onset is frequently sudden. Eventually, subictericia, slight albuminuria, and the Faget's sign (the relative slow pulse with rising temperature) can be present. The patient's recovery is complete without intercurrences. This clinical presentation is common among young children with antibodies passively acquired from their mothers and people with long time contact with YFV and/or other flaviviruses closely related to it. This clinical presentation is frequently misdiagnosed and only recognized during outbreaks or epidemics, when active surveillance is implemented, the suspect case definition is broadly amplified, and serologic surveys are used to diagnose these cases.

Moderate form: patients present with a sudden onset of high fever, headache, dizziness, muscle and joint pains, and nausea in the first 3–5 days. Faget's sign can be present. Some patients also present with nausea and ocular pain. The headache and muscle pains especially backache can be severe. Other patients have also skin hemorrhages such as petechiae, ecchymoses, or other kinds of small hemorrhages, including epistaxis, melena, menorrhage, and eventually other mucosal bleeding. The evolution lasts for 5–7 days of disease, and recovery is slower with convalescence of at least 1–2 weeks with malaise and muscle pain. In general, these patients present with a slight increase in the serum levels of aminotransferases, Gama GT, and bilirubin, as well as the creatinine and blood urea nitrogen (BUN) (Tuboi et al. 2007).

Severe presentation: This is the classic yellow fever; the patients present all symptoms of the moderate form, but the symptomatology is more severe, in general dramatic. The jaundice is apparent in skin and sclerotic and the signs of hepatic and renal failure are also too clear. Hemorrhages including black vomit (stomach hemorrhage) and uterine and mucosal hemorrhages are more intense and are basically due to the intense hepatic injury and accumulation of coagulation factors produced in the liver (Bailey et al. 2020); albuminuria is intense (++++/+4). The evolution of these patients can be faster with 5 days or longer course with 10 or more days. The convalescent period is common to last for 4–4 weeks. In fatal cases, death usually occurs between 7 and 10 days of disease, but some deaths can be registered up to 4 weeks and these in general are due to cardiac arrest (Monath 2001; Vasconcelos 2003; Monath and Vasconcelos 2015; Tuboi et al. 2007).

It is important to mention that moderate and severe cases are frequently characterized by distinct periods of disease: Period of infection: this corresponds to the infectious period and viremia. During this period, mosquito can become infected if they bite patients. During this time, symptoms are characterized by high fever (~39° C), headache, malaise, nausea, and joint and muscle pains. This period lasts for three to 5 days and is followed by a period of remission. This period is not easily recognized and cannot be present in some severe cases. When present, it lasts for 12–48 h and is followed for the period of intoxication. This period is characterized by an increase in the severity of symptoms. During this period, the YFV is not recovered from the blood, but is easily detected in the viscera, especially the liver. Clinically, patients present with symptoms and signs of liver and kidney failures, but fever, joint, and muscle pains become more severe. This period is not present in mild presentation of yellow fever (Monath 2001; Vasconcelos 2003).

1.5 Diagnosis

The specific diagnostic of yellow depends on the time of disease, kind of biological specimen, and clinical situation of patients. Indeed, in the first days of disease, during viremia, that is, infection period, blood samples (1–2 mL) are more indicated for viremic investigation, especially attempts of virus isolation in cell culture or by molecular approaches including real-time RT-PCR (RT-qPCR). This test is the gold standard method for the virologic diagnosis of YFV infections. Theoretically, all genomic part can be used for PCR in the molecular diagnostics of YFV; however, segments of the envelope (E), NS5 genes, and 3'NCR are more utilized to synthesize primers and probes. Several protocols have been published elsewhere with good results (Domingo et al. 2012, 2018; Hughes et al. 2018).

After the first week of disease symptoms, serologic tests, such as ELISA for IgM and IgG detection, are preferable to detect anti-YFV antibodies. The IgM ELISA is the serologic gold standard method. The presence of IgM against YFV in non-vaccinated persons is suggestive of recent or current infection. Normally, collections of 3–5 mL of blood are enough to obtain serum for serologic testing including retesting if necessary to confirm the YFV infection. In reference laboratories, the hemagglutination-inhibition (HI) test, fixation-complement (FC) test, and plaque reduction neutralization test (PRNT) are also used to confirm serologic diagnosis of yellow fever (Vasconcelos et al. 2001). The use of these techniques requires two blood samples: **the first** in acute phase and **the second** in the convalescent phase with an interval of 2–3 weeks. When tested together, in general, we observe the serologic conversion, that is, the change of negative or low titers in acute serum samples to positive in high titers in the convalescent-phase samples. The serologic conversion to YFV is indicative of recent infection in a non-vaccinated person.

In patients with fatal outcome, an autopsy to obtain viscera samples from liver, heart, kidney, lung, and others is recommended, or alternatively ultrasound-guided biopsies can substitute autopsy which in general are more appropriate for obtaining

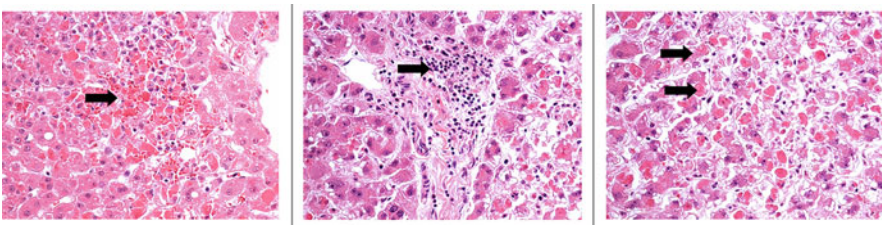


Fig. 1.1 Histopathological aspects of the liver during yellow fever. (**a**) In the hepatic parenchyma hemorrhagic area with hemorrhage resulting from vascular alterations induced by the yellow fever virus and by proinflammatory cytokines is noted. (**b**) In the portal tract, we observe mild inflammatory infiltration of lymphocytes. (**c**) We can see multiple Councilman corpuscles representing the apoptotic hepatocytes induced by the yellow fever virus infection and anti-inflammatory cytokines, such as TGF-β

authorization of patient's relatives to collect these and other specimens. Viscera samples can be used to attempt virus isolation and RT-qPCR and in this case should be preferably stored at -80° C or to detect viral antigens by immunohistochemistry (IHC). In this case, samples should not be frozen; instead they should be stored at room temperature (~25° C) and preserved in 10% buffered-formalin solution (Hall et al. 1991).

The RT-qPCR protocol is similar to the approach used for diagnostics of serum samples. But viscera samples should be macerated and/or cells are lyzed before submitting to molecular technique.

The IHC is similar to the procedures of other flaviviruses such as dengue and zika. The detection of YFV antigens in the cytoplasm is easily seen in optical microscope (Fig. 1.1).

1.6 Treatment

Specific antiviral drugs are not approved for treatment of yellow fever, and consequently the treatment of severe cases is based on measures to support life of ill people. Patients with severe illness should be admitted to intensive care units (ICU). For more detailed information on the supportive treatment of hospitalized patients in ICU, we recommend to consult Kallas et al. (2019) and Ho et al. (2019).

1.7 Control and Prevent Measures

Urban epidemics can be prevented by vector control programs. Index levels more than 5% in receptive areas where the vaccination rate is very low are at risk for urban transmission. Although this is true, it was demonstrated in Africa that urban transmission is only sustainable when vector indexes are high than 20%. This occurs because *Aedes aegypti*, an exceptional dengue and zika virus vector, is not a good

vector for YFV (Miller et al. 1989). In fact, during an epidemic in Nigeria in the 1980s the expansion of yellow fever was slow and this probably occurred due to the receptivity of *Aedes aegypti* to YFV. It has been hypothesized that in the large yellow fever epidemics in the past centuries (1800s and 1900s) when the indexes were not developed yet, the vector indexes were probably too high, another possibility that is associated with the lineage vector. Some authors have proposed that in the past the *Aedes aegypt*i lineage was more competent to transmit YFV because it was from African origin, and that presently the circulating lineage is the Asian lineage that would be less competent to transmit YFV, but excellent to transmit other flaviviruses like the serotypes of dengue and also the zika virus (Monath 2001; Monath and Vasconcelos 2015).

It is not possible to prevent epizootics in nature, but the occurrence of human cases is preventable by vaccination.

The 17D vaccine (Theiler and Smith 1937a, b) has been used for more than 80 years and probably saved millions of lives. A single dose of vaccine is sufficient to immunize people for at least 10 years. Recently, the WHO has recommended a single shot to immunize people probably for life (WHO 2014). Nonetheless, additional research is necessary to define with more scientific data the real persistence of YFV antibodies in neutralizing titers after a single shot or two or more shots of the YFV 17D vaccines, especially in children. Indeed, some well-defined studies support the need of an additional YFV 17D vaccine dose among children after 10 years of the first vaccination (Campi-Azevedo et al. 2016; Domingo et al. 2018; Vasconcelos and Barrett 2019).

17D vaccines are safe and antigenic for more than 98% of vaccinees. Unfortunately, in 2001 the occurrence of several cases in Brazil and the USA of viscerotropic disease resembling the wild-type disease was demonstrated; the severity of cases was reported and the case fatality rate has been estimated at around 25–40% and the incidence ranging from one case for 100,000–1 million vaccines. The susceptibility to these cases is rare but severe adverse events are not demonstrated yet has. Individual susceptibility of unknown origin, possible of genetic background, has been hypothesized (Vasconcelos et al. 2001; WHO 2014).

Recently, due to the shortage of YFV 17D vaccines and following the emergence of yellow fever in Africa, the vaccine was fractioned 1:10 and administered in Africa with good results during the urban epidemic in Kinshasa, Democratic Republic of Congo, in 2016, as well as in Mbarara (Uganda) and Kilifi (Kenya). The follow-up of vaccines showed neutralizing antibodies in high percentage after and in identical titer levels of standard 17D dose in inducing seroconversion after 28 days post-vaccination and without major safety concern. These results support the use of fractional dosage in the general adult population for outbreak response in situations of vaccine shortage (Roukens et al. 2018). Additional studies, however, are necessary to investigate if this fractional dose is also efficient to protect children against yellow fever.

References

Bailey AL, Kang LI, de Assis Barros D'Elia Zanella LGF, Silveira CGT, Ho YL, Foquet L, Bial G, McCune BT, Duarte-Neto AN, Thomas A, Raué HP, Byrnes K, Kallas EG, Slifka MK, Diamond MS (2020) Consumptive coagulopathy of severe yellow fever occurs independently of hepatocellular tropism and massive hepatic injury. Proc Natl Acad Sci USA 117(51): 32648–32656. https://doi.org/10.1073/pnas.2014096117

Barrett AD, Monath TP (2003) Epidemiology and ecology of yellow fever virus. Adv Virus Res. 61:291–315. https://doi.org/10.1016/s0065-3527(03)61007-9

Basu A, Chaturvedi UC (2008) Vascular endothelium: the battlefield of dengue viruses. FEMS Immunol Med Microbiol 53(3):287–299

Bonaldo MC, Gómez MM, dos Santos AA, de FVS A, Ferreira-de-Brito A, de Miranda RM et al (2017) Genome analysis of yellow fever virus of the ongoing outbreak in Brazil reveals polymorphisms. Mem Inst Oswaldo Cruz. 112(6):447–451. https://doi.org/10.1590/0074-02760170134

Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde (2018) Boletim Epidemiológico Secretaria—Emergência epidemiológica de febre amarela no Brasil, no período de dezembro de 2016 a junho de 2018. 48. Brasília, DF

Brennörfer ED, Weiland M, Frelin L, Derk E, Ahlén G, Jiao J, Bode JG, Sällberg M (2010) Anti-tumor necrosis factor α treatment promotes apoptosis and prevents liver regeneration in a transgenic mouse model of chronic hepatitis C. Hepatology 52(5):1553–1563

Bryant JE, Holmes EC, Barrett AD (2007 May 18) Out of Africa: a molecular perspective on the introduction of yellow fever virus into the Americas. PLoS Pathog. 3(5):e75. https://doi.org/10.1371/journal.ppat.0030075

Campi-Azevedo AC, Teixeira-Carvalho A, Antonelli LR et al (2016) Booster dose after 10 years is required following 17DD-YF-primary vaccination. Hum Vaccin Immunother 12:491–502

Chambers TJ, Hahn CS, Galler R, Rice CM (1990) Flavivirus genome organization, expression, and replication. Annu Rev Microbiol.:649–688. https://doi.org/10.1146/annurev.mi.44.100190.003245

Chisari FV, Ferrari C (1995) Hepatitis B virus immunopathogenesis. Ann Rev Immunol 13(1): 29–60

Councilman WT (1981) Report on etiology and prevention of yellow fever. N S W Public Health Bull 2:151–159

Cunha MDP, Duarte-Neto AN, Pour SZ, Ortiz-Baez AS, Černý J, Pereira BBS, Braconi CT, Ho YL, Perondi B, Sztajnbok J, Alves VAF, Dolhnikoff M, Holmes EC, Saldiva PHN, Zanotto PMA (2019 Dec 31) Origin of the São Paulo yellow fever epidemic of 2017–2018 revealed through molecular epidemiological analysis of fatal cases. Sci Rep. 9(1):20418. https://doi.org/10.1038/s41598-019-56650-1

Delatorre E, de Abreu FVS, Ribeiro IP, Gómez MM, Dos Santos AAC, Ferreira-de-Brito A, Neves MSAS, Bonelly I, de Miranda RM, Furtado ND, Raphael LMS, da Silva LFF, de Castro MG, Ramos DG, Romano APM, Kallás EG, Vicente ACP, Bello G, Lourenço-de-Oliveira R, Bonaldo MC (2019) Distinct YFV lineages co-circulated in the Central-Western and Southeastern Brazilian regions from 2015 to 2018. Front Microbiol. 10:1079. https://doi.org/10.3389/fmicb.2019.01079. eCollection 2019

Domingo C, Patel P, Yillah J, Weidmann M, Méndez JA, Nakouné ER, Niedrig M (2012 Dec) Advanced yellow fever virus genome detection in point-of-care facilities and reference laboratories. J Clin Microbiol. 50(12):4054–4060. https://doi.org/10.1128/JCM.01799-12

Domingo C, Charrel RN, Schmidt-Chanasit J, Zeller H, Reusken C (2018 Jul 12) Yellow fever in the diagnostics laboratory. Emerg Microbes Infect. 7(1):129. https://doi.org/10.1038/s41426-018-0128-8

Gibney KB, Edupuganti S, Panella AJ, Kosoy OL, Delorey ML, Lanciotti RS, Mulligan MJ, Fischer M, Staples JE (2012) Detection of anti-yellow fever vírus immunoglobulin M antibodies at 3–4 years following yellow fever vaccination. Am. J. Trop. Med. Hyg. 87(6):1112–1115

Hall WC, Crowell TP, Watts DM, Barros VL, Kruger H, Pinheiro F, Peters CJ (1991 Oct) Demonstration of yellow fever and dengue antigens in formalin-fixed paraffin-embedded human liver by immunohistochemical analysis. Am J Trop Med Hyg. 45(4):408–417. https://doi.org/10.4269/ajtmh.1991.45.408

Ho YL, Joelsons D, Leite GFC, Malbouisson LMS, Song ATW, Perondi B, Andrade LC, Pinto LF, D'Albuquerque LAC, Segurado AA (2019 Jun 11) Severe yellow fever in Brazil: clinical characteristics and management. Hospital das Clínicas Yellow Fever Assistance Group. J Travel Med. 26(5):taz040. https://doi.org/10.1093/jtm/taz040

Hudson NP (1928) The pathology of experimental yellow fever in the macacus rhesus. Am. J Pathol 4(5):395–429

Hughes HR, Russell BJ, Mossel EC, Kayiwa J, Lutwama J, Lambert AJ (2018 May 25) Development of a real-time reverse transcription-pcr assay for global differentiation of yellow fever virus vaccine-related adverse events from natural infections. J Clin Microbiol. 56(6):e00323-18. https://doi.org/10.1128/JCM.00323-18

Jentes ES, Poumerol G, Gershman MD, Hill DR, Lemarchand J, Lewis RF, Staples JE, Tomori O, Wilder-Smith A, Monath TP (2011 Aug) The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 11(8):622–632. https://doi.org/10.1016/S1473-3099(11)70147-5

Kallas EG, D'Elia Zanella LGFAB, Moreira CHV, Buccheri R, Diniz GBF, Castiñeiras ACP, Costa PR, Dias JZC, Marmorato MP, Song ATW, Maestri A, Borges IC, Joelsons D, Cerqueira NB, Santiago E, Souza NC, Morales Claro I, Sabino EC, Levi JE, Avelino-Silva VI, Ho YL (2019 Jul) Predictors of mortality in patients with yellow fever: an observational cohort study. Lancet Infect Dis. 19(7):750–758. https://doi.org/10.1016/S1473-3099(19)30125-2

Kraemer MUG, Faria NR, Reiner RC, Golding N, Nikolay B, Stasse S et al (2017 Mar) Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015–16: a modelling study. Lancet Infect Dis. 17(3):330–338. https://doi.org/10.1016/S1473-3099(16)30513-8

Leal SG, Romano APM, Monteiro RV, Melo CB, Vasconcelos PFC, Castro MB (2016) Frequency of histopathological changes in Howler monkeys (Alouatta sp.) naturally infected with yellow fever vírus in Brazil. Rev. Soc. Bras. Med. Trop. 49(1):29–33

Miller BR, Monath TP, Tabachnick WJ, Ezike VI (1989 Dec) Epidemic yellow fever caused by an incompetent mosquito vector. Trop Med Parasitol. 40(4):396–399

Monath TP (2001) Yellow fever: an update. Lancet. Infect. Dis. 1(1):11–20

Monath TP, Vasconcelos PFC (2015 Mar) Yellow fever. J Clin Virol. 64:160–173. https://doi.org/10.1016/j.jcv.2014.08.030

Monath TP, Brinker KR, Chandler FW, Kemp GE, Cropp CB (1981) Pathophysiologic correlations in a rhesus monkey model of yellow fever: with special observations on the acute necrosis of B cell areas of lymphoid tissues. Am J Trop Med Hyg 30(2):431–443

Moreira-Soto A, Torres MC, Lima de Mendonça MC, Mares-Guia MA, Dos Santos Rodrigues CD, Fabri AA, Dos Santos CC, Machado Araújo ES, Fischer C, Ribeiro Nogueira RM, Drosten C, Sequeira PC, Drexler JF, Bispo de Filippis AM (2018 Sep) Evidence for multiple sylvatic transmission cycles during the 2016–2017 yellow fever virus outbreak. Brazil. Clin Microbiol Infect. 24(9):1019.e1–1019.e4. https://doi.org/10.1016/j.cmi.2018.01.026

Mutebi JP, Barrett AD (2002 Nov) The epidemiology of yellow fever in Africa. Microbes Infect. 4(14):1459–1468. https://doi.org/10.1016/s1286-4579(02)00028-x

Quaresma JAS, Barros VL, Fernandes ER, Pagliari C, Takakura C, Vasconcelos PFC, Andrade HF Jr, Duarte MIS (2005) Reconsideration of histopathology and ultrastructural aspects of the human liver in yellow fever. Acta Trop 94(2):116–127

Quaresma JAS, Barros VL, Fernandes ER, Pagliari C, Guedes F, Vasconcelos PFC, Andrade Junior HF, Duarte MIS (2006) Immunohistochemical examination of the role of Fas ligand and lymphocytes in the pathogenesis of human liver yellow fever. Virus. Res 116(1/2):91–97

Quaresma JAS, Barros VL, Pagliari C, Fernandes ER, Guedes F, Takakura CFH, Andrade HF Jr, Vasconcelos PFC, Duarte MIS (2006) Revisiting the liver in human yellow fever: Virus-induced apoptosis in hepatocytes associated with TGF-β, TNF-α and NK cells activity. Virology 345: 22–30

Quaresma JAS, Duarte MIS, Vasconcelos PFC (2006) Midzonal lesions in yellow fever: a specific pattern of liver injury caused by direct virus action and in situ inflammatory response. Med. Hypotheses. 67:618–621

Quaresma JAS, Barros VL, Pagliari C, Fernandes ER, Andrade Jr HF, Vasconcelos PFC, Duarte MIS. Hepatocyte lesions and cellular immune response in yellow fever infection. Trans. R. Soc. Trop. Med. Hyg. v. 101, n. 2, p. 161–168, Feb. 2007.

Quaresma JAS, Pagliari C, Medeiros DBA, Duarte MIS, Vasconcelos PFC (2013) Immunity and immune response, pathology and pathologic changes: progress and challenges in the immunopathology of yellow fever. Rev. Med. Virol. 23(5):305–318

Rice CM, Lenches EM, Eddy SR, Shin SJ, Sheets RL, Strauss JH (1985) Nucleotide sequence of yellow fever virus: implications for flavivirus gene expression and evolution. Science 229:726–733

Roukens AHE, van Halem K, de Visser AW, Visser LG (2018) Long-term protection after fractional-dose yellow fever vaccination: follow-up study of a randomized, controlled, noninferiority trial. Ann Intern Med 169:761–765

Rowan PJ, Dunn NJ, Serag-El HB, Kunik ME (2007) Views of hepatitis C virus patients delayed from treatment for psychiatric reasons. J. Viral. Hepat. 14(12):883–889

Stokes A, Bauer JH, Hudson NP (1928) The transmission of yellow fever to Macacus rhesus: preliminary note. J Am Med Assoc. 90:253–255

Tesh RB, Guzman H, da Travassos Rosa APA, Vasconcelos PFC, Dias LB, Bunnell JE, Zhang H, Xiao SY (2001) Experimental yellow fever virus infection in the Golden Hamster (Mesocricetus auratus). 1. Virologic, Biochemical and Immunologic studies. J Infect Dis 183(10):1431–1436

Theiler M (1930) Studies on the action of the yellow fever virus in mice. Ann Trop Med 24:249–272

Theiler M, Smith HH (1937a May 31) The effect of prolonged cultivation in vitro upon the pathogenicity of yellow fever virus. J Exp Med. 65(6):767–786. https://doi.org/10.1084/jem.65.6.767

Theiler M, Smith HH (1937b) The use of yellow fever virus modified by in vitro cultivation for human immunization. J Exp Med. 65(6):787–800. https://doi.org/10.1084/jem.65.6.787

Tigertt WD, Berge TO, Gochenour WS, Gleiser CA, Eveland WC, Bruegge CV, Smetana HF (1960) Experimental yellow fever. Trans NY Acad Sci 22:323–333

Tuboi SH, Costa ZG, Vasconcelos PFC, Hatch D (2007) Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998–2002. Trans R Soc Trop Med Hyg 101(2):169–175

Vasconcelos PFC (2003 Apr) Yellow fever. Rev Soc Bras Med Trop. 36(2):275–293. https://doi.org/10.1590/S0037-86822003000200012

Vasconcelos PFC (2010 Dec) Yellow fever in Brazil: thoughts and hypotheses on the emergence in previously free areas. Rev Saude Publica. 44(6):1144–1149

Vasconcelos PFC, Barrett ADT (2019 Dec) Are booster doses of yellow fever vaccine needed. Lancet Infect Dis. 19(12):1275–1276. https://doi.org/10.1016/S1473-3099(19)30411-6

Vasconcelos PFC, Monath TP (2016) Yellow fever remains a potential threat to public health. Vector-Borne Zoonotic Dis. 16(8):566–567. https://doi.org/10.1089/vbz.2016.2031

Vasconcelos PFC, Costa ZG, da Travassos Rosa ES, Luna E, Rodrigues SG, Barros VLRS, JP DS, Monteiro HAO, Oliva OFP, Vasconcelos HB, Oliveira RC, Sousa MRS, Barbosa da Silva J, Cruz ACR, Martins EC, da Travassos Rosa JFS (2001) An epidemic of jungle Yellow fever in Brazil, 2000. Implications of climatic alterations in disease spread. J Med Virol 65(3):598–604

Vasconcelos PFC, da Travassos Rosa APA, Rodrigues SG, da Travassos Rosa ES, Dégaller N, da Travassos Rosa JFS (2001) Inadequate management of natural ecosystem in the Brazilian

Amazon region results in the emergence and reemergence of arboviruses. Cad Saúde Públ 17: 155–164

Vasconcelos PFC, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VLRS, Monath TP, Rodrigues SG, Laval C, Costa ZG, Vilela MFG, Santos CLS, Papaiordanou CMO, Alves VAF, Andrade LD, Sato HK, da Travassos Rosa ES, Froguas GB, Lacava E, Almeida LMR, Cruz ACR, Rocco IM, Santos RTM, Oliva OFP (2001) Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 358:91–97

Vasconcelos PFC, Bryant JE, da Travassos Rosa APA, Tesh RB, Rodrigues SG, Barrett ADT (2004 Sep) Genetic divergence and dispersal of yellow fever virus. Brazil. Emerg Infect Dis. 10(9): 1578–1584. https://doi.org/10.3201/eid1009.040197

Vieira WT, Gayotto LC, De Lima CP, De Brito T (1983) Histopathology of the human liver in yellow fever with special emphasis on the diagnostic role of the Councilman body. Histopathology 7(2):195–208

Wang E, Weaver SC, Shope RE, Tesh RB, Watts DM, Barrett AD (1996 Nov 15) Genetic variation in yellow fever virus: duplication in the 3′ noncoding region of strains from Africa. Virology 225(2):274–281. https://doi.org/10.1006/viro.1996.0601

WHO (2014) Vaccines and vaccination against yellow fever: WHO position paper, June 2013—recommendations. Vaccine 33:76–77

Xiao SY, Zhang H, Guzman H, Tesh RB (2001) Experimental yellow fever virus infection in the Golden Hamster (*Mesocricetus auratus*). 2. Pathology. J. Infect. Dis 183(10):1437–1444

Chikungunya

2

Luciano Pamplona de Góes Cavalcanti, André Machado Siqueira, José Alfredo de Sousa Moreira, and André Ricardo Ribas Freitas

Abstract

Chikungunya is a viral disease transmitted to humans by infected mosquitoes. It is an acute febrile illness caused by the chikungunya virus (CHIKV)—an arbovirus belonging to Togaviridae and the genus Alphavirus. It was initially described in Africa, where it circulates in wild cycles involving vectors (genus Aedes) and non-human primates. The term "chikungunya" is derived from the Makonde language of the Bantu people. It means "that which bends up" or "stooped walk" because of the incapacitating arthralgia caused by the disease.

Keywords

Aedes aegypti · Aedes albopictus · Togaviridae · Alphavirus · CHIKV

L. P. de Góes Cavalcanti (✉)
Faculdade de Medicina, Universidade Federal do Ceará and Centro Universitário Christus, Fortaleza, Brazil

A. M. Siqueira
Instituto Nacional de Infectologia (INI), Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
e-mail: andre.siqueira@ini.fiocruz.br

J. A. de Sousa Moreira
Instituto Nacional de Infectologia - FIOCRUZ, Rio de Janeiro, Brazil

A. R. R. Freitas
Faculdade São Leopoldo Mandic, Sao Paulo, Brazil
e-mail: andre.freitas@slmandic.edu.br

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_2

2.1 An Overview

Chikungunya is a viral disease transmitted to humans by infected mosquitoes. It is an acute febrile illness caused by the chikungunya virus (CHIKV)—an arbovirus belonging to Togaviridae and the genus Alphavirus. It was initially described in Africa, where it circulates in wild cycles involving vectors (genus *Aedes*) and non-human primates. The term "chikungunya" is derived from the Makonde language of the Bantu people. It means "that which bends up" or "stooped walk" because of the incapacitating arthralgia caused by the disease.

It has a wide worldwide distribution and has caused great concern, mainly due to the impact generated to health services and the fact that part of the infected patients is unable to perform their daily activities, causing severe economic impacts due to reduced productivity (Mohan et al. 2010; Donalísio et al. 2015; Krutikov and Manson 2016).

Chikungunya is transmitted by the mosquito vectors *Aedes aegypti* and *Aedes albopictus*. Infected travelers can import chikungunya into new areas, in areas with *Ae. aegypti* and/or *Ae. albopictus* mosquitoes and local transmission can follow (i.e., in Italy, where the first outbreak occurred in 2007).

Several large outbreaks with high attack rates have been documented, affecting one-third to three-quarters of the population in areas where the virus is circulating. From 2005 to 2006, Reunion Island reported a large outbreak involving approximately 34% of the islands' residents.

One of the challenges imposed by CHIKV has been identifying suspected individuals correctly in the co-circulation of other arboviruses that present similarly in tropical regions and are transmitted by the same mosquito vectors chikungunya virus (i.e., Dengue, Zika, and Mayaro). The viruses can cocirculate in a geographic region, and coinfections have been documented; however, whether the dual infection has been associated with worse outcomes than mono-infection remains further investigated.

The laboratory diagnosis has mainly focused on either RNA or virus-specific antibody detection through RT-PCR and ELISA techniques. However, such diagnostic technologies require complex instrumentation and are not easy to perform outside sophisticated laboratories in urban settings where trained personnel are available. Therefore, these tests are not accessible or affordable to patients at the lower healthcare system levels, where most CHIKV outbreaks occur. In contrast, rapid diagnostic tests (RDTs) promise to overcome some of these challenges by bridging many gaps along the diagnostic test pathway in CHIKV-endemic areas.

Herein, we aim to comprehensively review the epidemiology, pathogenesis, diagnosis, treatment, prevention, and prognosis of the chikungunya infection, focusing on Latin America.

2.2 Chikungunya: A Global Public Health Concern

Chikungunya is a global public health concern. The disease was first described in 1952 in the Makonde Plains, along the borders between Tanzania and Mozambique. It emerged as an acute febrile illness with exanthem and arthralgia. However, it differed from previous dengue reports by presenting severe joint pain (Robinson 1955). In 1953, an epidemic in Newala, Tanzania, allowed for the first time the isolation of the virus from the serum of a febrile patient and clarified some issues related to viral pathogenesis (Ross 1956). Since then, CHIKV has been responsible for emerging and re-emerging outbreaks in several tropical and temperate regions worldwide.

The virus remained restricted in some tropical regions of the world until 2004, when it re-emerged with an outbreak off the coast of Kenya, with approximately half a million cases spreading to Comoros, Mauritius, Reunion Island, and the other Indian Ocean islands between 2005 and 2006 (González-Sánchez and Ramirez-Arroyo 2018). In Europe, the first autochthonic outbreak was reported in Emilia-Romagna, Italy, in 2007. In 2010, there were reports of cases in India, Indonesia, Myanmar, Thailand, Maldives Islands, and Taiwan. France and the United States also registered cases between 2010 and 2014 (Delisle et al. 2015; González-Sánchez and Ramirez-Arroyo 2018).

In the Americas, CHIKV began in December 2013, on the Caribbean Island of Saint Martin, after an investigation of febrile disease with laboratory results negative for dengue (Zeller et al. 2016). The emerging CHIKV belonged to the Asian genotype and spread to 17 countries in South America by December 2014. Since it is first reported, local transmission has been identified in more than 50 countries in the Caribbean, North America, South America, and Central America (Henry et al. 2017; Wahid et al. 2017).

Chikungunya was considered, until recently, to be the cause of benign disease. However, this understanding of the disease is being changed. Until the chikungunya emergence that began in 2004 in the Indian Ocean, few cases of deaths from chikungunya had been. In Réunion, several death certificates mentioned chikungunya as one of the diseases leading directly to death or as an associated event challenging the conventional view of the non-lethal nature of CHIKV (Renault et al. 2007). Reports of hospitalized and laboratory-confirmed chikungunya cases that progressed to death reinforced the severity of this disease (Economopoulou et al. 2009). Upon arrival in the Americas, mortality studies in different countries show an excess of deaths in epidemic periods compared to previous non-epidemic years, suggesting that these analyzes can estimate the impact of chikungunya in situations where not all deaths from the disease are correctly diagnosed (Freitas et al. 2017, 2018a, b, c, 2019). Recent necropsy studies have demonstrated viral antigens in different tissues, confirming chikungunya's systemic and potentially fatal character (Sharp et al. 2021).

2.3 The Biology of the Chikungunya Virus

The Chikungunya virus (CHIKV) is a simple-taped ribonucleic acid (RNA) virus, which belongs to the family *Togaviridae,* genus *Alphavirus,* measuring 60–70 nm in diameter and consisting of four non-structural proteins and three structural proteins. The surface of the lipid envelope is located viral glycoproteins E1 and E2, which are associated with heterodimers, forming 80 trimers, besides the presence in the periphery of glycoprotein E3. The nucleocapsid consists of a c protein of the viral capsid and an RNA molecule (Strauss and Strauss 1986; Uchime et al. 2013).

Twenty-nine arboviruses belonging to this genus are classified into seven distinct antigenic complexes (Barmah Forest, Eastern Equine Encephalitis, Middelburg, Ndumu, Semliki Forest, Venezuelan Equine Encephalitis, and Western Equine Encephalitis). CHIKV belongs to the Semliki Forest complex, which also involves other pathogens causing fever, exanthem, and arthralgias of medical importance, such as the O'nyong nyong (ONNV), Mayaro (MAYV), and Ross River (RRV) viruses (Solignat et al. 2009).

The human–mosquito–human transmission cycle begins when an arthropod vector feeds on a vertebrate host in a viremic state. During this period (extrinsic incubation), a wide range of mechanisms is activated in the mosquito to fight viral infection. However, arboviruses have strategies to overcome these barriers in the mosquito and multiply until they reach their salivary glands, which will be excreted during blood repast, thus infecting a susceptible new host. In humans bitten by an infected mosquito, symptoms of the disease usually occur after an (intrinsic) period of incubation. After this period, the viremia in the host enables the renewal of the cycle from a blood repast of a susceptible vector (Conway et al. 2014; Lum and Ng 2015; Liang et al. 2015).

2.4 The Immunopathogenesis of Chikungunya

The pathogenesis of CHIKV infection in humans is not fully defined. However, recent epidemics have helped to provide information about cells and organisms involved in viral replication.

The CHKV is transmitted by *Aedes* spp. mosquitoes' bites but can also result from form maternal-fetal transmission. After initially replicating in the skin, the virus disseminates to the liver and joints through the blood and lymphatic circulation. The incubation period between transmission and development of symptoms is 2–4 days. During this period, there is rapid and robust viral replication reaching up to 108 particles/ml. The CHIKV is known for its arthritogenic potential and tropism for joint tissue. However, apart from the blood, it can also be found to infect stromal cells of the central nervous system (potentially leading to meningoencephalitis), muscle, skin fibroblasts, liver, spleen, and other connective tissue cells.

CHIKV has a direct cytopathic activity that leads to apoptotic cell death in cultures and is likely to dominate its properties in vivo. The viraemic acute phase is accompanied by high levels of IFN-I and other inflammatory cytokines. The virus

is cleared of the circulation after usually 7 to 10 days when it is also possible to identify specific antibodies against CHIKV. Antibodies against CHIKV are believed to be long-lived and promote life immunity against reinfection. Unlike other viral infections, IgM against CHIKV can be detected for more than 10 months after initial infections, with some individuals presenting positivity for more than 5 years. It has been suggested that virus particles persistence in the joint tissues could lead to the maintenance of IgM detection and correlate with chronic joint manifestations. Nevertheless, this is still to be confirmed, and studies in this area are still being done.

2.5 Global Genetic Diversity of Chikungunya Virus

CHIKV has a single serotype, and, until that time, it is believed that it confers protective immunity throughout the life of the recovered individuals (Sahadeo et al. 2015).

Phylogenetic analysis studies based on genotypic and antigenic characteristics show the existence of three genotypes and one lineage, which were named according to the first site of isolation: Western or West African genotype (WA), Eastern or East/Central/South African genotype (ECSA), Asian genotype and the Indic Ocean Lineage (IOL), which emerged from the Genotype ECSA (Powers and Logue 2007; Tsetsarkin et al. 2007; Arankalle et al. 2007; Sudeep and Parashar 2008; Volk et al. 2010; Nunes et al. 2015a, b).

The lineage of the Indian Ocean (IOL), derived from ECSA, was first reported between 2005 and 2006, being responsible for explosive epidemics in the Indian Ocean Islands and Asia between 2005 and 2011 (Schuffenecker et al. 2006; Volk et al. 2010; Nunes et al. 2015a, b), spreading throughout several regions of the Eastern Hemisphere, causing outbreaks in more than 60 countries (Rezza et al. 2007; Tsetsarkin et al. 2007; Kumar et al. 2008, Pulmanausahakul et al. 2011). The expansion of this lineage was attributed to adaptive mutations in position 226 of the gene encoding glycoprotein E1 that provided physical conditioning advantage to Aedes albopictus without reducing the physical conditioning of *Aedes aegypti*, allowing a rapid diversification of the lineage (Sahadeo et al. 2015).

In 2013, the Asian genotype was detected in the Caribbean region and spread to 38 countries in the Americas. In Brazil, in addition to the Asian genotype detected in Amapá and probably imported from French Guiana, the circulation of the ECSA genotype in Bahia and Rio de Janeiro was also evidenced, probably from Angola where this genotype was already endemic (Vega-Rúa et al. 2014). Genetic analysis showed the circulation of two CHIKV East-Central-South African (ECSA) lineages in the northeast of Brazil. It revealed no unique virus genomic mutation associated with fatal outcomes (Lima et al. 2020). Thus, Brazil presents itself in a differentiated context in the CHIKV epidemic that occurred in the Americas, between 2014 and 2017, with the co-circulation of viral strains of two distinct genotypes. In addition, the dispersion of the ECSA genotype in Brazil created an environment conducive to outbreaks similar to those observed in the Indian Ocean islands due to the presence of *Aedes aegypti* and *Aedes albopictus* (Vega-Rúa et al. 2014).

2.6 Approach to Chikungunya Diagnosis in the Context of Other Acute Febrile Illnesses Prevalent in Latin America

At different stages of the disease, chikungunya can be confused with other arbovirus infections, such as dengue and Zika. From a clinical perspective, there is no clinical algorithm robust enough to distinguish between these three arboviruses. Hence, testing for dengue and Zika should also be pursued. Clinical guidelines in Latin America recommend patients to be managed in the initial phase as dengue, as lack of early intervention can result in high rates of complications. We recommend that front-line clinicians, in the face of acute febrile illness, (1) conduct a broad differential diagnosis considering a syndrome-based approach; (2) recognize the alarming signs of severe febrile illness; and (3) stratify the mortality risk with prediction scores. Table 2.1 shows the primary febrile syndromes and their main etiologies in Latin America.

The diagnosis of CHIKV infection should be suspected in patients with acute onset of fever and polyarthralgia accompanied by relevant epidemiologic exposure (residence in or travel to area where mosquito-borne transmission of CHIKV has been reported). The prominent laboratory abnormalities are lymphopenia, thrombocytopenia, and mild changes in hepatocellular enzymes. During a CHIKV outbreak that occurred between October 2018 and July 2019 in Rio de Janeiro, Brazil, we found that predictors independently associated with RT-PCR confirmed CHIKV infection was the presence of cough [OR: 0.30 (0.13–0.69)], joint pain [OR: 11.87 (5.35–26.32)], rash [OR: 7.07 (3.06–16.30)], temperature (OR: 1.67 (1.16–2.40)], and leukocytopenia [OR: 3.57 (1.24–10.28)].

CHIKV infection can be detected through direct methods such as viral culture and detection of the virus genetic material or indirect methods using serological methods. Viral cultures are usually not used for clinical and surveillance purposes. They can detect the virus up to 4 days after the onset of symptoms. RT-PCR is considered the gold standard for diagnosing acute infection and can detect the viral genetic material up to 7 days after onset of symptoms when sensitivity can be close to 100%. Although the virus has been detected up to 10 days of symptoms, sensitivity can drop to around 40%, making this approach inappropriate for discarding infection. Other molecular methods have been developed, most notably LAMP (loop-mediated isothermal amplification) assays. However, its use has not yet been disseminated to clinical and public health settings. So far, unlike other arboviral infections, there is no antigen-based test for point-of-care diagnosis, which makes it more difficult for health professionals to reach a conclusive diagnosis.

Serological methods have been used for post-acute (after 10 days of symptoms onset) diagnosis and community serosurveys. IgG levels can be present for years, acting as a good marker for past infection and as an epidemiological tool to determine the seroprevalence of a population.

Most of the commercial kits available are based on ELISA techniques. They have reliable results, and point-of-care rapid diagnostic tests are under development. As previously mentioned, IgM can persist detectable for months or years and should not be used isolated to infer recent infection. Cross-reactivity can be detected with other

Table 2.1 The differential diagnosis for acute febrile illness according to presenting symptoms in Latin America

Syndromes	Common etiologies	Less common etiologies
Fever with respiratory symptoms	Influenza virus, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*	Q fever, *Burkholderia pseudomallei*, Hantavirus spp., *Leptospira* spp., *Histoplasma* spp., *Paracoccidioides brasiliensis* complex, *Strongyloides stercolaris*, *Legionella* spp.,
Fever with jaundice	*Leptospira* spp., *Plasmodium* spp., viral hepatitis, *Salmonella* spp.	YF, arenavirus
Fever with diarrhea	*Norovirus, Escherichia coli*, *Salmonella* spp., *Shigella*, *Campylobacter* spp., *Giardia intestinalis*	Liver flukes, *Vibrio* spp., *Cryptosporidium, Schistosoma mansoni*, intestinal amebiasis
Fever with rash or eschar	Rickettsiosis, DENV, CHIKV, ZIKV, acute HIV	*Sporothrix* spp., *Bartonella* spp., *Spirilum minus*
Fever with CNS manifestations	DENV, ZIKV, CHIKV *Streptococcus pneumoniae*, *Haemophilus influenza*, *Leptospira* spp., *Toxoplasma*, *P. falciparum*	Free-living amebae (i.e., *Naegleria fowleri*, *Angiostrongylus cantonensis*), neurosyphilis, WNV, SL, Rocio, rabies, EEE, WEE, VEEV, YF, *P vivax, T cruzi*
Fever with hemorrhagic manifestations	*Plasmodium* spp., DENV, CHIKV, ZIKV, rickettsiosis, *Leptospira* spp.	Arenavirus, hantavirus, *T cruzi,* YF
Undifferentiated non-malarial fever illness	DENV, CHIKV, ZIKV, *Salmonella* spp., *Toxoplasma*, rickettsiosis, *Leptospira* spp., bacterial sepsis, acute HIV	OROV, MAYV, VEEV, SLE, *Ehrlichia* spp., *Coxiella burnetti*, *Bartonella* spp., *Brucella* spp., *Trypanosoma cruzi*

DENV: dengue virus; CHIKV: chikungunya virus; EEE: eastern equine encephalitis virus; HIV: human immunodeficiency virus; OROV: Oropuche virus; SLE: Saint Louis encephalitis virus; MAYV: Mayaro virus; VEEV: Venezuelan equine encephalitis virus; WNV: West Nile virus; WEE: western equine encephalitis; YF: yellow fever; ZIKV: Zika virus

alphaviruses, especially the ones in the Semliki Forest serocomplex, such as Mayaro (MAYV), O'nyong-nyong (OONV), and Ross River viruses (RRV), making it more difficult to distinguish in regions of co-circulation of these viruses.

2.7 Global Availability of Chikungunya RDTs

We recently conducted a scoping review of the global landscape of CHIKV rapid diagnostic tests currently under development or commercially available (Moreira J et al. unpublished data). We found that the in vitro diagnostic medical device manufacturers are primarily concentrated on CHIKV antibody-based RDTs, and their accuracy overall performs poorly. It should not be used in clinical settings as long as they suffer significant improvements. Conversely, antigen-based RDTs,

although still in a development phase, promise to have a high level of sensitivity and specificity across the distinct CHIKV genotypes.

Given the problems associated with the existing diagnostic strategies for CHIKV, there is a clear and urgent need for new, appropriate diagnostic tools for CHIKV that meet the ideal product profile of "REASSURED" diagnostics. The characteristics of the diagnostics products mentioned above are defined by a set of criteria which includes: (1) Real-time connectivity; (2) Ease of specimen collection; (3) Environmental friendliness; (4) Affordable by those at risk of infection; (5) Sensitive (few false-negatives); (6) Specific (few false-positives); (7) User-friendly (simple to perform and requiring minimal training); (8) Rapid (to enable treatment at first visit) and Robust (does not require refrigerated storage); (9) Equipment-free; and (10) Delivered to those who need it. Few products right now meet the ideal "REASSURED" profile, and new research and investments are required to develop those that match the profile needed. Pertinent questions about feasibility, acceptability, cost-effectiveness, sustainability policy implications must be addressed before the widespread use of CHIKV RDTs in endemic countries. More importantly, we also need to address the impact of CHIKV RDTs into integrated fever case management and how its implementation translates into a better prescription practice for acute febrile patients (i.e., reducing unnecessary antibiotic prescription).

2.8 Clinical Manifestations: Neonates, Children, and Adults

After the incubation period, the viremic host initiates an acute clinical picture, which may evolve to a post-acute or chronic phase of the disease. The clinical picture of the acute phase is very similar to dengue, with sudden onset of high fever, headache, arthralgia, muscle pain, exanthem, nausea, and fatigue (Nayar and Albur 2017; Burt et al. 2017). The main characteristic of the disease is the presence of polyarthralgia described in more than 90% of patients in the acute phase, which causes essential physical dysfunction, significantly impacting the quality of life of affected patients. The work disability caused by the disease in an economically active age group further expands the magnitude of the problem for the affected population (Burt et al. 2014; Rodriguez-Morales et al. 2016).

In its different phases, joint pain is the most frequent and disabling symptom in chikungunya infection—the aggravating factor of being intense and not responsive to analgesics (De Andrade et al. 2010). However, patients usually report joint clinical improvement 7–10 days after symptoms (Nunes et al. 2015a, b).

In some cases of the disease are reported atypical manifestations, which may be: neurological, severely affecting CNS with meningitis, encephalitis, myelitis, paralysis, ataxia, convulsions, Guillain–Barré syndrome, behavioral disorders, among others (Arpino et al. 2009; Chandak et al. 2009; Zacks and Paessler 2010; Rust 2012; Bale 2015). They may present cardiac manifestations (myocarditis, pericarditis, heart failure, arrhythmia, and hemodynamic instability), renal (nephritis and acute renal failure), dermal (photosensitivity hyperpigmentation, vesiculobullous

dermatosis, and aphthous ulcerations), and ocular (optic neuritis, iridocyclitis, episcleritis, retinitis, and uveitis).

Severe forms of acute infection have been observed in different age groups, not only in elderly patients. These forms involve the central, respiratory, and urinary nervous systems. Occasionally, decompensation of pre-existing chronic diseases, particularly cardiovascular, respiratory, renal, and autoimmune diseases, may occur.

Patients with severe forms must be hospitalized, and a portion may need intensive care such as respiratory, hemodynamic, or dialysis support. In Reunion Island, of 610 patients, 84 (14%) needed ICU, and 65 (11%) died.

Unlike dengue and Zika, the musculoskeletal manifestations of CHIK, as previously mentioned, undergo a chronic process requiring adequate knowledge from health professionals for the long-term follow-up of these patients. After the acute phase, symptoms may persist to a post-acute (up to 3 months) and chronic (> 3 months). Joint involvement after the acute phase may assume different clinical patterns. The rate of sub-acute joint symptoms ranges from 50% to nearly 90% in some studies, and more than 10% of patients progress to the persistence of symptoms for months or years (Van Aalst et al. 2017).

In the chronic phase, arthralgia is characterized by fluctuations in pain intensity, with recurrences generally affecting the same joints involved in the acute phase, causing a reduction in range of motion and worsening quality of life (Burt et al. 2014). The main predictors of chronicity are advanced age, female gender, initial intensity of joint pain, detection of CHIKV-RNA after 7 days of symptom onset (Van Aalst et al. 2017; Huits et al. 2018).

The first signs and symptoms start between the 1st and 15th days of life. The most common signs and symptoms are fever, rash, refusal of breastfeeding, skin hyperpigmentation, and edema of extremities. Neurological complications are most frequent and manifest as meningoencephalitis, encephalitis, hypotonia, irritability, hyperalgesia, and seizures. Clinical manifestations of organs and systems can manifest as respiratory failure, hemodynamic instability, gastrointestinal symptoms, and septic shock. Other serious complications such as intracranial hemorrhage, pericarditis, myocarditis, pericardial effusion, and necrotizing enterocolitis have also been reported (Ferreira et al. 2021).

Although it affects the entire population, regardless of age and gender, younger children and the elderly are more susceptible to the severe form of the disease and more significant progression to death (Fig. 2.1).

2.8.1 Chikungunya Clinical Presentation in Children Versus Adults

There are limited data on pediatric-specific presentation of CHIKV. Ritz N and colleagues observed up to 40% of asymptomatic infection rates in children. This proportion is much higher than in adults. During a CHIKV outbreak in Rio de Janeiro, 2018–2019, we observed that children frequently reported rash (70.8% vs. 48.7%), and arthralgia was less present (66.7% vs. 94.7%) compared

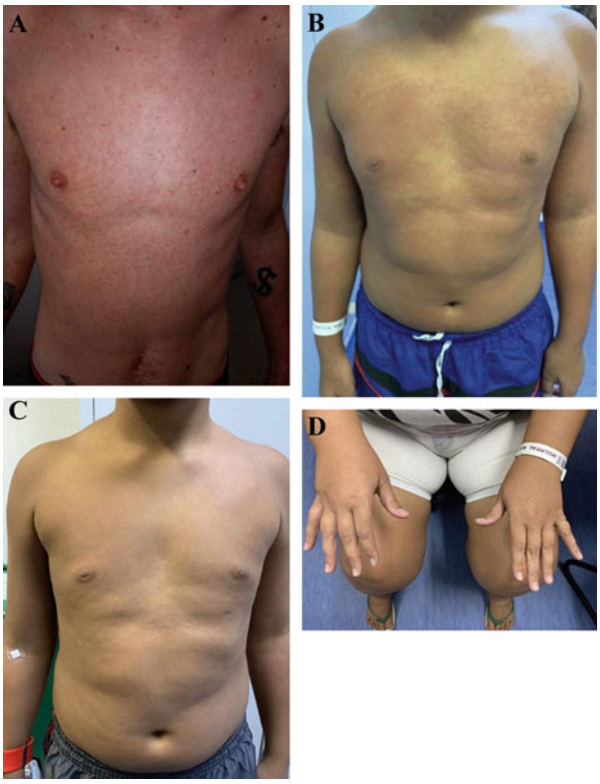


Fig. 2.1 (**a**) A maculopapular rash during the acute infectious phase of chikungunya. The rash was distributed over the entire body, resolved after a few days, and was followed by desquamation; (**b**) Eight-year-old male complaints of acute onset high-grade fever, maculopapular rash (mainly over the limbs, face, and trunk), and bilateral polyarthralgia; (**c**) The same child comes back 2-week on for clinical and laboratory evaluation. The rash has resolved, and he is entirely asymptomatic. (**d**) Acute arthritis involving the metacarpophalangeal and proximal interphalangeal joints in a patient with chikungunya arthritis. Arthralgia is usually bilateral and symmetric, involves distal joints more than proximal joints, and is associated with morning stiffness

Table 2.2 Main differences regarding Chikungunya clinical manifestations in children against adults

Characteristics	Children	Adults
Asymptomatic disease	35–40% (rare in neonates and infants)	16–27%
Neurologic	Headache (15%)	Headache (40–81%)
Musculoskeletal	Myalgia and arthralgia (30–50%)	Arthritis/arthralgia, symmetric, more commonly affecting distal joints (87–99%)
Mucocutaneous	Oral ulcers (rare)	Oral ulcers (16%)
Skin	Maculopapular rash (33–60%)	Maculopapular rash on trunk and limbs (35–50%)

with the adult's counterpart. Table 2.2 summarizes the primary clinical manifestation between children and adults.

2.9 Treatment: Acute Phase, Post-Acute, and Chronic Arthritis

2.9.1 Acute Phase

To date, there is no specific antiviral treatment for chikungunya. The therapeutic approach, therefore, is symptomatic support, hydration, and rest. Evidence that rest is a protective factor in avoiding evolution to the post-acute phase is critical. In the acute phase, the objectives are to control fever and pain, treat dehydration or involvement of other organs, prevent iatrogenic risk, maintain functional capacity, and avoid dissemination to relatives and contacts (Brasil, Ministério da Saúde 2017).

To control pain, analgesics such as dipyrone or paracetamol can be used (oral paracetamol 60 mg/kg/dia maximum 4 g/day and dipyrone 1 g 4 times a day), or opioids (codeine 50–100 mg 4 times a day and tramadol 50–100 mg 4 times a day), the treatment can be done in monotherapy or combination. In the presence of neuropathic pain, tricyclic antidepressants and anticonvulsants should be used (oral amitriptyline 25–50 mg/day, oral pregabalin 50–150 mg 2–4 times a day, and oral gabapentin 300 mg 2–3 times a day).

The use of non-steroidal anti-inflammatory (NSAID) is contraindicated in the first days until the differential diagnosis with dengue has been removed due to the higher risk of bleeding. Aspirin is also contraindicated in the acute phase due to the risk of Reye syndrome and bleeding.

Special attention needs to be paid to the risks of self-medication, overdoses, and adverse effects of the medications used in the post-acute phase. In addition to simple analgesics or weak opioids, NSAIDs can be used once the diagnosis of dengue has been removed.

2.9.2 Post-Acute and Chronic Arthritis

Several treatments have been developed for the subacute and chronic forms of chikungunya, and several alternatives have been tried with varying success. In general, the initial treatment is with non-steroidal anti-inflammatory drugs (NSAIDs, ibuprofen 400 mg three times daily, diclofenac 50 mg twice daily, naproxen 250 mg twice daily, aceclofenac 200 mg daily), in unresponsive cases, corticosteroids can be used (oral prednisolone, 5–10 mg/day.

More complicated cases are treated with disease-modifying antirheumatic drugs (DMARDs) hydroxychloroquine, 5 mg/kg/day, maximum 400 mg daily; methotrexate, 10–25 mg/week with folic acid 1 mg/day; sulfasalazine, 1–2 g/day (Pathak et al. 2019). Chronic patients who present with neuropathic pain also may respond well to treatment with tricyclic antidepressants and anticonvulsants (Oral amitriptyline 25–50 mg/day, oral pregabalin 50–150 mg 2–4 times a day, and oral gabapentin 300 mg 2–3 times a day) (Figs. 2.2, 2.3, and 2.4).

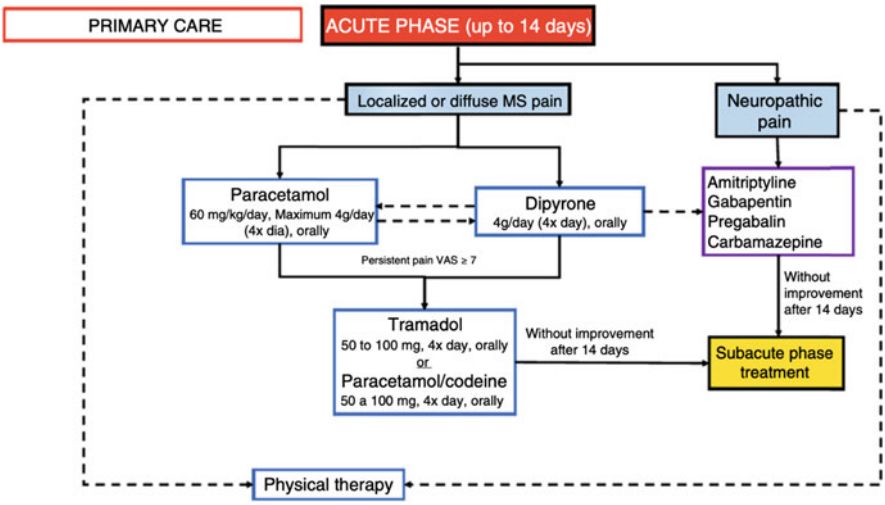


Fig. 2.2 Therapy for the acute phase of Chikungunya infection according to the Brazilian Society of Rheumatology (Rev Bras Reumatol 2017; 57 (S2): S438–S451)

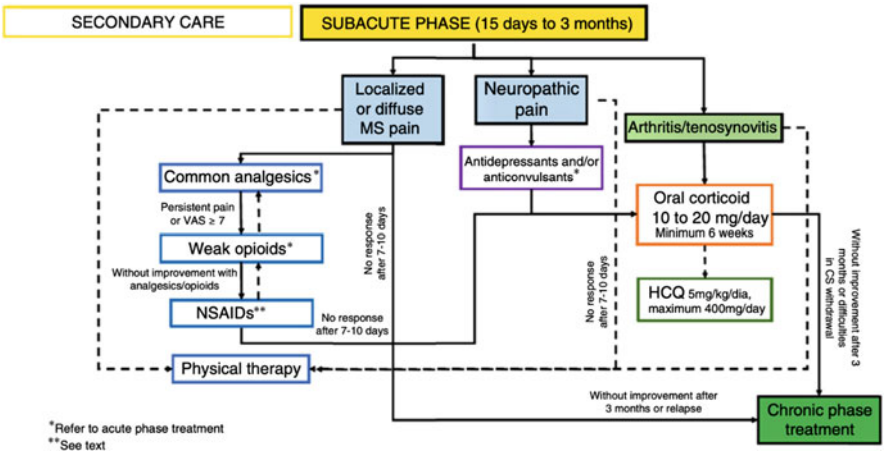


Fig. 2.3 Therapy for the post-acute phase of Chikungunya infection according to the Brazilian Society of Rheumatology (Rev Bras Reumatol 2017; 57 (S2): S438–S451)

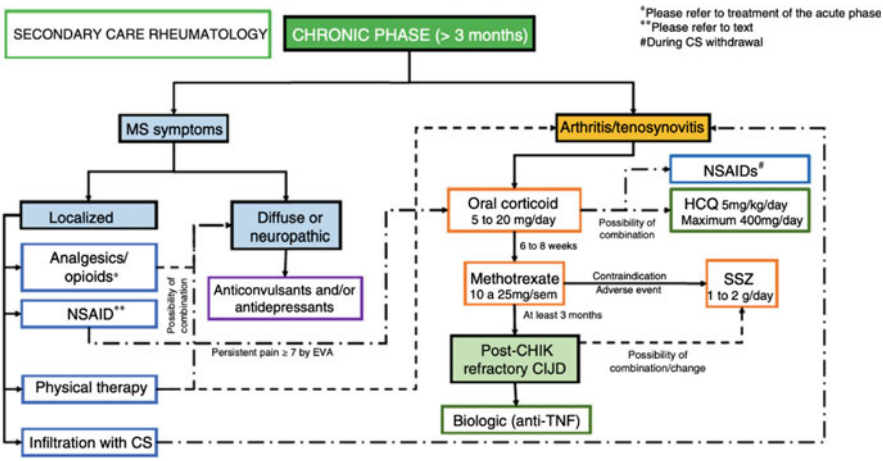


Fig. 2.4 Therapy for the chronic phase of Chikungunya infection according to the Brazilian Society of Rheumatology (Marques et al. 2017)

2.10 Prevention and Control

2.10.1 Vaccine Development

The ongoing Coronavirus disease 2019 (COVID-19) pandemic has brilliantly taught us the importance of vaccine development of emerging infections and its impact on controlling disease dynamics and morbi-mortality. Chikungunya vaccine development is interesting because promise candidates are in the pipeline in phase 1 and 2 trials. Such candidates apply different vaccine platforms for delivery such as inactivation, attenuation, chimeric constructions with different viral backbones, viral proteins, DNA, and virus-like particles.

The most advanced vaccine candidates, a measles-vectored vaccine (Reisinger et al. 2018) and a virus-like particles vaccine (Chen et al. 2020), have reached high seroconversion rates in humans but required more than a single shot to achieve it.

In a randomized trial (Reisinger et al. 2018), including more than 260 healthy adults in non-chikungunya-endemic regions, a live-attenuated, measles-vectored vaccine expressing CHIKV structural proteins (MV-CHIKV) induced neutralizing antibodies against CHIKV after one or two immunizations. Seroconversion rates in those who received MV-CHIKV ranged from 50 to 93% after one dose and 86–100% after two doses. Immune responses were durable up to 6 months after one or two doses, and the vaccine was safe and well-tolerated.

In another randomized phase 2 trial (Chen et al. 2020) of a CHIKV virus-like particle vaccine, 400 adults in CHIKV-endemic Caribbean countries received two intramuscular injections or a placebo. Among those seronegative at baseline, 88% had at least a fourfold increase from baseline neutralization titers. The immune

response was durable up to 72 weeks after vaccination, and the vaccine was safe and well-tolerated. Phase 3 trials are desperately needed to understand better the efficacy, safety, and long-term immune response.

These two trials and others have raised important questions about correlates of protection, duration of protection, and whether vaccines are effective against infection or symptomatic disease. In the future, a suitable vaccine might be available for each situation—that is, explosive outbreak, endemic countries, travelers, military, and people with underlying medical conditions. The difficulties of implementing clinical efficacy trials are notorious because of the epidemiological pattern of CHIKV (cyclical movement characterized by remote outbreaks interspersed with periods of epidemiological silence). However, we hope that such barriers will be overcome and make way for other promising candidates.

2.10.2 Mosquito Protection

While we do not have an efficient vaccine, the main prevention strategies are linked to controlling its main vectors, the mosquitoes of the genus Aedes (*Aedes aegypti* and *Aedes albopictus*). Despite the new control technologies described in recent years, nothing has been enough for effective and long-lasting control of these vectors. Individuals with CHIKV infection may reduce the spread of infection to others by following precautions to avoid mosquito bites during the first week of illness (i.e., viremia phase).

Guidelines regarding the safe and effective use of insect repellents in order to maximize effectiveness and minimize side effects were issued by the United States Environmental Protection Agency. The most widely used insect repellents are DEET (N, N-diethyl-3-methylbenzamide), Icaridin (Picaridin) (KBR 3023), PMD (P-menthane-3,8-diol), BioUD (2-undecanone), IR3535, and Metofluthrin. These agents are not equal in efficacy and provide varying degrees of protection against different arthropods vectors. Experimental studies have shown that repellents protection is reduced by swimming, washing, sweating, wiping, exercise, and rainfall.

2.11 Summary and Take-Home Messages

- Chikungunya (CHIK) is an arbovirus caused by the chikungunya virus (CHIKV), virus of the Togaviridae family, Alphavirus genus.
- The clinical picture of the acute phase can be very similar to dengue and Zika, with sudden onset of high fever and malaise. Polyarthralgia often begins two to 5 days after onset of fever and commonly involves multiple joints. Arthralgia is usually bilateral and symmetric, involves distal joints more than proximal joints, and is associated with morning stiffness. The most common skin manifestation is macular or maculopapular rash. Severe complications (i.e., meningoencephalitis, cardiopulmonary failure, kidney injury, and death) have been described more frequently in older individuals and those with underlying comorbidities.

- Patients commonly develop chronic musculoskeletal manifestations, including inflammatory polyarthritis, polyarthralgia, and tenosynovitis during and following acute infection. Inflammatory arthritis can persist for weeks, months, or years. The chronic manifestations usually involve joints affected during the acute illness and can be relapsing or unremitting and incapacitating. Multiple predictors of chronicity have been described including age > 40, severity of acute disease, and underlying osteoarthritis.
- Given the remarkable and rapid growth of its incidence in the Americas, it affected a considerable proportion of naïve-individuals, in a short period, causing significant attack rates. In Brazil, where the first autochthonous cases were registered in 2014, epidemics were already registered in the following year in several regions, especially in the northeast.
- Despite the production of guidelines for clinical management in several countries, there are still many gaps that need to be addressed; highlighting: chronicity rate, risk factors for progression to more severe forms and deaths, the persistence of the disease, and evaluation of which the best drug or non-drug strategies are more suitable for management in the different stages of the disease.
- There is no specific antiviral therapy for the treatment of CHIKV infection, and management during the acute phase is supportive, including rest, fluids, and anti-inflammatory or analgesic drugs. For patients with chronic arthritis who are unable to taper corticosteroid without recurrence of symptoms, disease-modifying antirheumatic drugs (i.e., methotrexate, sulfasalazine) are recommended.
- There is an essential diversity of factors related to the evolution of the infection, involving demographic factors (age and sex), genetic, virological, pre-existing diseases (DM, obesity, and rheumatologic diseases), and used therapies (immunosuppressive and biological).
- The health, economic and psychosocial impact caused during chikungunya epidemics, in addition to the high mortality rates recently revealed, as well as the overload caused on health systems, which need to respond efficiently to this emergency, make chikungunya one of the most critical arboviruses to be controlled. Besides that, accumulated experience of Brazil, with recent epidemics, has highlighted that the current chikungunya case classification does not encompass the actual needs presented by some instances with atypical features, nor does it contribute to the management of potentially severe cases. As the circulation of CHIKV increases on all continents, we will need a prospective case classification.
- On the other hand, choosing rational empiric therapy for patients with febrile syndromes in low-resource settings is complicated because many of them may be caused by neglected tropical diseases. Such infections are severe and treatable but often clinically indistinguishable without confirmatory tests. Making matters worse, very little epidemiological data underpin clinicians' assessment of prior probability in vast areas of Latin America. In this context, many vital questions remain unanswered.

References

Arankalle VA et al (2007) Genetic divergence of chikungunya viruses in India (1963–2006) with special reference to the 2005–2006 explosive epidemic. J Gen Virol 88(7):1967–1976

Arpino C, Curatolo P, Rezza G (2009) Chikungunya and the nervous system: what we do and do not know. Rev Med Virol 19(3):121–129

Bale JF (2015) Epidemiology, diagnosis virus and immune-mediated encephalitides: treatment and prevention. Pediatr Neurol 53:3–12

Brasil, Ministério da Saúde, Secretaria de Vigilância em Saúde (2017) Chikungunya: manejo clínico. Ministério da Saúde, Brasília

Burt F, Chen W, Mahalingam S (2014) Chikungunya virus and arthritic disease. Lancet Infect Dis 14(9):789–780

Burt FJ et al (2017) Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. Lancet Infect Dis

Chandak NH et al (2009) Neurological complications of chikungunya virus infection. Neurol India 57(2):177

Chen GL, Coates EE, Plummer SH, Carter CA, Berkowitz N (2020) Effect of a chikungunya virus–like particle vaccine on safety and tolerability outcomes a randomized clinical trial. JAMA 323(14):1369–1377. https://doi.org/10.1001/jama.2020.2477

Conway MJ et al (2014) Role of the vector in arbovirus transmission. Virology 1:71–88

de Andrade DC et al (2010) Chronic pain associated with the chikungunya fever: long lasting burden of an acute illness. BMC Infect Dis 10:31

Delisle E, Rousseau C, Broche B, Leparc-Goffart I, L'Ambert G, Cochet A, Prat C et al (2015) Chikungunya outbreak in Montpellier, France, September to October 2014. Euro Surveill 20(17):ii–21108 Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21108

Donalísio MR et al (2015) Chikungunya no Brasil: um desafio emergente. Rev Bras Epidemiol 18(1):283–285

Economopoulou A et al (2009) Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Réunion. Epidemiol Infect 137:534–541

Ferreira FCPDADM, da Silva ASV, Recht J, Guaraldo L, Moreira MEL et al (2021) Vertical transmission of chikungunya virus: one systematic review. PLoS One 16(4):e0249166

Freitas ARR, Cavalcanti L, Von ZAP, Donalisio MR (2017) Excess mortality related to chikungunya epidemics in the context of co-circulation of other arboviruses in Brazil. PLOS Curr Outbreaks:140491. https://doi.org/10.1371/currents.outbreaks.14608e586cd321d8d5088652d7a0d88412

Freitas ARR, Alarcón-Elbal PM, Paulino-Ramírez R, Donalisio MR (2018a) Excess mortality profile during the Asian genotype chikungunya epidemic in the Dominican Republic. Trans R Soc Trop Med Hyg 112(10):443–449. https://doi.org/10.1093/trstmh/try07211

Freitas ARR, Alarcón-Elbal PM, Donalisio MR (2018b) Excess mortality in Guadeloupe and Martinique, islands of the French West Indies, during the chikungunya epidemic of 2014. Epidemiol Infect 146(16):2059–2065. https://doi.org/10.1017/S095026881800231510

Freitas ARR, Donalisio MR, Alarcón-Elbal PM (2018c) Excess mortality and causes associated with chikungunya, Puerto Rico, 2014–2015. Emerg Infect Dis 24:2352–2355. https://doi.org/10.3201/eid2412.17063913

Freitas ARR, Gérardin P, Kassar L, Donalisio MR (2019) Excess deaths associated with the 2014 chikungunya epidemic in Jamaica. Pathog Globe Health 113(1):27–31. https://doi.org/10.1080/20477724.2019.1574111

González-Sánchez JA, Ramirez-Arroyo GF (2018) Chikungunya virus: history, geographic distribution, clinical picture, and treatment. P R Health Sci J 37:187–194

Henry M, Francis L, Asin V, Polson-Edwards K, Olowokure B (2017) Chikungunya virus outbreak in Sint Maarten, 2013–2014. Rev Panam Salud Publica 41(21)

Huits R, De Kort J, Van Den Berg R, Chong L, Tsoumanis A et al (2018) Chikungunya virus infection in Aruba: diagnosis, clinical features and predictors of post-chikungunya chronic polyarthralgia. PLoS One 13(4):e0196630. https://doi.org/10.1371/journal.pone.0196630
Krutikov M, Manson J (2016) Chikungunya virus infection: an update on joint manifestations and management. Rambam Maimonides Med J 7(4):e0033. https://doi.org/10.5041/RMMJ.10260
Kumar NP et al (2008) A226V mutation in virus during the 2007 chikungunya outbreak in Kerala, India. J Gen Virol 89(8):1945–1948
Liang G, Gao X, Gould EA (2015) Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control. Emerg Microbes Infect 4(1):1–5. https://doi.org/10.1038/emi.2015.18
Lima STS et al (2020) Fatal outcome of chikungunya virus infection in Brazil. Clin Infect Dis:1–8
Lum F-M, Ng LFP (2015) Cellular and molecular mechanisms of chikungunya pathogenesis. Antivir Res 120:165–174
Marques CDL et al (2017) Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. Part 2—treatment. Rev Bras Reumatol Engl Ed 57(S2):S438–S451
Mohan A et al (2010) Epidemiology, clinical manifestations, and diagnosis of chikungunya fever: lessons learned from the re-emerging epidemic. Indian J Dermatol 55(1):54
Nayar G, Albur M (2017) Chikungunya. BMJ 356:j250
Nunes MR et al (2015b) Emergence and potential for spread of chikungunya virus in Brazil. BMC Med 13:102
Nunes MRT et al (2015a) Emergence and potential for spread of chikungunya virus in Brazil. BMC Med 13(1):1
Pathak H, Mohan MC, Ravindran V (2019) Chikungunya arthritis. Clin Med (Lond) 19(5): 381–385. https://doi.org/10.7861/clinmed.2019-0035
Powers AM, Logue CH (2007) Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. J Gen Virol 88(9):2363–2377
Pulmanausahakul R et al (2011) Chikungunya in Southeast Asia: understanding the emergence and finding solutions. Int J Infect Dis 15(10):e671–e676
Reisinger EC, Tschismarov R, Beubler E, Wiedermann U, Firbas C, Loebermann M et al (2018) Immunogenicity, safety, and tolerability of the measles-vectored chikungunya virus vaccine MV-CHIK: a double-blind, randomised, placebo-controlled and active-controlled phase 2 trial. Lancet 392(10165):2718–2727. https://doi.org/10.1016/S0140-6736(18)32488-7
Renault P, Solet JL, Sissoko D, Balleydier E, Larrieu S, Filleul L, Lassalle C, Thiria J, Rachou E, de Valk H, Ilef D, Ledrans M, Quatresous I, Quenel P, Pierre V (2007) A major epidemic of chikungunya virus infection on Reunion Island, France, 2005–2006. Am J Trop Med Hyg 77(4): 727–731. PMID: 17978079
Rezza G et al (2007) Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 370(9602):1840–1846
Robinson MC (1955) An epidemic of virus disease in Southern Province, Tanganyika territory, in 1952–1953. Trans R Soc Trop Med Hyg, Oxford 49(1):28–32
Rodriguez-Morales AJ et al (2016) Post-chikungunya chronic arthralgia: a first retrospective follow-up study of 39 cases in Colombia. Clin Rheumatol 35(3):831–832
Ross RW (1956) The Newala epidemic: III. The virus: isolation, pathogenic properties and relationship to the epidemic. Epidemiol Infect 54(2):177–191
Rust RS (2012) Human arboviral encephalitis. Semin Pediatr Neurol 19(3):130–151
Sahadeo NMH et al (2015) Molecular characterisation of chikungunya virus infections in Trinidad and comparison of clinical and laboratory features with dengue and other acute febrile cases. PLoS Negl Trop Dis 9(11)
Schuffenecker I et al (2006) Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak. PLoS Med 3(7):e263

Sharp TM, Keating MK, Shieh WJ et al (2021) Clinical characteristics, histopathology, and tissue Immunolocalization of chikungunya virus antigen in fatal cases. Clin Infect Dis 73(2):e345–e354. https://doi.org/10.1093/cid/ciaa837

Solignat M, Gay B, Higgs S, Briant L, Devaux C (2009) Replication cycle of chikungunya: a re-emerging arbovirus. Virology 393(2):183–197

Strauss EG, Strauss JH (1986) Structure and replication of the alphavirus genome. In: The togaviridae and flaviviridae. Springer, New York, pp 35–90

Sudeep AB, Parashar D (2008) Chikungunya: an overview. J Biosci 33(4):443–449

Tsetsarkin KA et al (2007) A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS Pathog 3(12):e201

Uchime O, Fields W, Kielian M (2013) The role of E3 in pH protection during alphavirus assembly and exit. J Virol 87(18):10255–10262. https://doi.org/10.1128/JVI.01507-13

Van Aalst M, Nelen CM, Goorhuis A, Stijnis C, Grobusch MP (2017) Long-term sequelae of chikungunya virus disease: a systematic review. Travel Med Infect Dis 15:8–22. https://doi.org/10.1016/j.tmaid.2017.01.004

Vega-Rúa A et al (2014) High level of vector competence of Aedes aegypti and Aedes albopictus from ten American countries as a crucial factor in the spread of chikungunya virus. J Virol 88(11):6294–6306

Volk SM et al (2010) Genome-scale phylogenetic analyses of chikungunya virus revealing dependent emergences of recent epidemics and various evolutionary rates. J Virol 84(13):6497–6504

Wahid B et al (2017) Global expansion of chikungunya virus: mapping the 64-year history. Int J Infect Dis 58:69–76

Zacks MA, Paessler S (2010) Encephalitic alphaviruses. Vet Microbiol 140(3):281–286

Zeller H, Bortel WV, Sudre B (2016) Chikungunya: its history in Africa and Asia and its spread to new regions in 2013–2014. J Infect Dis 214(5):436–440

3 Zika Virosis: A Known, But Long Time Underestimated Disease That Got New and High Attention Before, During, and After the Olympic Games in Brazil 2016

Heinz Mehlhorn

Abstract

Infections due to the so-called Zika virus had been known since 1947. However, it reached only worldwide attention when numerous human infections were noted before, during, and after the Olympic Games in Brazil in the year 2016.

Keywords

Zika virus · Transmission pathways · Prevention of infection

3.1 Introduction

The outbreak or the official notice of the spreading of the so-called Zika virus fever in Brazil at the end of the year 2015 just some months before the start of the Olympic Games in the year 2016 (August 5, 2016–21, 2016) shocked not alone the sports world, but also many people living in whole South America, Central America as well as in the Southern regions of the USA and also many people around the globe, who had made plans to participate at the Olympic Games in and around Rio de Janeiro (Martins et al. 2021). This outbreak was astonishing and surprising, since the normal population was not aware that this agent (a virus) was already known since 1947, when it was found in females of the mosquito species *Aedes africanus* and other related species (*Aedes aegypti* syn. *Stegomyia aegypti*, *A. albopictus*, *A. hensilli,* etc.). Years before it had also been proven that monkeys and humans had been infected in many countries in Africa, Asia, and the Caribbean. However, in many countries of South America medical care and research in this field had not been very

H. Mehlhorn (✉)
Department of Parasitology, Heinrich Heine University, Duesseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_3

effective, although in some regions 73% of the people had been proven to be infected, wherefrom, however, only 18% of the tested persons showed clear, significant symptoms of disease. Thus infections had not been considered as very important, especially since mostly poor people living under poor dwelling conditions had been infected and had no or poor contacts to physicians who would have been able to diagnose the disease (Plourde and Bloch 2016). Furthermore, the symptoms varied in their intensity and thus low-graded symptoms had not been registered.

3.2 The Zika Virus

The name (Zika) of this disease has its origin in the fact that its detection occurred during a Yellow fever expedition in the so-called Zika forest in Uganda (Africa). Furthermore, the name Zika is today used in several countries as a first name as well as family name for both males and females This dangerous 50 nm sized organism (ZIKV) belongs to the so-called positive-sense single-stranded RNA viruses within the family of Flaviviridae, which contains a bunch of several other mosquito-borne viruses being important due to their clinical importance (e.g., like those inducing the Yellow fever or the Guillain-Barré disease, which is the inducer of the Guillain-Barré syndrome in adult humans and the microcephaly in babies).

The Zika virus was first isolated in the year 1947 from a macaque monkey hit by high fever and later (1954) also detected in humans in Nigeria. This new virus was later found, too, in the intestine of mosquitoes of the species *Aedes africanus* as well as in many other species of this genus. Again later this virus has been detected to be widespread throughout Africa, Asia and Oceania, South and North America (Plourde and Bloch 2016). Later it reached worldwide attention, when it was found before and after the Olympic Games in Rio de Janeiro, Brazil, in the year 2016. The public attention was very high due leading to the fact that, that un- and newborn children had been severely hit by developing microcephaly, so that the WHO declared the Zika virus a so-called Public Health Emerging of International Concern in February 2016. Why the observed severeness of the disease was so intensive remained unclear, since before and after this outbreak humans became much less hit.

The Zika virus, which has been shown to be a single-stranded RNA virus in the family of Flaviviridae, which are known to include many other mosquito-transmitted viruses of high clinical importance such as Yellow fever virus (YFV), has a genome containing 10,794 nt encoding 3419 aa as it is in the case in other flaviviruses, too (Kuno and Chang 2007).

3.3 Transmission of the Zika Virus

This virus is predominantly transmitted during the bloodsucking act of female mosquitoes of the genus *Aedes*, which is known as vector of many agents of disease. The first proof was shown already in 1948 during experimental studies using *Aedes*

africanus mosquitoes (Dick et al. 1952). The Zika virus was also isolated from other mosquitoes of the genus *Aedes* (e.g., *A. africanus*, *A. hensilli*, *A. albopictus*). In the year 1956 experiments showed, that the virus can be transported without problems by *Aedes aegypti* and that the virus survived inside the female mosquitoes for at least 10 weeks. Similar data were achieved, when further species like *Aedes hensilli*, *A. polynesiensis* were proven to have transmitted this virus in French Polynesia. In Asia *Aedes aegypti* mosquitoes apparently have reached a predominant position as vectors of different viruses thus indicating that it apparently had been widely spread without being detected. According to the Brazilian Information (SINASC) the prevalence of microcephaly from 2000 to 2014 was 5.5 per 100,000 persons, while this rate increased to 54.6 per 100,000 humans. The reasons remained not understood, since actually the severe cases have again significantly decreased. In any way today the disease occurs still in low rates in many countries. This might be due to the import via travellers (Freitas et al. 2020). The spreading of this virus is also increased due to the fact that there are further pathways of transmission, since this virus was also found in human sperm fluids, in blood preservations, or in fluids during the birth process.

3.4 Clinical Symptoms

After an incubation period of about 2–6 days symptoms may occur in (only) about 20% of the infected persons. The most common symptoms are fever, exanthema, muscle pain, cephalgias, gastrointestinal symptoms, conjunctivitis, which, however, mostly decrease within a few days. It was noted that in special cases persons could die from symptoms of the Guillain-Barré syndrome, which had been found rather often in patients in French Polynesia (Meyer 2021). The rate of cases of microcephaly, which was enormous in the period before and after the Olympic Games in Brazil 2016, has decreased considerably in recent times.

3.5 Prevention

Since apparently bloodsucking mosquitoes seem to be the most important vectors (besides sexual transmission), the use of repellents (i.e., icaridin) is strongly recommended when visiting regions with an abundance of the mosquitoes of the genus *Aedes*. Although the spread of the Zika virus is currently (2022) considerably low, it is strongly recommended when worldwide visiting rural regions with high prevalence of mosquito species of the genus *Aedes*. Especially pregnant women should protect themselves from *Aedes* mosquito bites if visiting tropical regions and should use condoms during sexual intercourse with persons returning from tropical regions. Since also sexual transmission seems reasonable, the use of condoms is recommended, since infected persons may not have symptoms of disease.

Furthermore, people, who had visited especially tropical regions and suffer from fever symptoms now, should inform their physician that they stayed in tropical or

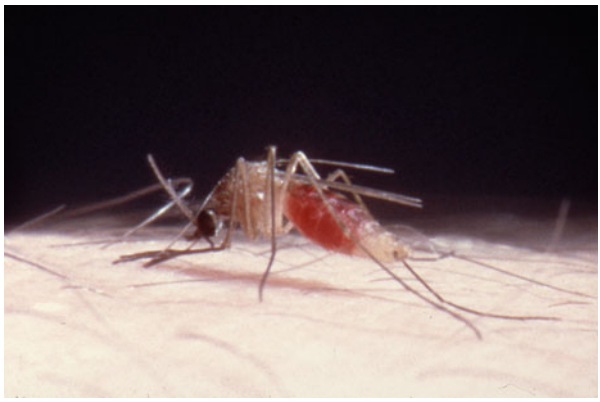


Fig. 3.1 Bloodsucking female of the mosquito species *Aedes aegypti*

subtropical regions before. Then he may find the cause of potential infections more easily (Fig. 3.1).

Bibliography

Abbasi A-N (2016) Zika virus infection; vertical transmission and fetal congenital anomalies. J Ayub Med Coll Abbottabad JAMC 28(1):1–2

Angelidou A, Michael Z, Hotz A, Friedman K, Emani S, LaRovere K et al (2018) Is there more to Zika? Complex cardiac disease in a case of congenital Zika syndrome. Neonatology 113:177–182

Besnard M, Eyrolle-Guignot D, Guillemette-Artur P, Lastere S, Bost-Bezeaud F, Marcelis L et al (2016) Congenital cerebral malformations and dysfunction in fetuses and newborns following the 2013 to 2014 Zika virus epidemic in French Polynesia. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 21(13)

Brady OJ, Osgood-Zimmerman A, Kassebaum NJ, Ray SE, de Araújo VEM, da Nóbrega AA, Frutuoso LCV, Lecca RCR, Stevens A, Zoca de Oliveira B, de Lima JM Jr, Bogoch II, Mayaud P, Jaenisch T, Mokdad AH, Murray CJL, Hay SI, Reiner RC Jr, Marinho F (2019) The association between Zika virus infection and microcephaly in Brazil 2015–2017: an observational analysis of over 4 million births. PLoS Med 16(3):e1002755

Braga JU, Bressan C, Dalvi APR, Calvet GA, Daumas RP, Rodrigues N et al (2017) Accuracy of Zika virus disease case definition during simultaneous dengue and chikungunya epidemics. PLoS One 12(6):e0179725

Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC, Nobre A et al (2016) Zika virus outbreak in Rio de Janeiro, Brazil: clinical characterization, epidemiological and virological aspects. PLoS Negl Trop Dis 10(4):e0004636

Brasil P, Pereira JP Jr, Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M et al (2016) Zika virus infection in pregnant women in Rio de Janeiro. N Engl J Med 375:2321–2334

Cardoso CW, Paploski IAD, Kikuti M, Rodrigues MS, Silva MMO, Campos GS et al (2015) Outbreak of exanthematous illness associated with Zika, chikungunya, and dengue viruses, Salvador, Brazil. Emerg Infect Dis 21:2274–2276

Carvalho-Sauer R, da Costa MCN, Barreto FR, Teixeira MG (2019) Congenital Zika syndrome: prevalence of low birth weight and associated factors. Bahia, 2015–2017. Int J Infect Dis 82:44–50

Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D et al (2016) Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. Lancet Lond Engl 387:2125–2132

Coelho AVC, Crovella S (2017) Microcephaly prevalence in infants born to Zika virus-infected women: a systematic review and meta-analysis. Int J Mol Sci 18(8). https://doi.org/10.3390/ijms18081714

Counotte MJ, Egli-Gany D, Riesen M, Abraha M, Porgo TV, Wang J et al (2008) Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barre syndrome: from systematic review to living systematic review. F1000 Research 7:196

Cugola FR, Fernandes IR, Russo FB, Freitas BC, Dias JLM, Guimarães KP et al (2016) The Brazilian Zika virus strain causes birth defects in experimental models. Nature 534:267–271

de Araujo TVB, Rodrigues LC, de Alencar Ximenes RA, de Barros Miranda-Filho D, Montarroyos UR, de Melo APL et al (2016) Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. Lancet Infect Dis 16: 1356–1363

De Oliveira Melo AS, Aguiar RS, Amorim MMR, Arruda MB, De Oliveira MF, Ribeiro STC et al (2016) Congenital Zika virus infection: beyond neonatal microcephaly. JAMA Neurol 73:1407–1416

de Paula FB, Ko AI, Khouri R, Mayoral M, Henriques DF, Maia M et al (2017) Glaucoma and congenital Zika syndrome. Ophthalmology 124(3):407–408

de Souza WV, Barreto de Araujo TV, de Albuquerque MFP, Braga MC, de Alencar Ximenes RA, Miranda-Filho de DB et al (2016) Microcephaly in Pernambuco state, Brazil: epidemiological characteristics and evaluation of the diagnostic accuracy of cutoff points for reporting suspected cases. Cad Saude Publica 32(4):e00017216

Dick GWA, Kitchen SF, Haddow AJ (1952) Zika virus (I). Isolations and serological specificity. Trans R Soc Trop Med Hyg 46:509–520

Faluyi U, Obadare O, Sangem A, Onuegbu CA, Medavarapu S (2016) Complications associated with Zika virus infection: a systematic review study. Am Sci Res J Eng Technol Sci ASRJETS 24:151–161

Fernandez MP, Parra Saad E, Ospina Martinez M, Corchuelo S, Mercado Reyes M, Herrera MJ et al (2017) Ocular histopathologic features of congenital Zika syndrome. JAMA Ophthalmol 135: 1163–1169

Franca GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD et al (2016) Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet Lond Engl 388:891–897

Freitas DA, Souza-Santos R, Carvalho LMA, Barros WB, Neves LM, Brasil P, Wakimoto MD (2020) Congenital Zika syndrome: a systematic review. PLoS One 15(12):e0242367

Guillemette-Artur P, Besnard M, Eyrolle-Guignot D, Jouannic J-M, Garel C (2016) Prenatal brain MRI of fetuses with Zika virus infection. Pediatr Radiol 46:1032–1039

Hennessey M, Fischer M, Staples JE (2016) Zika virus spreads to new areas—region of the Americas, May 2015–January 2016. Am J Transplant 16:1031–1034

Honein MA, Dawson AL, Petersen EE, Jones AM, Lee EH, Yazdy MM et al (2017) Birth defects among fetuses and infants of US women with evidence of possible Zika virus infection during pregnancy. Jama-J Am Med Assoc 317:59–68

Kuno G, Chang GJ (2007) Full-length sequencing and genomic characterization of Bagaza, Kedougou, and Zika viruses. Arch Virol 152:687–696

Liang B, Guida JP, Costa ML, Mysorekar IU (2019) Host and viral mechanisms of congenital Zika syndrome. Virulence 10:768–775

Lowe R, Barcellos C, Brasil P, Cruz OG, Honório NA, Kuper H, Carvalho MS (2018) The Zika virus epidemic in Brazil: from discovery to future implications. Int J Environ Res Public Health 15(1):96

MacNamara FN (1954) Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Trans R Soc Trop Med Hyg 48:139–145

Marchette NJ, Garcia R, Rudnick A (1969) Isolation of Zika virus from *Aedes aegypti* mosquitoes in Malaysia. Am J Trop Med Hyg 18:411–415
Martins MM, Medronho RA, Cunha AJLAD (2021) Zika virus in Brazil and worldwide: a narrative review. Paediatr Int Child Health 41:28–35
Mattar S, Ojeda C, Arboleda J, Arrieta G, Bosch I, Botia I et al (2017) Case report: microcephaly associated with Zika virus infection, Colombia. BMC Infect Dis 17(1):423–423
Meyer CG (2021) Tropenmedizin - Infektionskrankheiten. 4th ed., Ecomed Medizin, Landsberg
Mehlhorn H (2016a) Animal parasites. Springer International, Switzerland
Mehlhorn H (2016b) Human parasites. Springer International, Switzerland
Mehlhorn H (2016c) Encyclopedia of parasitology, 4th edn. Springer, Berlin
Morris JK, Rankin J, Garne E, Loane M, Greenlees R, Addor M-C et al (2016) Prevalence of microcephaly in Europe: population based study. BMJ 354:i4721–i4721
Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau V-M (2015) Potential sexual transmission of Zika virus. Emerg Infect Dis 21:359–361
Nishiura H, Kinoshita R, Mizumoto K, Yasuda Y, Nah K (2016) Transmission potential of Zika virus infection in the South Pacific. Int J Infect Dis 2016 Apr; 45:95–97
Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F et al (2014) Zika virus infection complicated by Guillain-Barre syndrome—case report, French Polynesia, December 2013. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 19(9) https://doi.org/10.2807/1560-7917
Parra-Saavedra M, Reefhuis J, Piraquive JP, Gilboa SM, Badell ML, Moore CA et al (2017) Serial head and brain imaging of 17 fetuses with confirmed Zika virus infection in Colombia, South America. Obstet Gynecol 130:207–212
Pessoa A, van der Linden V, Yeargin-Allsopp M, Carvalho MDCG, Ribeiro EM, Van Naarden BK et al (2018) Motor abnormalities and epilepsy in infants and children with evidence of congenital Zika virus infection. Pediatrics 141(Suppl 2):S167–S179
Plourde AR, Bloch EM (2016) A literature review of Zika virus. Emerg Infect Dis 22:1185–1192
Pomar L, Malinger G, Benoist G, Carles G, Ville Y, Rousset D et al (2017) Association between Zika virus and fetopathy: a prospective cohort study in French Guiana. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol 49:729–736
Puntasecca CJ, King CH, LaBeaud AD (2021) Measuring the global burden of chikungunya and Zika viruses: s systematic review. PLoS Negl Trop Dis 15(3):e0009055
Santana MB, Lamas CC, Athayde JG, Calvet G, Moreira J, De Lorenzo A (2019) Congenital Zika syndrome: is the heart part of its spectrum? Clin Microbiol Infect 25:1043–1044
Schaub B, Gueneret M, Jolivet E, Decatrelle V, Yazza S, Gueye H et al (2017) Ultrasound imaging for identification of cerebral damage in congenital Zika virus syndrome: a case series. Lancet Child Adolesc Health 1(1):45–55
Simeone RM, Shapiro-Mendoza CK, Meaney-Delman D, Petersen EE, Galang RR, Oduyebo T et al (2016) Possible Zika virus infection among pregnant women—United States and territories. MMWR Morb Mortal Wkly Rep 65(20):514–519
Sousa AQ, Cavalcante DIM, Franco LM, Arau'jo FMC, Sousa ET, Valenca-Junior JT et al (2017) Postmortem findings for 7 neonates with congenital Zika virus infection. Emerg Infect Dis 23:1164–1167
Tsui I, Moreira MEL, Rossetto JD, Vasconcelos Z, Gaw SL, Neves LM, Zin OA, Haefeli L, Silveira Filho JCB, Gomes SC Jr, Adachi K, Pone MVDS, Pone SM, Pereira JP Jr, Belfort R, Arumugaswami V, Brasil P, Nielsen-Saines K, Zin AA (2018) Eye findings in infants with suspected or confirmed antenatal Zika virus exposure. Pediatrics 142(4):e20181104
Tsui I, Neves LM, Adachi K, Gaw SL, Pereira JP, Brasil P et al (2019) Overlapping spectrum of retinochoroidal scarring in congenital Zika virus and toxoplasmosis infections. Ophthalmic Surg Lasers Imaging Retina 50(12):779–784
van der Linden V, Pessoa A, Dobyns W, Barkovich AJ, van der Junior HL, ELR F et al (2016) Description of 13 infants born during October 2015-January 2016 with congenital Zika virus

infection without microcephaly at birth—Brazil. MMWR Morb Mortal Wkly Rep 65(47): 1343–1348

van der Linden V, Petribu de NCL, Pessoa A, Faquini I, Paciorkowski AR, van der Linden H et al (2019) Association of severe hydrocephalus with congenital Zika syndrome. JAMA Neurol 76: 203–210

Ventura LO, Ventura CV, Lawrence L, van der Linden V, van der Linden A, Gois AL et al (2017) Visual impairment in children with congenital Zika syndrome. J AAPOS 21(4):295–299.e2

Vesnaver TV, Tul N, Mehrabi S, Parissone F, S˘trafela P, Mlakar J et al (2017) Zika virus associated microcephaly/microencephaly—fetal brain imaging in comparison with neuropathology. BJOG Int J Obstet Gynaecol 124:521–525

Vieira CJD, Pereira LP, Dias DA, Aguiar LB, Maia JC, Costa JIF et al (2017) Presumed Zika virus related congenital brain malformations: the spectrum of CT and MRI findings in fetuses and newborns. Arq Neuropsiquiatr 75:703–710

WHO (2016) La Directora General de la OMS resume el resultado del Comite´ de Emergencia sobre el virus de Zika [Internet]. WHO. [cited 2017 Oct 23]. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/es/

WHO (2019a) Zika virus [Internet]. World Health Organization. [cited 2019 Oct 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/zika-virus

WHO (2019b) Countries and territories with current or previous Zika virus transmission [Internet]. Available from: https://www.who.int/emergencies/diseases/zika/countries-with-zika-and-vectors-table.pdf

Wilder-Smith A, Chang CR, Leong WY (2018) Zika in travellers 1947–2017: a systematic review. J Travel Med 25(1)

Important Infectious Diseases in Latin America and the Caribbean: Plague

4

Matheus Filgueira Bezerra and Alzira Maria Paiva de Almeida

Abstract

In this chapter, we present a review of the historical, epidemiological, clinical, and diagnostic aspects of plague, a zoonosis caused by the bacterium *Yersinia pestis,* which has rodents as its main host but can also be conveyed to humans and other mammals. Within an updated panorama of the plague in Latin America, we discuss the dynamics of this disease in a twentieth-century context to address topics such as the entry of the disease in Latin American countries, prevention and control strategies and their impact on societies, the rodent hosts and flea vectors as well as other factors contributing to the establishment of natural foci on the continent, and the current epidemiological situation of the disease.

Keywords

Plague · *Yersinia pestis* · Epidemiology · Latin America · rodent hosts · flea vectors

4.1 Introduction

Plague is a flea-transmitted disease caused by the gram-negative bacterium *Yersinia pestis.* There were at least three pandemics in the past. Although treatable with antibiotics, there is a lack of long-term efficient vaccines. This disease still threatens individuals living mostly in remote areas in rural regions in several countries across Africa, Asia, and the Americas. Many parallels can be traced between the ongoing COVID-19 pandemic and the historic bubonic plague pandemics: there is an

M. F. Bezerra · A. M. P. de Almeida (✉)
National Reference Laboratory for Plague, Fiocruz PE, Recife, PE, Brazil
e-mail: matheus.bezerra@fiocruz.br; alzira.almeida@fiocruz.br

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_4

overload of healthcare services and health professionals, economic disruption, and social conflicts caused by isolation measures. Although popularly recognized from history classes as the deadly disease that caused devastation in the Middle Age, plague remains a disease of epidemic potential. Across centuries, this vector-borne infection became the emblematic symbol of an epidemic disease, as it claimed millions of lives over the centuries, shaping the way of life, science, and arts across civilizations (Bramanti et al. 2016).

The first official reports of bubonic plague in Latin America took place in 1899 in port zones from Paraguay, Brazil, and Argentina. In the following years, plague was reported in Uruguay (1901), Mexico (1902), Chile (1903), Peru (1903), Panama (1905), Ecuador (1908), Venezuela (1908), Cuba (1912), Puerto Rico (1912), Bolivia (1921), and El Salvador (1955). Plague was introduced in Latin America by the arrival of ships with contaminated crew and rats, causing outbreaks in port cities. In many of these countries, the disease escaped the seaport zones and spread out by inland transportation of goods. Reaching rural sites, plague flipped to wild rodents from local fauna, establishing several natural foci where the ecological conditions were congenial for its persistence (Moll and O'Leary 1940; Pollitzer 1954; Pollitzer and Meyer 1965).

Since its first reports, the occurrence of human plague cases was recorded almost annually in those countries, and after different periods of persistence, the last cases were reported in Cuba (1915), Puerto Rico (1921), Mexico (1923), Chile (1931), Uruguay (1932), Argentina (1958), and Venezuela (1963). Although Colombia and the Guianas share some climatic and geographic aspects with other plague-affected neighbors, there are no reports of the establishment of plague foci in these regions (Faccini-Martínez Sotomayor 2013). Currently, four countries are still considered endemic for plague in Latin America: Bolivia, Brazil, Ecuador, and Peru.

The broad access to the use of antibiotics in post-exposure prophylaxis and efficient vector and host control measures may have contributed to reduction in human cases. However, the mechanisms that have driven the disease to its current state of quiescence in these countries are not yet fully understood (Faccini-Martínez Sotomayor 2013; Schneider et al. 2014; Bertherat 2019). Plague has a complex cycle with natural foci that remain active or may reemerge after several decades. Understanding plague transmission dynamics across different ecosystems and social contexts is crucial to establish effective surveillance strategies, capable of recognizing eventual issues that may precede spillovers to human populations (Zeppelini et al. 2016).

In this chapter, we present a review of the epidemiological, clinical, and diagnostic aspects of this zoonosis and an updated panorama of plague and where it remains in Latin America.

4.2 Plague: One of the Oldest and Most Feared Diseases of Mankind

Genomic sequences of *Y. pestis* found in 5000 years-old tooth pulps in remains from Eurasian populations point toward an endemic presence of plague at that time. In literature, records from the *First Book of Samuel* describe the rodent-related "Plague from Ashdod" (today's Israel) that afflicted the Philistines, dating back to 1320 B.C. (Barbieri et al. 2021; Bramanti et al. 2016).

During the Christian era, at least three major plague pandemics are well characterized: The Justinian Plague (542–602 A.D.), which started in Egypt and spread widely through Asia, Africa, and Europe with an estimated death toll of 100 million people. It is believed that the pandemic had a significant contribution to the failure of Justinian I in the reconquest and reunification of the western Roman Empire. The second plague pandemic started in Asia and reached Europe and North Africa, enduring from the XIV until the XVI century. It claimed the lives of one-third of the European population in the period from 1346 to 1353, which nowadays is commonly known as the Black Death. The third pandemic started in the Chinese province of Yunnan after a fast populational expansion due to extraction of cooper and minerals and quickly spread with the opening of trade routes. After reaching Hong Kong in 1894, the disease spread globally through steamships, reaching lands without prior contact with the disease (Pollitzer 1954). It was during the third pandemic, with the availability of new scientific equipment that plague could be better studied. Observations from scientists such as Alexander Yersin, Shibasaburo Kitasato, Paul-Louis Simond, and Masanori Ogata brought fundamental information about plague's pathogen, hosts, and vectors (Butler 2014). With these data coming into light, health authorities had for the first time a fair opportunity to fight against the spread of the disease.

4.2.1 A Forgotten Zoonosis with a Potential for Public Health Emergency of International Concern (PHEIC)

Despite its declining incidence worldwide, plague remains a disease of global interest due to its epidemic potential, high case fatality rate when untreated, its ability to rekindle after decades of epidemiological silence, and its potential use as a biological weapon. This ability to resurge could be evidenced in multiple situations: when the plague reappeared in Algeria in 2003 after over 50 years of quiescence (Bertherat et al. 2007); in the Peruvian coastal district of Mórrope in 1994, after 70 years quiescence (Rodriguez-Morales et al. 2019); in Ecuador, 12 deaths from related individuals exposed to sick guinea pigs (cuyes) in 1998, after 12 years of quiescence (Gabastou et al., 2000); and in Brazil, there was an outbreak in the state of Paraiba in 1986, after 8 years of quiescence in the area (Tavares et al. 2012).

As per the International Health Regulations (IHR) (2008), the pneumonic form of plague is one of the notifiable diseases listed as a potential Public Health Emergency of International Concern (PHEIC). However, political interest (and related funds) is

usually more focused on biohazard reduction than development and support for control programs in most endemic countries. According to the IHR, an event needs to fulfill at least two of the four criteria to be a potential PHEIC: it would be a serious public health problem; unusual or unexpected; significant risk of international spread; and significant risk to trade and tourism. Pneumonic plague is one of the few diseases on the IHR notification list. Indeed, the disease has been classified among the zoonosis of top priority interest from a One Health perspective (http://www.onehealthinitiative.com).

Cumulative field observations in plague foci combined with the critical review of data issuing from paleomicrobiological, anthropological, and historical studies continue to shed new light on questions related to the reservoirs, sources, transmission, and vectors of *Y. pestis* and to provide new avenues for addressing these questions (Barbieri et al. 2021). It had been shown that plague spillovers to human populations require the combination of some factors: the wild rodent population to be above a certain threshold continuously for some years, a high flea/host ratio, and proper climate conditions.

4.2.2 *Yersinia pestis*, the Plague Bacillus

Out of the 25 species described in the *Yersinia* genus to date, only three are known to cause disease in human and other mammals: *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica*. While *Y. pestis* is the causative agent of plague, the other two species cause gastrointestinal infections. Evolutionary genomic studies estimate that *Y. pestis* diverged from *Y. pseudotuberculosis* up to 28,000 years ago. Since its first description, the plague microbial received the names *Bacterium pestis*, *Bacillus pestis*, *Pasteurella pestis*, and finally, *Yersinia pestis*, in reference to the French-Swiss scientist Alexander Yersin who isolated the bacterium for the first time in Hong Kong (Butler 2014; Demeure et al. 2019) parallel to Kitasato.

Yersinia pestis is a nonmotile gram-negative bacillus that belongs to the Enterobacteriaceae family, categorized in the Biohazard Class 3 and Bioterrorism Agents Group A (Demeure et al. 2019; Inglesby et al. 2000). It is a facultative anaerobic microorganism that can be cultured on basic agar media. The bacterium is sensitive to UV radiation and chloride-based disinfectants, and despite its short half-life in dry metallic surfaces, it can remain viable for years in biological environments such as sputum, flea feces, bone marrow, and other protected tissues. Experimental and field data suggest that *Y. pestis* can survive in rodent burrows, digestive tract of parasites, and even free-life soil protozoa (Gage 2012; Perry and Fetherston 1997).

When compared to other pathogenic bacteria, *Y. pestis* strains are considerably conserved. The recent technical advances and growing accessibility to next-generation sequencing methods, combined with extraction protocols able to retrieve *Y. pestis* DNA from the teeth of ancient remains, allowed a better understanding of plague evolution. Phylogenetic analysis of *Y. pestis* genomes revealed five distinct branches, that were related to population declines dated back to the Neolithic Age or later pandemics described by history. The analysis of genomic sequence from

ancient samples also suggested that, after diverging from *Y. pseudotuberculosis*, the early strains of *Y. pestis* were unable to produce biofilm and had their dispersion limited to human-to-human transmission, predominating the pneumonic or septicemic clinical forms rather than bubonic (Barbieri et al. 2021; Demeure et al. 2019; Vogler et al. 2016).

Y. pestis virulence can be attributed to several genes found across three plasmids (pFra, pPst, and pYV) and its 4.650 kilobase chromosome. Among these virulence factors, the Yersiniabactin is probably one of the most relevant, as in its absence, *Y. pestis* infection causes only mild to moderate symptoms. This molecule presents a high affinity for Fe^{3+}, allowing its uptake by the bacterium in the low-iron environment, commonly observed in hosts due to the increased expression of ferritin, a positive acute-phase protein (Demeure et al. 2019).

Another well-described virulence factor are the *Yersinia* effector proteins (Yops), which are encoded by the pYV plasmid and are able to subvert host cell pathways, triggering cell death and inhibiting inflammatory cytokines. These factors are injected in host cells by the type three secretion system (T3SS), a needle-like structure containing the LcrV protein on the tip, able to trespass the host cell membrane. The pFra plasmid, exclusively found in *Y. pestis*, encodes the capsular fraction 1 protein (F1), which intermediates escape from phagocytosis and phospholipase D (toxin murine), which increases survival in the digestive tract of the fleas. The pPst plasmid, also specific of *Y. pestis*, encodes the plasminogen activator (Pla), which facilitates the spread of the bacteria from the flea bite site (Demeure et al. 2019; Perry and Fetherston 1997).

4.2.3 Transmission of Plague

Humans can be exposed to flea bites outdoors or at the household environment, when people, domestic animals (especially cats), or peridomestic rodents bring infected fleas inside the house. Although the bubonic form transmitted by the flea is the most common situation, other transmission routes that have been reported are discussed below:

- Lung infection by *Y. pestis* may be transmitted human to human or animal to human through air droplets, resulting in a much aggressive disease if compared to the bubonic form.
- Gastrointestinal plague can result from the ingestion of undercooked contaminated meat and perhaps from the manual transfer of infected fluids to the mouth during the handling of infected animal tissues.
- Plague can also be transmitted during the skinning and handling of carcasses of wild animals such as rabbits and hares, prairie dogs, wildcats, and coyotes.
- Some Andean communities' custom to capture and grind hair lice with the teeth, which when contaminated induces an oropharyngeal syndrome with formation of peritonsillar abscess and pneumonia.

Of note, direct inoculation of mammal-adapted organisms is associated with primary septicemia and high case fatality rates. These severe forms can be at least partially explained by the fact that many of the *Y. pestis* virulence factors expressed at 37 degrees are already present at the moment of the contamination.

4.2.4 Animal Hosts of Plague

Plague is essentially a zoonotic flea-transmitted disease, able to infect a broad range of mammal species that can be considered main or incidental hosts and contribute to the dynamics between wildlife and human cases. Of the 351 species reported as hosts for plague, 279 belong to the order Rodentia (279 species). Others are Carnivora (31 species), Lagomorpha (14 species), Eulipotyphla (13 species), Artiodactyla (seven species), Primates (two species), Didelphimorphia (two species), Scandentia (one species), Hyracoidea (one species), and Afrosoricida (one species) (Mahmoudi et al. 2020).

In South America, at least 50 wild rodent species have been identified as plague hosts, in addition to one lagomorph and two marsupials. Upon a taxonomic revision and update, many species involved with plague in Brazil, Peru, Ecuador, and Bolivia have undergone taxonomic changes (Bonvicino et al. 2015). Table 4.1 shows the rodent species involved with plague in the four endemic countries in Latin America.

Multiple studies performed worldwide reveal an exuberant diversity of hosts and vector communities that interplay with climate and geographic features, resulting in unique and intricate panorama for each plague focus. Therefore, it is of most importance to understand the dynamics of plague at a regional level, in order to design adequate surveillance and control measures. Although more commonly perceived as a human hazard condition, plague is also considered an anthropogenic invader and has the potential to cause significant impact on local ecosystems (Zeppelini et al. 2016).

Plague surveillance must take into consideration that domestic animals also have an important role in transmission dynamics. The domestic carnivores may transport infected carcasses and fleas to the home environment. While infected cats usually progress with severe symptoms, dogs tend to show mild or no symptoms. Raising guinea pigs (*Cavia porcellus*, popularly known as *cuyes*) inside homes is a common use of some Andean communities that presents an additional risk factor for outbreaks. These animals become infected and multiply the infection by sharing their fleas with humans.

4.2.5 Insect Vectors of *Yersinia pestis*

Although rodents may acquire the infection by direct contact with contaminated soil, vector transmission plays a major role in the dissemination of plague in animal populations. Mainly the fleas (*Siphonaptera*; approximately 80 species found infected) but also other hematophagous insects, such as human lice (*Pediculus*

Table 4.1 First and the last occurrences of human cases, the current plague areas, the rodent hosts, and flea vectors in the four endemic countries in Latin America

Country	First occurrence		Last occurrence	Current plague areas, hosts, and vectors		
	Year	Locality		Plague areas (Department/State)	Rodent hosts	Flea vectors
Bolivia	1903	La Paz	2018	La Paz, Chuquisaca, Santa Cruz, Tarija	*Rattus rattus, Calomys boliviae (Hesperomys fecundus); Calomys venustus (Hesperomys v. venustus); Graomys griseoflavus (G. cachinus, G. chacoensis, G. g. griseoflavus, G. medius) Oligoryzomys flavescens (Oryzomys flavescens); Oligoryzomys longicaudatus (Oryzomys longicaudatus); Oxymycterus paramensis; Tapecomys wolffsohni (Phyllotis wolffsohni); Rhipidomys leucodactylus (Rhipidomys equatoris); Dasyprocta azarae (Dasyprocta variegata boliviae); Galea littoralis littoralis (G.m. leucoblephara); and the Lagomorpha Sylvilagus brasiliensis (S. b. gibsoni)*	*Xenopsylla cheopis, Pulex irritans, Tiamastus cavicola, Polygenis spp., Ctenocephalides spp.,*
Brazil	1899	Santos/SP	2005	Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Bahia, Minas Gerais, Rio de Janeiro	*Rattus rattus, Akodon cursor, Calomys expulsus, Cerradomys langguthi, Holochilus sciureus, Necromys lasiurus, Nectomys squamipes, Oligoryzomys stramineus, Oxymycterus dasytrichus, Galea spixii, Thrichomys laurentius*	*Xenopsylla cheopis, Polygenis b. jordani, P. tripus, Ctenocephalides felis, Pulex irritans*

(continued)

Table 4.1 (continued)

Country	First occurrence		Last occurrence	Current plague areas, hosts, and vectors		
	Year	Locality		Plague areas (Department/State)	Rodent hosts	Flea vectors
Ecuador	1908	Guayaquil, Santa Rosa, Manabí, El Oro	2008	Chimborazo, Tungurahua, Cotopaxi, Loja	*Rattus norvegicus, Rattus rattus, Mus Musculus, Cavia porcellus (cuyes), Aegialomys xanthaeolus (Oryzomys xanthaeolus), Akodon dolores, Akodon mollis, Oligoryzomys flavescens (Oryzomys flavescens), Oligoryzomys longicaudatus (Oryzomys longicaudatus), Phyllotis andium (Phyllotis fruticicolus), Sciurus stramineus, Sigmodon peruanus (Sigmodon peruanus, Sigmodon puna)*, and *Simosciurus nebouxii*	*Pulex irritans, Xenopsylla cheopis*, *Tiamastus cavicola, Polygenis litargus, P. bohlsi*, *P. brachimus, Nopsosilla londinenses*
Peru	1902	Callao	2018	Mórrope, La Libertad, Piura, Ancash, Tumbes, Lambayeque, Cajamarca, Amazonas	*Rattus rattus, Rattus norvegicus, Aegialomys xanthaeolus (Oryzomys xanthaeolus), Akodon dolores, Akodon orophilus (Akodon mollis orophilu), Hylaeamys perenensis, Oecomys spp., Rhipidomys leucodactylus (Rhipidomys equatoris), Simosciurus nebouxii (Sciureus stramineus nebouxii), Oryzomys andinus*, *Cavia tschudii,* the domestic *Cavia porcellus (cuyes),* the tree squirrel *Sciurus stramineus* and the cottontail rabbits (Lagomorpha) *Sylvilagus andinus* and *S. ecaudatus.*	*Xenopsylla cheopis, Polygenis litargus*, *Hectopsylla spp.*, *Tiamastus cavicola*

humanus), have been reported to transmit plague. Table 4.1 shows the flea species involved with plague in the four endemic countries in Latin America. Two major routes of plague transmission by fleas have been described so far: the mass transmission (early phase) and the biofilm-dependent transmission (Hinnebusch et al. 2017).

The early phase transmission (EPT) was described shortly after the discovery of the flea as a vector for plague. After feeding on an infected animal's blood, the flea mouthparts are contaminated with a small amount of plague bacilli; within a short window of time, they can infect the next animal bitten by the flea. Further experiments demonstrated that this mechanism has a low efficiency, due to the small number of individual bacteria transferred to the host, requiring multiple fleas to establish an infection. On the other hand, the biofilm-dependent transmission is based on the ability of *Y. pestis* to produce a bacterial biofilm that blocks the passage of food in the proventricular valve of the flea's midgut. Within a few days, the infected flea suffers from starvation and tries desperately to feed, biting multiple animals. During the bite, the host blood reaches the flea's midgut, gets contaminated with bacilli from the biofilm, and due to the blockage, is returned to the biting point in the host's skin. Due to the higher number of bacilli transferred to the host and the increased number of exposed hosts, this vectorial mechanism is significantly more efficient than EPT (Hinnebusch et al. 2017).

On the top of its role as vector, the flea can also act as a plague reservoir, as it can survive for months inside rodent burrows. The microclimate inside the burrows also prolonged *Y. pestis* viability in flea feces. *Xenopsylla cheopis*, the so-called rat flea, has cosmopolitan geographic distribution, is found in many plague foci and is considered the main plague vector. *Pulex irritans*, known as the "human flea," is widely distributed over the globe and is suspected to have contributed to the Black Death during the Medieval Age, promoting human-to-human flea transmission in the absence of commensal rats and the *X. cheopis* (Gage 2012).

4.2.6 Clinical Features

The spectrum of clinical manifestations in plague patients ranges from extremely severe clinical forms to asymptomatic cases and is influenced by the overall health status of the patient, the virulence, inoculum load, and most importantly, the site of entry of the infection. The main clinical forms of the disease are bubonic plague, pneumonic plague, and septicemic plague. Other less frequent forms may occur, such as pharyngeal, gastrointestinal, meningeal, primary cutaneous, and endophthalmic plague. Nonspecific signs and symptoms include chills, fever, myalgias, arthralgias, and weakness (Bin-Saeed et al. 2005; Butler 2014; Edmunds et al. 2008; Perry and Fetherston 1997).

The bubonic form is characterized by swelling of cervical, axillary, or inguinal lymph nodes, depending on the site of the flea bite (Fig. 4.1). Septicemic plague affects the bloodstream and can be contracted by handling infected animals. Hematogenous dissemination of the bacteria to other organs and tissues may cause

Fig. 4.1 (**a**) Plague patient with inguinal bubo, and B–F risk factors for plague. (**b**) domestic Cavia porcellus (cuyes) raised as food source; (**c**) rural settings in remote areas with food sources and potential nesting for rodents; (**d**) contamination of domestic animals in close contact with wild fauna; (**e**) vulnerable indigenous communities; (**f**) improper storage of crops in patio area

intravascular disseminated coagulation and endotoxic shock, producing dark discoloration in the extremities. Pneumonic plague affects the lungs and can spread from person to person, through contaminated air droplets. Pneumonic plague can also evolve from a bubonic or septicemic plague left untreated. In this case, symptoms include breath shortness, chest pain, and coughing blood or watery mucous. Shock and respiratory failure can become fatal, requiring rapid diagnosis, and treatment with antibiotics is important for a full recovery. The incubation period is from 3 to 6 days for the bubonic form, and 1–3 days for the pneumonic form (Butler 2014; Perry and Fetherston 1997).

4.2.7 Laboratorial Diagnosis of Plague

In case of suspected diagnosis of plague, a range of laboratorial tests can provide useful information. For an adequate results interpretation, it is important to take into consideration the time from initial symptoms and the clinical form of the disease (Fig. 4.2).

4.2.7.1 Serology

Serological diagnosis of plague is divided into indirect and direct tests. Direct tests rely on the detection of *Y. pestis*-specific antigens, more commonly the F1 capsular antigen by ELISA or rapid diagnostic test (RDT). These tests are ideal for early days of symptoms and can be applied to distinct types of samples, such as sputum, serum,

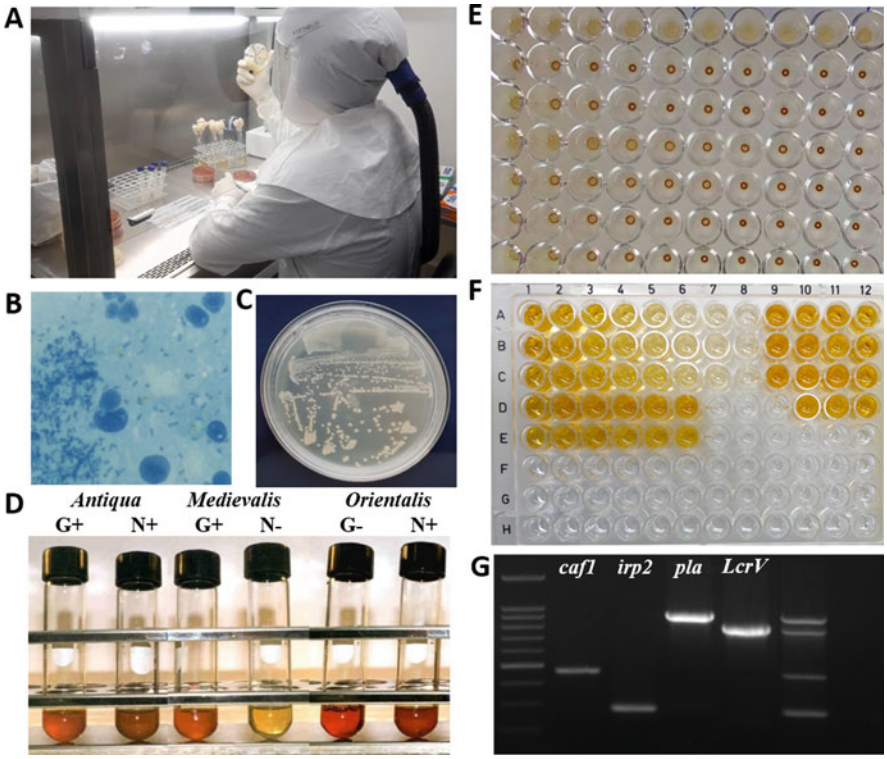


Fig. 4.2 (**a**) Handling *Yersinia pestis* in BSL3; (**b**) Mouse spleen smear stained by Loeffler's methylene blue method; (**c**) *Yersinia pestis* colonies in BAB medium and phage lysis; (**d**) Biochemical tests of glycerol fermentation and nitrate reduction (South America strains are Biovar *orientalis*); (**e**) Hemagglutination test; (**f**) ELISA test; (**g**) M-PCR (*caf1, irp2, pla, lcrV*)

urine, and bubo aspirates. Indirect methods rely on the detection of anti-F1 antibodies in serum by using assays such as hemagglutination, ELISA-IgG (specie-specific), or ELISA Protein A (multi-species, Fig. 4.2). Anti-F1 IgG antibodies are detectable from 8 days after disease onset, reaching a titer plateau after 2 weeks and lasting for years. These features implicate that samples collected during the first week may cause false-negative results, but allow proper diagnosis in late days of onset and are the best option to detect previously exposed hosts in epidemiologic surveillance of plague foci (Demeure et al. 2019; Valles et al. 2020).

4.2.7.2 Bacteriology

Laboratorial isolation of *Y. pestis* in culture is considered the gold-standard technique for plague diagnosis. *Y. pestis* can be cultivated in non-selective medium, such as blood agar base, Luria-Bertani, and brain heart infusion, or gram-negative selective medias, such as agar MacConkey or the antibiotic-based agar CIN (novobiocin-irgasan-cefsulodin). On optimal growth temperature (28 °C), *Y. pestis* can take up to

8 days to form colonies and in liquid culture shows a flocculate growth without turbid media. The bacteriophage lysis test is used for confirmation of suspected colonies. Further biochemical tests such as glycerol fermentation and nitrate reduction can be used to further characterize the Biovar. Additionally, bipolar plague bacilli can be visualized in microscopy of the biological samples using Loeffler's methylene blue staining method.

Although very important, bacteriology presents some limitations, as the procedures must be performed in a level-3 biosafety facility (BSL-3), the slow bacterial growth may take up to 8 days, and results are released when patients are already under antibiotic treatment (Fig. 4.2). Results can also be confirmed by analysis of peptide profile of the bacterium extracts in MALDI-TOF. Due to reports of resistant strains of *Y. pestis*, it is recommended to perform antibiotic sensitivity tests in the isolates, including streptomycin, gentamicin, chloramphenicol, tetracycline, trimethoprim, and ciprofloxacin (Demeure et al. 2019; Perry and Fetherston 1997; Valles et al. 2020).

Of note, there are reports of false-positive results in automatic microbiology equipment as the adopted setup of biochemical tests may misinterpret results from *Shigella* spp., *Acinetobacter* spp., *Pseudomonas* spp., and some environmental non-fermenting bacilli isolates. Therefore, it is highly recommended that *Y. pestis* diagnosis by automated equipment should be confirmed with other tests or sample should be sent to a reference laboratory before reporting results to patients and local healthcare authorities (Almeida et al. 2020).

4.2.7.3 Molecular Biology

Several protocols for molecular diagnosis of plague have been described, including nested-PCR, multiplex-PCR, and LAMP, among others (Fig. 4.2). Usually, the reactions are based on the primers or probes targeting the *caf1* and *pla* genes. Other genes including *inv, irp2*, and *LcrV* may also be evaluated for identification of virulence factors, but these genes are shared with other species of bacteria and, therefore, have limited diagnostic value (Demeure et al. 2019; Valles et al. 2020).

4.2.8 Treatment

Plague is treatable with antibiotics and due to the severity and rapid progression of the disease, an early therapeutic intervention is mandatory for an effective response. Although samples for bacterial culture are usually collected before treatment, antibiotic therapy must not wait for laboratorial results and start as soon as possible. Healthcare team should pay attention to biosafety measures, especially in case of lung symptoms, when the patient must stay in strict isolation (Butler 2014; Inglesby et al. 2000).

Some antimicrobials from the beta-lactam and macrolide groups may present a misleading sensitivity in antibiogram while having poor results in clinical practice and should be avoided. Aminoglycosides, such as streptomycin and gentamicin, are the frontline options, but doxycycline, chloramphenicol, fluoroquinolones, and

trimethoprim sulfamethoxazole also show positive results. As streptomycin production has stopped in many countries, a combination of gentamicin and doxycycline had been shown to be similarly effective. Treatment should take between 10 and 14 days, and clinical improvements can be observed from the second or third day of therapy (Butler 2014).

4.2.9 Plague as an Occupational Disease

Farmers, hikers, campers, hunters, and individuals occupationally exposed to wild rodents in endemic areas such as anthropologists, archeologists, geologists, and spelunkers are at greater risk of exposure. Researchers and students of biological areas, veterinarians, and zoo employees are exposed to the risk of becoming infected in the exercise of their activities, regardless of whether they are carried out in focal or free areas. Health professionals, such as doctors, nurses, laboratory staff, community, and health agents, are also exposed.

In 2009, an experienced researcher died from septicemia caused by an attenuated *Y. pestis* strain that he manipulated in a laboratory project. Although this strain is widely used because it does not cause disease in humans, the researcher had hemochromatosis and the excess of iron in his organism may have contributed to a more aggressive infection by this strain (MMWR 2011). Cases have also been reported in point-of-care assistance professionals. In 2010, a physician and a medical student gave assistance to a patient suspected of bacterial pneumonia or H1N1 without using protective equipment. Unfortunately, both professionals contracted the disease and the 21-year old student died (Donaires et al. 2010). In 2007, a biologist working at the Grand Canyon National Park (USA) died from pneumonic plague after examining the carcass of a deceased mountain lion during his research in the park (Wong et al. 2009).

4.2.10 Prevention

4.2.10.1 Measures Taken During the Twentieth Century Epidemics in South America

Due to its iconic potential for devastation, the arrival of plague in Latin America in the early twentieth century forced the major ports in South America to adopt preventive measures. These included quarantines, fumigating commercial ships and cargos with sulfur and cyanide-based toxic gas with machines such as Clayton and Aparato Marot upon arrival at the port, and setting rat traps in the docks surroundings (Engelmann 2018).

Once the disease entered the cities, the so far overlooked public health agencies, quarantine hospitals, clinical laboratories, and research institutes were promptly established. Preventive measures focused on decontaminating sewers and households, combating the accumulation of trash in the streets, and organizing highly dense human habitations. Several affected cities across the continent

underwent drastic urbanistic restructuring, encompassing housing conditions, street paving, and sewage systems. In the Ecuadorian city of Guayaquil, wooden houses and even historic buildings were destroyed and rebuilt with other materials such as cement and zinc foil. The new houses had their floor uplifted from the ground, the windows were enlarged for extra sunlight exposure, and hollow walls were prohibited (Palacios and Estévez 2006; Padilla 2007).

During the epidemics in Rio de Janeiro, the Brazilian capital at the time, the sanitary doctor Oswaldo Cruz established a policy of rewarding the population for the capture of rats. Documents reveals that as much as 1.6 million rats were captured and incinerated between 1903 and 1907 in the city. Although this measure could successfully reduce the spread of the disease, some citizens were found to be intentionally farming rats over profit, entailing its suspension (Nascimento and Silva 2013).

4.2.10.2 Prevention Nowadays

There is currently no commercially available vaccine or preventive medication against plague. Educative programs should be constantly carried out in the endemic regions and publicity regarding preventive measures should take into consideration the cultural and ethnic characteristics of the communities. Messages considered offensive and disrespectful to local culture and beliefs may have undesirable effects, including low compliance with the proposed measures.

General recommendations include:

- Avoid rodent populations nearby the household area by removing any food sources or potential nesting materials.
- Avoid direct contact with rodents or wild animals that prey on rodents. Animal remains can also maintain plague viable for days.
- Treat domestic animals for fleas.
- Houses constructed with thatched walls and roofs or adobe walls are highly vulnerable to rodent activities (seen in plague-endemic areas of Andean countries). Improper storage of crops in patio areas or in the roof provides easy food access for rodents, facilitating transmission of plague (Fig. 4.1).
- Build deposits for grain and food production in rural houses.
- In case of human pneumonic plague, individuals directly exposed must undergo post-exposure chemoprophylaxis with antibiotics and the use of masks must be implemented in the community.

4.3 Introduction of Plague Into Latin America and the Caribbean

The plague entered Latin America along the Atlantic Coast in April 1899 in Montevideo (Uruguay) conveyed by the Dutch sailboat Zeier, from Rotterdam, carrying a cargo of rice from India. During the journey to South America, when the sealed packs of sugar were first opened in Las Palmas, in the Canary Islands,

dead rats were found inside the containers. In the following days, two men from the crew fell sick and one died. In Montevideo, the cargo was transferred to the Argentine steamboat Centauro, which departed on April 19 crossing the port of Buenos Aires, La Plata, and the Paraguay River (death of rats was registered on board in this trip) and arrived in Asunción (Paraguay) on April 26. Four sailors got sick and just one recovered. The deaths were initially attributed to other conditions, such as typhoid fever, and plague diagnosis was not considered due to the inland position of the city. However, 37 soldiers got sick in August of the same year and having their installations burned could not stop the disease from spreading to the rest of Asuncion and smaller cities along railway lines (Moll and O'Leary 1940; Pollitzer 1954; Pollitzer and Meyer 1965).

Interestingly, large amounts of the contaminated rice cargo that introduced plague in Paraguay also disembarked in Montevideo during the same trip, without reports of plague cases. This was at least partially attributed to the poorer sanitary conditions in the port from Asuncion and the lack of sulfuric gas-based disinfection machines known as Aparato Marot, used in commercial ships at that time (Engelmann 2018). From 1899 to 1913, the plague reached the Argentinian cities of Rosario (1899), Buenos Aires (1899), Tucumán (1900), Córdoba (1907), Bahía Blanca (1913), and others. Due to the quick rise of cases in Rosario and Buenos Aires, a medical committee directed by Carlos Malbrán instituted control measures, such as reporting suspicious cases, isolation of patients and contact tracing, and disinfection of houses and cargos (Moll and O'Leary 1940; Pollitzer and Meyer 1965).

In October 1899, the disease also reached Brazil conveyed by ships with rice cargoes coming from Rangoon (Burma, Southeast Asia) via Porto (Portugal), infecting first the port city of Santos and then Sao Paulo and spread in the coastal cities reaching the ports from the south to the north of the country by 1912. Rio de Janeiro, the capital of Brazil at that time, registered a plague epidemic with over 960 officially recorded deaths until 1907 (Moll and O'Leary 1940; Pollitzer and Meyer 1965). While the infection has disappeared from Sao Paulo, several natural foci have become established in the states of Pernambuco, Paraíba, Piauí, Ceará, Rio Grande do Norte, Alagoas, Bahia, and northern Minas Gerais which constitute the "focus of the Northeast," and also in the Serra dos Órgãos (Rio de Janeiro) which remains to date (Baltazard 2004; Giles et al. 2011; Tavares et al. 2012).

In the Pacific coast of South America, the plague entered through the port of Callao, Lima (Peru), in December 1902 with the arrival of a ship loaded with rice from Bangkok (Thailand), to spread to other coastal cities and the countryside. In Ecuador, the disease was introduced through Guayaquil and Santa Rosa by the ships from Paita (Piura, Peru) in February 1908. In Chile, the disease appeared for the first time in the port of Iquique and later, in Valparaíso, in 1903, after the arrival of ships from Callao. Due to the isolation and distance from the coast, Bolivia did not present official cases of plague until 1921; however, there are unconfirmed reports of plague cases in La Paz in September 1903. Historic records suggest that plague may have been introduced in Venezuela in 1908 by a ship from Guayaquil that disembarked goods in La Guaira (Vargas State, Venezuela) (Moll and O'Leary 1940; Pollitzer and Meyer 1965). Figure 4.3 shows the years with notification of human plague cases per country in Latin America and the Caribbean from 1899 to 2020.

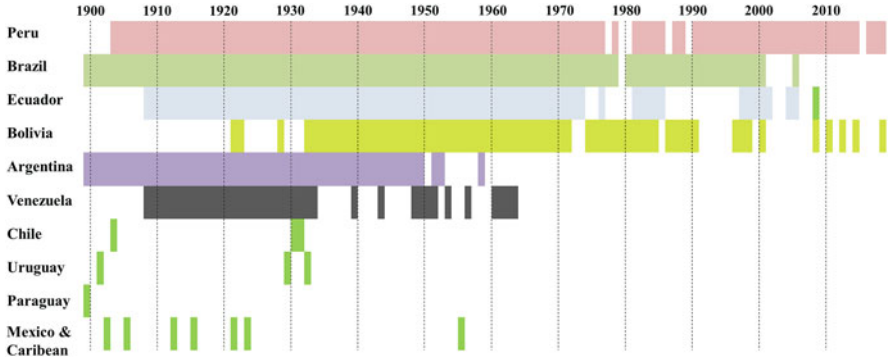


Fig. 4.3 Occurrence of plague cases in Latin America and the Caribbean from 1899 to 2020

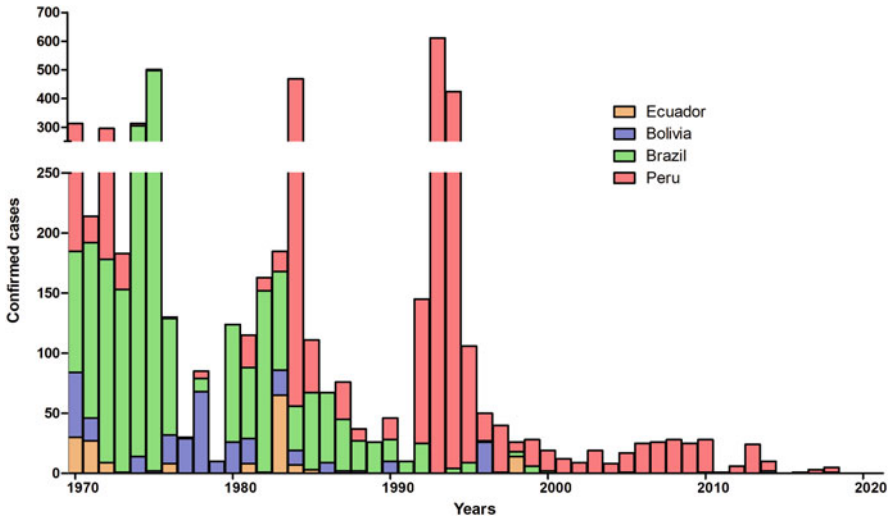


Fig. 4.4 Plague cases during the last 50 years: 1970–2020 in the four endemic countries

4.3.1 Establishment of Plague Foci in South America.

Currently, four countries are considered endemic for plague in Latin America (Bolivia, Brazil, Ecuador, and Peru), as the disease seems highly established in these countries according to the regular occurrence of cases since its introduction. In the last 50 years (1970–2020), these four countries notified to the WHO 5286 cases and 264 deaths (5% deaths). Most of the cases (2487; 47%) and deaths (163; 61,7%) were from Peru. Brazil notified 2187 cases (41.4%) and 33 deaths (12.5%). Bolivia reported 440 (8.3%) cases and 58 deaths (22%); Ecuador reported 172 (3.3%) cases and 10 deaths (3.8%). Fig. 4.4 shows the annual occurrence of plague cases in these

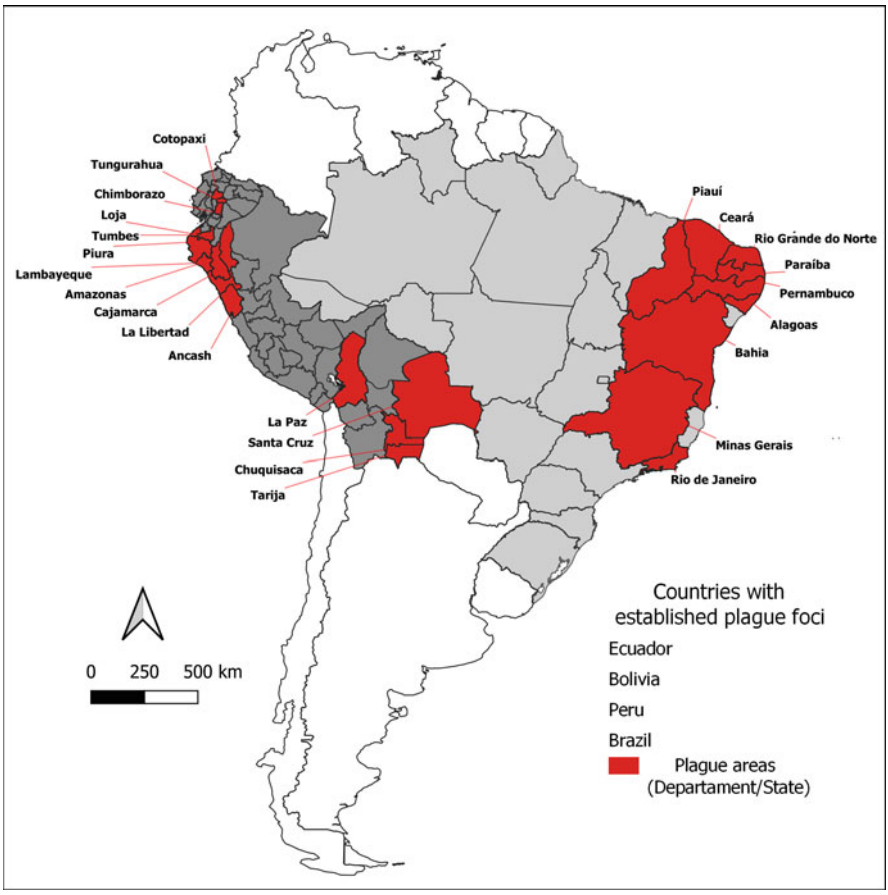


Fig. 4.5 Map of South America showing the plague areas (Department/State) in the four countries considered endemic

four countries in the last 50 years, and Fig. 4.5 shows a map of the countries considered endemic for plague in Latin America at the department/state/province level.

The countries that were affected only during the first years after the arrival of plague (Cuba, Chile, Mexico, Panama, Paraguay, Puerto Rico, and Uruguay) are considered to be unlikely to have a reemergence. In these countries, cases were sparse events, registered in regions close to introduction sites and now silent for over 70 years. On the other hand, Argentina and Venezuela are considered to have potential of reemergence, as they had multiple outbreaks over time and last case was notified less than 40 years ago (Rodriguez-Morales et al. 2019). Therefore, similarly to the four endemic countries, it is important to maintain epidemiologic surveillance of the historical plague foci in Argentina and Venezuela.

In a recent study, the investigation of the spatiotemporal dispersion of human cases in a plague focus from Northeast Brazil revealed a pattern that may be representative of several plague foci in Latin America: after a brief ports phase (approximately 1899–1910), the disease traveled inland to smaller cities, causing urban-delimited outbreaks. Next, during the period of epidemiological silence, the bacterium was transmitted from the urban commensal rats to species from the local fauna. The infection of wild rodents occasioned the establishment of new natural foci in the wild-sylvatic areas, followed by resurgence of plague in rural zones after years of epidemiological silence (Fernandes et al. 2021).

4.3.2 Plague on the Atlantic Coast of South America

4.3.2.1 Brazil

During the 50 years period of 1970–2020, there were 2187 cases with 33 deaths (case fatality rate 1.5%) in Brazil. During the 1970s, Brazil was the country that has had the highest occurrence of human plague infection in the Americas. Cases occurred every year, with a peak of 496 cases reported to the WHO in 1975. The last outbreaks of plague in Brazil were recorded in the states of Bahia (1975), Ceará and Pernambuco (1974/1975), and Paraíba (1986/1987). Ever since, all foci have tended to quiescence, as only three cases were laboratory confirmed in the 1990s and one in 2005, in the state of Ceará. Isolated suspected cases have still been recorded, but without laboratory confirmation. Furthermore, the *Y. pestis* bacterium was no more identified in rodents nor flea by the routine surveillance activities since 1987, and serologic testing for antibodies against the *Y. pestis* F1 antigen in sentinel animals is declining over time.

Practically since the arrival of the plague in Brazil, a surveillance and control program adapted to the epidemiological situation, ecological and demographic characteristics, and scientific and technological conditions has been implemented. For decades, surveillance consisted of searching *Y. pestis* in rodents and fleas or detecting specific anti-plague (anti-F1) antibodies by hemagglutination (HA) among sentinel animals (dogs and cats) in the focal areas. An analysis of the results revealed higher sensitivity of serological testing among domestic dogs. Therefore, surveillance has been restricted to the analysis of serological samples from free-roaming dogs (Fig. 4.1), and since 2007, rodent and flea monitoring has been discontinued (Tavares et al. 2012).

Several studies on the various elements involved in the epidemiological cycle of plague have been carried out in Brazil, identifying the potential rodent reservoirs of the infection, their habitats and behaviors, and their susceptibility to the plague, besides the flea species, vector ability, and their role in plague transmission (Fernandes et al. 2020; Tavares et al. 2012). The rodent species involved in plague in Brazil are the *Necromys lasiurus, Cerradomys langguthi, Calomys expulsus, Akodon cursor, Holochilus sciureus, Nectomys squamipes, Oligoryzomys stramineus, Oxymycterus dasytrichus, Galea spixii, Thrichomys laurentius*, and *Rattus rattus.* The species *Necromys lasiurus* was recognized as the epizootic

(amplifier) host, spreading the infection to other species and further spillover to the human populations. Therefore, the growth of *Necromys* populations and the rise of its flea index (the ratio between fleas - the vector and rodents - the host) were acknowledged as a warning signal of the plague threat. The species *Galea spixii* and *Rattus rattus* are relatively resistant and are supposed to participate in the long-term maintenance of the infection in the focal areas (Fernandes et al. 2020).

The flea species involved in plague in Brazil are *Polygenis bohlsi jordani* and *P. tripus* (ectoparasites of wild rodents), *Xenopsylla cheopis* (rat flea), *Pulex irritans* (known as the human flea, is ubiquitous and also parasite of domestic animals), *Ctenocephalides felis* (ectoparasite of dogs and cats), and *Adoratopsylla antiquorum* (parasite of small marsupials, carnivores, predators of rodents) (Fernandes et al. 2020). Studies on the plague transmission by *P. b. jordani* and *P. tripus* using flea colonies raised in the laboratory demonstrated that they are efficient plague vectors. The flea *Polygenis b. jordani* parasitizes practically all rodent species of the North-east foci; therefore, it was incriminated for the epizootization of the plague among the rodents and for the genesis of most of the human plague cases (Baltazard 2004).

Plague diagnosis was initially limited to bacteriological analysis: culture from biological samples on peptone agar plates, animal inoculations, and the bacteria identification using anti-plague phage. Animal inoculation was gradually abandoned due to biosafety issues. Between 1966 and 1997, a total of 907 *Y. pestis* strains were isolated from rodents, fleas, and humans. These cultures are deposited in the *Yersinia* spp. collection (Fiocruz—CYP) (http://cyp.fiocruz.br/index?services). The Brazilian strains belong to the *Orientalis* variety that spread during the third pandemic and have been studied from various approaches (Tavares et al. 2012; Leal et al. 2015). Whole-genome sequencing of several *Y. pestis* strains isolated from different sources and periods provided evidence for the hypothesis of only a single introduction of the plague in Brazil (Vogler et al. 2019).

4.3.3 Plague on the Pacific coast of South America

4.3.3.1 Peru

The plague entered Peru in 1903, through the ports of Callao and Pisco, and then spread throughout the coast and to the interior of the country. In the La Libertad region, northern Peru, it entered through the port of Pacasmayo and settled in the Piura, Lambayeque, Cajamarca, and La Libertad regions. Currently, plague areas persist in northern Peru in the departments of Cajamarca (Chota, San Miguel, and San Pablo provinces), La Libertad, Lambayeque, Piura (Ayabaca, Huancabamba, Piura provinces, Mórrope), and Ancash (southern part) (Moll and O'Leary 1940; Pollitzer and Meyer 1965).

Between 1970 and 2020, there were 2487 cases with 163 deaths (case fatality rate 6.5%) in Peru. Cases were almost annually reported during the whole period until 2019, and no cases occurred in 2020. Since the 1970s, there was a downward trend in the incidence of human plague in Peru until 1984, when a large outbreak occurred, affecting large areas of the departments of Cajamarca and Piura (413 cases,

31 deaths) and from 1992 to 1994 (1151 cases, 54 deaths). In 1994, plague reemerged on the coast (Mórrope), after 70 years, and in 2009 reemerged in La Libertad after 12 years of quiescence (25 cases). New foci emerged in 2013 (24 cases) (Bertherat 2019; Dávalos et al. 2001; Pareja-Ramos et al. 2013).

In 1993, a collaborative effort between Peruvian government and PAHO structured a national program of control and prevention of plague, focused on avoiding the arrival of plague in highly populated urban zones. To achieve this goal, measures were delineated according to the following priorities: (1) improvement of grain storage conditions; (2) epidemiological and ecological investigation of plague natural foci in a $> 10.000\ km^2$ area; (3) use of pesticide and training of local teams in regions with plague activity; and (4) educational measures with local populations. Altogether, the program had effective results, as it reduced the lethality rate of the disease to 2%; installed a network of surveillance laboratories; and reduced the domestic farming of "cuyes" through informing the population of its risks. Despite the success of the program, Peru still is the country with more recent cases in Latin America (Ruiz et al. 1996).

The most common wild rodents and most frequently found infected with plague in Peru are *Aegialomys xanthaeolus (=Oryzomys xanthaeolus), Akodon dolore, Akodon orophilus (=Akodon mollis orophilu), Hylaeamys perenensis, Oecomys spp., Rhipidomys leucodactylus (=Rhipidomys equatoris), Simosciurus nebouxii (=Sciureus stramineus nebouxii), Oryzomys andinus (=Phyllotis fruticicolus), Cavia tschudii,* the tree squirrel *Sciurus stramineus*, and the cottontail rabbits (Lagomorph) *Sylvilagus andinus* and *S. ecaudatus* (Arrieta et al. 2001; Bonvicino et al. 2015; Pozo et al. 2005; Ruiz 2001).

The fleas associated with plague are *Polygenis litargus*, parasite of *Simosciurus nebouxii (=Sciureus stramineus nebouxii), Hectopsylla* spp. and *Tiamastus cavicola*, parasite of *Cavia tschudii*, and the domestic *Cavia porcellus* (cuyes) (Arrieta et al. 2001; Pozo et al. 2005; Ruiz 2001).

4.3.3.2 Ecuador

During the 50 years period of 1970–2020, there were 172 cases with 10 deaths (case fatality rate 5.8%) in Ecuador. After 1970 (30 cases, 1 death) and 1971 (27 cases), plague cases decreased and became sporadic, between periods of quiescence and important outbreaks. In 1983, an outbreak affecting 65 people occurred, and further cases occurred in 1984 (seven cases, one death) and 1985 (three cases, two deaths). After 12 years of quiescence, the last outbreak occurred in 1998 in Chimborazo Province with 14 cases and four deaths, out of which two had laboratory evidence of pneumonic plague. They were all members of the same family and the origin of their infection was associated with exposure to sick guinea pigs (cuyes). The presence of plague antibody among dogs from the communities provided evidence of a recent plague epizootic in the area. After that episode, no other cases were registered in Ecuador, but plague foci still persist in the southern part of Ecuador in Loya province (Chimborazo, Tungurahua, Cotopaxi, Loja) (Bertherat 2019; Gabastou et al. 2000; Ruiz 2001).

Plague-associated rodents in Ecuador are *Rattus norvegicus, Rattus rattus, Mus musculus*, and the domestic *Cavia porcellus* or "cuyes" in the intradomiciliary environment and the wild species *Aegialomys xanthaeolus (=Oryzomys xanthaeolus), Akodon dolores, Akodon mollis, Oligoryzomys flavescens (=Oryzomys flavescens), Oligoryzomys longicaudatus (=Oryzomys longicaudatus), Phyllotis andium (=Phyllotis fruticicolus), Sciurus stramineus, Sigmodon peruanus (=Sigmodon peruanus, Sigmodon puna)*, and *Simosciurus nebouxii (=Sciureus stramineus nebouxii)* (Bonvicino et al. 2015; Ruiz 2001).

The squirrel *Simosciurus nebouxii (*formerly *Sciurus stramineus nebouxi)* is comparatively resistant to plague and purportedly one of the plague reservoirs during the interepizootic periods. The species *Akodon mollis* and *Aegialomys xanthaeolus* (formerly *O. xanthaeolus*) are highly susceptible and undergo acute epizootics.

The fleas associated with plague are *Pulex irritans* and *Xenopsylla cheopis* intradomiciliary, *Tiamastus cavicola* parasite of the domestic *Cavia porcellus* (cuyes), and *Polygenes litargus, P. bohlsi bohlsi*, *P. brachimus*, and *Nopsosilla londinenses* parasites of the wild species *Aegialomys xanthaeolus* (formerly *Oryzomys xanthaeolus)*, *Akodon mollis*, and *Simosciurus nebouxii (*formerly *Sciurus stramineus nebouxi)* (Ruiz 2001).

4.3.3.3 Bolivia

After the first reports of plague in Bolivia in the early 1920s, plague has spread widely throughout the country (Padilla 2007; Pollitzer and Meyer 1965). Today, there are two widely separated foci, one in the northwest in La Paz Department in Franz Tamayo and Nor Yungas Provinces and the other in south central Bolivia in the departments of Chuquisaca, Santa Cruz, Tarija. During the 50 years' period of 1970–2020, there were 440 cases with 58 deaths (case fatality rate 13.2%). Human plague was recorded annually during the first two decades until 1990, except for the years 1972, 1973, 1985, and 1989. There were 409 cases with 51 deaths (case fatality rate 12.5%) in this 20 years' period. No case was reported in the following 5 years; then there were 26 cases in 1996 and 1 case in 1997. After that, only a single case and death were reported in the years 2010 and 2018 and 2 cases and a death in 2014 (Bertherat 2019; Faccini-Martínez Sotomayor 2013; Ruiz 2001).

The rodents associated with plague in Bolivia are *Rattus rattus, Calomys boliviae (=Hesperomys fecundus), Calomys venustus (=Hesperomys v. venustus), Graomys griseoflavus (=G. cachinus, G. chacoensis, G. g. griseoflavus, G. medius), Oligoryzomys flavescens (=Oryzomys flavescens), Oligoryzomys longicaudatus (=Oryzomys longicaudatus), Oxymycterus paramensis, Tapecomys wolffsohni (=Phyllotis wolffsohni), Rhipidomys leucodactylus (=Rhipidomys equatoris), Dasyprocta azarae (=Dasyprocta variegata boliviae), Galea littoralis littoralis (=G.m. leucoblephara), and the* Lagomorph *Sylvilagus brasiliensis (=S. b. gibsoni)*, and the fleas are *Xenopsylla cheopis, Pulex irritans, Tiamastus cavicola, Polygenis spp.,* and *Ctenocephalides spp.* (Bonvicino et al. 2015; Ruiz 2001).

The species *Graomys griseoflavus* is considered particularly important, because it inhabits both in the wild and intradomiciliary. Therefore, it can interchange plague between these environments.

4.3.4 Important Considerations of Plague in Latin America

Plague affects mostly poor populations in rural settings in remote areas; affected regions have high poverty and poor socioeconomic levels and poor sanitation, household hygiene, and living conditions. Indigenous communities from the Andean region are considered vulnerable to plague, due to the increased exposure to wildlife, cultural habits, and poorer access to healthcare services. The houses built with inadequate materials are vulnerable to the invasion of rodents or fleas; improper storage of crops and the accumulation of garbage attract rodents and favor their reproduction by providing them with a source of food and at the same time facilitate transmission of the disease to humans (Fig. 4.1).

Some customs and traditions may impact the risk of human plague such as holding funeral wakes and offering the deceased's clothing to relatives, favoring human-to-human transmission in many Andean communities. Raising guinea pigs (*Cavia porcellus)* called "cuyes" inside homes as food source (Fig. 4.1). These animals are frequently infected and can pass the infection on to humans through infected fleas or directly by handling. They can harbor the flea species *Tiamastus cavicola* and *P. irritans,* which have been found naturally infected with plague, and *Hectopsylla* spp.

Overall, nowadays in Latin America the cases are essentially sporadic and have the bubonic form, associated with farming activities in rural areas. Sporadic outbreaks are purportedly transmitted by the human flea *P. irritans* (anthroponotic plague). In urban areas, in the coastal pacific cities, *R. norvegicus* and *R. rattus* are common hosts, and it is assumed that their fleas' parasite (*X. cheopis*) is involved in plague transmission in human settlements.

Human cases and outbreaks usually are preceded by intensive plague epizootics of wild rodents. Climatic disturbances (e.g., increased rainfall) increase the food sources for rodents, resulting in fast population growth and invasion of human dwellings by *Y. pestis*-infected rodents and fleas. Deforestation provokes the displacement of wildlife and the incursion of humans into plague-infected areas and results in the migration of rodents and fleas to urban areas (e.g., significant increase in rodents in La Hermelinda the largest supply center in the city of Trujillo, Peru, in 2012) (Pareja-Ramos et al. 2013).

4.4 Final Remarks

Currently, the global incidence of human plague is the lowest reported by the WHO in 30 years. Most cases are reported in Madagascar, followed by the Democratic Republic of the Congo. Sporadic cases have also been reported annually in other

regions outside Africa, such as China, Mongolia, USA, Peru, and Bolivia. It is well established that plague can remain in epidemiological silence for several decades and suddenly spill over into human populations, and despite the current downward trend, we must remain vigilant and maintain rigorous epidemiological surveillance (Bertherat 2019).

Due to its widespread presence in wildlife reservoirs, the eradication of plague is a momentarily unattainable objective. Attempts to eradicate plague from ecosystems by some countries (USA, USSR) were ineffective and, consequently, discontinued (Gage 2012; Jones et al. 2019). The PAHO (2009) established as the GOAL Indicator for plague the absence of fatal cases and domiciliary outbreaks and recommends the following priorities: improved capacity in early detection (diagnosis), risk analysis (host and vectors surveillance in natural foci), and establishment of plans regarding control measures in case of outbreaks. Ultimately, the best prevention of plague is to secure a good human living condition, with access to the basic needs, education, and a wholesome environment. Healthcare and research institutions must be solid and prepared to contain emergencies.

Many aspects remain to be clarified regarding the epidemiology of plague transmission in Latin America, particularly those related to the wild rodent reservoirs and flea vectors. Epidemiological surveillance and diagnosis are very poor in most of the countries from the region. It is important that each endemic country maintain well-trained teams and adequate diagnostic supplies to stand ready for prompt diagnosis, treatment, and control measures in case of emergencies.

Despite the human tragedy and economical losses caused by this scourge in South America during the early twentieth century, the plague brought into the attention of the authorities the importance of investing in science, public health, urban planning, and social welfare to prevent the quick spread of epidemics. This disease reshaped not only the fast-growing South American metropolis of Rio de Janeiro and Buenos Aires, but also many others all around the world (Surat, India) into cleaner and healthier cities. Moreover, it motivated the creation of renowned research institutes, such as Fiocruz, Butantan, and Carlos Malbrán, which are a landmark in the combat of infectious diseases in South America and benefit the population until nowadays.

As in 2020 a new pandemic brings the world down to its knees, the scenario evocates many of the challenges faced by Latin American societies during the third plague pandemics. Insights from the disruptive advances achieved during epidemics from the past are key to comprehend and overcome the current COVID-19 pandemic.

References

Almeida AMP, Sobreira M, Leal NC, Tavares C (2020) Does the plague still threaten us? Rev Soc Bras Med Trop 53:1–3

Arrieta M, Soto R, Gonzáles R, Nombera J, Holguín C, Monje J (2001) Características de la población de roedores y pulgas en áreas de diferente riesgo para peste de tres provincias del departamento de Piura-Perú. Rev Med Exp 18:90–97

Baltazard M (2004) La démarche exemplaire d'un épidémiologiste de terrain: M. Baltazard et les foyers de peste du nordest brésilien. Bull Soc Pathol Exot 97:93–118

Barbieri R, Signoli M, Chevé D, Costedoat C, Tzortzis S, Aboudharam G, Raoult D, Drancourt M (2021) *Yersinia pestis*: the natural history of plague. Clin Microbiol Rev 34:e00044–e00019. https://doi.org/10.1128/CMR.00044-19

Bertherat E (2019) Plague around the world in 2019. WER WHO 94:289–292. Available from: http://www.who.int/wer

Bertherat E, Bekhoucha S, Chougrani S, Razik F, Duchemin JB, Houti L et al (2007) Plague reappearance in Algeria after 50 years, 2003. Emerg Infect Dis 13:1459–1462

Bin-Saeed AA, AL-Hamdan NA, Fontaine RE (2005) Plague from eating raw camel liver. Emerg Infect Dis 11(9):1456–1457

Bonvicino CR, Oliveira JA, Estrela PC, D'Andrea PS, Almeida AMP (2015) A taxonomic update of small mammal plague reservoirs in South America. Vector Borne Zoonotic Dis 10:571–579

Bramanti B, Stenseth NC, Walløe L, Lei X (2016) Plague: a disease which changed the path of human civilization. In: Yang R, Anisimov A (eds) *Yersinia pestis*: retrospective and perspective. Springer, Dordrecht, pp 1–26

Butler T (2014) Plague history: Yersin's discovery of the causative bacterium in 1894 enabled, in the subsequent century, scientific progress in understanding the disease and the development of treatments and vaccines. Clin Microbiol Infect 20:202–209. https://doi.org/10.1111/1469-0691.12540

Dávalos V, Arrieta M, Olguín C, Laguna V, Pun M (2001) Outbreak of bubonic plague in Jacocha, Huancabamba, Perú. Rev Soc Bras Med Trop 34:87–90. https://doi.org/10.1590/S0037-86822001000100013

Demeure CE, Dussurget O, Fiol GM, Le Guern AS, Savin C, Pizarro-Cerdá J (2019) *Yersinia pestis* and plague: an updated view on evolution, virulence determinants, immune subversion, vaccination, and diagnostics. Gen Imm. https://doi.org/10.1038/s41435-019-0065-0

Donaires L, Céspedes M, Valencia P, Salas J, Luna M, Castañeda A et al (2010) Peste neumónica primaria con transmisión intrahospitalaria en La Libertad, Perú, 2010. Rev Peru Med Exp Salud Pública 27:326–336

Edmunds DR, Williams ES, O'toole D, Mills KW, Boerger-Fields AM, Jaeger PT, Bildfell RJ, Dearing P, Cornish TE (2008) Ocular plague (*Yersinia pestis*) in mule deer (*Odocoileus hemionus*) from Wyoming and Oregon. J Wild Dis 44(4):983–987

Engelmann L (2018) Fumigating the hygienic model city: bubonic plague and the sulfurozador in early-twentieth-century Buenos Aires. Med Hist 62(3):360–382. https://doi.org/10.1017/mdh.2018.37

Faccini-Martínez Sotomayor HA (2013) Reseña histórica de la peste en Suramérica: una enfermedad poco conocida en Colombia. Biomedica 33:8–27. https://doi.org/10.7705/biomedica.v33i1.814

Fernandes DLR, Filgueira MB, Sobreira M, Leal NC, Reis CRS, Almeida AMP (2020) Rodent hosts and flea vectors in Brazilian plague foci: a review. Int Zool 0:1–10. https://doi.org/10.1111/1749-4877.12480

Fernandes DLR, Gomes ECS, Filgueira MB, Guimarães RJPS, Almeida AMP (2021) Spatiotemporal analysis of bubonic plague in Pernambuco, Northeast of Brazil: case study in the Municipality of Exu. PLoS One 16(4):1–14

Gabastou J, Proaño J, Vimos A, Jaramillo G, Hayes E, Gage K et al (2000) An outbreak of plague including cases with probable pneumonic infection, Ecuador, 1998. Trans R Soc Trop Med Hyg 94:387–391. https://doi.org/10.1016/S0035-9203(00)90114-7

Gage KL (2012) Factors affecting the spread and maintenance of plague. In: Almeida AMP, Leal NC (eds) Advances in *Yersinia* Research, vol 954. Springer Science & Business Media, pp 79–94

Giles J, Peterson AT, Almeida AMP (2011) Ecology and geography of plague transmission areas in Northeastern Brazil. PLoS Negl Trop Dis 5:e925

Hinnebusch BJ, Jarrett CO, Bland DM (2017) "Fleaing" the Plague: Adaptations of *Yersinia pestis* to its insect vector that lead to transmission. Ann Rev Microbiol 71:215–232. https://doi.org/10.1146/annurev-micro-090816-093521

Inglesby TV, Dennis DT, Henderson DA et al (2000) Plague as a biological weapon: medical and public health management. JAMA 283(17):2281–2290. https://doi.org/10.1001/jama.283.17.2281

Jones SD, Atshabar B, Schmid BV, Zuk M, Amramina A, Stenseth NC (2019) Living with plague: lessons from the Soviet Union's antiplague system. PNAS 116:9155–9163. https://doi.org/10.1073/pnas.1817339116

Leal NC, Sobreira M, Araújo AFQ et al (2015) Viability of *Yersinia pestis* subcultures in agar-stabs. LAM 62:91–95

Mahmoudi A, Krytufek B, Sludsky A, Schmid BV, Almeida AMP, Lei X, Bertherat E, Ramasindrazana B, Yeszhanov A, Stenseth NC, Mostafavi E (2020) Plague reservoir species throughout the world. Integr Zool. https://doi.org/10.1111/1749-4877.12511

MMWR (2011) Fatal laboratory-acquired infection with an attenuated *Yersinia pestis* strain—Chicago. Illinois 60:7

Moll AA, O'Leary SB (1940) Plague in the Americas: an historical and quasi epidemiological survey. Bull PAHO 19:576–584

Nascimento DR, Silva MAD (2013) The bubonic plague in the city of Rio de Janeiro and the public strategies to combat it (1900–1906). Revista Territórios Fronteiras Cuiabá 6(2):109–124

Padilla M (2007) La peste bubónica en Chuquisaca. Rev Inst Med Su 73:1–7

PAHO (2009) Resolution CD49.R19. elimination of neglected diseases and other poverty-related infections. Forty-ninth directing council. Pan American Health Organization, Washington, DC

Palacios M, Estévez E (2006) La peste en el Ecuador, sus inicios y control. Rev Ecuat Hig Med Trop 43:43–50

Pareja-Ramos JJ, Bazán-Ruiz S, Maguiña-Vargas C (2013) Plague in Peru. Threat of urban epidemic outbreak in La Libertad. Acta Med Per 30(4)

Perry RD, Fetherston JD (1997) *Yersinia pestis*—etiologic agent of plague. Clin Microb Rev 10:35–66

Pollitzer R (1954) Plague. WHO, Geneva, Switzerland. Available from: https://apps.who.int/iris/handle/10665/41628

Pollitzer R, Meyer KF (1965) Plague in the Americas, vol 115. Scientific Publication, PAHO Washington

Pozo E, Troncos G, Palacios A, Arévalo F, Carrión G, Laguna A (2005) Distribución y hospederos de pulgas (Siphonaptera) en la provincia de Ayabaca, Piura 1999. Rev Peru Med Exp Salud 22:316–320

Rodriguez-Morales AJ, Escalera-Antezana JP, Alvarado-Arnez LE (2019) Is plague globally reemerging? Infect 23(1):7–9. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0123-93922019000100007&lng=en. https://doi.org/10.22354/in.v23i1.748

Ruiz A (2001) Plague in the Americas. Emerg Infect Dis 7:539–540. https://doi.org/10.3201/eid0707.017718

Ruiz A, Navarro A, Vargas E, Sánchez J, Sato A, Escobar E (1996) Peste bubónica en el Perú: un enfoque multisectorial de control. Bol Sanit Panam 121:363–367

Schneider MC, Najera P, Aldighieri S, Galan DI, Bertherat E et al (2014) Where does human plague still persist in Latin America? PLoS Negl Trop Dis 8(2):e2680. https://doi.org/10.1371/journal.pntd.0002680

Tavares C, Aragão AI, Leal NC, Leal-Balbino TCA, Oliveira MBM, Oliveira GM, Almeida AMP (2012) Plague in Brazil: from now and then. In: Almeida AMP, Leal NC (eds) Advances in *Yersinia* research, vol 954. Springer Science & Business Media, pp 69–77

Valles X, Stenseth NC, Demeure C, Horby P, Mead PS, Cabanillas O et al (2020) Human plague: an old scourge that needs new answers. PLoS Negl Trop Dis 14:2020

Vogler AJ, Keim P, Wagner DM (2016) A review of methods for subtyping *Yersinia pestis*: from phenotypes to whole genome sequencing. Infect Genet Evol 37:21–36. https://doi.org/10.1016/j.meegid.2015.10.024

Vogler AJ, Sahl JW, Leal NC et al (2019) A single introduction of *Yersinia pestis* to Brazil during the 3rd plague pandemic. PLoS One 14(1):e0209478. https://doi.org/10.1371/journal.pone.0209478

WHO (2008) International health regulations (2005). WHO, Geneva

Wong D, Wild MA, Walburger MA, Higgins CL et al (2009) Primary pneumonic plague contracted from a mountain lion carcass. Clin Infect Dis 49:e33–e38. https://doi.org/10.1086/600818

Zeppelini CG, Almeida AMP, Estrela PC (2016) Zoonoses as ecological entities: a case review of plague. PLoS Negl Trop Dis 10:e0004949

Trypanosoma Cruzi: An Ancient and Successful Enzootic Parasite

5

Ana Maria Jansen, Raphael Testai de Souza, Andre Luiz Rodrigues Roque, and Samanta Cristina das Chagas Xavier

Abstract

Despite the growing global awareness of the importance of environmental preservation and the interdependence of plant, animal, and environmental health, there are still few long-term studies of free-living wild animal parasites. The difficulty in setting up multidisciplinary teams for this kind of study may constitute a plausible explanation. This is the case of trypanosomiasis by *T. cruzi*, the etiologic agent of Chagas disease that is a pan-infective multi-host parasite, dispersed in the wild environment of all Brazilian biomes. In addition to discussing the issue of parasitism of wild animals by *T. cruzi* and the outbreaks of acute Chagas disease in humans, we present a cartographic approach that allows us to determine the environmental suitability of the transmission of *T. cruzi* and, therefore, may be used as a predictive tool of the transmission of *T. cruzi* in the wild environment. The cartography is particularly interesting in cases such as trypanosomiasis (*T. cruzi*), allowing to model areas with high adequacy of the parasite's enzootic cycle; therefore, of risk of human disease if any project in the environment is being planned. This approach reduces the need for fieldwork (expensive and difficult), especially in a country with continental dimensions as Brazil.

A. M. Jansen (✉) · A. L. R. Roque · S. C. das Chagas Xavier
Laboratório de Biologia de Tripanosomatídeos, Instituto Oswaldo Cruz, Rio de Janeiro, RJ, Brazil
e-mail: jansen@ioc.fiocruz.br

R. T. de Souza
Laboratório de Biologia de Tripanosomatídeos, Instituto Oswaldo Cruz, Rio de Janeiro, RJ, Brazil

Programa de Pós-graduação Stricto sensu em Biologia Computacional e Sistemas do, Instituto Oswaldo Cruz (PGBCS/IOC/Fiocruz), Rio de Janeiro, RJ, Brazil

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_5

Keywords

Euglenozoa · Polykinetoplast · Kinetoplastea · Trypanosomatidae · Trypanosoma cruzi

5.1 Parasites: General Aspects

All organisms associate and interact so that living beings are, therefore, interdependent. These interactions are dynamic and may acquire distinct peculiarities both at an individual level and along its coevolutionary process on a temporal and spatial scale. Perhaps the most common and most successful type of association among living organisms is termed parasitism, in which the energy flow is unilateral. It is estimated that parasites make up the majority of living species (Dobson et al. 2008), and, very importantly, parasites seldom occur in single infections but rather in mixed infections (including at least the host resident microbiota). These assemblages constitute communities that also undergo constant adjustments. Cooperation and competition are some of the interactions that take place among these community members. Parasites are very important pieces of the complex life interaction nets. Parasites forge biodiversity and deeply influence the ecology, evolution, and behavior of free-living species (Kuris et al. 2008; Dunne et al. 2013) to such a degree that they were considered as "ecosystem engineers" by Hatcher et al. (2012).

Heinrich Anton de Bary (1879) who coined the term symbiosis (living together) refers to the capacity of distinct species of living together, in 1879. It did not enter into Bary's elegant definition any allusion to benefit, illness, or pathogenicity. Many authors still associate parasitism, with unilaterality of damage or benefits, which is a rather simplistic way of interpreting a phenomenon as complex as parasitism, which is modulated by so many variables. Also very common is the use of the terms virulence and pathogenicity as synonyms. Here, we prefer to use the term virulence to define the proliferative competence of a parasite in its host and the term pathogenicity as the capacity of the parasite to inflict harm to its host. These attributes do not always coincide. Thus, *Trypanosoma evansi* is able to maintain high rates of trypomastigotes multiplying in the blood of capybaras (*Hydrochoerus hydrochaeris*) without causing damage to this animal species. That is, *T. evansi* is virulent but not pathogenic for this mammal species (Herrera et al. 2004). It is also important to point out that virulence and pathogenicity are not exclusive attributes of the parasite, but are the resultant from the set of peculiarities of each partner of this interaction. That is, one same species of parasite can be pathogenic or virulent for one host species but not for another. This is true at the individual level within a host species or also genotype of the parasite species.

A point that presents many gaps in knowledge is the possible synergistic or antagonistic effects resulting from mixed infections both by different genotypes of a same parasite species or by concomitant infections by distinct species of parasites. From a classical point of view, virulence and pathogenicity are solely attributes of the parasite. So that, throughout the coevolutionary process, successful parasites are

proposed as those that established a "balanced" relationship with their hosts because, if parasites kill the host, it will also disappear. This concept has been revised as is become increasingly clear that, virulence and pathogenicity can be, and often are, fitness traits of the parasite for ensuring its transmission. Long-lasting parasitemias or the decrease or even loss of mobility of an animal, increases the chances of transmission of the parasite by enhancing the encounter with vectors or predators.

Although parasitism is the most common "*modus vivendi*" among living beings and, in spite of being a widely studied subject, there is still a relative lack of knowledge of parasites of free-living wild animals. In fact, only nowadays the study of wild animal parasites that do not include pets or animals of economic interest is gaining increasing interest. This is due to the growing awareness of the interdependence of all living beings which even means an interdependence of health, as well as the recognition of the importance of including parasites in studies of biodiversity. Indeed, parasites are an important part of biodiversity.

Paradoxically, there are still relatively few publications and studies of free-living wild animal parasites. Part of the scarcity of studies of free-living wild animals is due to the lack of specific reagents for diagnosis, but also, and mainly, due to the difficulty of their capture and management and the impossibility of forming cohorts for follow-up. Most of the data are obtained from punctual collections of samples that are very probably biased since very young or very old or ill individuals will certainly not be able to walk into a trap. This means that these data only reflect a snapshot of the enzootic situation. Here, in addition to discussing the issue of parasitism of wild animals by *T. cruzi* and the outbreaks of acute Chagas disease in humans, we present a cartographic approach that allows us to determine the environmental suitability of the transmission of *T. cruzi* and; therefore, means a and predictive tool on the transmission of *T. cruzi* in the wild environment.

5.1.1 Origin of Parasitism

A canonical statement about the origin of parasitism proposes a long coevolutionary process between host and parasite to explain the distribution of parasites among living being taxa. This hypothesis completely disregards that, despite suffering selective pressures exerted by their hosts, parasites have their own evolutionary peculiarities and are not simply appendages of their hosts' evolutionary history (Araujo et al. 2015). Additionally, in the above-mentioned scenario, host switching should be rare, which contrasts with the increasingly frequent description spill over events; that is, parasites previously described as specific to one host species or genre, parasitizing totally distinct taxa (Hoberg and Brooks 2008, 2015).

Agosta and Klemens (2008) termed as "Ecological host fitting" the ability of a parasite to use novel resources or to colonize new species and tissues forming novel associations without having a previous contact with them. This process (according to these authors) results from the set of traits and adaptive competences that these parasites already have had at the time they encounter the new host/tissue.

Over the past two decades, much attention has turned to understanding a phenomenon common to absolutely all, if not all, life forms including parasites—the genetic parasites that include transposable elements, plasmids, viruses, and others. Parasite-host interactions are deeply imbricated in the process of evolution of living beings. Parasitic DNA, or transposon, are short sequences of DNA that propagate in the host cell genome. By inserting into new DNA locations in the genome, transporting genetic information from one location in the genome to another, the result can either increase your potential for adaptation to a new environment represented by a new tissue or even to a new host or, on the contrary, result in its extinction. Indeed, sequences derived from transposable elements constitute large fractions of the genomes of diverse eukaryotes, parasites or not but are not quite as prominent in prokaryotes (Carmody et al. 2016; Iranzo et al. 2016).

5.1.2 The Euglenozoa

Euglenozoa are the living relatives of some of the earliest unicellular eukaryotes. The most characteristic aspect of this group is the presence of an expressive amount of extranuclear DNA located in the mitochondria (kDNA). This kDNA presents distinct distribution patterns that distinguish three main groups: (1) organisms that display compressed kDNA located near the flagellar pocket (the eukinetoplast or the true kinetoplastids), (2) organisms that display scattered kDNA in the mitochondrial lumen that may be distributed as regular clusters termed polykinetoplast, and (3) kDNA as diffuse masses the so-named pankinetoplast.

Euglenozoa have extremely diverse lifestyles and a range of features that were never observed in other eukaryotes very probably due to the limited knowledge of the free-living representatives of this group. In fact, almost nothing is known about free-living protists in general (Adl et al. 2019). Nevertheless, the increasing awareness of the emergence of parasitic diseases reinforced the importance of studying spill-over phenomena and, consequently, the evolutionary processes underlying the adaptation of a free-living organism to a parasitic lifestyle.

5.1.3 The Kinetoplastea

Kinetoplastids are perhaps the organisms among the protists that display a higher degree of abundance and richness (Pawlowski et al. 2012). The class Kinetoplastea includes the orders Trypanosomatida, Eubodonida, Parabodoida, Neobodonida, and Prokinetoplastida (Adl et al. 2019; Moreira et al. 2004). Trypanosomatida is perhaps the most studied group of Kinetoplastea because they include agents of diseases of human, animal, and plant of economic value. Compared with other groups of protists, Kinetoplastids are highly adaptable and widespread and are among those eukaryotes that diverged earlier from the ancestral group (Lukeš et al. 2014). Within the Kinetoplastid lineage, adaptation to parasitism is proposed as having evolved only once. The steps that have been taken by these organisms to adapt to the parasitic

lifestyle are still far from being clarified and probably will depend on the availability of the genomes of their free-living closest relatives (Lukeš et al. 2014).

5.1.4 The Trypanosomatidae

Trypanosomatidae are characterized by the presence of one elongated mitochondrion that displays a particular region that harbors flagellum and a particular region, the kinetoplast, harbors a uniquely arranged extra nuclear DNA (kDNA) which may vary according to systematic morphological characteristics (Kaufer et al. 2017). These ancient eukaryotic organisms that are obligate parasites and are found in all vertebrate classes are widely distributed in nature and are basically distributed into two major phylogenetic lineages: the Terrestrial clade composed of trypanosomes of mammals, snakes, lizards, crocodilians and birds and the Aquatic Clade that includes trypanosomes of fishes chelonians, anurans and platypus and are frequently transmitted by leeches. These two main clades, in turn, branch out into numerous other clades (Stevens et al. 2001; Hamilton et al. 2005, 2007).

Regarding mammalian trypanosomes, an intense debate started in the early twentieth century with (Leger 1904, apud Lankester 2016) proposing diametrically opposed hypotheses. Namely: (1) the origin of mammalian Trypanosomas would have been the consequence of the adaptation of monogenetic Trypanosomatids from insects ingested by mammals, initially to the digestive tract and later to other tissues and organs and (2) the acquisition of hematophagic habits by insects led to the adaptation from monogenetic Trypanosomatides of insects to the blood of mammals that served as their food source. This debate lasted a few decades and currently the insect first hypothesis is a consensus. In fact, these hypotheses were proposed long before the amplitude of the universe of these protozoans was known and long before the current methodological possibilities. These hypotheses were, therefore, constructed from inductive reasoning without empirical evidence. However, the insect first hypothesis remains valid to the present.

Taxonomy of Trypanosomatids was up to less than a decade ago, defined by morphological characteristics such as the presence of one or two flagella, presence and aspect of the flagellar pocket, position and characteristics of kDNA, and morphology of evolutionary stages (d'Avila-Levy et al. 2015). According to their life cycle, two major groups are recognized in the Trypanosomatidae family: the monoxenous species, that complete their life cycle in one single host species, predominantly insects (mainly Dipterans and Hemipterans) and that make up the majority of Trypanosomatids and those that have included in their life cycle, besides insects, a vertebrate host and therefore are termed, dixenous Trypanosomatids. Phylogenic inferences concluded that dixeny in Trypanosomatidae has been acquired in multiple and independent events (Lukeš et al. 2014, 2018). As in any other biological phenomenon, the boundaries between these two groups are far from being rigid and exceptions as well as intermediate situations exist. Actually, most likely other still unknown types of interactions and survival strategies exist among the Trypanosomatids.

There are Trypanosomatids that adapted to phytophagous insects and are able to parasitize many families of vascular plants, using nectar seed albumen latex, phloem, and fruit sap (Camargo 1999). Other Trypanosomatids perform their life cycle inside other protists as is the case of *Herpetomonas* that parasitize ciliates (Fokin et al. 2014). Still others harbor viruses and bacteria that have been acquired independently from several environmental (including hosts) sources. The association of Trypanosomatids with viruses is being increasingly studied and demonstrated to be another important piece for understanding the pathogenicity of these parasites. Metatranscriptomic surveys detected numerous Trypanosomatid viruses, some of which have been associated with the increase of pathogenicity in the *Leishmania* genus. These findings that are still very incipient show how there are still so many aspects to reveal in relation to the pathogenicity and virulence of parasites and also show how reductionist it is to classify parasites as pathogenic or not (Grybchuk et al. 2018).

The members of Trypanosomatidae include the etiologic agents of important zoonoses namely the trypanosomiasis and leishmaniasis. Among trypanosomiasis are Chagas disease and sleeping sickness in humans and nagana and surra in cattle, besides other potentially disabling trypanosomiasis of domestic wild animals and humans. In common, these taxa are widely dispersed and display huge genetic diversity. Also, monoxenous, that is, insect-restricted Trypanosomatids, display genetic diversity besides being highly dispersed in nature demonstrating that they are not that restricted to insects. In fact, encounters of Trypanosomatids of the genus *Chritidia* in wild mammals and even in humans have been increasingly reported (Ghobakhloo et al. 2019; Rangel et al. 2019; Dario et al. 2021). Trypanosomatids themselves may be parasitized by procariota and even viruses, a phenomenon whose consequences for the mammalian host are far from known. Among insects, the Coleoptera and Diptera demonstrate the higher prevalence of infection by monoxenous Trypanosomatids in comparison to other insect taxa.

Dixeny, that is, the ability of using two hosts, typical of *Trypanosoma* spp. that circulate between invertebrate and vertebrate hosts is described as a derived trait. Some Trypanosome species are described as being restricted to just one vertebrate host species in contrast to others that are able to parasitize a wide spectrum of vertebrate species. The recent findings of the bee parasitizing species, *Crithidia mellificae* in the blood and other tissues of several mammalian have signaled that at least this species, seems to be one step to be a generalist as well as a dixenic Trypanosomatid as well (Dario et al. 2021). Monoxenous Trypanosomatids infecting vertebrates is not a new phenomenon. In experimental conditions, it was possible to infect chicken embryos with a hemipteran-derived *Crithidia* isolate. Two other axenic culture-derived monoxenous species (*Leptomonas* sp. and *Crithidia* sp.) were able to survive and stimulate the humoral immune response when directly injected into the scent glands of the marsupial species *Didelphis aurita* (McGhee 1959; Sá et al. 1980; Deane and Jansen 1988).

Actually, little is known about the real host restriction, that is, the competence of *Trypanosoma* spp. to infect distinct mammal species or its ability to spill over to other species, a point of fundamental importance under one health perspective. Our

group has found several examples of biological plasticity of this taxon. Thus, we have already found *T. dionisii* described as restricted to bats infecting a human (Dario et al. 2017), *T. lainsoni*, originally described in rodents but already diagnosed in marsupials and bats (Rodrigues et al. 2019); and *T. cascavelli*, a parasite described in *Crotalus durissus* rattlesnake and later diagnosed infecting the marsupials *Monodelphis americana*, *Marmosa demerarae*, and *Didelphis albiventris* (Dario et al. 2017; Rodrigues et al. 2019). These and many other examples help us to understand the trends of the phenomena that occur, turning it possible to make predictions of the potential distributions of the parasite genotypes.

5.2 Trypanosoma Cruzi

Trypanosoma cruzi is a highly successful parasite in that it displays a huge heterogeneity, parasitizes hundreds of mammalian species, in these is able to thrive in almost all mammalian cell types and is transmitted by dozens of triatomine species. Besides, almost all its evolutive stages are infective since all of its evolutionary stages are capable of infecting as also epimastigotes are increasingly being described as infective (De Souza and Barrias 2020). Currently, genotypes of *T. cruzi* are assembled in 6 DTUs (Discrete Typing Units) and the genotype Tcbat, described as associated with these mammals that in short time will be named TcVII (Zingales et al. 2009).

Transmission of *T. cruzi* in nature takes place within a complex trophic network, in which each animal species plays a different role, in space and time, in terms of its maintenance and infective potential (Roellig et al. 2009). Thus, the transmission of *T. cruzi* is maintained through a complex trophic network, in which the nodes are the different species and the edges the interactions between them (Jansen et al. 2015, 2018), resulting in different enzootic scenarios (Fig. 5.1). That is, each region is unique, has a characteristic transmission network, which needs to be understood and known, so that areas of epidemiological risk can be recognized and, thus, correctly guide prevention and control measures, directing the actions of health agents and local residents (Roque and Jansen 2008).

According to Jansen et al. (2015), DTU distributions have not yet been unambiguously associated with hosts biomes or habitats. Through an analysis of data collected from 9000 wild mammals species from eight orders, it could be seen that: (1) TcI is the most widely distributed genotype in Brazil, with 58% of *T. cruzi* isolates; (2) TcII (17%), although less frequent than TcI, is also widely distributed; (3) *T. cruzi* hybrid genotypes (TcV and TcVI) are less prevalent, being extremely rare in Brazil, at rates of 0.3%; and (4) TcIII and TcIV are widely distributed but occur at significantly lower rates of 3% and 2.5%. Regarding hybrids, the authors highlight three non-mutually exclusive explanations: (1) these DTUs depend on simultaneous infection with other DTUs or parasites to be transmitted; (2) these DTUs are kept in nature in very low parasitemias, undetectable by the methods used; and/or (3) it was unsuccessful in sampling its suitable reservoir species (Jansen et al. 2015).

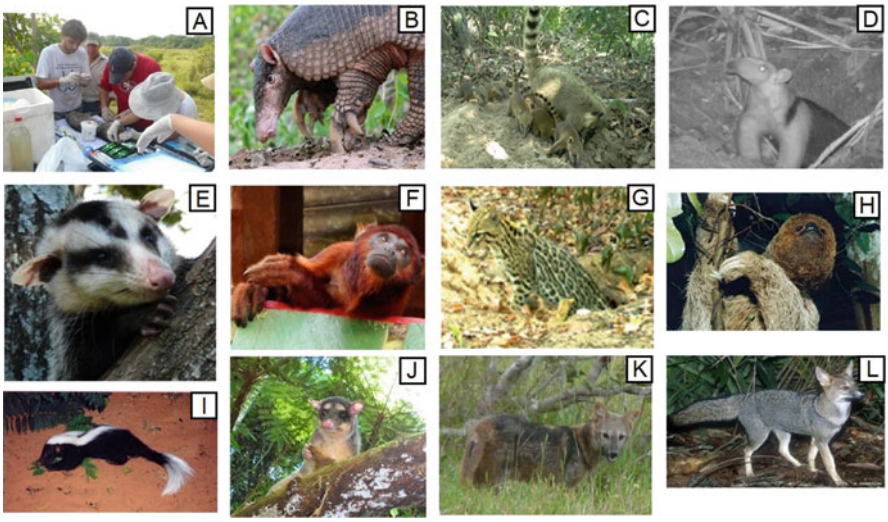


Fig. 5.1 Main mammalian hosts involved in the *Trypanosoma cruzi* transmission network in the wild environment in Brazil. Some of these species (B, C, D, G, and L) are considered environmental engineers, creating new habitats that will be explored by other species. (**a**) Field team, (**b**) *Priodontes maximus*, (**c**) *Nasua nasua*, (**d**) *Tamandua tetradactyla*, (**e**) *Didelphis albiventris*, (**f**) *Alouatta seniculus*, (**g**) *Leopardus pardalis*, (**h**) *Bradypus variegatus*, (**i**) *Mephitis mephitis*, (**j**) *Philander opossum*, (**k**) *Cerdocyon thous*, (**k**) *Lycalopex vetulus*

The map in Fig. 5.2 represents the distribution of *T. cruzi* DTUs, and their mixed infections with other Trypanosomatids and between his DTUs in Brazil, which is a country with continental dimensions and a wide variety of environments and biocenoses. This map is an update of the Trypanosomatids database distributions from the work of Jansen et al. (2020). *T. cruzi* is primarily a wild enzooty that was transmitted among the mammalian fauna that consisted in South America, basically of the orders Cingulata, Pilosa, and Didelphimorphia. As other taxa entered the continent, they were incorporated into the transmission cycle of this parasite. Thus, primates and caviomorph rodents arrived in the Americas 35 myr ago; carnivores and other taxa during the great exchange of mammals, which took place 5 years ago myr (Webb 1976; Flynn and Wyss 1998). And how did humans enter this complex *T. cruzi* transmission network? The classic hypothesis proposed that Chagas disease emerged among the prehistoric populations of the Andes when they started to domesticate animals, changed to sedentary habits, and adopted agriculture. These changes in their lifestyle habits happened approximately 6000 years ago. This was coincident with the domestication of guinea pigs (*Cavia* sp.) and grain storage that attracted rodents (Cortez et al. 2010). Wild triatomine was attracted by these easy food sources and adapted to the clay constructions of these ancient populations. However, molecular analysis of human mummies showed that *T. cruzi* infection in humans and Chagas disease were already common in prehistoric populations of South America and North America, long before this period. Data obtained by the

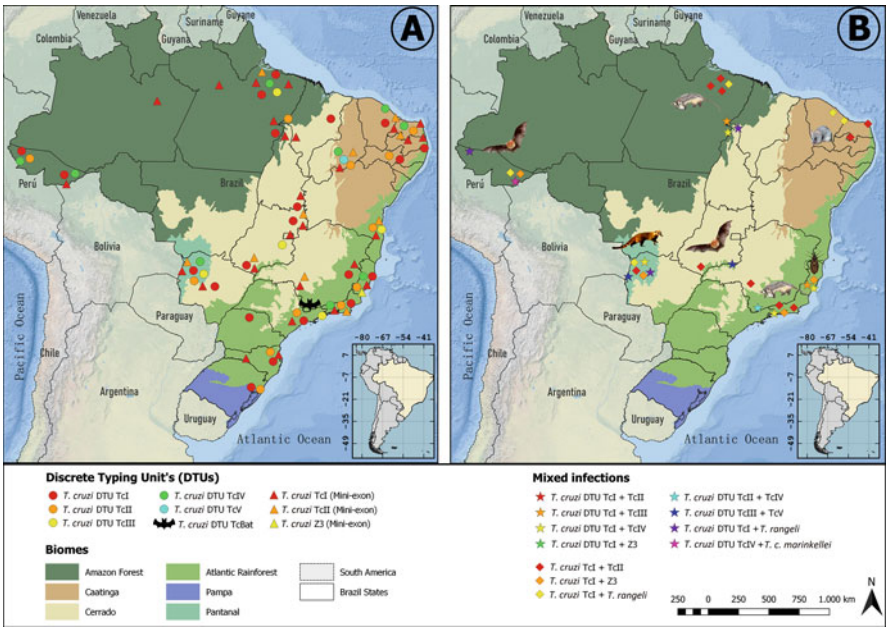


Fig. 5.2 (**a**) Spatial distribution of *Trypanosoma cruzi* DTUs in Brazilian biomes according to the isolates deposited in the Coltryp, (**b**) Spatial distribution of the observed mixed infections between *Trypanosoma cruzi* DTUs and others Trypanosomatids, and their most representative hosts in different Brazilian biomes. **Coltryp:** Coleção de *Trypanosoma* de mamíferos Silvestres, Domésticos e Vetores (http://coltryp.fiocruz.br)

analysis of mummified human tissues up to 9000 BP by molecular tools showed that Chagas disease was extant among prehistoric nomad people of Brazil and other countries of the American continent, showing that the entrance of humans in the zoonotic transmission cycle of *T. cruzi* probably started as soon as they arrived in the American continent ground 16,000 BP (Aufderheide et al. 2004; Lima et al. 2008; Fernandes et al. 2008). Typical Intestinal and heart lesions of Chagas disease lesions as well as amastigote nests were already described in mummified tissues of Andean cultures in the past (Rothhammer et al. 1985; Fornaciari et al. 1992; Guhl et al. 1997, 1999, 2000).

Triatoma infestans was the first triatomine species to be associated with human dwellings, dispersed to other parts of the American continent. In Bolivia up to the present time, *T. infestans* remains a public health problem mainly in the Andean areas since individuals from the wild colonies reinfest the houses, making the constant control of them, essential. The classical hypothesis on the origin of Chagas disease proposed that the dispersion of *Triatoma infestans* occurred during colonial times, when precarious dwellings made of mud that were disseminated throughout Brazil offered a suitable niche to which *T. infestans* became adapted (Dias 2000).

5.2.1 Intergovernmental Efforts to Interrupt the *Trypanosoma cruzi* Transmission by *Triatoma infestans*

At the present time, it became clear that, despite the multiples scenarios of *T. cruzi* transmission to humans, one in special highlights as the responsible for the vast majority of the thousands of yearly new cases: the contaminative transmission vectored by the domiciliary kissing bug *Triatoma infestans.* This vector species originated in the Andean Valleys of Bolivia, where it is found in the sylvatic environment (Cortez et al. 2010). The adaptation process to human housing probably occurred concomitantly with the beginning of human settlements close to forest environments and simultaneously to the process of domestication and breeding of guinea pigs that started to be maintained in breeding cages adjacent to these settlements (Cortez et al. 2010). This animal species breeding, from which it was expected to provide food supply for humans, also showed to be an important food source for hematophagous insects, including kissing bugs. After Americas' colonization, the greater movement of people and supplies helped to establish the domestic colonies of *T. infestans,* previously adapted to the human dwellings of the Bolivian Valleys, in different parts of Latin America, especially the Southern Cone.

Although derived from wild populations of *T. infestans,* still present in sylvatic areas of Bolivia and Paraguay, the vector populations that were disseminated throughout Brazil and other countries below the Amazon basin, was eminently domestic, fully adapted to this environment. As a result, *T. infestans* never become sylvatic in Brazil and this peculiarity helped to spread the parasite in the so-called domestic transmission cycles. The scenario that dominated the *T. cruzi* transmission to humans, maintaining high levels of Chagas disease incidence was based on an etiological agent transmitted by a single vector species that inhabited exclusively the intra-domiciliary wall cracks. Despite the elevated number of infested domiciles in a continental geographic dispersion, one single and homogeneous measure would expect to substantially impact *T. cruzi* transmission: the intra-domiciliary elimination of this vector. The insecticide spraying in human dwellings and attachments started to be implemented in 1975 in Brazil, when the Chagas Disease Control Program was created. The constant entomological and serological surveys defined the priority areas where the insecticide spraying would take place (Ramos Jr. and Carvalho Ramos and de Carvalho 2001). Along with this practical action, educational campaigns and house improvements (gradually replacing adobe for brick houses) were also established as complementary actions. Moreover, the modification of population profile, from about 70% of population living in rural areas in the 1950s to no more than 12% in the 2000s, also positively impact the in-house *T. cruzi* transmission. As a result, only about two decades after the implementation of these associated measures, the *T. cruzi* transmission by *T. infestans* was severally impacted.

In 2006, Brazil was certified as free of *T. cruzi* transmission by *T. infestans* (Schofield et al. 2006). Residual foci of *T. infestans* colonies are still observed in few areas, especially in semi-arid parts of Bahia state and in Rio de Grande do Sul state, in the extreme of south Brazil (Bedin et al. 2021). However, no *T. cruzi* infection is

observed in these colonies and this scenario is also observed in other Southern Cone countries and regions that are already certified (or in the process of certification) as free of *T. infestans* vectorial transmission. Currently, the better conditions of housing hamper the adaptation of other (sylvatic) vector populations to human dwellings. However, several triatominae species are described as having this potential, mainly: *Triatoma braziliensis, T. pseudomaculata, T. sordida*, and *Panstrongylus megistus* (Costa and Lorenzo 2009; Costa et al. 2021). The colonization process of these insects is generally associated with homes built with poor health conditions and rudimentary building techniques, such as mud and adobe huts (Walter et al. 2005; Gürtler and Yadon 2015). However, it is known that behavior change and insect's adaptation to a new (and completely different) environment, as is the case of the human domiciles for sylvatic vectors, constitute a long evolutionary process for triatomines (Schofield and Dias 1999). The good news is that the resistance ratios to deltamethrin in Brazil are considered low (RR50 < 8.0) (Pessoa et al. 2015). The *T. infestans* control, associated with the virtually absence of *T. cruzi* transmission due to blood and tissue transfusions, achieved some years before, led authorities to consider that in a few years, no more new cases of Chagas disease would be noticed. However, the maintenance of the sylvatic cycle, the presence of infected and sylvatic vectors inhabiting peridomestic areas and, mainly, the constant and increased human's exposition to wild environments, rapidly remembered all of us that the elimination of the transmission of an enzootic parasite is a goal not suitable to be achieved.

5.2.2 Chagas Disease After *T. Infestans* Control: Distinct Scenarios of Transmission and the Consequent Disease Outbreaks

Even 1 year before Brazil was certified as free of the *T. cruzi* intradomiciliary transmission by *T. infestans,* one major outbreak due to oral transmission was noticed in the margin of a highway that led to some rich destinies in South Brazil, just after the Carnival holiday. Thirty-three cases, dozens of hospital admission, and four deaths characterized this event that is still nowadays the higher Chagas disease outbreak noticed in Brazil. The sanitary investigation confirmed the consumption of contaminated sugarcane juice as the causative event of transmission to different families (Steindel et al. 2008). Despite the initial attempts to correlate any specific characteristic of the sugarcane plantations with triatomines, studies performed at that moment described the maintenance of *T. cruzi* in wild fauna (especially opossums) and the presence of infected *T. tibiamaculata* in palm trees very close to the establishment as the origin of human infections (Roque et al. 2008). The lack of care in the storage of sugarcane, as well as the lack of barriers to prevent the entry of insects attracted by light, resulted in infected insects (perhaps just one) being crushed together with the sugarcane, infecting the juice and leading to the oral infection of dozens of people. The terrible truth that emerged from this event was that wherever an infected sylvatic triatomine entered an establishment attracted to the light and was ground up or defecated into food, an oral outbreak of Chagas disease could occur.

Infected triatomines in forested areas around houses and dwellings is the common scenario in every rural area of entire country. In this way, as for example observed in Redenção, Ceará State, in Northern Brazil, Chagas disease oral outbreaks would be likely to occur anywhere and in an unexpected way (Roque et al. 2008).

The unexpected pattern cannot be attributed to the Amazon basin, where the majority of cases are currently reported (Santos et al. 2020). In this area, human dwellings are inserted inside the forest, and wild and domestic mammals interact in the same manner in the wild and domestic environment (Fig. 5.3). The fact that insects are attracted to light and contaminate food does not differ from the scenario above described.

In these areas, dog *T. cruzi* infection showed not only to be an efficient indicator of reduction of wild mammalian fauna richness but also signalize for the presence of small wild mammals with high parasitemia. The lower richness of small mammal species is discussed as a risk factor for the re-emergence of Chagas disease (das Xavier et al. 2012). This scenario requires a new approach to identify hotspot transmission areas and implement control measures. Monitoring of *T. cruzi* infection in dogs may be a valuable tool for detecting the fauna lower richness of small wild mammals and elucidating the transmission cycle of *T. cruzi* in the wild (das Xavier et al. 2012). The difference in the amazon basin is that houses rarely have windows or other protection against insect entry, the wooden cracks in the walls allow insects' free access to the houses and, in some areas, the habit of process açaí fruit (*Euterpe oleracea*) juice outside the houses, under artificial lighting, and precariousness sanitary and educational conditions is not an exceptional situation. On the contrary, it is a cultural rule that is related to familiar outbreaks and usually occurs in the more hot and dry period of year, coincident to the açaí harvest and triatomine's more often flying activities. Sometimes, infected bugs from one area (usually a sylvatic one) infest the panniers that transport the fruits for another area (usually an urban area) and are crushed with the fruits, resulting in human cases far from the origin of the infected bugs. This is the explanation for Belém, one of the largest urban areas in the Brazilian Amazon region, reporting the higher incidence of Chagas disease cases in Brazil. *T. cruzi* remote transmission by the transport of açaí baskets contaminated by infected triatomines has also been described. To this peculiar route of parasite dissemination, authors named as *Distantiae transmission* (Xavier et al. 2014). There are also areas in the Amazon where *T. cruzi* transmission occurs by oral or contaminative routes, by invading triatomines. The Chagas disease outbreaks associated to urban areas are much easier to be detected, both due to the usually higher number of infected people and the better health conditions in these urban centers. On the contrary, the familiar outbreaks in pristine areas where access to health professionals is difficult and people are usually not aware of the mechanisms of transmission and common symptoms (usually confused with malaria, common in the whole Amazonia) are underestimated in a still unknown magnitude.

As first hypothesized for sugarcane, also the açaí fruit (and its palms) was believed to present some characteristics that could attract and maybe favor the triatomines' presence. But this was further not confirmed because açaí palm trees usually present poor accumulation of organic material, the most important aspect

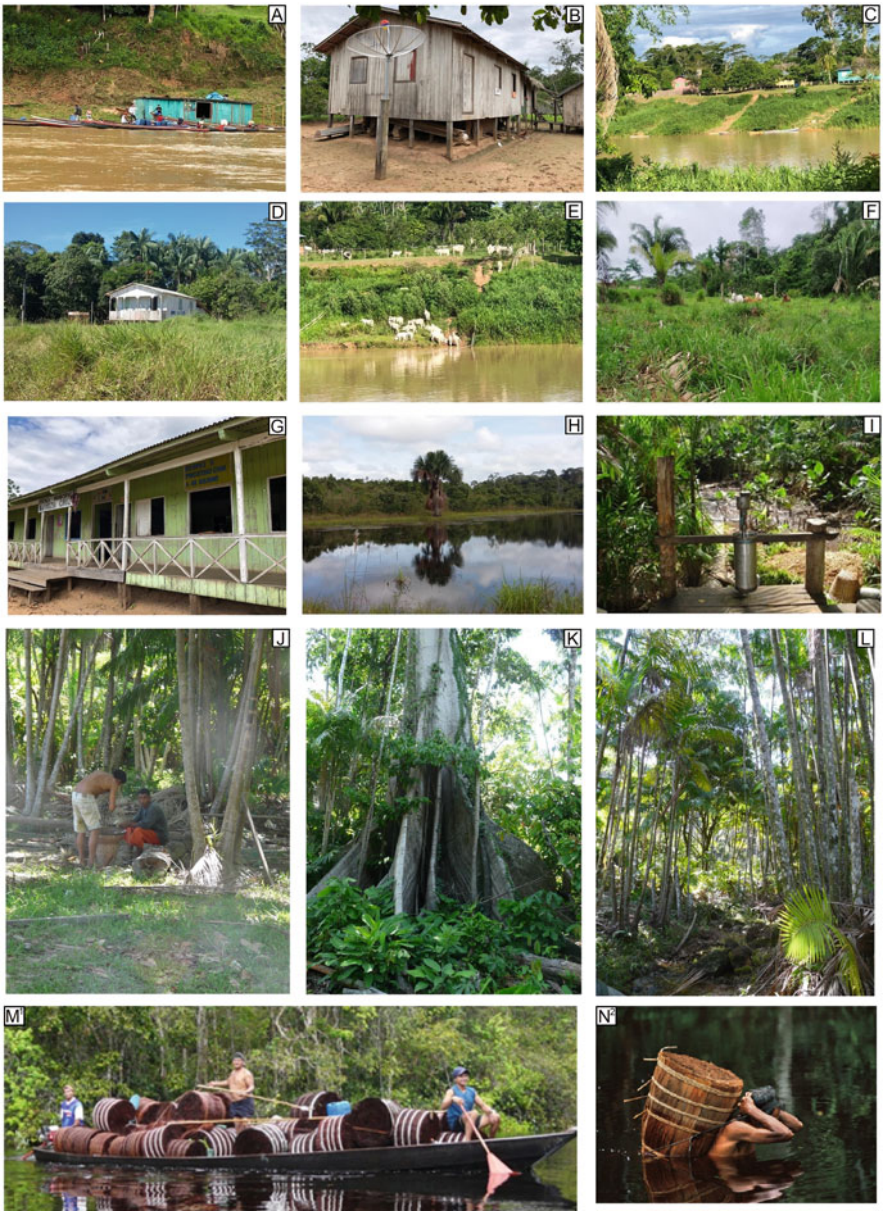


Fig. 5.3 Main scenarios of *Trypanosoma cruzi* transmission in areas of acute Chagas disease outbreaks in the Amazon biome. (**A**) Transport from the islands that provide the majority of the açaí fruit; (**B, C** and **D**) typical house in the Amazon, highlighting its proximity to the forest; (**E** and **F**) livestock areas in the Amazon; (**G**) rural school; (**H**) palm trees; (**I**) Community açaí fruit whisk in house's backyard; (**J** and **L**) The açaí palm, *Euterpe oleracea* and fruit collection; (**K**) samaúma (*Ceiba pentandra*); (**M**[1] and **N**[2]) occupational Chagas disease among piaçava (*Leopoldinia piassaba*) palm fiber gatherers (**M**[1]: https://thomazrural.com.br/2014/08/21/novo-preco-minimo-da-piacava/, **N**[2]: Araquém Alcântara, www.terrabrasilimagens.com.br)

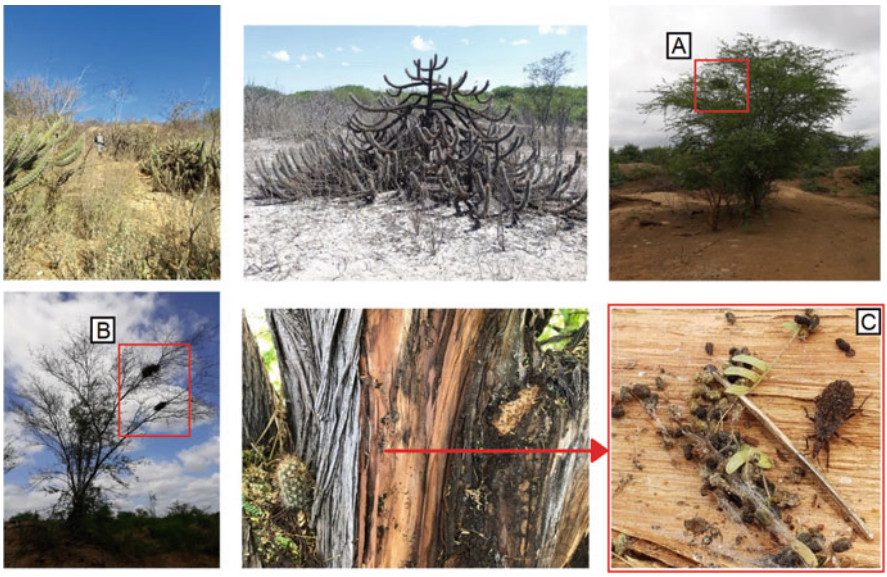


Fig. 5.4 *Trypanosoma cruzi* transmission scenario in the municipality of Ibimirim, in the state of Pernambuco, associated with the outbreak of acute Chagas disease, in the Caatinga biome. (**a** and **b**) Bird nests with the presence of *Triatoma pseudomaculata*, (**c**) *Triatoma pseudomaculata*

related to the presence of triatomines in Amazon trees (Abad-Franch et al. 2010). So, insects are probably attracted to the açaí fruit panniers during its storage and transportation as a consequence of the released of volatile gases, heat, light, and wind present on the banks of rivers, from where they are transported in small boats to the places where they will be sold (Jansen et al. 2020). The cases related to the consumption of other palm fruits juice, also as common as açaí in the Amazon region, as the bacaba (*Oenocarpus bacaba*) and the patawa tree (*Oenocarpus bataua*), shows that the *T. cruzi* transmission is associated to the way the fruit is processed (poor sanitary education bad food manipulation practices) and not with the characteristics of the fruit itself. In the case of outbreaks resulting from the consumption of bacaba juice contaminated with infected bug feces, cultural differences in consumption usually result in the infection of a greater number of people from a single contaminated juice, as observed in Ananás, Tocantins State, Brazil (Jansen et al. 2020).

Finally, not only beverages are associated with the outbreaks of Chagas disease in Brazil. Solid food as babaçu palm heart (Jansen et al. 2020) and also the direct contact of infected bug feces with mouth, as was the case of a 2-year-old boy (Dario et al. 2016) were also reported. Intriguingly, a recent outbreak that represented one of the largest even reported in Brazil (Ibimirim municipality, Brazil, in 2019) led to the infection of more than 30 people, and the food supply associated with the infections was never defined. Infected triatomines were found in a garden that provided vegetables for people staying there (Fig. 5.4). *T. cruzi* was isolated from a local

Didelphis albiventris, that is, there was enzootic transmission of the parasite in the area, which led to the never proven hypothesis of contamination of vegetables that were ingested without proper hygiene.

As can be seen, the current scenario of Chagas disease requires a different approach from the one adopted for the control of *T. infestans* in Brazil, which consisted of massive house spraying. The success of this measure was partly due to the fact that in Brazil *T. infestans* did not adapt to the wild environment.

The epidemiological scenario of Chagas disease is complex and requires the adoption of new surveillance and monitoring tools mainly in areas presenting more than one transmission mechanisms. *T. cruzi* transmission in the wild is focal; therefore, cartography is a highly promising tool in detecting hot-spots transmission areas and different epidemiological scenarios of Chagas disease.

Chagas disease outbreaks will continue to challenge the health authorities concerning the heterogeneity of clinical signs presented by the patients (which vary according to the initial parasite load and route of infection), environmental scenario (proximity of infected mammals and/or vectors) to which humans are exposed and, mainly, due to the lack of knowledge of the numerous variables involved in these outbreaks. For sure, such different scenarios of transmission point to different (and locally specific) control measures which only will be effective if planned and executed under a transdisciplinary focus. This is particularly true for the açaí production area of the Pará state in Brazil. Although apparently the cases of Chagas disease in these areas display the same common epidemiological history, that is, the consumption of the same infection source (açaí juice) and infection route (oral), there are local differences that need to be evaluated. Was the infection acquired inside houses by triatomine that invade the houses and fell into some food bowl or did the infected insects attracted by light feel in the açaí mixer? Were the characteristics of the enzootic cycle also similar?

There are many steps of preparation of the açaí juice before consuming it during which, there may have been contamination: harvesting and transporting the fruits, softening the fruits in warm water and finally the way people obtain the pulp of the fruit. These steps may be regionally peculiar; therefore, contamination can occur in each of these stages according to the açaí juice preparation schedule.

The collection of açaí is done manually and the açaí bunches are placed on the ground. Then, the fruits are placed in a large container with water at approximately 60 °C to soften the fine pulp of the fruit, thus facilitating its extraction. Afterward, the fruits are generally pulped in handcrafted mechanical devices called "açaí mixers." These açaí mixers are normally exposed to environment since they are located in areas close to the kitchen, which allows insects to be attracted by artificial lighting (açaí is prepared in the morning and evening twilight) and to fall into the açaí mixer or into the freshly prepared juice. The even poorer riverside populations do not have açaí mixers thus, they pulp the fruit manually and sometimes even heat the water up to 60 °C and, what is worse, they do not change the water. In the rainy season, rivers often become muddy and the population uses stored rainwater, that is, all waste of clean water needs to be avoided. In addition, there is also the fact that the baskets full of fruit waiting on the pier to be transported to the larger cities, eliminate

CO_2, which is an attraction factor for triatomines. The outbreaks of Chagas disease in Amazonas would certainly diminish significantly if the fruit juice was properly prepared. In fact, the number of outbreaks of Chagas disease through oral transmission has steadily increased due to the national and international interest in açaí.

5.2.3 The Niche Modeling as a Promising Method to Forecast *Trypanosoma Cruzi* High Transmission Areas

The ecological niche of a parasite is its host that, in turn, is subject to different types of selective pressures, whether biotic, such as predation, food opportunity, competition, reproductive investment, or abiotic, such as climate conditions. Thus, it is not possible to understand parasitism without considering environmental conditions and at all the intrinsic and complex interactions that occur in this environment. The ecological niche modeling used to study host–parasite interactions seeks to comprehend and explain all the complexity of the host–parasite interaction in a given environment.

Although Ecological Niche Modeling (ENM) is widely used to study the distribution of mammals and vectors in geographic and environmental space, it only recently has increasingly gained interest in the study of parasites. Parasitism is a phenomenon that involves the interaction between different species, with different degrees of dependence in a given environment that therefore presents spatial and temporal peculiarities. Actually, Cartographic studies, with applications of Geoprocessing tools, can contribute to a better understanding of the parasite/host/environment triad.

The definition of the Ecological Niche began to be discussed at the beginning of the twentieth century by Joseph Grinnell (1917) and Charles Elton (1927) under two distinct focuses, the first based on the importance of the environmental characteristics, and the second related to kind of interactions between species. For Grinnell (1917), the geographic distribution of species is a response to environmental variables, treating environmental and habitat requirements as defining factors of their home ranges, allowing their presence, survival, and reproduction. However, Elton (1927) defined the ecological niche as the functional relationship of species in community, and the interaction between them as the factor that influences the geographic distribution.

Although these two approaches seem antagonistic in the definition of niche, in reality, they are complementary to each other, their first interconnection occurring in Hutchinson's (Hutchinson 1957) innovative and elegant definition of ecological niche as the sum of all the environmental factors that act on a given organism, like a hyper-volume with n-dimensions. Hutchinson (1957) separated the ecological niche in i) the Fundamental Niche (FN), which corresponds to the environmental characteristics that allow the species to live indefinitely, and ii) the Realized Niche (RN), which, due to the competition between species and local environmental characteristics favors the more adapted species by competitive exclusion (Gause 1936).

What are the ecological interactions involved in the environment/host/parasite triad? Specifically concerning *T. cruzi*: its host species—mammals and triatomine vectors—have their own ecological niches, which are related to biotic and abiotic characteristics in the geographic space, while the parasite has its niche in the host organism, and is, therefore, influenced by the niche itself (of the mammal or vector) (Jansen et al. 2015). In this interaction, the parasite may negatively affect the phenotypic characteristics and behavior of the host, influencing its morphology, foraging, and habitat use, due to pathological consequences and the energy costs involved in the movement, restricting the host's niche to the niche of the infected host (Rohde 1994; Britton and Andreou 2016). However, this is still a possibility without a concrete answer, due to the difficulty of measuring these impacts of *T. cruzi* on free-living wild host health (Jansen et al. 2015).

ENM applications have demonstrated to be able to clarify directly or indirectly the ecology of the environment/host/parasite triad, both for the identification of areas of the potential presence of infection in hosts, as well as for the identification of suitable areas for the presence of mammals, hosts, and vectors (Gurgel-Gonçalves et al. 2012; Meyer et al. 2014; Ramsey et al. 2015; Parra-Henao et al. 2016a, b; Cáceres et al. 2016; Izeta-Alberdi et al. 2016; Ferro e Silva et al. 2018; Kindler et al. 2020).

Geospatial analysis is based on the concept of landscape epidemiology (Pavlovsky 1939) and is a tool that has been increasingly used in studies of vector-borne multi-host parasites. Understanding the landscape where transmission takes place makes it possible to model and identify possible high transmission areas and consequently the risk of disease of a target species. The knowledge of the wild cycle of *T. cruzi* transmission depends on the understanding of the ratio between the richness diversity of potential of reservoir mammals, vectors and their function in the ecosystem, rate of infection prevalence, parasitemic level and pattern of infection. For this reason, data on the distribution of triatomine and wild and domestic mammal hosts are used in combination with environmental, anthropogenic, demographic, and socioeconomic factors to model the risk of transmission of *T. cruzi* and its DTUs.

There are some diversity metrics that should be considered. Thus, the beta-diversity concept was originally developed to estimate the variation in species composition of free-living organisms, in which spatial renewal is due to the replacement of species by others, from location to location (turnover). Nesting, a parasite can optimally exploit a subset of host species that are regionally restricted (nested host communities), which may reflect a non-random situation of species loss as a consequence of any factor that promotes orderly disaggregation (Baselga 2010; Krasnov et al. 2011; Izeta-Alberdi et al. 2016).

Baselga (2010) proposed a technique to separate the effect of turnover (species replacing rates in different regions) and nesting in the calculation of beta-diversity, as they are additive and antagonistic. An additive partition of beta-diversity that provides the two separate components of spatial rotation and nesting underlying the total amount of beta-diversity, two families of beta-diversity measures for peer and multi-site situations. Each family comprises a measure responsible for all aspects of beta-diversity, which is additively decomposed into two measures responsible for

pure spatial turnover and nesting components, respectively. Attributing the different beta-diversity patterns to their respective biological phenomena is essential to analyze the causality of processes underlying biodiversity.

Parasite specificity is often measured as the number of host species that a parasite is able to infect, sometimes even without considering the genetic distance between these host species. However, this situation can be totally changed in the temporal scale and in accordance with an eventual alteration of the local faunal composition. In fact, the immigration of new species to a particular location can result in the expansion (or reduction) of the host spectrum that will be exploited by a particular parasite. This becomes even more complex in the case of the transmission cycle of a heterogeneous, multi-host, and pan-infective parasite such as *T. cruzi*. To capture these spatial nuances of host specificity, it was proposed to use an index to assess the rate of host species replacement between localities at beta-specificity a β (SPF), which is derived from studies of spatial patterns in the diversity of plants and animals. It was concluded that: (1) beta-specificity is statistically independent of traditional parasite metrics and (2) it is also independent of the size of the studied geographic area or of the host and parasite sampling effort. In addition, beta-specificity considers the phylogenetic proximity in order to distribute β (SPF) values between species, that is, more related species have β (SPF) values more similar than expected by chance. However, most possible combinations of local specificity (alpha specificity) or global (gamma specificity) and beta-specificity are observed, suggesting that adding a spatial component to host use studies will reveal a new facet of specificity. This emergence provides a new perspective on parasite specificity at a scale relevant to studies ranging from biogeography to evolution to the rate and extent of parasite transmission (Krasnov et al. 2011).

Considering mammalian hosts and vectors Izeta-Alberdi et al. (2016) performed, based on metadata, the analysis of beta-specificity for all DTUs of *T. cruzi*. These authors found values that point to a high rate of species renewal in different areas of the American continent. Concerning triatomine and three orders of mammals it was concluded that, on a geographic scale, *T. cruzi* is an opportunistic parasite since its free beta-specificity for species exchange was greater than the nesting (reduction of host diversity) for all 7 DTUs. The beta-diversity of DTU was generally high, indicating highly diverse host numbers across regions.

In addition to the beta-specificity analysis, Izeta-Alberdi et al. (2016) performed ecological niche modeling for the 6 DTUs (TcI-TcVI) across the American continent, individually, finding that, according to the models, TcIV extends from the Nearctic region of Mexico, through the southeastern US to Argentina; TcIII projects a narrower range, from southern Mexico to Argentina, with less coverage on the drier Pacific coast; TcI is distributed throughout the Neotropical region from mid-Mexico to northeastern Argentina; TcII has a much more sparse geographic projection, occurring mainly in Central America and in the non-Amazonian regions of Venezuela and southern Brazil; and TcV and TcVI are more concentrated, although focused on the non-equatorial Neotropical regions of the continent (Mexico, Central America, southern Brazil, Bolivia).

An application for these niche concepts on parasitology was proposed Villalobos et al. (2019), in which the Maxent machine learning algorithm was applied to model areas with potential environmental suitability for the presence of triatomines and their infection by *T. cruzi*. As a result, it was identified that the infection limited the ability of triatomines to move, keeping them with the greatest suitability in the centroid of the vector distribution.

This technique is known as Ecological Niche Modeling (ENM), which aims to estimate the Existing Fundamental Niche ("potential niche") of a species using the variations of the environmental characteristics where its points of occurrence are located and predicting the areas of potential suitability for the presence of this species (Peterson 2011). Data on the presence of the target species and the environmental variables are processed in machine learning algorithms and statistical methods by Multiple Regression (MR: Multiple Regression); Linear Models (GAM: Generalized Additive Models); Classification Trees (CTA: Classification Tree Analysis); Genetic Algorithms (GA: Genetic Algorithm); Neural Networks (MN: Neural Networks); DOMAIN; FloraMap; Maxent, among others (Soberon and Peterson 2005; de Siqueira 2005; Giannini et al. 2012).

Ferro and Silva et al. (Ferro e Silva et al. 2018), used ecological niche modeling to identify areas with a potential risk of transmission of *T. cruzi* in the state of Paraná, using climatic and landscape variables in separate approaches, modeling the distribution areas of the triatomines *Panstrongylus megistus*, *Panstrongylus geniculatus, Rhodnius neglectus, Rhodnius prolixus*, and *Triatoma sordida*. To analyze their models, Ferro and Silva et al. (Ferro e Silva et al. 2018) developed the Ecoland approach, which is based on the possibility that models that use only climate variables and models that use only landscape variables can result in contradictory distribution patterns of suitability for a species. Climatic and landscape variables, such as temperature, precipitation, relative humidity, vegetation and wind speed and its temperature, are factors that admittedly influence the life dynamics, dispersion, and search for food sources of triatomines (Forattini et al. 1978; Zeledon and Rabinovich 1981; Gonçalves et al. 1998; Abrahan et al. 2011; dos Santos et al. 2013; Parra-Henao et al. 2016a).

This approach performs a comparative analysis by applying map algebra between the models generated in a climatic approach and in a landscape approach at a municipality level. Subsequently, the classification of high, medium, and low concordance and discordance between these approaches is performed resulting in a simplified way of mapping areas of potential distribution of triatomines.

An application of ENM for niche analysis of *T. cruzi* infection in the Southeast and South of the Atlantic Forest biome was performed. This study aimed at Ecological Niche Modeling for triatomines as well as *T. cruzi* infected and uninfected *Didelphis aurita*. *T. cruzi* infection was determined by blood culture in axenic medium and positive testing *D. aurita* pointed to potential transmission areas. The two main triatomine species *Triatoma vitticeps* and *Panstrongylus megistus* were used as explanatory biotic variables for *T. cruzi* infection in *D. aurita*.

The modeling of *D. aurita* was carried out under two approaches, one that used only climate variables, and one that considered only landscape variables. Four

Table 5.1 Environmental variables climate and landscape, used in the modeling of *Triatoma vitticeps* and *Panstrongylus megistus* in the Southeast and South of the Atlantic Forest biome

Variables	Spatial resolution
Mean diurnal range (BIO 2)	30 arc-second (~1 km^2)[a]
Max temperature of warmest month (BIO 5)	30 arc-second (~1 km^2)[a]
Annual precipitation (BIO 12)	30 arc-second (~1 km^2)[a]
Precipitation of wettest month (BIO 13)	30 arc-second (~1 km^2)[a]
Precipitation of driest month (BIO 14)	30 arc-second (~1 km^2)[a]
Wind speed range	30 arc-second (~1 km^2)[a]
Water vapor pressure range	30 arc-second (~1 km^2)[a]
Normalized difference vegetation index (NDVI)	30 arc-second (~1 km^2)[b]

[a] Worldclim (https://www.worldclim.org/data/worldclim21.html)
[b] Google Earth Engine (https://developers.google.com/earth-engine/datasets/catalog)

models were produced (Uninfected *D. aurita*, climate and landscape, and infected *D. aurita* climate and landscape). The division of these models aimed to analyze the different areas of suitability for the presence of the marsupial and its infection in climate and landscape models (Ferro e Silva et al. 2018). The modleR package of MNE was used, in the R programming language, performing the modeling with the algorithms: Bioclim, Maxent, Random Forest, SVM (Support Vector Machine), GLM (Generalized Linear Model), Mahalanobis Distance, DOMAIN and BRT (Boosted Regression Trees).

Weather data were acquired from the Wordclim website, and landscape data from the Google Earth Engine (GEE) platform and the IBGE website. The variables used for the modeling of triatomines and *D. aurita* are shown in Tables 5.1 and 5.2.

An analysis of climate models + landscape was performed using the Ecoland method (Ferro e Silva et al. 2018), applying a map algebra between the models to verify the locations of agreement and disagreement between these two approaches. For this, the Districts (available on the IBGE website) were defined as the analysis scale, which were classified into three categories of environmental suitability (β), being high ($\beta \geq 66.67\%$), medium ($33.33\% \leq \beta < 66.67\%$) and low ($0 \leq \beta < 33.33\%$). For the analysis by Ecoland for *D. aurita*, in addition to relating the climate and landscape models, the sum of the niche models of *T. vitticeps* and *P. megistus* was also included.

Through these models, it was possible to identify the different scenarios in which *D. aurita* can act as a potential reservoir in three areas where cases and/or outbreaks of acute Chagas disease—ACD occurred in the Southeast and South of the Atlantic Forest biome.

5.2.3.1 Modeling *Didelphis Aurita* and Its *Trypanosoma Cruzi* Infection: Navegates—Santa Catarina, Brazil

Figure 5.5 shows a comparative analysis performed between the climate and landscape models and the Ecoland analysis, respectively, for the municipality of Navegantes-SC, area of the ACD outbreak in 2005 (Roque et al. 2008), when comparing climate and landscape models for *D. aurita* and its infection by *T. cruzi*

Table 5.2 Climate and landscape variables used in modeling *Didelphis aurita* and its infection by *Trypanosoma cruzi* (positive blood culture)

Variables	Resolution
Mean diurnal range (BIO 2)	30 arc-second (~1 km^2)[1]
Temperature seasonality (BIO 4)	30 arc-second (~1 km^2)[b]
Max temperature of warmest month (BIO 5)	30 arc-second (~1 km^2)[b]
Mean temperature of wettest quarter (BIO 8)	30 arc-second (~1 km^2)[b]
Mean temperature of driest quarter (BIO 9)	30 arc-second (~1 km^2)[b]
Annual precipitation (BIO 12)	30 arc-second (~1 km^2)[b]
Precipitation of wettest month (BIO 13)	30 arc-second (~1 km^2)[b]
Precipitation seasonality (BIO 15)	30 arc-second (~1 km^2)[b]
Normalized difference vegetation index (NDVI)	30 arc-second (~1 km^2)[a]
Euclidean distance to nearest location with human presence	~1 km^2 (GHSL)[b]
Euclidean distance to the nearest drainage section	(~1 km^2)[c]
Ecological niche model of *Triatoma vitticeps*	30 arc-second (~1 km^2)
Ecological niche model of *Panstrongylus megistus*	30 arc-second (~1 km^2)

The variables "*Triatoma vitticeps* ecological niche model" and "*Panstrongylus megistus* ecological niche model" were included only in the modeling of *D. aurita* infected by *T. cruzi*
[a] Google Earth Engine (https://developers.google.com/earth-engine/datasets/catalog);
[b] Worldclim (https://www.worldclim.org/data/worldclim21.html);
[c] Brazilian Institute of Geography and Statistics—IBGE—(11,000,000 e 125,000) (https://www.ibge.gov.br/geociencias/downloads-geociencias.html).

Navegantes demonstrated high climatic and landscape suitability for the presence of *D. aurita*, with values ranging from [63%–69%] and [36%–98%], respectively. Infected *D. aurita*, were found inside the areas with environmental suitability [27%–71%] and [17%–97%], respectively.

By the comparative analysis of the Ecoland approaches between the models of the presence of *D. aurita* and *D. aurita* infected by *T. cruzi* (Fig. 5.5), Navegantes presents an agreement between climate and landscape for high suitability in the *D. aurita* model, with averages of 68.5%, 97%. However, paradoxically it is an area that displays low suitability for the presence of *T. vitticeps* and *P. megistus* (25.03%). This result indicates that other species may are acting as vectors. In fact, *Triatoma tibiamaculata* was the species found in palm trees at the site of the ACD outbreak (Roque et al. 2008), and this is a species that demonstrated suitability in this municipality (Galvão 2014).

Navegantes was classified by the Ecoland model as displaying high suitability for the presence of *D. aurita* infected by *T. cruzi*, with an average value of 70.4% for climate and 95.3% for landscape. This showing that this municipality display high suitability, for the presence of *D. aurita* and for its infection by *T. cruzi* and role as a reservoir for *T. cruzi* in the area as proposed by Roque et al. (Roque et al. 2008), based on parasitological and serological tests. These intensities of suitability can be better visualized on the map of Fig. 5.6.

Finally, the joint analysis of Ecological Niche Modeling and Ecoland proved to be a sensitive method for identifying areas of suitability for the presence of *D. aurita*,

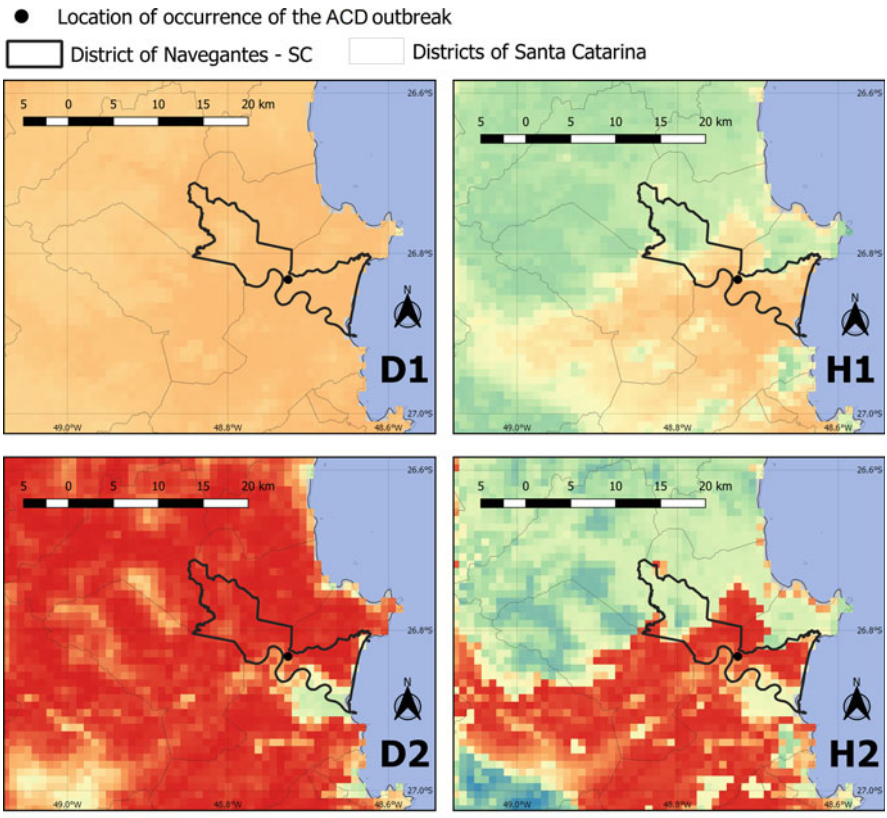


Fig. 5.5 Comparison between climate models and landscape for *Didelphis aurita* and *Didelphis aurita* infected by *Trypanosoma cruzi* in the municipality of Navegantes—Santa Catarina, Brazil. **D1** Ecological niche model of *D. aurita* in the climatic approach, for the district of Navegantes—SC, **H1** Ecological niche model of *D. aurita* infected by *T. cruzi* in the climatic approach, for the district of Navegantes—SC, **D2** Ecological niche model of *D. aurita* in the landscape approach, for the district of Navegantes—SC, **H2** Ecological niche model of *D. aurita* infected by *T. cruzi* in the landscape approach, for the district of Navegantes—SC

infected or not by *T. cruzi*. In Navegantes-SC, in the area of Chagas disease outbreak, it was indicated as being highly suitable for the presence of *D. aurita*, with and without *T. cruzi infection*. The high suitability of a given region is a necessary, but not sufficient, condition for the performance of *D. aurita* as a reservoir for *T. cruzi*. As an example, Ecoland demonstrated that *D. aurita* has different importance as a reservoir of *T. cruzi* in different locations of the Atlantic Forest.

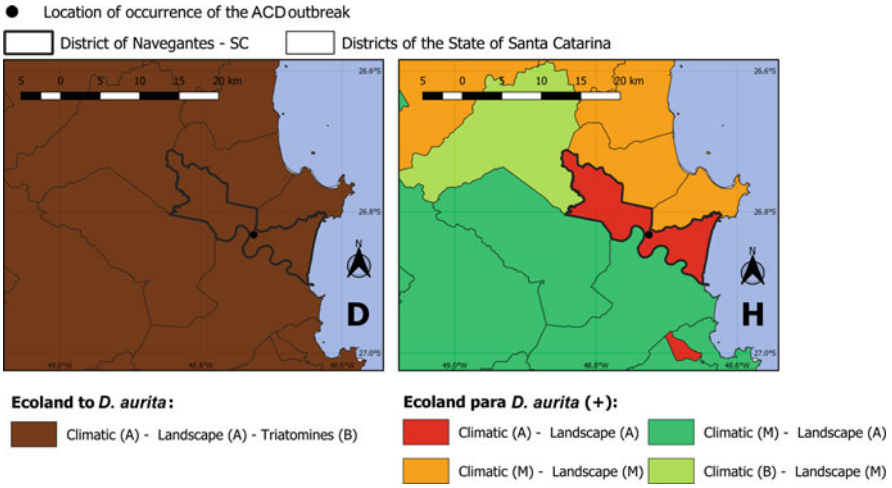


Fig. 5.6 Comparison between Ecoland for *Didelphis aurita* and its infection by *Trypanosoma cruzi* in the city of Navegantes—Santa Catarina, Brazil. **D** Ecoland analysis for the distribution of *D. aurita*, in the district of Navegantes—SC, **H** Ecoland analysis for the distribution of *D. aurita* infected by *T. cruzi*, in the district of Navegantes—SC

5.2.3.2 Modeling *Didelphis Aurita* and Its *Trypanosoma Cruzi* Infection: Guarapari—Espírito Santo, Brazil

In Espírito Santo, Dario et al. (2016) carried out a study to investigate a fatal case of ACD that occurred in the city of Guarapari, by the oral contamination of a child that put his fingers in the mouth after manipulating an infected *T. vitticeps*. The characterization of heart tissue demonstrated that this child was infected by *T. dionisii* and *T. cruzi* TcI, TcII, TcIII and TcIV genotypes. Later, Dario et al. (2017) confirmed the hypothesis that, in the region, bats act as the main reservoirs of *T. cruzi*, while *T. vitticeps* is the main triatomine vector found in this area, with high rates of single and mixed infections by *T. cruzi and T. dionisii*. Dogs of the locality displayed negative results for *T. cruzi* infection by serological and parasitological tests. The same results were observed in the local small wild mammals except one opossum *D. aurita*. High rates of *T. cruzi* infection were observed in the adult *T. vitticeps* that very often invaded the local houses infected with the same DTUs that have been observed in the heart tissue of the infected child. Rare nymphs were found but no sign of triatomine colonization could be observed.

When comparing the climate and landscape models for *D. aurita* without and with *T. cruzi* infection, in Fig. 5.7, the D1 model showed high climatic suitability for the presence of marsupial in the municipality of Guarapari, from 67% to 83%, while for its infection by *T. cruzi* (H1) the suitability was drastically reduced to values from 25% to 87%, where only its coastline has suitability above 40%. For the landscape, almost all of its territory (approximately 98%) presents suitability above 50%, D2, with pixels with high suitability prevailing. However, for the H2 model, the landscape followed the same pattern that occurred for the D1 and H1 models, in which

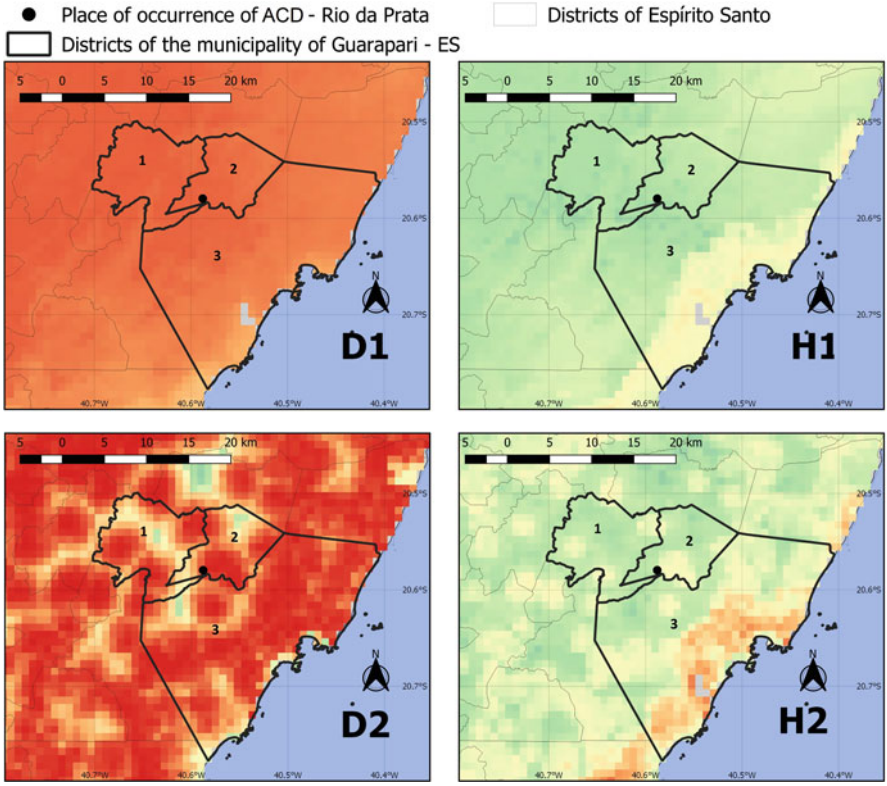


Fig. 5.7 Comparison between climate and landscape models for *Didelphis aurita* and its infection by *Trypanosoma cruzi* in the city of Guarapari—Espírito Santo, Brazil. **D1** Ecological niche model of *D. aurita* in the climatic approach, for the districts of the municipality of Guarapari—ES, **H1** Ecological niche model of *D. aurita* infected by *T. cruzi* in the climatic approach, for the districts of the municipality of Guarapari—ES, **D2** Ecological niche model of *D. aurita* in the landscape approach, for the districts of the municipality of Guarapari—ES, **H2** Ecological niche model of *D. aurita* infected by *T. cruzi* in the landscape approach, for the districts of the municipality of Guarapari—ES, **1** Todos os Santos, **2** Rio Calçado, **3** Guarapari

only the coast of the municipality (Guarapari) as indicated with medium and high suitability, ranging from 22% to 85%, while in the locality (Rio da Prata) were the case of ACD occurred, ranged between 22% and 50%, with more pixels of low adequacy than average.

By analyzing *D. aurita's* Ecoland (Fig. 5.8), the three districts of Guarapari were classified as having high climate, landscape, and presence of triatomines. As for *D. aurita* infected by *T. cruzi*, the two most coastal districts were classified with the agreement of medium suitability for climate and landscape, while the innermost district was classified as low for climate and medium for landscape.

These results indicate that, although Guarapari is a municipality with very high suitability for the presence of *D. aurita*, it is not suitable for the occurrence of

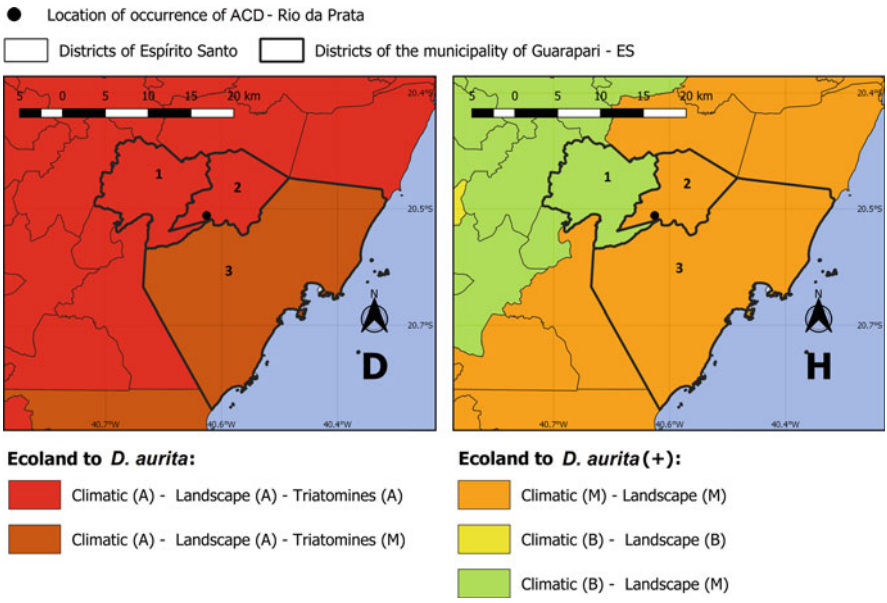


Fig. 5.8 Comparison between Ecoland approaches for *Didelphis aurita* and its infection by *Trypanosoma cruzi* in the city of Guarapari—Espírito Santo, Brazil. **D** Ecoland analysis for the distribution of *D. aurita*, for the districts of the municipality of Guarapari—ES, **H** Ecoland analysis for the distribution of *D. aurita* infected by *T. cruzi*, for the districts of the municipality of Guarapari—ES, **1** Todos os Santos, **2** Rio Calçado, **3** Guarapari

D. aurita infected by *T. cruzi*, despite the high suitability for the presence of triatomines (mainly *T. vitticeps*). Thus, these results are in agreement with the work of Dario et al. (2017), indicating none of the sylvatic animal does act as the main host of *T. cruzi* in the region, in addition show that CD cases can occur without an enzootic cycle near residential areas.

This is an example of the complexity diversity of the epidemiological scenarios of Chagas disease. But the already mentioned other cases and outbreaks in different epidemiological scenarios, show the importance of taking a comprehensive and multidisciplinary look at each situation. All together show that effective control strategies must consider socioeconomic and cultural aspects of each vulnerable population. But, regardless of the strategy, investing in education and scientific dissemination will be a mandatory path to reduce the occurrence of Chagas disease outbreaks.

Prehistoric people very probably became infected by oral and by the contaminative route. Consumption of raw meat was not exceptional as well as the contact with triatomines in natural shelters where our ancestors sought shelter to rest from excessive heat or storms. Again, as pointed above, oral route is turning important. In fact, over time, Chagas disease assumed and still assumes different epidemiological pictures, always in accordance with the human "*modus vivendi*" but always

mostly related to the most socially vulnerable people. It is currently mainly a food-borne disease and one of the more neglected diseases.

References

Abad-Franch F, Ferraz G, Campos C, Palomeque FS, Grijalva MJ, Aguilar HM, Miles MA (2010) Modeling disease vector occurrence when detection is imperfect: infestation of Amazonian palm trees by Triatomine bugs at three spatial scales. PLoS Negl Trop Dis 4(3):e620. https://doi.org/10.1371/journal.pntd.0000620

Abrahan LB, Gorla DE, Catalá SS (2011) Dispersal of *Triatoma infestans* and other Triatominae species in the arid Chaco of Argentina: flying, walking or passive carriage? The importance of walking females. Mem Inst Oswaldo Cruz 106(2):232–239. https://doi.org/10.1590/S0074-02762011000200019

Adl SM, Bass D, Lane CE, Lukeš J, Schoch CL, Smirnov A, Agatha S, Berney C, Brown MW, Burki F, Cárdenas P, Čepička I, Chistyakova L, del Campo J, Dunthorn M, Edvardsen B, Eglit Y, Guillou L, Hampl V, Heiss AA, Hoppenrath M, James TY, Karnkowska A, Karpov S, Kim E, Kolisko M, Kudryavtsev A, Lahr DJG, Lara E, Gall LL, Lynn DH, Mann DG, Massana R, Mitchell EAD, Morrow C, Park JS, Pawlowski JW, Powell MJ, Richter DJ, Rueckert S, Shadwick L, Shimano S, Spiegel FW, Torruella G, Youssef N, Zlatogursky V, Zhang Q (2019) Revisions to the classification, nomenclature, and diversity of eukaryotes. J Eukaryot Microbiol 66(1):4–119. https://doi.org/10.1111/jeu.12691

Agosta SJ, Klemens JA (2008) Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution. Ecol Lett 11(11):1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Araujo SBL, Braga MP, Brooks DR, Agosta SJ, Hoberg EP, von Hartenthal FW, Boeger WA (2015) Understanding host-switching by ecological fitting. PLoS One 10(10):e0139225. https://doi.org/10.1371/journal.pone.0139225

Aufderheide AC, Salo W, Madden M, Streitz J, Buikstra J, Guhl F, Arriaza B, Renier C, Wittmers LE, Fornaciari G, Allison M (2004) A 9,000-year record of Chagas' disease. PNAS 101(7):2034–2039. https://doi.org/10.1073/pnas.0307312101

Baselga A (2010) Partitioning the turnover and nestedness components of beta diversity. Glob Ecol Biogeogr 19(1):134–143. https://doi.org/10.1111/j.1466-8238.2009.00490.x

Bedin C, Wilhelms T, Villela MM, da Silva GCC, Riffel APK, Sackis P, de Mello F (2021) Residual foci of *Triatoma infestans* infestation: surveillance and control in Rio Grande do Sul, Brazil, 2001-2018. Rev Soc Bras Med Trop 54. https://doi.org/10.1590/0037-8682-0530-2020

Britton JR, Andreou D (2016) Parasitism as a driver of trophic niche specialisation. Trends Parasitol 32(6):437–445. https://doi.org/10.1016/j.pt.2016.02.007

Cáceres NC, de Moraes WM, Melo GL, Meloro C, Sponchiado J, dos Carvalho RS, de Bubadué JM (2016) Which factors determine spatial segregation in the south American opossums (*Didelphis aurita* and *D. albiventris*)? An ecological niche modelling and geometric Morphometrics approach. PLoS One 11(6):e0157723. https://doi.org/10.1371/journal.pone.0157723

Camargo EP (1999) Phytomonas and other Trypanosomatid parasites of plants and fruit**this review is dedicated to the memory of Franklin G. Wallace, a pioneer in the modern taxonomy of Trypanosomatids. In: Baker JR, Muller R, Rollinson D (eds) Advances in parasitology. Academic Press, pp 29–112

Carmody RN, Dannemann M, Briggs AW, Nickel B, Groopman EE, Wrangham RW, Kelso J (2016) Genetic evidence of human adaptation to a cooked diet. Genome Biol Evol 8(4):1091–1103. https://doi.org/10.1093/gbe/evw059

Cortez MR, Monteiro FA, Noireau F (2010) New insights on the spread of *Triatoma infestans* from Bolivia—implications for Chagas disease emergence in the southern cone. Infect Genet Evol 10(2):350–353

Costa J, Lorenzo M (2009) Biology, diversity and strategies for the monitoring and control of triatomines—Chagas disease vectors. Mem Inst Oswaldo Cruz 104:46–51. https://doi.org/10.1590/S0074-02762009000900008

Costa J, Dale C, Galvão C, Almeida CE, Dujardin JP (2021) Do the new triatomine species pose new challenges or strategies for monitoring Chagas disease? An overview from 1979–2021. Mem Inst Oswaldo Cruz 116. https://doi.org/10.1590/0074-02760210015

d'Avila-Levy CM, Boucinha C, Kostygov A, Santos HLC, Morelli KA, Grybchuk-Ieremenko A, Duval L, Votýpka J, Yurchenko V, Grellier P, Lukeš J (2015) Exploring the environmental diversity of kinetoplastid flagellates in the high-throughput DNA sequencing era. Mem Inst Oswaldo Cruz 110:956–965. https://doi.org/10.1590/0074-02760150253

Dario MA, Rodrigues MS, da Barros JHS, das Xavier SCC, D'Andrea PS, Roque ALR, Jansen AM (2016) Ecological scenario and *Trypanosoma cruzi* DTU characterization of a fatal acute Chagas disease case transmitted orally (Espírito Santo state, Brazil). Parasites Vectors 9(1): 477. https://doi.org/10.1186/s13071-016-1754-4

Dario MA, Lisboa CV, Costa LM, Moratelli R, Nascimento MP, Costa LP, Leite YLR, Llewellyn MS, das Xavier SCC, ALR R, Jansen AM (2017) High *Trypanosoma* spp. diversity is maintained by bats and triatomines in Espírito Santo state. Brazil PLoS One 12(11): e0188412. https://doi.org/10.1371/journal.pone.0188412

Dario MA, Lisboa CV, Silva MV, Herrera HM, Rocha FL, Furtado MC, Moratelli R, Rodrigues Roque AL, Jansen AM (2021) *Crithidia mellificae* infection in different mammalian species in Brazil. Int. J. Parasitol.: Parasites Wildlife 15:58–69. https://doi.org/10.1016/j.ijppaw.2021.04.003

das Xavier SCC, Roque ALR, dos Lima VS, Monteiro KJL, Otaviano JCR, da Ferreira Silva LFC, Jansen AM (2012) Lower richness of small wild mammal species and Chagas disease risk. PLoS Negl Trop Dis 6(5):e1647. https://doi.org/10.1371/journal.pntd.0001647

de Bary A (1879) Die Erscheinung der Symbiose. Verlag von Karl J, Trübner, Strassburg

de Siqueira MF (2005) Uso de modelagem de nicho fundamental na avaliação do padrão de distribuição geográfica de espécies vegetais. Text, Universidade de São Paulo

De Souza W, Barrias ES (2020) May the epimastigote form of *Trypanosoma cruzi* be infective? Acta Trop 212:105688. https://doi.org/10.1016/j.actatropica.2020.105688

Deane MP, Jansen AM (1988) From a mono to a digenetic life-cycle: how was the jump for flagellates of the family Trypanosomatidae? Mem Inst Oswaldo Cruz 83:273–275. https://doi.org/10.1590/S0074-02761988000300002

Dias JCP (2000) Vigilância epidemiológica em doença de Chagas. Cad Saúde Pública 16:S43–S59. https://doi.org/10.1590/S0102-311X2000000800005

Dobson A, Lafferty KD, Kuris AM, Hechinger RF, Jetz W (2008) Homage to Linnaeus: how many parasites? How many hosts? PNAS 105(Supplement 1):11482–11489. https://doi.org/10.1073/pnas.0803232105

dos Santos JE Jr, Viola MG, Lorosa ES, de Machado EMM, Ruas Neto AL, Corseuil E (2013) Evaluation of natural foci of *Panstrongylus megistus* in a forest fragment in Porto Alegre, state of Rio Grande do Sul. Brazil Rev Soc Bras Med Trop 46(5):575–583. https://doi.org/10.1590/0037-8682-0149-2013

Dunne JA, Lafferty KD, Dobson AP, Hechinger RF, Kuris AM, Martinez ND, McLaughlin JP, Mouritsen KN, Poulin R, Reise K, Stouffer DB, Thieltges DW, Williams RJ, Zander CD (2013) Parasites affect food web structure primarily through increased diversity and complexity. PLoS Biol 11(6):e1001579. https://doi.org/10.1371/journal.pbio.1001579

Elton CS (1927) Animal ecology. University of Chicago Press

Fernandes A, Iñiguez AM, Lima VS, de Souza SMM, Ferreira LF, Vicente ACP, Jansen AM (2008) Pre-Columbian Chagas disease in Brazil: *Trypanosoma cruzi* I in the archaeological remains of a human in Peruaçu Valley, Minas Gerais, Brazil. Mem Inst Oswaldo Cruz 103:514–516. https://doi.org/10.1590/S0074-02762008000500021

Ferro e Silva AM, Sobral-Souza T, Vancine MH, Muylaert RL, de Abreu AP, Pelloso SM, de Barros Carvalho MD, de Andrade L, Ribeiro MC, de Toledo MJO (2018) Spatial prediction of

risk areas for vector transmission of *Trypanosoma cruzi* in the state of Paraná, southern Brazil. PLoS Negl Trop Dis 12(10):e0006907. https://doi.org/10.1371/journal.pntd.0006907

Flynn JJ, Wyss AR (1998) Recent advances in south American mammalian paleontology. Trends Ecol Evol 13(11):449–454. https://doi.org/10.1016/S0169-5347(98)01457-8

Fokin SI, Schrallhammer M, Chiellini C, Verni F, Petroni G (2014) Free-living ciliates as potential reservoirs for eukaryotic parasites: occurrence of a Trypanosomatid in the macronucleus of *Euplotes encysticus*. Parasit Vectors 7(1):203. https://doi.org/10.1186/1756-3305-7-203

Forattini OP, Ferreira OA, da Silva EOR, Rabello EX (1978) Aspectos ecológicos da Tripanossomíase americana: XII—Variação regional da tendência de *Panstrongylus megistus* à domiciliação. Rev Saúde Pública 12(2):209–233. https://doi.org/10.1590/S0034-89101978000200013

Fornaciari G, Castagna M, Viacava P, Tognetti A, Bevilacqua G, Segura E (1992) Chagas' disease in Peruvian Inca mummy. Lancet 339(8785):128–129. https://doi.org/10.1016/0140-6736(92)91043-8

Galvão C (2014) Vetores da doença de Chagas no Brasil. Sociedade Brasileira de Zoologia 289. https://doi.org/10.7476/978859820309

Gause GF (1936) The principles of biocoenology. Q Rev Biol 11(3):320–336. https://doi.org/10.1086/394511

Ghobakhloo N, Motazedian MH, Naderi S, Ebrahimi S (2019) Isolation of *Crithidia* spp. from lesions of immunocompetent patients with suspected cutaneous leishmaniasis in Iran. Trop Med Int Health 24(1):116–126. https://doi.org/10.1111/tmi.13042

Giannini TC, Siqueira MF, Acosta AL, Barreto FCC, Saraiva AM, Alves-dos-Santos I (2012) Desafios atuais da modelagem preditiva de distribuição de espécies. Rodriguésia 63(3):733–749. https://doi.org/10.1590/S2175-78602012000300017

Gonçalves TCM, de Oliveira E, Dias LS, Almeida MD, Nogueira WO, de Pires FDÁ (1998) An investigation on the ecology of *Triatoma vitticeps* (Stal, 1859) and its possible role in the transmission of *Trypanosoma cruzi*, in the locality of Triunfo, Santa Maria Madalena Municipal District, state of Rio de Janeiro. Brazil Mem Inst Oswaldo Cruz 93(6):711–717. https://doi.org/10.1590/S0074-02761998000600002

Grinnell J (1917) The niche-relationships of the California thrasher. Auk 34(4):427–433. https://doi.org/10.2307/4072271

Grybchuk D, Akopyants NS, Kostygov AY, Konovalovas A, Lye L-F, Dobson DE, Zangger H, Fasel N, Butenko A, Frolov AO, Votýpka J, d'Avila-Levy CM, Kulich P, Moravcová J, Plevka P, Rogozin IB, Serva S, Lukeš J, Beverley SM, Yurchenko V (2018) Viral discovery and diversity in Trypanosomatid protozoa with a focus on relatives of the human parasite *Leishmania*. PNAS 115(3):E506–E515. https://doi.org/10.1073/pnas.1717806115

Guhl F, Jaramillo C, Yockteng R, Vallejo GA, Caárdenas-Arroyo F (1997) *Trypanosoma cruzi* DNA in human mummies. Lancet 349(9062):1370. https://doi.org/10.1016/S0140-6736(05)63207-2

Guhl F, Jaramillo C, Vallejo GA, Yockteng R, Cárdenas-Arroyo F, Fornaciari G, Arriaza B, Aufderheide AC (1999) Isolation of *Trypanosoma cruzi* DNA in 4,000-year-old mummified human tissue from northern Chile. Am J Phys Anthropol 108(4):401–407. https://doi.org/10.1002/(SICI)1096-8644(199904)108:4<401::AID-AJPA2>3.0.CO;2-P

Guhl F, Jaramillo C, Vallejo GA, Cárdenas A-AF, Aufderheide A (2000) Chagas disease and human migration. Mem Inst Oswaldo Cruz 95:553–555. https://doi.org/10.1590/S0074-02762000000400018

Gurgel-Gonçalves R, Galvão C, Costa J, Peterson AT (2012) Geographic distribution of Chagas disease vectors in Brazil based on ecological niche modeling. J Trop Med 2012:1–15. https://doi.org/10.1155/2012/705326

Gürtler RE, Yadon ZE (2015) Eco-bio-social research on community-based approaches for Chagas disease vector control in Latin America. Trans R Soc Trop Med Hyg 109(2):91–98. https://doi.org/10.1093/trstmh/tru203

Hamilton PB, Stevens JR, Gidley J, Holz P, Gibson WC (2005) A new lineage of trypanosomes from Australian vertebrates and terrestrial bloodsucking leeches (Haemadipsidae). Int J Parasitol 35(4):431–443. https://doi.org/10.1016/j.ijpara.2004.12.005

Hamilton PB, Gibson WC, Stevens JR (2007) Patterns of co-evolution between trypanosomes and their hosts deduced from ribosomal RNA and protein-coding gene phylogenies. Mol Phylogenet Evol 44(1):15–25. https://doi.org/10.1016/j.ympev.2007.03.023

Hatcher MJ, Dick JT, Dunn AM (2012) Diverse effects of parasites in ecosystems: linking interdependent processes. Front Ecol Environ 10(4):186–194. https://doi.org/10.1890/110016

Herrera HM, Dávila AMR, Norek A, Abreu UG, Souza SS, D'Andrea PS, Jansen AM (2004) Enzootiology of *Trypanosoma evansi* in Pantanal. Brazil Veterinary Parasitol 125(3):263–275. https://doi.org/10.1016/j.vetpar.2004.07.013

Hoberg EP, Brooks DR (2008) A macroevolutionary mosaic: episodic host-switching, geographical colonization and diversification in complex host–parasite systems. J Biogeogr 35(9): 1533–1550. https://doi.org/10.1111/j.1365-2699.2008.01951.x

Hoberg EP, Brooks DR (2015) Evolution in action: climate change, biodiversity dynamics and emerging infectious disease. Phil Trans R Soc B: Biol Sci 370(1665):20130553. https://doi.org/10.1098/rstb.2013.0553

Hutchinson GE (1957) Concluding remarks. Cold Spring Harb Symp Quant Biol 22(0): 415–427. doi:https://doi.org/10.1101/SQB.1957.022.01.039

Iranzo J, Puigbò P, Lobkovsky AE, Wolf YI, Koonin EV (2016) Inevitability of genetic parasites. Genome Biol Evol 8(9):2856–2869. https://doi.org/10.1093/gbe/evw193

Izeta-Alberdi A, Ibarra-Cerdeña CN, Moo-Llanes DA, Ramsey JM (2016) Geographical, landscape and host associations of *Trypanosoma cruzi* DTUs and lineages. Parasites Vectors 9(1):631. https://doi.org/10.1186/s13071-016-1918-2

Jansen AM, Xavier SCC, Roque ALR (2015) The multiple and complex and changeable scenarios of the *Trypanosoma cruzi* transmission cycle in the sylvatic environment. Acta Trop 151:1–15. https://doi.org/10.1016/j.actatropica.2015.07.018

Jansen AM, das Xavier SCC, Roque ALR (2018) *Trypanosoma cruzi* transmission in the wild and its most important reservoir hosts in Brazil. Parasites Vectors 11(1):502. https://doi.org/10.1186/s13071-018-3067-2

Jansen AM, das Xavier SC, C, Roque ALR (2020) Landmarks of the knowledge and *Trypanosoma cruzi* biology in the wild environment. Front Cell Infect Microbiol 10. https://doi.org/10.3389/fcimb.2020.00010

Kaufer A, Ellis J, Stark D, Barratt J (2017) The evolution of Trypanosomatid taxonomy. Parasit Vectors 10(1):287. https://doi.org/10.1186/s13071-017-2204-7

Kindler JTP, Zapata J, Ordonez E, Toulkeridis T, Zapata A (2020) The use of GIS in the predictive ecological niche modeling of vector species of the American trypanosomiasis disease (Chagas), in Ecuador. In: 2020 seventh international conference on eDemocracy & eGovernment (ICEDEG). IEEE, Buenos Aires, Argentina, pp 165–174

Krasnov BR, Mouillot D, Shenbrot GI, Khokhlova IS, Poulin R (2011) Beta-specificity: the turnover of host species in space and another way to measure host specificity. Int J Parasitol 41(1):33–41. https://doi.org/10.1016/j.ijpara.2010.06.001

Kuris AM, Hechinger RF, Shaw JC, Whitney KL, Aguirre-Macedo L, Boch CA, Dobson AP, Dunham EJ, Fredensborg BL, Huspeni TC, Lorda J, Mababa L, Mancini FT, Mora AB, Pickering M, Talhouk NL, Torchin ME, Lafferty KD (2008) Ecosystem energetic implications of parasite and free-living biomass in three estuaries. Nature 454(7203):515–518. https://doi.org/10.1038/nature06970

Lankester ER (2016) A treatise on zoology; part I: introduction and protozoa first fascicle. Leopold Classic Library

Leger L (1904) Les affinites de l'*Herpetomonas subulata* et la phylogenie des trypanosomes. Comp R Sances Soc Biol Ses Fil 67:615

Lima VS, Iniguez AM, Otsuki K, Ferreira LF, Araújo A, Vicente ACP, Jansen AM (2008) Chagas disease in ancient hunter-gatherer population. Brazil Emerg Infect Dis 14(6):1001–1002. https://doi.org/10.3201/eid1406.0707

Lukeš J, Skalický T, Týč J, Votýpka J, Yurchenko V (2014) Evolution of parasitism in kinetoplastid flagellates. Mol Biochem Parasitol 195(2):115–122. https://doi.org/10.1016/j.molbiopara.2014.05.007

Lukeš J, Butenko A, Hashimi H, Maslov DA, Votýpka J, Yurchenko V (2018) Trypanosomatids are much more than just trypanosomes: clues from the expanded family tree. Trends Parasitol 34(6):466–480. https://doi.org/10.1016/j.pt.2018.03.002

McGhee RB (1959) The infection of avian embryos with *Crithidia* species and *Leishmania Tarentola*. J Infect Dis 105(1):18–25. https://doi.org/10.1093/infdis/105.1.18

Meyer ALS, Pie MR, Passos FC (2014) Assessing the exposure of lion tamarins (*Leontopithecus* spp.) to future climate change. Am J Primatol 76(6):551–562. https://doi.org/10.1002/ajp.22247

Moreira D, López-García P, Vickerman K (2004) An updated view of kinetoplastid phylogeny using environmental sequences and a closer outgroup: proposal for a new classification of the class Kinetoplastea. Int J Syst Evol Microbiol 54(5):1861–1875. https://doi.org/10.1099/ijs.0.63081-0

Parra-Henao G, Cardona ÁS, Jaramillo-O N, Quirós-Gómez O (2016a) Environmental determinants of the distribution of Chagas disease vector *Triatoma dimidiata* in Colombia. Am J Trop Med Hyg 94(4):767–774. https://doi.org/10.4269/ajtmh.15-0197

Parra-Henao G, Suárez-Escudero LC, González-Caro S (2016b) Potential distribution of Chagas disease vectors (Hemiptera, Reduviidae, Triatominae) in Colombia, based on ecological niche modeling. J Trop Med:1439090. https://doi.org/10.1155/2016/1439090

Pavlovsky EN (1939) Natural nidality of transmissible diseases. Peace Publishers, Moscow

Pawlowski J, Audic S, Adl S, Bass D, Belbahri L, Berney C, Bowser SS, Cepicka I, Decelle J, Dunthorn M, Fiore-Donno AM, Gile GH, Holzmann M, Jahn R, Jirků M, Keeling PJ, Kostka M, Kudryavtsev A, Lara E, Lukeš J, Mann DG, Mitchell EAD, Nitsche F, Romeralo M, Saunders GW, Simpson AGB, Smirnov AV, Spouge JL, Stern RF, Stoeck T, Zimmermann J, Schindel D, de Vargas C (2012) CBOL protist working group: barcoding eukaryotic richness beyond the animal, plant, and fungal kingdoms. PLoS Biol 10(11):e1001419. https://doi.org/10.1371/journal.pbio.1001419

Pessoa GCD, Rosa ACL, Bedin C, Wilhelms T, de Mello F, Coutinho HS, Fonseca EOL, dos Santos RF, Diotaiuti L (2015) Susceptibility characterization of residual Brazilian populations of *Triatoma infestans* Klug, 1834 (Hemiptera: Reduviidae) to deltamethrin pyrethroid. Rev Soc Bras Med Trop 48:157–161. https://doi.org/10.1590/0037-8682-0011-2015

Peterson AT (ed) (2011) Ecological niches and geographic distributions. Princeton University Press, Princeton, N.J

Ramos AN Jr, de Carvalho DM (2001) Os diferentes significados da certificação conferida ao Brasil como estando livre da doença de Chagas. Cad Saúde Pública 17:1403–1412. https://doi.org/10.1590/S0102-311X2001000600011

Ramsey JM, Peterson AT, Carmona-Castro O, Moo-Llanes DA, Nakazawa Y, Butrick M, Tun-Ku E, de la Cruz-Félix K, Ibarra-Cerdeña CN (2015) Atlas of Mexican Triatominae (Reduviidae: Hemiptera) and vector transmission of Chagas disease. Mem Inst Oswaldo Cruz 110:339–352. https://doi.org/10.1590/0074-02760140404

Rangel DA, Lisboa CV, Novaes RLM, Silva BA, de Souza RF, Jansen AM, Moratelli R, Roque ALR (2019) Isolation and characterization of Trypanosomatids, including *Crithidia mellificae*, in bats from the Atlantic Forest of Rio de Janeiro, Brazil. Plos Negl Trop Dis 13(7):e0007527. https://doi.org/10.1371/journal.pntd.0007527

Rodrigues MS, Lima L, das Xavier SCC, Herrera HM, Rocha FL, Roque ALR, Teixeira MMG, Jansen AM (2019) Uncovering *Trypanosoma* spp. diversity of wild mammals by the use of DNA from blood clots. Int J Parasitol: Parasites Wildlife 8:171–181. https://doi.org/10.1016/j.ijppaw.2019.02.004

Roellig DM, Ellis AE, Yabsley MJ (2009) Oral transmission of *Trypanosoma cruzi* with opposing evidence for the theory of Carnivory. J Parasitol 95(2):360–364. https://doi.org/10.1645/GE-1740.1

Rohde K (1994) Niche restriction in parasites: proximate and ultimate causes. Parasitology 109 (Suppl):S69–S84. https://doi.org/10.1017/s0031182000085097

Roque ALR, Jansen AM (2008) Importância dos animais domésticos sentinelas na identificação de áreas de risco de emergência de doença de Chagas. Rev Soc Bras Med Trop 41:4

Roque ALR, D'Andrea PS, Jansen AM, Duarte ACM, Xavier SCC, da Rocha MG (2008) *Trypanosoma cruzi* transmission cycle among wild and domestic mammals in three areas of orally transmitted Chagas disease outbreaks. Am J Trop Med Hyg 79(5):742–749. https://doi.org/10.4269/ajtmh.2008.79.742

Rothhammer F, Allison MJ, Núñez L, Standen V, Arriaza B (1985) Chagas' disease in pre-Columbian South America. Am J Phys Anthropol 68(4):495–498. https://doi.org/10.1002/ajpa.1330680405

Sá MFGD, Sá CMD, Veronese MA, Filho SA, Gander ES (1980) Morphologic and biochemical characterization of *Crithidia brasiliensis* sp. n.*. J Protozool 27(3):253–257. https://doi.org/10.1111/j.1550-7408.1980.tb04248.x

Santos EF, Silva ÂAO, Leony LM, Freitas NEM, Daltro RT, Regis-Silva CG, Del-Rei RP, Souza WV, Ostermayer AL, Costa VM, Silva RAANR Jr, Sousa AS, Gomes YM, Santos FLN (2020) Acute Chagas disease in Brazil from 2001 to 2018: a nationwide spatiotemporal analysis. PLoS Negl Trop Dis 14(8):e0008445. https://doi.org/10.1371/journal.pntd.0008445

Schofield CJ, Dias JCP (1999) The southern cone initiative against Chagas disease. In: Baker JR, Muller R, Rollinson D (eds) Advances in parasitology. Academic Press, pp 1–27

Schofield CJ, Jannin J, Salvatella R (2006) The future of Chagas disease control. Trends Parasitol 22(12):583–588. https://doi.org/10.1016/j.pt.2006.09.011

Soberon J, Peterson AT (2005) Interpretation of models of fundamental ecological niches and species' distributional areas. Biodiv Inf 2(0). https://doi.org/10.17161/bi.v2i0.4

Steindel M, Kramer Pacheco L, Scholl D, Soares M, de Moraes MH, Eger I, Kosmann C, Sincero TCM, Stoco PH, Murta SMF, de Carvalho-Pinto CJ, Grisard EC (2008) Characterization of *Trypanosoma cruzi* isolated from humans, vectors, and animal reservoirs following an outbreak of acute human Chagas disease in Santa Catarina State, Brazil. Diagn Microbiol Infect Dis 60(1):25–32. https://doi.org/10.1016/j.diagmicrobio.2007.07.016

Stevens JR, Noyes HA, Schofield CJ, Gibson W (2001) The molecular evolution of Trypanosomatidae. In: Advances in parasitology. Academic Press, pp 1–53

Villalobos G, Nava-Bolaños A, De Fuentes-Vicente JA, Téllez-Rendón JL, Huerta H, Martínez-Hernández F, Rocha-Ortega M, Gutiérrez-Cabrera AE, Ibarra-Cerdeña CN, Córdoba-Aguilar A (2019) A reduction in ecological niche for *Trypanosoma cruzi*-infected triatomine bugs. Parasit Vectors 12(1):240. https://doi.org/10.1186/s13071-019-3489-5

Walter A, do Rego IP, Ferreira AJ, Rogier C (2005) Risk factors for reinvasion of human dwellings by sylvatic triatomines in northern Bahia state, Brazil. Cad Saúde Pública 21:974–978. https://doi.org/10.1590/S0102-311X2005000300034

Webb SD (1976) Mammalian faunal dynamics of the great American interchange. Paleobiology 2(3):220–234

Xavier SC, Roque AL, Bilac D, de Araújo VA, da Costa Neto SF, Lorosa ES, Ferreira da Silva LFC, Jansen AM (2014) *Distantiae* transmission of *Trypanosoma cruzi*: a new epidemiological feature of acute Chagas disease in Brazil. PLoS Negl Trop Dis 8(5):e2878. https://doi.org/10.1371/journal.pntd.0002878

Zeledon R, Rabinovich JE (1981) Chagas disease: an ecological appraisal with special emphasis on its insect vectors. Annu Rev Entomol 26(1):101–133. https://doi.org/10.1146/annurev.en.26.010181.000533

Zingales B, Andrade S, Briones M, Campbell D, Chiari E, Fernandes O, Guhl F, Lages-Silva E, Macedo A, Machado C, Miles M, Romanha A, Sturm N, Tibayrenc M, Schijman A (2009) A new consensus for *Trypanosoma cruzi* intraspecific nomenclature: second revision meeting recommends TcI to TcVI. Mem Inst Oswaldo Cruz 104(7):1051–1054. https://doi.org/10.1590/S0074-02762009000700021

6 The Social and Environmental Determinants of the Leishmaniases in the Americas

Oscar Daniel Salomón and Guilherme Loureiro Werneck

Abstract

The leishmaniases are vector-borne diseases caused by protozoan parasites of the genus *Leishmania* and transmitted by the bite of female phlebotomine sand flies. In the Americas, the transmission cycle is primarily zoonotic both for American cutaneous leishmaniasis (ACL) endemic in 18 countries and American visceral leishmaniasis (AVL) endemic to 13 countries. The range of parasites, vectors, reservoirs, and epidemiological scenarios involved in the transmission of leishmaniases, their distribution, and geographical expansion are challenges for theoretical analysis as well as for the design of control strategies. Therefore, to contribute to knowledge but also to the preventive program interventions, in this chapter we will focus on the environmental and socioeconomic determinants of the spatial and temporal distribution of the leishmaniases in the Americas, from the eco-epidemiology as conceptual framework to remote sensing image analysis as an analytical tool, approaching the theme by looking at the main elements involved in the transmission cycle: vectors, reservoirs, and humans.

Keywords

American cutaneous leishmaniasis · American visceral leishmaniasis · Eco-epidemiology · Remote sensing · Edge effect

O. D. Salomón (✉)
Instituto Nacional de Medicina Tropical- INMeT ANLIS Dr CG Malbran, Puerto Iguazú, Argentina

G. L. Werneck
Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_6

6.1 Introduction

The spatial and temporal variability in the occurrence of infectious diseases reflects the intrinsic characteristics of the transmission dynamics and the heterogeneity in the distribution of risk factors (Anderson and May 1992). To understand the causal mechanisms underlying these distinct spatiotemporal patterns, it is necessary to consider that not all risk factors for infectious diseases are restricted to individual or local features (Werneck et al. 2007). Contextual ecological factors may be important determinants of infection rates in subjects notwithstanding their individual-level risk factors. For instance, individuals (or small areas) with no significant high exposure levels may be at high risk just because the prevalence of infection is high among closely connected regions.

The incidence of zoonotic vector-borne diseases, such as the leishmaniases in the Americas, involves multiple levels of determination (Werneck et al. 2007; Shaw 2007; Belo et al. 2013a, b; Buzanovsky et al. 2020). For instance, environmental factors, such as temperature and land use, affect the size, longevity, and distribution of the vector populations. Poor living conditions increase the degree of contact between persons, reservoirs, and vectors. Malnutrition and genetic factors may contribute to poor outcomes after infection. The transmission of the leishmaniases often leads to geographical clustering of cases and hotspots of high incidence (Bern et al. 2008), suggesting that contextual level variables interact with individual- and local-level risk factors to trigger disease occurrence.

6.2 The Leishmaniases

The leishmaniases are a group of vector-borne diseases caused by protozoan parasites of the genus *Leishmania* and transmitted by the bite of female sand flies from over 90 species (WHO 2010). The leishmaniases are among the most important neglected tropical diseases, affecting mostly the poor populations in developing countries, contributing to the maintenance of the poverty cycle.

There are three basic clinical presentations of the leishmaniases: visceral, cutaneous, and mucocutaneous (WHO 2010). The main etiologic agents of cutaneous leishmaniasis (CL) are *L. major*, *L. tropica*, and *L. aethiopica* in the Old World and *L. mexicana*, *L. braziliensis*, *L. guyanensis*, and *L. amazonensis* in the New World. Mucocutaneous leishmaniasis (MCL) is mainly attributed to *L. braziliensis* and *L. panamensis* (both species from the subgenus *Viannia*). The *Leishmania donovani* complex (*L. donovani* and *L. infantum* [syn: *L. chagasi*]) is responsible for visceral leishmaniasis (VL). Other recognized clinical presentations are leishmaniasis recidivans, diffuse cutaneous leishmaniasis, and post-kala-azar dermal leishmaniasis.

The World Health Organization (WHO) estimates the incidence of 700,000–1 million new cases of leishmaniases each year worldwide, more than 90% from CL. More than 90% of MCL cases occur in Bolivia, Brazil, Ethiopia, and Peru. Visceral leishmaniasis is the most severe clinical form of the leishmaniases and is

often fatal if not adequately treated. Between 50 and 90,000 new cases of VL occur worldwide annually, with case fatality rates between 5 and 10% (WHO 2021).

In the Americas, from 2001 to 2019, 1,028,054 CL/MCL and 65,934 VL cases were reported. American CL/MCL (ACL) is endemic to 18 countries, and, in 2019, 77% of the cases reported occurred in five countries: Brazil, Colombia, Peru, Nicaragua, and Bolivia. American VL (AVL) is endemic to 13 countries, and in 2019, 97% of the reported cases were from Brazil (PAHO 2020).

The leishmaniasis transmission cycle is primarily zoonotic with a few exceptions outside the Americas, mainly in the Indian subcontinent (VL) and in the Middle East and some areas of North Africa (CL caused by *L. tropica*). The domestic dog is considered the main reservoir of AVL in urban areas, and marsupials and wild canids are thought to maintain the cycle in the sylvatic environment. The main vector of AVL is the sand fly *Lutzomyia longipalpis*, although other species have been incriminated (e.g., *Lu. cruzi* and *Pintomyia evansi*). The transmission cycles of ACL show high variability, involving different *Leishmania* species, reservoirs (e.g., dogs, rodents, marsupials, anteaters, and sloths), and vectors (e.g., *Nyssomyia flaviscutellata*, *Ny. whitmani*, *Ny. intermedia*, *Ny. umbratilis*, *Ny. shawi*, *Migonemyia migonei*, *Lu. peruensis*, and *Bichromomyia olmeca*, among many others).

With such variety of transmission cycles, a range of factors have been pointed as determinants of the spatial and temporal distribution of AVL and ACL (Almeida and Werneck 2014; Alves et al. 2016; Belo et al. 2013a, b; Buzanovsky et al. 2020; Falcão de Oliveira et al. 2020; Hernández et al. 2019; Silva Santana Cruz et al. 2021; Salomon 2021; Valero and Uriarte 2020). Among the multiple and complex variables that these studies have associated with the introduction, propagation, and dissemination of leishmaniases, socioeconomic and environmental variables are frequently cited. In particular, environmental changes due to migration movements, disorderly occupation of city's outskirts, high population density, inadequate living conditions, climate variables, land use, and land cover features have been highlighted.

In this chapter, we will focus on the environmental and socioeconomic determinants of the spatial and temporal distribution of the leishmaniases in the Americas, approaching the theme by looking at the main elements involved in the transmission cycle: vectors, reservoirs, and humans.

6.3 The Vectors of Leishmaniasis

The definition of leishmaniases often includes the requirement of transmission of the etiologic agent *Leishmania* sp. by female Phlebotominae insects (PAHO 2020), but this concept has been limited once the parasite cycle and vectorial competence for parasites related to *L. henrietti* was demonstrated in *Ceratopogonidae dipterans* (Panahi et al. 2020; Cotton 2017), given the continuity over time of some *Leishmania* species transmitted in mammals by vertical or horizontal routes. On the other hand, infection without apparent clinical manifestations, a phenomenon recorded in

most known *Leishmania* species, is excluded from the definition, which also includes clinical signs in its most rigorous form, which does not diminish the epidemiological importance of the asymptomatic mammals.

Approximately 1000 species of the subfamily Phlebotominae (order: Diptera; suborder: Nematocera; family: Psychodidae) have been described. Its greatest diversity is found in both subtropics – except New Zealand and the islands of Oceania, although there are species that colonize up to 50° north latitude in Canada and 40° south latitude in Argentina, and there are stable populations in areas with altitudes below sea level, such as the Dead Sea, and at more than 3000 m above sea level. In the Americas, 536 species are recognized. Those that represent a health risk belong to the genus *Lutzomyia*, according to the Lewis classification revised by Young, the most widely used at the programmatic level, but in the Galati classification, which is more widely used in the academic field, 23 genera are recognized (Akhoundi et al. 2016; Shimabukuro et al. 2017).

Adult phlebotomine sand flies are small insects, usually up to 3 mm in length. They have dense pilosity and a hirsute appearance on the body and wings; the thorax is gibbous and hides the head in dorsal view; the wings at rest are arranged in a "V" shape. Morphological characters used to discriminate between species are useful most of the times (Galati et al. 2017), but not within species complexes or very close sibling species. In *Lu. longipalpis* complex, the main vector of *L. infantum* in the Americas, populations with behavioral ("love songs"), physiochemical (pheromones), biochemical (cuticular hydrocarbons), and genetic differences are described, which may generate reproductive barriers and be associated with different vectorial capacities. However, despite the potential use of molecular means such as barcoding (Rodrigues et al. 2018), the determination using morphological taxonomy requires currently entomological laboratories with trained technicians and quality control, a challenge for programmatic transfer still pending in most countries.

Phlebotomine sand flies are insects of complete metamorphosis; its life cycle involves eggs up to 0.5 mm long and 0.15 mm wide, followed by four larval stages, which increase their morphological complexity and size (from less than 1–4 mm, followed by a relatively immobile pupa, which then becomes an adult). Larvae are terrestrial, are saprophagous, and develop in temperate, humid microenvironments rich in organic matter, usually with good canopy cover. Due to the difficulty in identifying natural breeding sites and the vagility of the pre-imaginal stages, anti-vectorial chemical interventions have so far been directed against adults. Under fixed experimental conditions of temperature and relative humidity, the life-cycle period of species of epidemiological interest is 6–10 days from female blood ingestion to oviposition, and 5–6 weeks to adult emergence, although there may be diapause due to adverse conditions. Adult females have longevities of 14–60 days, with ovipositions of 30 up to 200 eggs (Lawyer et al. 2017). Adults are usually active from dusk to dawn and remain during the day resting in shadowy places. Their adult dispersal radius by active flight does not exceed 100–200 m, and is less when the insects are released from a food source, although there are records of specimens found up to 2 km from the release site. Actually the dispersal radius as in many insects should be understood as concentric circles of probability. Adults, males and

females, feed on sugary solutions of vegetables or aphids for their metabolism. Females require blood to complete their ovarian cycle, although autogeny has been described in some species. Non-hematophagous males could reach the host first and attract females, with whom they copulate once the latter have ingested blood, thus ensuring the presence of fertilizable oocytes (PAHO 2020).

Ten percent of the described species of Phlebotominae are associated with the transmission of 20 species and subspecies of Trypanosomatida protozoa of the genus *Leishmania* to mammalians, by regurgitation during blood ingestion. Sand flies are also known to be vectors of other pathogens, bacteria such as *Bartonella bacilliformis* (Wachter et al. 2020), and bunyavirus such as those causing sand fly fever, summer meningitis, and vesicular stomatitis (Marklewitz et al. 2019). The subgenera of *Leishmania* are characterized, in turn, according to the site of adhesion and development of the parasite in the digestive tract of the vector, taking as reference the anterior region of the proctodeum where the Malpighian tubules open as peripyloric (*Viannia*), suprapyloric (*Leishmania*), and hypopyloric (*Sauroleishmania*), regions of adhesion corresponding to different histological and functional structures and to different embryological origins. Under controlled experimental conditions, *L. infantum*, agent of AVL, has metacyclic forms in 3 to 4 days in its American vectors after ingestion, and *L. braziliensis*, agent of ACL, in 4–6 days. However, to incriminate a species as a vector, studies of competence and vectorial capacity are necessary; especially considering that in sites with high host prevalence, fragments of parasitic DNA can be found in the blood-food content of many hematophagous ectoparasites, where parasites do not amplify, but could participate in mechanical transmission, for example in social grooming in non-human primates (Martínez et al. 2020).

According to different authors, the criteria to incriminate a Phlebotominae species as a vector, and specifically as a vector of transmission to humans, include (1) the association in time, space, and environment between vector (blood feeding source), reservoirs (zoophily), and humans (anthropophily); (2) the identity between parasites repeatedly isolated from vectors without recent blood meals and those isolated from reservoirs and human cases; (3) the association in time, space, and environment between infection in mammalian hosts and the vector, with consistent parasite density and infection rate; (4) the growth and amplification of the parasite in the vector in the presence of metacyclic promastigotes in the stomodeal valve or anterior midgut; and (5) the experimental infection of the vector during blood ingestion, and afterward the vector infective bite (Maroli et al. 2013). Vector-competent Phlebotominae can be classified from species-specific to permissive ones, while vector capacity is defined by intrinsic and extrinsic factors. Intrinsic factors include the enzymatic time pattern during blood digestion and the peritrophic matrix, parasite anchorage to the intestinal wall according to different mechanisms (Coutinho-Abreu et al. 2020), the magnitude of parasite amplification, anterior migration, metacyclogenesis, and the mechanisms of regurgitation and multiple bites (Serafim et al. 2018). Among these "injected" factors, the immune response of the host to the vector's saliva may have protective functions for the host in case of previous non-infective bites; however, the vasodilator maxadilan from *Lu.*

longipalpis saliva is a facilitator of infection together with macrophage recruiters or capillary permeability promoters, as well as the immunomodulation of the insect's digestive microbiota egested during the bite (Dey et al. 2018), microbiota that is also involved in the vector–parasite interactions (Campolina et al. 2020). Extrinsic factors depend on the bioecological and behavioral aspects of the vector already mentioned above, and on the characteristics of the vector–reservoir complex, such as the attraction of vector females to infected reservoirs (Staniek and Hamilton 2021), as well as behavioral and cultural factors that modulate the probability of contact between the infected vector and the host.

6.4 Eco-Epidemiology and Vectors

To say that vector-borne diseases are only transmitted where the vector species of the pathogen is present and that transmission is dense-dependent is almost a tautology; however, this statement carries the implicit conceptual framework of Pavlovsky's nidality (Pavlovsky and Pious Jr 1966) and landscape epidemiology (Kitron 1998), the physical and biological conditions of the environment in which the species colonization is most successful. Adding reservoir nidality and pathogen circulation can encompass much of the definition in time and space of biological risk. However, three concepts complicate this static picture:

Biological risk only indicates the possibility of transmission, but to characterize and even quantify the real probability of transmission, the exposure of the susceptible individual must be included, and human exposure is given by social, cultural, and economic factors, which can be separated from biological factors for analytical purposes but actually form an integral multidimensional eco-epidemiological momentum (Susser and Susser 1996). So, for instance in ACL only when it is controlled by social exclusion, the climate becomes the most significant factor of risk (Chaves et al. 2008).

The associations between vector or reservoir abundance or biological risk and environmental and social determinants are valid only for the scales of time and space in which they were recorded and analyzed, as these variables may even have opposite signs at different scales. Therefore, the same determinant can be counterbalanced or canceled when different scales are mixed.

The variables that determine the possibility and probability of risk of transmission are neither qualitatively nor quantitatively stable in time or space.

In relation to the last point, we must consider that the usually slow process of species adaptation has been pressured in the last century by forces of unprecedented magnitude and speed due to anthropogenic actions, including changes in land use, planned and unplanned urbanization, voluntary and forced movement of people, and the frequency of extraordinary climatic events (climate crisis). Pathogens, insect vectors, and some reservoirs, with their reproductive "r" strategy of relatively short cycles, many individuals, and genetic diversity, have a good chance of adapting and thriving in these fluctuating scenarios, albeit through different strategies. *Aedes* and their arboviruses, rodents and their fleas, and pathogens, thanks to their plasticity for

environmental adaptation, have managed to exploit human environments accompanying the process of urbanization taking advantage of this unprecedented concentration of food resources in the domestic environment and cities, including the blood source of these "human and animal monocultures"; in the case of parasites such as *Trypanosoma cruzi*, given the decrease in the event of direct vector–human contact, the oral route of transmission becomes important for parasite sustainability as the vertical mother–child route, with the possibility of evolving toward "commensal" strains with little or no morbidity.

Leishmaniases are no exception to these processes, but in the Americas the course of ACL and AVL shows two different alternatives, although both take advantage of the effect of the concentration of human and animal blood resources in the urban, rural, and rururban domestic environment; the decrease in competition for these resources by decreasing the richness of Phlebotominae species and increasing the prevalence of those better ones adapted to the anthropized landscape: indoor human dwellings for rest (endophily) and feed (endophagy); multiple artificial sites for shelter, feed of vegetable carbohydrates, breed in sites enriched of organic matter (Manteca et al. 2021), soil-related differential microbiota and illegal waste sites as in *Phlebotomus papatasi* (Chelbi et al. 2020; Kakumanu et al. 2021); and even larval passive dispersal facilitated by land translocation, and parasite dispersal by transit or traffic of domestic reservoirs such as dogs, and intensified vertical transmission in these through animal crossbreeding.

However, as stated above, the adaptive strategies of ACL and AVL parasites differ between them. The parasites of ACL circulated in the Americas with man as an incidental host before the European conquest. Parasites and vectors presented then already a wide diversity of species adapted to different environments, from the Andean highlands to the tropical rainforest, although usually without association with arid and rocky environments as in other regions of the world, so the common name sand fly is not representative of American species. Spatial segregation as a force of speciation originated by changes in geological periods, such as the formation of the inter-Andean valleys or the isthmus of Panama. But once the European colonial society was installed, at the same time as there was a progressive change in land use, the system of forced and massive migrations in conditions of servitude of the indigenous people, known as "mita" and "yanaconazgo," and the same displacements of the colonial armies, going into virgin forests, possibly generated a first dispersion of infected people, domestic animals and pets, and new cycles of transmission. These cycles, in areas where there was no previous transmission, could have involved permissive vectors and new reservoirs according to the Stockholm paradigm (Brooks et al. 2019), with transmission dynamics due to multi-host reservoir and multi-vector communities rather than a single vector or reservoir (Viana et al. 2014). This multiplicity of pathogens and ecological fittings of Phlebotominae and mammals involved conferred to ACL a preconditioning of plasticity that initiated the rapid changes of the twentieth century and the enormous magnitude of environmental fragmentation it entailed allowed the ACL vector–parasite–reservoir system to persist, despite forecasting of dilution or extinction of the disease due to the disappearance of primary vegetation woods. Although there

are still no examples in America of a typical urban cycle of ACL, as we will see later, at the focus spatial scale there is a strong pressure toward the adaptation of vectors to anthropized environments, and at the microscale, domestic spaces are generated where the risk of transmission is already permanently installed, or the vector has periodical colonizations from "wild" source populations through metapopulation dynamics (Levins 1969).

A different scenario is that of AVL, for which there is a broad consensus that *L. infantum* parasite was introduced to the Americas from infected humans and dogs arriving from the Iberian Peninsula. In this relatively recent opportunity of an invasive parasite transmitted by Phlebotominae from the Old World in search of a local vector, *L. infantum* achieved its American dream by encountering the neotropical Phlebotominae *Lu. longipalpis*. Although today other vector species have already been described and several species have been incriminated as permissive vectors, which could play a major role in several outbreaks, *Lu. longipalpis* remains the main vector of AVL in most of the continent (Salomón et al. 2015). This situation implies that, unlike ACL with its interspecific diversity, the permanence of AVL in a changing world used intraspecific diversity as a strategy, of a species that demonstrated environmental plasticity from a complex with wide genetic diversity (Araki et al. 2009), which has allowed its rapid dispersal and adaptation to urbanized environments. Again, these mechanisms of adaptation and generation of transmission risk must be discriminated in spatiotemporal scales as we will see below.

6.4.1 American Cutaneous Leishmaniasis

As previously mentioned, ACL transmission comprises a diversity of Phlebotominae vectors and reservoir mammals (PAHO 2019). But despite this wide range of epidemiological scenarios and extension of geographical distribution from the USA (Kipp et al. 2020) to Argentina, the event "vector-to-human transmission" is a phenomenon usually restricted in time and space and manifested by focal outbreaks, even in hyperendemic areas with recurrent peaks of cases that do not respond to a regular seasonal pattern.

These epidemic outbreaks have sometimes been recorded in recent years on the basis of notifications from urban centers, which has led to the proposal of urbanization of the ACL. However, the risk is often associated at focus scale with vector mobilization during urban growth processes or land occupation in the periphery with deforestation of primary or secondary vegetation, or it is related to intra-urban vegetation patches due to microheterogeneity of the landscape, gallery forests associated with rivers, proximity to the green belt, parks-reserves, and zoos (Salomon 2019). Thus, rather than urbanization, ACL transmission despite the urban focus scale corresponds, from the vector scale perspective, to a non-urban micro-habitat. So, the spatial distribution of risk is actually related to the organization of space in cities, planned and unplanned urbanization with the creation of environmental interfaces where vector populations circulate, and socio-economic segregation of the human population. This last point may affect the two extremes of

the socioeconomic pyramid, at the vertex with the creation of private neighborhoods responding to the trend of return to nature, a community quantitatively not very important but with great visibility, social and political agency, and media presence, and at the base the fragile sectors, displaced to marginal areas of low real state value, usually floodable. This last scenario is the one that reinforces the association between the risk of ACL with inequity in the distribution of wealth and the social determination of the disease in peri-urban areas, due to increased vulnerability or exposure, related to determinants such as housing quality and overcrowding, access to the health system and public services, illiteracy, income, and hierarchy in the labor relationship, a context that in turn reduces the agency capacity of these groups to change their social and health situation.

The interface or "edge effect" used to explain many cases of transmission in urbanized environments actually serves as a conceptual framework to understand most epidemic outbreaks of ACL, also in non-urban environments (Quintana et al. 2010). This edge effect at higher resolution scales can be characterized according to the duration of human exposure as ephemeral, transient, and permanent, and according to the location of the life cycle of the vector and the actual site of human exposure in forest cycle – forest transmission, forest cycle - peridomestic transmission, peridomestic cycle - peridomestic transmission.

Ephemeral exposure is related to infections due to human exposure to the wild cycle in wild environments (hunters, military, researchers, tourists, migrants, and intensive extractive activities such as mining, lumbering, and tropical crops). They can generate outbreaks reported at health centers far from the actual sites of transmission when groups are exposed, as after military demobilization (Mubayi et al. 2018). The human incidence curve is usually narrow, related to gender and age exposed.

Exposure in transient edges originates in temporary camps, recreational activity close to the forest, and with wild cycles and peridomestic transmission during peri-urban growth or expansion of subsistence farms. Larger outbreaks are generated due to agro-industrial deforestation fronts, extensive fires as in the Amazonia, and focal ones due to commercial agricultural practices close to the forest ecotone such as organic soil enrichment in cultures of cocoa, coffee, banana, and sugar cane (Alexander et al. 2009; da Silva et al. 2000; Carrada Figueroa et al. 2014), and large development projects, sometimes accompanied by massive migrations of susceptible populations with high social vulnerability (Furtado et al. 2016; Zorrilla et al. 2017). The human incidence curve is usually wider than in ephemeral exposure, falls as the transient edge disappears, and if there is peridomestic-indoor transmission, does not differ by gender or age.

Permanent edges imply the establishment of urban environments with relatively long-standing interphases between the forest and domestic landscapes, which can generate microclimatic particularities and outbreaks associated with extraordinary climatic events. The risk is still associated with the proximity to forest borders (Moreno et al. 2020), but some vector species can colonize the peridomestic area, at least as sink populations in a metapopulation dynamics, and so increase the indoor transmission risk. Regarding the extraordinary climatic events, there are time lags

between the trigger event and the peak of adult vectors due to population cycle periods and expansion of breeding area, or with the wild reservoirs due to the increase of food or displacement, and a further lag time with the human cases due to the intrinsic cycle of the parasite (Salomón et al. 2004; Lewnard et al. 2014). The human incidence curve is usually sigmoid, saturating as long as the border remains, similar between genders, but increasing with age due to the probability of exposure. However, the border as a generator of risk of infection or exposure to Phlebotominae vectors still requires a more detailed analysis from the approach of gender and age by activities and risk perception, independent of the differential clinical susceptibility according to sex (Lockard et al. 2019).

The conceptualization of risk associated with edge effect also allows thinking about different control strategies, in addition to ephemeral personal protection for ephemeral edges. Transient chemical barriers have been tested in transitory fields or transitory on the way to be permanent (Perich et al. 1995; Feliciangeli et al. 2003), together with physical barriers as buffer areas (Esterre et al. 1986), and domiciliary chemical interventions during the season of highest vector activity (Acosta et al. 2017; Cabrera et al. 2018). Environmental management trials, although they have given encouraging results (Gouveia et al. 2012. Reinhold-Castro et al. 2013), are difficult to extrapolate programmatically beyond microfocal recommendations.

When the scale of analysis is changed to a third subnational jurisdiction, it is observed that 36% of Latin American municipalities (n 4951) present ACL transmission. These municipalities by degree of similarity in environmental and socioeconomic determinants were grouped into seven clusters; the risk of transmission was positively associated, in decreasing order of magnitude with the Amazonian, Andean, and Savannah clusters (Maia-Elkhoury et al. 2021). The Amazonian cluster is the one with the largest extension, geographical continuity, and environmental homogeneity, still indicating the relative importance of the wild cycle. The Andean conglomerate, on the other hand, with its fragmentation into valleys separated by mountain barriers, presents a great diversity of epidemiological scenarios and focal situations, from endemic transmission in the semiarid highlands, settlements due to mining prospecting, to interventions in high altitude rainforests with transmission records 2000 m above sea level. Risk communities in the Savannah conglomerate are usually located in environmental transition zones, with components of rural peridomestic transmission, although socio-environmental alterations in "hot spots" can generate large-scale outbreaks, as a result of the exploitation and transport of gas in "La Convención" in Peru (Torres-Slimming 2010; Gutiérrez et al. 2017). This conglomerate approach suggests that environmental surveillance of ACL in areas with a high probability of transmission is cost-effective, if the impact of interventions to prevent or mitigate changes in exposure and risk is adequately assessed. Consistently leishmaniasis should be incorporated into prospection environmental risk studies for development projects, as malaria is currently included in water or irrigation projects, and environmental surveillance should be integrated into entomological and epidemiological surveillance.

6.4.2 American Visceral Leishmaniasis

About the principal vector for AVL, *Lu. longipalpis*, as it was stated above, the genetic polymorphism of this species complex, a biological platform with ongoing cryptic speciation and introgression processes, provides plasticity but poses a problem for the extrapolation of research results, as local populations can present different vectorial and spreading capacity (Casaril et al. 2019). In this sense, geographic dispersal and urbanization have been associated with the pheromone chemotype (S)-9-methylgermacrane-B, in contrast to the cembrene-1 chemotype (Casanova et al. 2015), although despite the reproductive barriers (Dos Reis and Alevi Dos Reis and Alevi 2020) it is also possible that dispersing populations hybridize along its spread with local populations, giving rise to haplotypes with urbanization potential and good adaptation to local conditions (Quintana et al. 2019).

In jungle environments *Lu. longipalpis* relative abundance is usually 5% or less (Thomaz-Soccol et al. 2018; de Souza Freitas et al. 2018), but reaches between 80% and 100% in colonized urban areas, while its absolute abundance can grow from 5 times to more than 250 times once the environment is anthropized (Oliveira et al. 2011; Vilela et al. 2011). In relation to the dispersal-urbanization of the vector observed mainly since 1980 (Salomón et al. 2015), this process has been associated at macroscale with environmental modifications due to the construction of roads, dams, and infrastructure works such as the Bolivia-Brazil gas pipeline in the State of Mato Grosso do Sul (Pasquali et al. 2019), unplanned urbanization, deforestation in "fishbone" shape, and road network and intensity of exchange between neighboring localities (Oliveira et al. 2018). These large developmental projects in turn entail massive migration of workers and their families and dogs, to seek opportunities for a better quality of life, increasing the probability of parasite dispersal and AVL outbreaks. In a recent colonized city 2 years may elapse between the first record of *Lu. longipalpis* and the first canine case and 1 year more for the first human case (Casanova et al. 2015; Oliveira et al. 2016).

Large cities, once colonized, act as radial sources of spreading to their network of satellite localities (Harvim et al. 2019), decreasing their dispersal speed or reorienting its direction as the vector encounters environments with less ecological fitting, as in the state of São Paulo where the dispersal goes from 200 km/year at the beginning of the spreading wave to less than 25 km/year (Oliveira et al. 2016). Similarly, within a city, from the initial colonization site *Lu. longipalpis* spread radially, in steps, to the closer peridomiciles where the environment is conducive to its development; however, accounting for spatial discontinuities at the macro-scale and micro-scale, at any scale passive transport cannot be ruled out associated with transport of plants with soil presumably carrying eggs or larvae, such as a the initial colonization of a city from a flower nursery or a cemetery (Prestes-Carneiro et al. 2019; Brazil 2013), or the association with plant pots at microscale in urbanized areas (Santini et al. 2012).

This dependence on soil and organic matter for breeding, even in the cities, as well as the flight radius and fidelity to blood food sources, explains that populations with good adaptation to the urban environment, at the microscale, are still associated

with the microheterogeneity of the landscape and persistence of green spaces, or its expression through indicators such as the normalized difference vegetation index (NDVI) (Quintana et al. 2019; Berrozpe et al. 2019). Therefore, the vectors have a contagious distribution clustered in few places, the so-called critical sites, with abundance differences of up to more than 1000 times between spatially close traps (Figueiredo et al. 2016; Quinnell and Dye 1994), while the spatial autocorrelation of urban abundance for *Lu. longipalpis* was estimated to be around 600–700 m (Fernández et al. 2013).

Another micro-scale variable usually associated with the presence and abundance of vectors, regardless of the characterization of the landscape as urban or rural or the specific attractiveness of each host, is the abundance of blood-food sources in the domestic environment, especially chickens, pigs, and dogs, and secondarily other animals such as cats, horses, cows, and even bats in caves (Salomon 2021). However, many linear analytical approaches that tried to correlate the number of phlebotomine with the number hosts of the same species or between species normalized as biomass did not show significant associations, probably due to the fact that the olfactory stimulus in insects increases not in linear shape but in jumps assimilable to quadratic functions (Andersson et al. 2013). Furthermore, other factors modify the linear relationships as the male's pheromone recruitment process depends on host density (Quinnell and Dye 1994), which arrests both sexes at the site of the trap, phenomenon that can be used to improve chemical control (Courtenay et al. 2019).

In addition to the aforementioned association with food sources, adult harborage conditions and breeding sites with fallen organic matter from fruit or deciduous trees and housing quality such as wall openings or the bathroom or kitchen outside the dormitory building are related to the risk of exposure (Luz et al. 2020). However, socioeconomic variables or their proxies are interdependent with environmental conditions when referring to vector distribution, mainly in urban scenarios where the area with highest captures of *Lu. longipalpis* is the intermediate one between the highly urbanized center and the rururban periphery, generally in the shape of ring (Fernández et al. 2010). On the other hand, sometimes the lack of association between vector abundance and domestic animals or vegetation may be due to the fact that the design involves their presence as a precondition to select the sites for sampling, and so these variables were controlled a priori (Costa et al. 2019). In the same way, the distance from the trap to the blood source and the size of the source can bias many results such as the outdoor/indoor abundance, gut content, and even the rate of infection. Birds are refractory to *Leishmania* development so *Lu. longipalpis* populations associated with chicken coops or roosting trees have low infections, but the poultry amplifies the size of these vector populations increasing the human risk at closer "verandas," where people stay unprotected during the hours of maximum phlebotomine activity (Santini et al. 2010; Andrade et al. 2009).

In relation to temporal patterns, at different spatial and temporal scales, where climatic or environmental variables by proxy (NDVI, NDWI) are associated with *Lu. longipalpis* population size or transmission indexes such as AVL canine or human incidence, these results should be interpreted with attention to the sampling design of

the dependent variable and the explanatory variables. Meteorological data concurrent with captures actually reflect the activity of already existing adult sand flies, but only previous climatic data, attending to egg–adult cycles, can be associated with population size. On the other hand, the critical variables may vary according to season, since in the dry season the water deficit or rainfall may be critical but in the rainy season it could be the temperature. In Argentinean cities, the NDVI and land surface temperature (LST) were the significant variables during the summer but low urban coverage during the winter in one focus, while in another locality the significant variables were LST with lags of 2 months, and NDVI and normalized difference water index (NDWI) with lags of 2 and 3 months (Gómez-Bravo et al. 2017; Berrozpe et al. 2019). In turn, environmental changes at the microscale landscape or in the abundance of domestic animals can modify the presence and abundance of the vector independently of seasonal or extraordinary climate conditions (de Oliveira et al. 2013; Holcman et al. 2013).

However, despite the difficulties in extrapolating the spatiotemporal determinants of *Lu. longipalpis* distribution at the scale of urban focus, the phenomenon of persistent clustering and the possibility of defining the factors that modulate it at the micro-focal scale create the opportunity to develop prevention and integrated control strategies. There, environmental management focused on surveillance or mitigation on the most likely hotspots/source populations would be more cost-effective than interventions on the entire community (Salomon 2021).

6.5 The Challenges to the Control of American Visceral Leishmaniasis in Urban Areas

AVL is endemic to 13 countries, but the vast majority of the human cases occur in Brazil (PAHO 2021). Although reports on the occurrence of AVL cases in urban areas have been described in Argentina (Salomón et al. 2012), Colombia (Zambrano-Hernandez et al. 2015), Paraguay (Canese 2010), and Venezuela (Aguilar et al. 1998), the process of urbanization in Brazil has been dramatic and more extensively and historically described (Costa 2008; Maia-Elkhoury et al. 2008; Nascimento et al. 2008; Oliveira et al. 2008; Rangel and Vilela 2008; Werneck 2008). A close look at the Brazilian case might be useful for informing surveillance and control activities in other Latin American countries.

Historically recognized as a rural endemic disease, there has been a gradual process of urbanization of AVL in Brazil, and the disease found in large cities the suitable conditions for its occurrence (Werneck 2008; Harhay et al. 2011). Major urban epidemics were first recorded in the 1980s in the capitals of the states of Piauí (city of Teresina), Rio Grande do Norte (city of Natal), and Maranhão (city of São Luís), all in the Northeast region of the country (Costa et al. 1990; Jeronimo et al. 1994; Rafael da Silva et al. 1997). Subsequently the disease spread to large cities in all other regions of the country.

The epidemiological scenario leaves no doubt about the magnitude of the process of urbanization and geographical expansion of AVL. From 1980 to 2019, more than

105,000 cases of AVL were reported in the country, leading to the death of more than 6400 people. The average number of cases registered annually increased from 1601 (1985–1989) to 3630 (2000–2004), stabilizing around 3300 annual cases since then. In the 1990s, only 10% of cases occurred outside the Northeast Region, but in 2010s, this figure reached more than 50% of cases, demonstrating the insidious territorial expansion of the disease. Between 2015 and 2019, the indigenous transmission of AVL was recorded in more than 1700 municipalities in 23 Federated Units.

The reasons why this traditionally rural disease emerged in urban centers are not clear, but environmental changes associated with migratory movements and population growth have been frequently implicated. On the one hand, the disorderly process of urban occupation results in precarious living conditions and environmental destruction, promoting favorable conditions for the reproduction of the vector, the sand fly *Lutzomyia longipalpis*, which easily adapts to the peridomestic conditions of depleted areas, exploiting the accumulation of organic matter generated by domestic animals and poor sanitary conditions (Rangel and Vilela 2008). On the other hand, dogs wandering on the outskirts of the city can become infected when they come into direct contact with the sylvatic transmission cycle and, when they return to the inner city, serve as amplifiers of the infection for other dogs and humans. Foxes, potential wild reservoirs of the parasite, have also come to be seen relatively frequently on the outskirts of some cities, rummaging through urban waste in search of food (Werneck and Costa 2005). In this context, the presence of a large number of susceptible people, infected reservoirs, and vectors in abundance constitute basic conditions for the occurrence of autochthonous cases of the disease in urban areas.

Control of urban AVL in Brazil has been a resounding failure (Barreto et al. 2011). The Brazilian program for visceral leishmaniasis control (PVLC) was launched in the beginning of the 1960s, and the main proposed control strategies were obligatory notification of human cases, opportune diagnostic and treatment of human cases, vector control with insecticides, and culling of seropositive dogs. Indeed, these strategies seemed to be appropriate for confronting an eminently rural disease for which the typical foci of high incidence of infection could be identified with relative ease. However, in the last 50 years there was no substantial update or revision of the control strategies recommended by the original PVLC, despite the immense transformations in the Brazilian society during this period. In particular, social changes involved an intense, fast, and excluding process of urbanization associated with population movements from rural areas, leading to social segregation, with the peripheries of the large metropolitan areas characterized by the lack of urban services, environmental destruction, and poor living conditions (Werneck 2018).

The main supports of the current measures to reduce transmission still are vector control with residual insecticides and culling of seropositive dogs, although the first is underused. What supports the use of vector control and reservoirs as intervention strategies on AVL is the assumption that the incidence of infection in humans is directly related to the number of infectious dogs and the vectorial capacity of sand

flies to transmit the infection (Dye 1996). However, even though there is a theoretical basis to support the use of these strategies and VL surveillance and control actions are currently focusing on the areas of greatest risk, in practice, these measures have not been successful in interrupting the process of geographic expansion of AVL in the country (Werneck 2016).

A fundamental reason for the ineffectiveness of these strategies is the need for a permanent surveillance system, with extensive use of human and financial resources. Other specific factors can contribute to the ineffectiveness of dog culling, including (1) the inadequate sensitivity of the diagnostic tests commonly used to detect infectious dogs, (2) eliminated dogs are almost immediately replaced by a new population that can acquire infection quickly in highly endemic areas, (3) the large time span between diagnosis and removal of the infected dog from the environment, (4) low priority of VL compared to other diseases, and (5) chronic shortages of humans, material, and financial resources for sustaining the activities (Nunes et al. 2008; Zuben and Donalísio 2016). Concerning vector control, the operational difficulties and high cost related to the sustained large-scale implementation of intra- and peridomestic household spraying with insecticides, associated with limited knowledge about the ecology and biology of sand flies in the urban environment and the need for a comprehensive entomological surveillance system that provides qualitative and quantitative information about the vector, are other factors that favor the maintenance of transmission (Maia-Elkhoury et al. 2008; Rangel and Vilela 2008). The situation is aggravated by other difficulties such as the growing judicialization against canine euthanasia promoted by nongovernmental organizations and veterinarians; the low impact of health education activities; and insufficient investment in environmental sanitation (Romero 2016; Zuben and Donalísio 2016).

The urbanization process brings new challenges to the AVL control programs. The intra-urban heterogeneities in the distribution of vectors and other risk factors, patterns of vector–host contact, and host's susceptibility give rise to a variety of eco-epidemiological transmission scenarios. Spatial distribution of urban AVL is markedly heterogeneous, which may lead to a substantial increase in the force of transmission (Woolhouse et al. 1997). For canine leishmaniasis, for example, it was estimated that spatial heterogeneity in contact rates between dogs and vectors was able to produce a 3.5-fold increase in transmission rates (Woolhouse et al. 1997). In this situation, population subgroups contribute more to transmission and others have no contribution at all. As a result, focusing on interventions in higher-risk groups can lead to a substantial reduction in infection rates (Koopman et al. 2005).

Thus, considering these heterogeneities is fundamental to guide the choice of intervention strategies to be implemented, since the effectiveness of control measures can be modified according to several factors, such as the level of baseline transmission in the area, number of susceptible people, size of the canine and vector populations, social vulnerability, sanitation services, household structure, and environmental features, including land use and climate (Werneck 2008). Since AVL is considered a disease in which the conditions for transmission depend mostly on local factors, these underlying heterogeneities are important factors modulating the

effectiveness of the interventions. Therefore, the choice of control measures to use against AVL should be based on the specific context to which it will be implemented. There is probably no means to reduce AVL transmission in urban areas without using a combination of interventions which should be delivered according to the different transmission scenarios, preferably targeting areas at highest risk (Werneck 2018).

6.6 Remote Sensing as a Tool for Exploring the Role of Environment in the Spread of Visceral Leishmaniasis

Many efforts have been made to develop methods with the aim of identifying areas at risk for AVL transmission, most of them based on spatial analysis of historical data on human disease. However, since only a fraction of individuals infected will develop clinical disease and the incubation period of AVL varies between 3 and 6 months, such approaches fail to provide an up-to-date scenario useful for informing where interventions should be focused. Indeed, there is a consensus that information on vector distribution would be the most useful for that purpose, but, at the same time, is difficult to be obtained systematically due to the insufficient knowledge about sand flies breeding sites and behavior and the operational problems involved in monitoring of insect population at large geographical scales. The heterogeneous landscape of cities requires that data on vectors be gathered with finer geographical resolution, adding more complexity to the process.

In the last few decades, researches have been exploring the use of remote sensing images to identify areas of high risk of transmission of different vector-borne diseases. Most of the initial successful approaches have used these techniques to predict the occurrence of breeding sites and abundance of arthropod vectors that transmit malaria. However, there are substantial differences in the ecology of malaria and AVL vectors, the latter breeding in smaller and often difficult to recognize habitats. For this reason, the use of remote sensing in AVL research has focused less on the prediction of AVL vectors and mainly on the cross-sectional identification of environmental features associated with the occurrence of the disease with the aim of producing maps of risk.

In this chapter, we present an example of potential use of RS imagery to describe the relationship between landscape features and the distribution of AVL in the city of Teresina, the site of the first registered large urban epidemic of AVL in Brazil (Costa et al. 1990) (Fig. 6.1).

In this example, we examined the role of environmental risk factors in the occurrence of AVL in a population-based case-control study. Cases were persons newly diagnosed with AVL and controls were chosen at random from a list of residential addresses. We used a Global Positioning System to identify the location of the household of each participant (Fig. 6.2A). A remote sensing image (Landsat-TM) was processed to generate a map of land use/land cover classes and values of the NDVI (Fig. 6.2B). Four environmental variables were extracted with a 300 m radius buffer zone around the house (total of 304 pixels). The first two variables, the

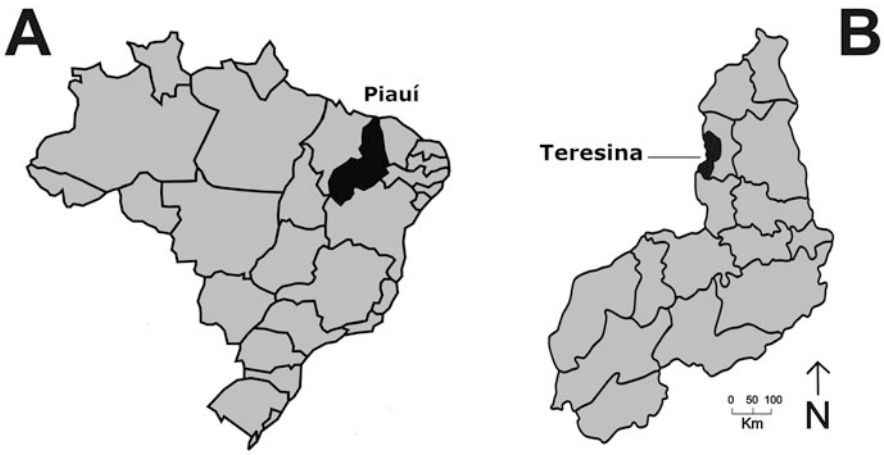


Fig. 6.1 (**a**) State of Piauí, Brazil and (**b**) The city of Teresina, Piauí State

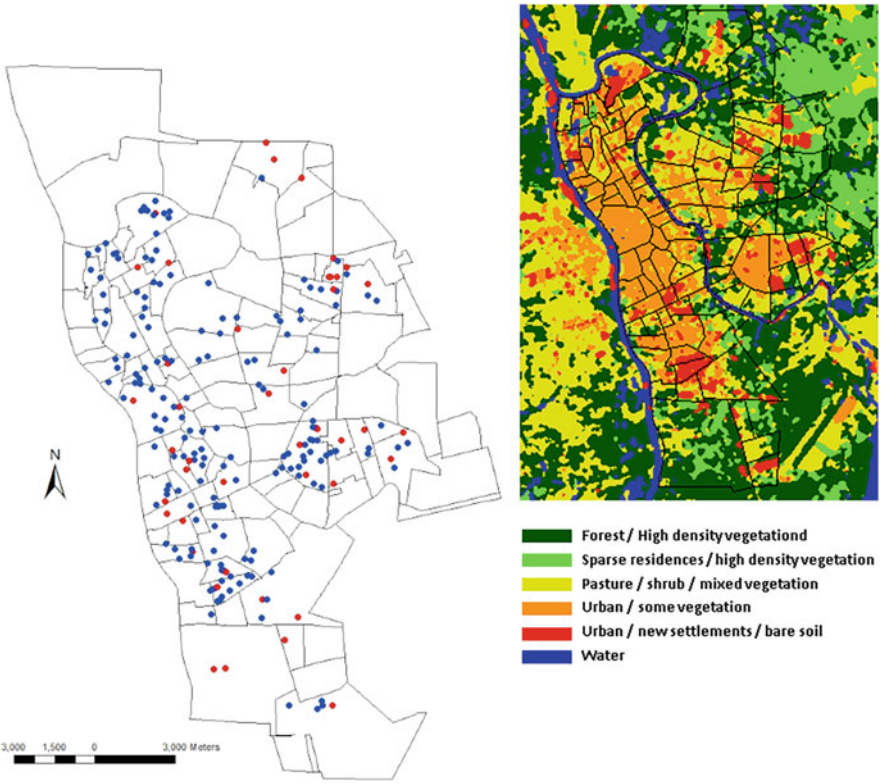


Fig. 6.2 (**a**) Geographical location of cases (red) and controls (blue); (**b**) Land use/land cover categories in Teresina's neighborhoods, 1995

"deforestation" and "urbanization" indices, were obtained by applying correspondence analysis to the land use/land cover classes. The deforestation index was a continuous variable with values varying from households located in new development settlements at one extreme to those located in highly residential areas with little vegetation on the other. The urbanization index was also a continuous variable ranging from values corresponding to households located in high-density residential areas to those in sparsely inhabited areas with abundant trees and vegetation. The third environmental variable, the "grass/pasture" index, was based on the percentage of pixels classified as pasture, grass, and bare soil in the buffer zone. The last environmental variable was the "commercial/residential" index, based on the percentage of the pixels in the buffer zone that were classified as mainly residential or commercial. All four indices entered in the model as binary factors (high/low) based on cutoff values suggested by classification tree models. The last set of variables used to describe the environment around the houses was the NDVI. In this study, we determined the minimum, the maximum, and the mean NDVI in the buffer zone, and recorded the values as high or low, based on the following cutoff values: 0.25 (maximum NDVI), 0.2 (mean), and − 0.2 (minimum).

After controlling for age, living conditions, and household characteristics, the risk of AVL was higher for persons living in areas with high percentage of land covered by grass or pasture, with high minimum NDVI, and with evidence of recent deforestation. Living in highly commercial and/or residential regions decreased the risk of VL by 85% (Table 6.1).

This example highlights the potential of remote sensing for the planning and execution of control programs. By using RS, it is possible to identify areas of high risk, based on environmental information that is associated with the incidence of AVL. Focusing control measures on these areas may be a useful strategy to increase their effectiveness, reduce operational costs, and contribute to the sustainability of control actions.

6.7 Closing Remarks

The distribution and geographic expansion of the leishmaniases in the Americas are strongly influenced by several factors. The transmission dynamics depends on the diversity of parasite, vector, and reservoir species, and on the local variation the various socioeconomic factors and man-made environmental transformations, leading to a diversity of epidemiological patterns of transmission. Despite strong theoretical models suggesting that certain interventions might be effective for controlling zoonotic leishmaniasis, the impact of such measures essentially depends on the spatial variability in the transmission rates, which is strongly determined by the distribution of the vector population. There is no simple solution for tackling the problem, but considering the heterogeneous spatial pattern of disease distribution and the lack of high levels of effectiveness of the available interventions, there is probably no means to reduce transmission without using a combination of

Table 6.1 Odds ratios (OR) and 95% confidence intervals (95% CI) for visceral leishmaniasis (VL) associated with environmental surrogates for level of exposure to infection defined for a 300 meters buffer around the household, Teresina, Brazil

Characteristic	Cases ($n = 44$)	Controls ($n = 176$)	Crude OR	95% CI	Adjusted OR[a]	95% CI[a]
Deforestation index						
Low	29	158	1.0			
High	15	18	5.11	2.30–11.3	2.13	0.73–6.27
Urbanization index						
Low	33	115	1.0		1.0	
High	11	61	0.62	0.29–1.31	0.35	0.12–1.03
Grass/pasture index						
Low	40	174	1.0		1.0	
High	4	2	10.6	1.87–60.2	13.6	1.74–106
Commercial/residential index						
Low	10	6	1.0			
High	34	170	0.11	0.04–0.33	0.15	0.04–0.63
Mean NDVI						
Low	39	174	1.0			
High	5	2	10.1	1.87–54.9	7.87	0.95–65.5
Minimum NDVI						
Low	3	42	1.0			
High	41	134	4.45	1.30–15.2	5.14	1.03–25.7
Maximum NDVI						
Low	10	65	1.0			
High	34	111	2.04	0.94–4.42	1.56	0.56–4.32

[a]Adjusted for age, living conditions and correlates of insect presence in the household

interventions delivered according to the different transmission scenarios, preferably targeting areas at highest risk.

References

Acosta MM, Santini MS, Pérez AA et al (2017) Evaluation of efficacy of impregnated curtains in experimental hen houses as a phlebotomine control tool in Northeast Argentina. Med Vet Entomol 31:161–166

Aguilar CM, Fernández E, Fernández R et al (1998) Urban visceral leishmaniasis in Venezuela. Mem Inst Oswaldo Cruz 93:15–16

Akhoundi M, Kuhls K, Cannet A et al (2016) A historical overview of the classification, evolution, and dispersion of *Leishmania* parasites and sandflies. PLoS NTDs. 10:e0004349

Alexander B, Agudelo LA, Navarro JF et al (2009) Relationship between coffee cultivation practices in Colombia and exposure to infection with *Leishmania*. Trans R Soc Trop Med Hyg 103:1263–1268

Almeida AS, Werneck GL (2014) Prediction of high-risk areas for visceral leishmaniasis using socioeconomic indicators and remote sensing data. Int J Health Geogr 13:13

Alves EB, Costa CH, de Carvalho FA et al (2016) Risk profiles for *Leishmania infantum* infection in Brazil. Am J Trop Med Hyg 94:1276–1281

Anderson RM, May RM (1992) Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford, p 17

Andersson P, Löfstedt C, Hambäck PA (2013) How insects sense olfactory patches—the spatial scaling of olfactory information. Oikos 122:1009–1016

Andrade AR, Nunes VL, Galati EA et al (2009) Epidemiological study on leishmaniasis in an area of environmental tourism and ecotourism, state of Mato Grosso do Sul, 2006–2007. Rev Soc Bras Med Trop 42:488–489

Araki AS, Vigoder FM, Bauzer LG et al (2009) Molecular and behavioral differentiation among Brazilian populations of *Lutzomyia longipalpis* (Diptera: Psychodidae: Phlebotominae). PLoS NTDs 3:e365

Barreto ML, Teixeira MG, Bastos FI et al (2011) Successes and failures in the control of infectious diseases in Brazil: social and environmental context, policies, interventions, and research needs. Lancet 377:1877–1889

Belo VS, Struchiner CJ, Werneck GL et al (2013a) A systematic review and meta-analysis of the factors associated with *Leishmania infantum* infection in dogs in Brazil. Vet Parasitol 195:1–13

Belo VS, Werneck GL, Barbosa DS et al (2013b) Factors associated with visceral leishmaniasis in the Americas: a systematic review and meta-analysis. PLoS NTDs 7:e2182

Bern C, Maguire JH, Alvar J (2008) Complexities of assessing the disease burden attributable to leishmaniasis. PLoS NTDs 2:e313

Berrozpe PE, Lamattina D, Santini MS et al (2019) Spatiotemporal dynamics of *Lutzomyia longipalpis* and macro-habitat characterization using satellite images in a leishmaniasis-endemic city in Argentina. Med Vet Entomol 33:89–98

Brazil RP (2013) The dispersion of *Lutzomyia longipalpis* in urban areas. Rev Soc Bras Med Trop 46:263–264

Brooks DR, Hoberg EP, Boeger WA (2019) The Stockholm paradigm: climate change and emerging disease. University of Chicago Press, Chicago

Buzanovsky LP, Sanchez-Vazquez MJ, Maia-Elkhoury ANS et al (2020) Major environmental and socioeconomic determinants of cutaneous leishmaniasis in Brazil—a systematic literature review. Rev Soc Bras Med Trop 53:e20190291

Cabrera OL, Santamaría E, Pardo RH (2018) Experimental hut to study the indoor behaviour and effects of insecticide-treated bednets on phlebotomine sand flies (Diptera: Psychodidae). Mem Inst Oswaldo Cruz 113:e180131

Campolina TB, Villegas LEM, Monteiro CC et al (2020) Tripartite interactions: *Leishmania*, microbiota and *Lutzomyia longipalpis*. PLoS NTDs 14:e0008666

Canese J (2010) Gran incremento de Leishmaniasis visceral humana en Paraguay. Pediatr (Asunción) 37:167–168

Carrada Figueroa GC, Leal Ascencio VJ, Jiménez Sastré A et al (2014) Transmission of cutaneous leishmaniasis associated with cacao (*Theobroma cacao*) plantations in Tabasco. Gac Med Mex 150:499–508

Casanova C, Colla-Jacques FE, Hamilton JG et al (2015) Distribution of *Lutzomyia longipalpis* chemotype populations in São Paulo state, Brazil. PLoS NTDs 9:e0003620

Casaril AE, Alonso DP, Franco KG et al (2019) Macrogeographic genetic structure of *Lutzomyia longipalpis* complex populations using next generation sequencing. PLoS One 14:e0223277

Chaves LF, Cohen JM, Pascual M et al (2008) Social exclusion modifies climate and deforestation impacts on a vector-borne disease. PLoS NTDs 2:e176

Chelbi I, Mathlouthi O, Zhioua S et al (2020) The impact of illegal waste sites on the transmission of zoonotic cutaneous Leishmaniasis in Central Tunisia. Int J Environ Res Public Health 18:66

Costa AT, Dias ES, Souza AGM et al (2019) Ecology of phlebotomine sand flies in an area of leishmaniasis occurrence in the Xakriabá Indigenous Reserve, Minas Gerais, Brazil. Rev Soc Bras Med Trop 52:e20180474

Costa CH (2008) Characterization and speculations on the urbanization of visceral leishmaniasis in Brazil. Cad Saude Publica 24:2959–2963

Costa CH, Pereira HF, Araújo MV (1990) Epidemia de leishmaniose visceral no estado do Piauí, Brasil, 1980–1986. Rev Saude Publica 24:361–372

Cotton JA (2017) The expanding world of human Leishmaniasis. Trends Parasitol 33:341–344

Courtenay O, Dilger E, Calvo-Bado LA et al (2019) Sand fly synthetic sex-aggregation pheromone co-located with insecticide reduces the incidence of infection in the canine reservoir of visceral leishmaniasis: a stratified cluster randomised trial. PLoS NTDs 13:e0007767

Coutinho-Abreu IV, Oristian J, de Castro W et al (2020) Binding of *Leishmania infantum* Lipophosphoglycan to the midgut is not sufficient to define vector competence in *Lutzomyia longipalpis* sand flies. mSphere 5:e00594-20

da Silva O, de Sousa ME, dos Santos FA (2000) La leishmaniose tégumentaire américaine dans la région sucrière du Pernambouc, Nord-Est du Brésil. Santé: Cahiers d'Etudes et de Recherches Francophones 10:123–126

De Oliveira EF, Silva EA, Casaril AE (2013) Behavioral aspects of *Lutzomyia longipalpis* (Diptera: Psychodidae) in urban area endemic for visceral leishmaniasis. J Med Entomol 50:277–284

de Souza Freitas MT, Dos Santos CFR, de Andrade EM et al (2018) New records of phlebotomine sand flies (Diptera: Psychodidae) from the state of Alagoas, northeast of Brazil. J Med Entomol 55:242–247

Dey R, Joshi AB, Oliveira F et al (2018) Gut microbes egested during bites of infected sand flies augment severity of Leishmaniasis via Inflammasome-derived IL-1β. Cell Host Microbe 23: 134–143

Dos Reis YV, Alevi KCC (2020) Hybridization in Phlebotominae (Diptera: Psychodidae): a mini-review. Infect Genet Evol 86:104593

Dye C (1996) The logic of visceral leishmaniasis control. Am J Trop Med Hyg 55:125–130

Esterre P, Chippaux JP, Lefait JF et al (1986) Evaluation d'un programme de lutte contre la leishmaniose cutanée dans un village forestier de Guyane française. Bull World Health Organ 64:559–565

Falcão de Oliveira E, Oliveira AG, Arruda CCP et al (2020) Spatio-temporal modeling of visceral leishmaniasis in Midwest Brazil: an ecological study of 18-years data (2001–2018). PLoS One 15(10):e0240218

Feliciangeli MD, Mazzarri MB, Campbell-Lendrum D et al (2003) Cutaneous leishmaniasis vector control perspectives using lambdacyhalothrin residual house spraying in El Ingenio, Miranda State, Venezuela. Trans R Soc Trop Med Hyg 97:641–646

Fernández MS, Salomón OD, Cavia R et al (2010) *Lutzomyia longipalpis* spatial distribution and association with environmental variables in an urban focus of visceral leishmaniasis, Misiones, Argentina. Acta Trop 114:81–87

Fernández MS, Santini MS, Cavia R et al (2013) Spatial and temporal changes in *Lutzomyia longipalpis* abundance, a Leishmania infantum vector in an urban area in northeastern Argentina. Mem Inst Oswaldo Cruz 108:817–824

Figueiredo HR, Santos MF, Casaril AE et al (2016) Sand flies (Diptera: Psychodidae) in an endemic area of leishmaniasis in Aquidauana municipality, Pantanal of Mato Grosso do Sul, Brazil. Rev Inst Med Trop Sao Paulo 58:87

Furtado NV, Galardo AK, Galardo CD et al (2016) Phlebotomines (Diptera: Psychodidae) in a hydroelectric system affected area from northern Amazonian Brazil: further insights into the effects of environmental changes on vector ecology. J Trop Med 9819723

Galati EAB, Galvis-Ovallos F, Lawyer P et al (2017) An illustrated guide for characters and terminology used in descriptions of Phlebotominae (Diptera, Psychodidae). Parasite 24:26

Gómez-Bravo A, German A, Abril M, Scavuzzo M, Salomón OD (2017) Spatial population dynamics and temporal analysis of the distribution of *Lutzomyia longipalpis* (Lutz & Neiva, 1912) (Diptera: Psychodidae:Phlebotominae) in the city of Clorinda, Formosa, Argentina. Parasit Vectors 10(1):352

Gouveia C, de Oliveira RM, Zwetsch A et al (2012) Integrated tools for American cutaneous Leishmaniasis surveillance and control: intervention in an endemic area in Rio de Janeiro, RJ, Brazil. Interdiscip Perspect Infect Dis 2012:568312

Gutiérrez JD, Martínez-Vega R, Ramoni-Perazzi J et al (2017) Environmental and socio-economic determinants associated with the occurrence of cutaneous leishmaniasis in the northeast of Colombia. Trans R SocTrop Med Hyg 111:564–571

Harhay MO, Olliaro PL, Costa DL et al (2011) Urban parasitology: visceral leishmaniasis in Brazil. Trends Parasitol 27(9):403–409

Harvim P, Zhang H, Georgescu P et al (2019) Transmission dynamics and control mechanisms of vector-borne diseases with active and passive movements between urban and satellite cities. Bull Math Biol 81:4518–4563

Hernández AM, Gutierrez JD, Xiao Y et al (2019) Spatial epidemiology of cutaneous leishmaniasis in Colombia: socioeconomic and demographic factors associated with a growing epidemic. Trans R Soc Trop Med Hyg:trz043

Holcman MM, Sampaio SM, Rangel O et al (2013) Spatial and seasonal distribution of *Lutzomyia longipalpis* in Dracena, a city in the western region of the state of São Paulo, Brazil, that is endemic with visceral leishmaniasis. Rev Soc Bras Med Trop 46:704–712

Jeronimo SM, Oliveira RM, Mackay S et al (1994) An urban outbreak of visceral leishmaniasis in Natal, Brazil. Trans R Soc Trop Med Hyg 88:386–388

Kakumanu ML, Marayati BF, Schal C et al (2021) Oviposition-site selection of *Phlebotomus papatasi* (Diptera: Psychodidae) sand flies: attraction to bacterial isolates from an attractive rearing medium. J Med Entomol 58:518–527

Kipp EJ, de Almeida M, Marcet PL et al (2020) An atypical case of autochthonous cutaneous Leishmaniasis associated with naturally infected Phlebotomine sand flies in Texas, United States. Am J Trop Med Hyg 103:1496–1501

Kitron U (1998) Landscape ecology and epidemiology of vector-borne diseases: tools for spatial analysis. J Med Entomol 35:435–445

Koopman JS, Simon CP, Riolo CP (2005) When to control endemic infections by focusing on high-risk groups. Epidemiology 16:621–627

Lawyer P, Killick-Kendrick M, Rowland T (2017) Laboratory colonization and mass rearing of phlebotomine sand flies (Diptera, Psychodidae). Parasite 24:42

Levins R (1969) Some demographic and genetic consequences of environmental heterogeneity for biological control. Bull Entomol Soc Am 15:237–240

Lewnard JA, Jirmanus L, Júnior NN (2014) Forecasting temporal dynamics of cutaneous leishmaniasis in Northeast Brazil. PLoS NTDs 8:e3283

Lockard RD, Wilson ME, Rodríguez NE (2019) Sex-related differences in immune response and symptomatic manifestations to infection with *Leishmania* species. J Immunol Res 2019: 4103819

Luz JGG, Carvalho AG, Naves DB (2020) Are backyard characteristics relevant factors for the occurrence of human visceral leishmaniasis in Central-Western Brazil? Trans R Soc Trop Med Hyg 114:276–283

Maia-Elkhoury AN, Alves WA, Sousa-Gomes ML et al (2008) Visceral leishmaniasis in Brazil: trends and challenges. Cad Saude Publica 24:2941–2947

Maia-Elkhoury AN, Magalhães Lima D, Salomón OD et al (2021) Interacción entre los determinantes medioambientales y socioeconómicos para el riesgo para leishmaniasis cutánea en América Latina. Rev Panam Salud Publica 45:e49

Manteca-Acosta M, Cavia R, Utgés ME, Salomón OD, Santini MS (2021) Peridomestic natural breeding sites of *Nyssomyia whitmani* (Antunes and Coutinho) in an endemic area of tegumentary leishmaniasis in northeastern Argentina. PLoS NTDs 15(8):e0009676

Marklewitz M, Dutari LC, Paraskevopoulou S (2019) Diverse novel phleboviruses in sandflies from the Panama Canal area, Central Panama. J Gen Virol 100:938–949

Maroli M, Feliciangeli MD, Bichaud L (2013) Phlebotomine sandflies and the spreading of leishmaniases and other diseases of public health concern. Med Vet Entomol 27:123–147

Martínez MF, Kowalewski MM, Giuliani MG (2020) Molecular identification of *Leishmania* in free-ranging black and gold howler monkeys (Alouatta caraya) in northeastern Argentina. Acta Trop 210:105534

Moreno M, Guzmán-Rodríguez L, Valderrama-Ardila C et al (2020) Land use in relation to composition and abundance of phlebotomines (Diptera: Psychodidae) in five foci of domiciliary transmission of cutaneous leishmaniasis in the Andean region of Colombia. Acta Trop 203: 105315

Mubayi A, Paredes M, Ospina J (2018) A comparative assessment of epidemiologically different cutaneous Leishmaniasis outbreaks in Madrid, Spain and Tolima, Colombia: an estimation of the reproduction number via a mathematical model. Trop Med Infect Dis 3:43

Nascimento EL, Martins DR, Monteiro GR et al (2008) Forum: geographic spread and urbanization of visceral leishmaniasis in Brazil. Postscript: new challenges in the epidemiology of *Leishmania chagasi* infection. Cad Saude Publica 24:2964–2967

Nunes CM, Lima VM, Paula HB et al (2008) Dog culling and replacement in an area endemic for visceral leishmaniasis in Brazil. Vet Parasitol 153:19–23

Oliveira AM, Vieira CP, Dibo MR et al (2016) Dispersal of *Lutzomyia longipalpis* and expansion of canine and human visceral leishmaniasis in São Paulo state, Brazil. Acta Trop 164:233–242

Oliveira AM, López RVM, Dibo MR et al (2018) Dispersion of *Lutzomyia longipalpis* and expansion of visceral leishmaniasis in São Paulo state, Brazil: identification of associated factors through survival analysis. Parasite Vectors 11:503

Oliveira CD, Morais MH, Machado-Coelho GL (2008) Visceral leishmaniasis in large Brazilian cities: challenges for control. Cad Saude Publica 24:2953–2958

Oliveira DM, Saraiva EM, Ishikawa EA et al (2011) Distribution of phlebotomine fauna (Diptera: Psychodidae) across an urban-rural gradient in an area of endemic visceral leishmaniasis in northern Brazil. Mem Inst Oswaldo Cruz 106:1039–1044

PAHO (2019) Manual de procedimientos para vigilancia y control de las leishmaniasis en las Américas. Organización Panamericana de la Salud, Washington DC

PAHO (2020) Leishmaniasis: epidemiological report in the Americas. Number 9. Pan American Health Organization, Washington DC

PAHO (2021). Atlas interactivo de Leishmaniasis En Las Américas. Aspectos clínicos y diagnósticos diferenciales. Organización Panamericana de la Salud, Washington DC

Panahi E, Shivas M, Hall-Mendelin S et al (2020) Utilising a novel surveillance system to investigate species of Forcipomyia (Lasiohelea) (Diptera: Ceratopogonidae) as the suspected vectors of *Leishmania macropodum* (Kinetoplastida: Trypanosomatidae) in the Darwin region of Australia. Int J Parasitol Parasites Wildl 12:192–198

Pasquali AKS, Baggio RA, Boeger WA et al (2019) Dispersion of *Leishmania* (*Leishmania*) *infantum* in central-southern Brazil: evidence from an integrative approach. PLoS NTDs 13: e0007639

Pavlovsky EN, Pious FK Jr (1966) Natural nidality of transmissible disease in relation to landscape epidemiology of Zooanthroponoses. University of Illinois Press, Urbana and London

Perich MJ, Hoch AL, Rizzo N et al (1995) Insecticide barrier spraying for the control of sand fly vectors of cutaneous leishmaniasis in rural Guatemala. Am J Trop Med Hyg 52:485–488

Prestes-Carneiro LE, Daniel LAF, Almeida LC (2019) Spatiotemporal analysis and environmental risk factors of visceral leishmaniasis in an urban setting in São Paulo state, Brazil. Parasit Vectors 12:251

Quinnell RJ, Dye C (1994) Correlates of the peridomestic abundance of *Lutzomyia longipalpis* (Diptera: Psychodidae) in Amazonian Brazil. Med Vet Entomol 8:219–224

Quintana MG, Salomón OD, De Grosso MS (2010) Distribution of phlebotomine sand flies (Diptera: Psychodidae) in a primary forest-crop interface. Salta, Argentina J Med Entomol 47: 1003–1010

Quintana MG, Pech-May A, Fuenzalida AD et al (2019) *Lutzomyia longipalpis* (Diptera: Psychodidae) Argentina-Bolivia border: new report and genetic diversity. Mem Inst Oswaldo Cruz 114:e190184

Rangel EF, Vilela ML (2008) *Lutzomyia longipalpis* (Diptera, Psychodidae, Phlebotominae) and urbanization of visceral leishmaniasis in Brazil. Cad Saude Publica 24:2948–2952

Reinhold-Castro KR, Fenelon VC, Rossi RM et al (2013) Impact of control measures and dynamics of sand flies in southern Brazil. J Vector Ecol 38:63–68

Rodrigues BL, Carvalho-Costa LF, Pinto IS et al (2018) DNA barcoding reveals hidden diversity of sand flies (Diptera: Psychodidae) at fine and broad spatial scales in Brazilian endemic regions for Leishmaniasis. J Med Entomol 55:893–901

Romero GA (2016) O controle de leishmaniose visceral no Brasil: transformar é preciso. Cad Saude Publica 32:S0102-311X2016000600402

Salomon OD (2019) Instructions on how to make an outbreak of American cutaneous Leishmaniasis. J Trop Med Health 3:146

Salomon OD (2021) *Lutzomyia longipalpis*, gone with the wind and other variables. Neotrop Entomol 50:161–171

Salomón OD, Wilson ML, Munstermann LE (2004) Spatial and temporal patterns of phlebotomine sand flies (Diptera: Psychodidae) in a cutaneous leishmaniasis focus in northern Argentina. J Med Entomol 41:33–39

Salomón OD, Mastrángelo AV, Santini MS et al (2012) Leishmaniasis visceral: senderos que confluyen, se bifurcan. Salud Colectiva 8(Supl:1):S49–S63

Salomón OD, Feliciangeli MD, Quintana MG (2015) *Lutzomyia longipalpis* urbanisation and control. Mem Inst Oswaldo Cruz 110:831–846

Santini MS, Salomón OD, Acardi SA (2010) *Lutzomyia longipalpis* behavior at an urban visceral leishmaniasis focus in Argentina. Rev Inst Med Trop Sao Paulo 52:187–192

Santini MS, Fernández MS, Pérez AA et al (2012) *Lutzomyia longipalpis* abundance in the city of Posadas, northeastern Argentina: variations at different spatial scales. Mem Inst Oswaldo Cruz 107:767–771

Serafim TD, Coutinho-Abreu IV, Oliveira F et al (2018) Sequential blood meals promote *Leishmania* replication and reverse metacyclogenesis augmenting vector infectivity. Nat Microbiol 3: 548–555

Shaw J (2007) The leishmaniases—survival and expansion in a changing world. A mini-review. Mem Inst Oswaldo Cruz 102:541–547

Shimabukuro PHF, de Andrade AJ, Galati EAB (2017) Checklist of American sand flies (Diptera, Psychodidae, Phlebotominae): genera, species, and their distribution. Zookeys 660:67–106

Silva AR, Viana GM, Varonil C (1997) Leishmaniose visceral (calazar) na Ilha de São Luís, Maranhão, Brasil: evolução e perspectivas. Rev Soc Bras Med Trop 30:359–368

Silva Santana Cruz C, Soeiro Barbosa D, Oliveira VC et al (2021) Factors associated with human visceral leishmaniasis cases during urban epidemics in Brazil: a systematic review. Parasitology 148:639–647

Staniek ME, Hamilton JGC (2021) Odour of domestic dogs infected with *Leishmania infantum* is attractive to female but not male sand flies: evidence for parasite manipulation. PLoS Pathog 17: e1009354

Susser M, Susser E (1996) Choosing a future for epidemiology: II. From black box to Chinese boxes and eco-epidemiology. Am J Public Health 86:674–677

Thomaz-Soccol V, Gonçalves AL, Piechnik CA, Baggio RA, Boeger WA, Buchman TL, Michaliszyn MS, Rodrigues Dos Santos D et al (2018) Hidden danger: unexpected scenario in the vector-parasite dynamics of leishmaniases in the Brazil side of triple border (Argentina, Brazil and Paraguay). PLoS NTDs 12(4):e0006336

Torres-Slimming P (2010) Globalización, el proyecto Camisea y la salud de los matsiguengas. Rev Peru Med Exp Salud Publica 27:458–465

Valero NNH, Uriarte M (2020) Environmental and socioeconomic risk factors associated with visceral and cutaneous leishmaniasis: a systematic review. Parasitol Res 119:365–384

Viana M, Mancy R, Biek R et al (2014) Assembling evidence for identifying reservoirs of infection. Trends Ecol Evol 29:270–279

Vilela ML, Azevedo CG, Carvalho BM et al (2011) Phlebotomine fauna (Diptera: Psychodidae) and putative vectors of leishmaniases in impacted area by hydroelectric plant, state of Tocantins. Brazil. PLoS One 6:e27721

Wachter S, Hicks LD, Raghavan R et al (2020) Novel small RNAs expressed by *Bartonella bacilliformis* under multiple conditions reveal potential mechanisms for persistence in the sand fly vector and human host. PLoS Negl Trop Dis 14:e0008671

Werneck GL (2008) Forum: geographic spread and urbanization of visceral leishmaniasis in Brazil. Introduction. Cad Saude Publica 24:2937–2940

Werneck GL (2016) The control of visceral leishmaniasis in Brazil: end of a cycle. Cad Saude Publica 32:S0102-311X2016000600201

Werneck GL (2018) Effectiveness of control strategies against visceral leishmaniasis in Brazil: there is no silver bullet. Rev Inst Adolfo Lutz, São Paulo 77:e1758

Werneck GL, Costa CHN (2005) Utilização de dados censitários em substituição a informações socioeconômicas obtidas no nível individual: uma avaliação empírica. Epidemiologia e Serviços de Saúde 14:143–150

Werneck GL, Costa CH, Walker AM et al (2007) Multilevel modelling of the incidence of visceral leishmaniasis in Teresina, Brazil. Epidemiol Infect 135:195–201

WHO (2010) Control of the leishmaniases: report of a meeting of the WHO expert committee on the control of Leishmaniases. WHO Press, Geneva

WHO (2021) World Health Organization. Leishmaniasis. http://www.who.int/news-room/fact-sheets/detail/leishmaniasis Accessed 15.05.2021

Woolhouse ME, Dye C, Etard JF et al (1997) Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc Natl Acad Sci USA 94:338–342

Zambrano-Hernandez P, Ayala-Sotelo MS, Fuya-Oviedo P et al (2015) Brote urbano de leishmaniasis visceral en Neiva. Colombia Rev Salud Publica (Bogota) 17:514–527

Zorrilla V, De Los Santos MB, Espada L et al (2017) Distribution and identification of sand flies naturally infected with *Leishmania* from the southeastern Peruvian Amazon. PLoS NTDs 11: e000602

Zuben AP, Donalísio MR (2016) Dificuldades na execução das diretrizes do Programa de Vigilância e Controle da Leishmaniose Visceral em grandes municípios brasileiros. Cad Saude Publica 32:S0102-311X2016000600401

Toxoplasmosis in South America

7

Heinz Mehlhorn

Abstract

The protozoan parasite *Toxoplasma gondii* is distributed worldwide and parasitizes animals as well as humans. The latter become infected by eating raw or undercooked meat of infected animals (e.g., that of pigs). Infections of pregnant women may lead to infections of the fetus introducing eventually very severe symptoms of disease or even death of the growing fetus. Thus, doctors should inform pregnant women to avoid raw meat.

Keywords

Toxoplasma gondii · Oocysts · Congenital toxoplasmosis · Raw meat as pathway of infection · Cats as vectors · Chemotherapy

7.1 Name

The genus name *Toxoplasma* has been selected in the years 1908/1909 by two French scientists working in North African countries: Charles Nicolle and Louis Manceaux. During their studies in Tunis dealing with the North African rodent *Ctenodactylus gundi*, both these scientists detected bow-like appearing protozoan stages, which they named *Toxoplasma gondii* based on the Greek terms *toxon* = arc bow and *plasma* = life, whereby they apparently mixed the official genus name **gundi** with ***gondii***. At first the authors thought that this parasite is related to the genus *Leishmania* (c.f. Ferguson 2009). At the same time (1908), this parasite was found in Brazil in rabbits by Splendore. Both scientific groups considered at first this

H. Mehlhorn (✉)
Department of Parasitology, Heinrich Heine University, Düsseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_7

parasite as a related organism belonging to the genus *Leishmania*. In the following years (1908–1937), many papers became published documenting that this organism occurs worldwide in a broad spectrum of hosts inducing often severe symptoms of disease. However, it took until 1937 to find out the true relationship of this apparently widespread parasite, when Sabin and Olitsky showed that *T. gondii* was an obligate intracellular parasite which could be transmitted by oral uptake of infected tissues. They also showed that eating raw *Toxoplasma*-contaminated meat may transmit this new parasite and first cases of diseased humans were described (Wolf and Cowen 1937). Starting in the year 1948, when Sabin and Feldman developed a serological technique characterizing antibodies against the now named organism *Toxoplasma gondii*. This protozoan parasite reached a worldwide broad attention. Since then, *Toxoplasma gondii* was found worldwide (Mehlhorn 2016a, b).

7.2 Geographic Distribution and Transmission of *Toxoplasma gondii*

The papers of Sabin and Olitski (1937), Sabin (1942), and Sabin and Feldman (1948) showed with the help of their serological methods that the newly described parasite *Toxoplasma gondii* has reached a worldwide distribution among humans and many vertebrate animals. It turned out that not only carnivorous host species including humans are involved but also those which ingest food contaminated by oocysts originating from cat feces (Fig. 7.1). Due to this flexibility, this parasite has reached worldwide distribution among felids and is considered to have reached the third place of the most common parasites among humans and vertebrate animals. It was shown in many trials that about 0.4–2% of all free-ranging cats are infected due to their common consumption of cyst containing mice/rats or by uptake of feces containing oocysts. It is estimated that worldwide about one-third of the human world population is infected.

7.3 Biology, Morphology

Domestic cats or closely related species are final hosts (Fig. 7.1) as well as free-roaming felids like lions and tigers. After ingestion of tissue cysts containing animals or by ingesting sporulated oocysts, the thus infected cats excrete non-sporulated oocysts, which measure 12 × 10 μm in size (Fig. 7.2). Inside the oocyst wall two sporocysts become developed each containing finally four infectious sporozoites (Fig. 7.3). Such tiny oocysts might be spread from excreted cat feces by insects like cockroaches or flies or just by wind onto human or animal food. This offers the significant possibility of infections of humans and many animals, which might become intermediate hosts. It is estimated that around 80% of the elderly human population (eating undercooked meat) or many free-roaming cats that catch infected mice have antibodies against *Toxoplasma gondii*.

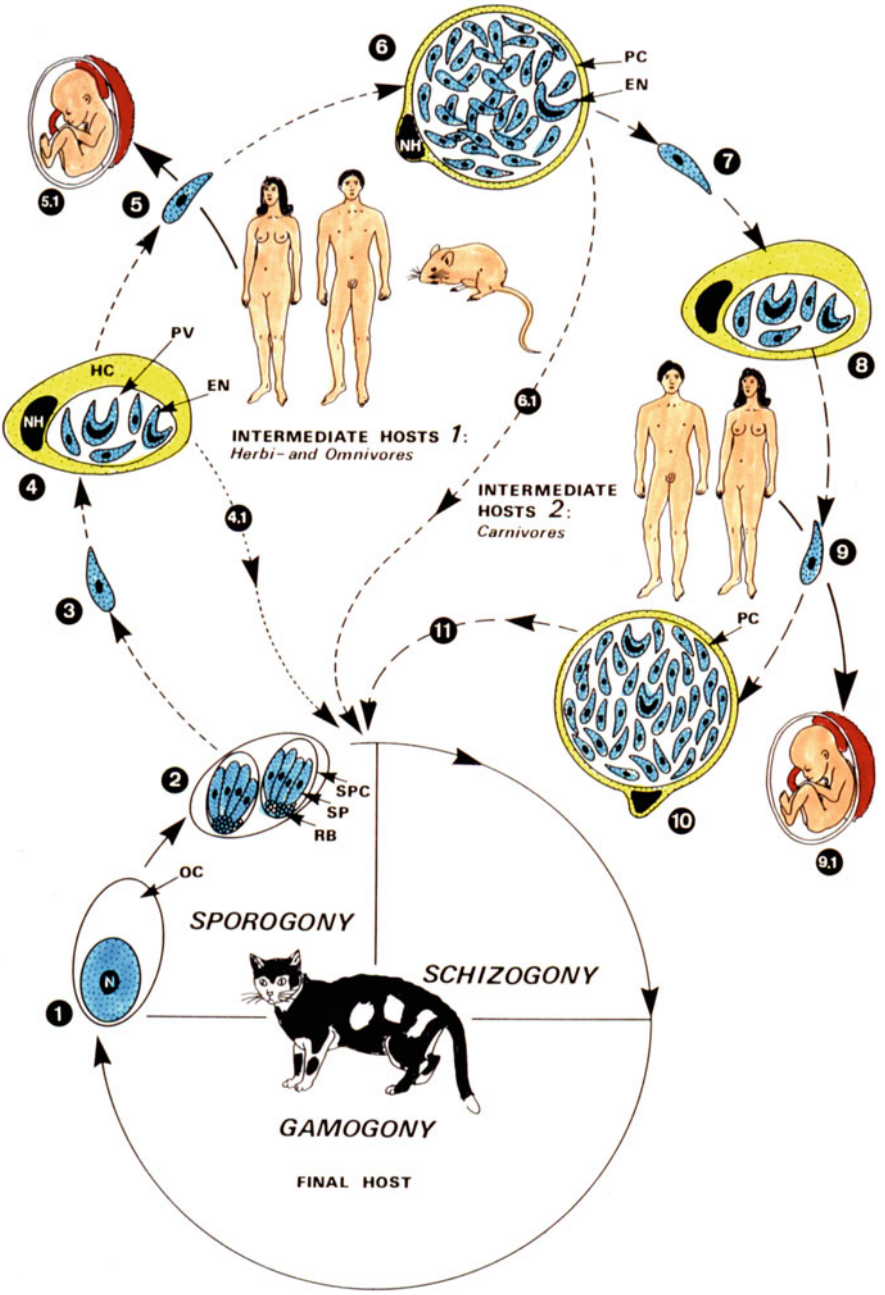


Fig. 7.1 Life cycle and transmission pathways of *Toxoplasma gondii*. The typical life cycle proceeds in the intestinal epithelium of felids (final host) which are infected by oral uptake of sporulated oocysts (**2**), ingestion of "pseudocysts" (**4.1, 8**) or tissue cysts (**6.1, 11**) with meat of various intermediate hosts (of 2 types). (**1**) Unsporulated oocysts are excreted with feces. (**2**) Sporulation (i.e., formation of sporocysts and sporozoites) occurs outside the final host. These stages may become spread by transport hosts such as flies and cockroaches. (**3**) After ingestion of

7.3.1 Pathway of Human Infections

Infections of humans may occur in different ways:

1. Oral uptake of sporulated oocysts (Fig. 7.3) by contact with cat feces or from hair of cats (cats like to lick both their anus and hair).
2. Oral uptake of oocysts (Fig. 7.3) that had been transported by flies from cat feces to human food or to lips of babies.
3. Oral uptake of tissue cysts in raw or undercooked meat of animals (e.g., in mild raw ham, salami, sausages, and steak tartar) (Figs. 7.6 and 7.7).
4. Intrauterine, diaplacental, or congenital transmissions. In the case of the first infection of females during pregnancy, *Toxoplasma* tachyzoites (Figs. 7.4 and 7.5). may pass the placenta and enter the fetus, which may become severely infected. Tests have shown that already 1% of the newborn had been infected.
5. Blood transfusions from latent infected people to previously noninfected persons. However, this pathway is apparently not very important in the case of *Toxoplasma* transmission, since the blood of patients contains in general rather few trophozoites/tachyzoites.

7.4 Symptoms of Disease (Toxoplasmosis)

7.4.1 Cats and Related Species

In the case of low -graded infections, clear clinical symptoms do either not occur or are not registered by the owners. However, in high-graded infections especially young cats show phases of watery diarrheas, which often stop without special

Fig. 7.1 (continued) oocysts by intermediate hosts of type 1, the sporozoites are set free inside its intestine and penetrate numerous types of extraintestinal cells (i.e., cells of the RES). (**4**) Inside the host cell the parasites reproduce by a typical binary fission (endodyogeny) leading to "pseudocysts" which are filled with merozoites (i.e., tachyzoites). (**4.1**) After ingestion of such pseudocysts, cats may become infected. (**5**) Free merozoite (tachyzoite) in blood or lymph fluid after bursting of a pseudocyst. (**5.1**) When the first infection occurs in pregnant women (or female animals), these merozoites may pass into the placenta and infect the fetus, leading to severe damage. (**6**) Formation of tissue cysts, mainly inside brain and muscle cells. After several endodyogenies these cysts (waiting stages) contain numerous cyst merozoites (bradyzoites, cystozoites) which are infectious for cats (**6.1**). (**7–10**) If carnivorous animals or humans (intermediate host of type 2) ingest such tissue cysts (**10**) as in intermediate hosts of type 1, diaplacental transmission (**9.1**) may also occur (see **Fig. 5.1**), leading to congenital toxoplasmosis. (**11**) Cats may also become infected by ingestion of tissue cysts from type 2 intermediate hosts. Then they pass oocysts after 3–5 days, whereas this prepatent period is longer after inoculation of pseudocysts (9–11 days) or oocysts (21–24 days). **EN** division by endodyogeny; **HC** host cell; **N** nucleus; **NH** nucleus of host cell; **OC** oocyst; **PC** primary cyst wall; **PV** parasitophorous vacuole; **RB** residual body; **SP** sporozoite; **SPC** sporocyst. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

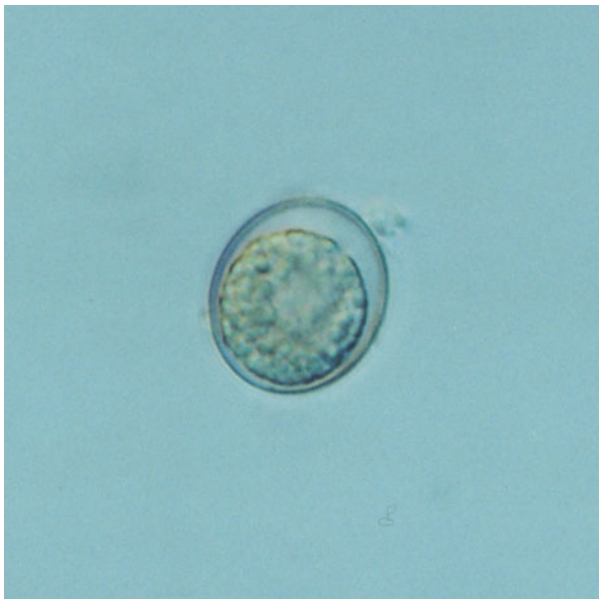


Fig. 7.2 Light micrograph of an oocyst of *Toxoplasma gondii* isolated from feces of an infected cat

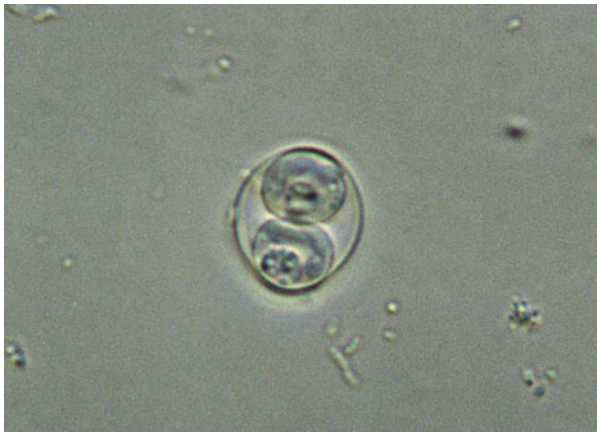


Fig. 7.3 Light micrograph of a sporulated oocyst of *Toxoplasma gondii* containing two sporocysts each with 4 sporozoites (found on soil)

treatment and the animals receive a rather solid immunity. Old cats and immunosuppressed animals may become severely sick—especially due to the loss of large amounts of water within excreted watery feces. Acute toxoplasmosis may also lead to serious damages of the brain and muscles of the legs and heart and thus limits the movements of infected hosts (vertebrate animals), which thus become an easy prey of the final hosts (cats).

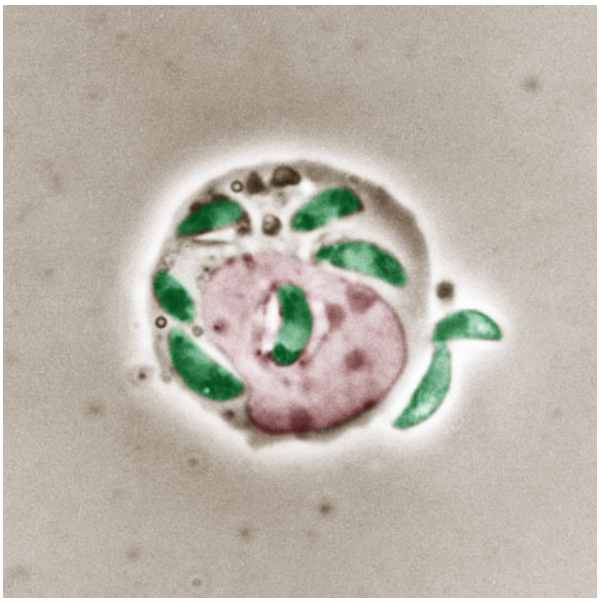


Fig. 7.4 Light micrograph of a human macrophage containing penetrated tachyzoites each within a separate vacuole. Two further tachyzoites start penetration of the cell. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

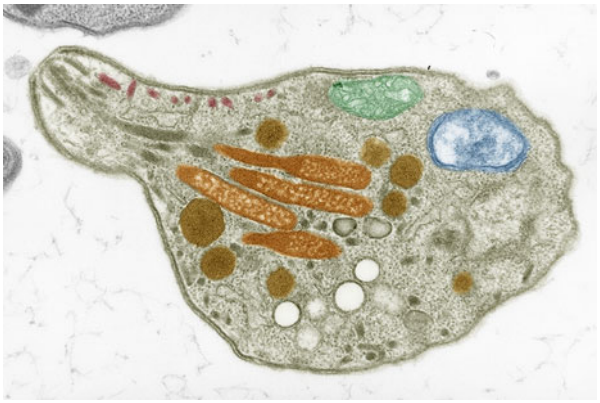


Fig. 7.5 Transmission electron micrograph of a section through the protruded anterior end of a tachyzoite showing sections of the typical organelles: mitochondrion: green; apicoplast: blue; rhoptries: grey + brown; conoid: gray at the top of the protrusion. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

7.4.2 Human Infections

As it is the case of diseases of animals, also human infections due to *T. gondii* might not be easily discovered, since the symptoms are unspecific and often low-graded (e.g., body pain, weakness), and thus, the disease might not be correctly diagnosed. In addition, there are different types of toxoplasmosis described occurring around the world.

7.4.2.1 Acquired Postnatal Toxoplasmosis

In this case, the infection starts due to the oral uptake of oocysts excreted by cats or by ingestion of the parasite stages in cysts of raw meat of infected animals belonging

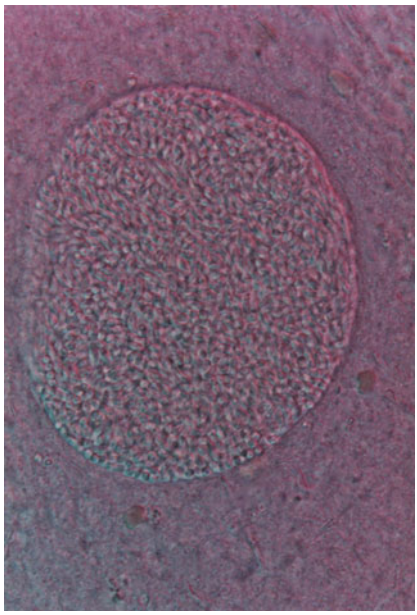


Fig. 7.6 Light micrograph of a *Toxoplasma* cyst in the brain of a mouse containing large numbers of banana-shaped, infectious tachyzoites (see Figs. 7.4, 7.5). Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

Fig. 7.7 Transmission electron micrograph of a cross section through a tissue cyst of *T. gondii*. Layers: outside red: muscle layer; yellow: destroyed muscle cell material; green: cover of the cyst inside the muscle cell; the inside is filled by sections through bradyzoites. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

to the human food chain (Fig. 7.1). Such an infection induces the following symptoms starting after a symptomless incubation period of about 2–3 weeks. This rather long time leads to the fact that the infected persons mostly do not remember when and where the infection occurred. Common symptoms are:

– Swelling of lymph nodes (adenitis)
– Infection of eyes (iridocyclitis, chorioretinitis, so-called ocular toxoplasmosis)
– Infection of the brain (meningoencephalitis)

– Infection of visceral organs (interstitial pneumonia, hepatitis, myocarditis, enterocolitis, myositis, skin eczema)
– Skin exanthema
– All of them may induce severe symptoms of disease (especially in persons with low immunostatus)

7.4.2.2 Congenital Toxoplasmosis

This disease is most dangerous for mothers and their unborn or very young children, if the mother is infected for the first time during pregnancy. In about 5% of the infections the agents of disease enter the unborn child. This may lead to severe damages, which may start immediately or increase even up to 20 years after the infection (e.g., diseased eyes). The development of a so-called hydrocephalus is unfortunately rather common as well as further spectrum fetopathies.

7.4.2.3 Ocular Toxoplasmosis (OT)

Studies have shown that the infection of eyes is much more common and severe in South America than in Europe and increases the damage due to the so-called posterior infectious uveitis.

7.4.2.4 Toxoplasmosis Due to Blood Transfusions

There had been reported several cases in the literature. However, the total number is rather low—probably due to the low number of tests and the mostly/often occurring rather mild symptoms.

7.5 Prophylaxis

Very young children, pregnant women (in case, they are still seronegative for *Toxoplasma*), and immunosuppressed persons should avoid contact with cats and cat feces and should not eat raw or undercooked meat (especially not that of free-ranging pigs). Deep-freezing of meat at ~20 °C for at least 24 h and cooking of meat at about 54 °C will potentially kill *Toxoplasma* stages inside the meat. Cats in private households should not be fed with raw meat. **Important:** Pregnant women should be tested for *Toxoplasma* antibodies at the very beginning of the pregnancy. In case that there are no existing *Toxoplasma* antibodies, this test must (!) be repeated at each of the following monthly investigations.

7.6 Incubation Period

Hours up to 2 days in cases of acute toxoplasmosis.

7.7 Prepatent Period

Depending on the pathogenicity and virulence of the *Toxoplasma* strain: 1–2 days up to several weeks.

7.8 Patency

Tissue cysts may exist for years within tissue cells without any symptoms. In cases of ruptures of these cysts, new phases of infections of other cells may occur (see chronic toxoplasmosis).

7.9 Diagnosis of Human Infections

Acute *Toxoplasma* infections may be diagnosed by detection of parasites (tachyzoites) in blood, in lymph node punctions, in fluids, or in biopsies of tissues. For the determination of the age of an infection, serological tests are used, which can be done by examination of the presence of the different antibody classes. **Fresh infections** are indicated by the early presence of the **IgM class**. If these antibodies are lacking or occur in lower numbers than those of the **IgG class**, an old infection is still present.

IgM antibodies can be diagnosed by the following tests:

- Double-sandwich IgM-ELISA (**DSIgM-ELISA**)
- Reverse-enzyme immunoassay (**REIA**)
- Immunosorbent agglutination assay (**ISAGA**)
- Enzyme immunoassay (**EIA**)

The following tests show a persistent infection for about 1 year. The **IgG antibodies** can be demonstrated by the following tests:

- Complement binding reaction (**KBR**)
- Coloring according to the Sabin and Feldman test (**SFT**)
- Indirect immunofluorescence test (**IIFT**)
- Enzyme-linked immunosorbent assay (**ELISA**)
- Direct agglutination test (**DAT**)

7.10 Determination of a First Infection of a Pregnant Woman

The **seroconversion** is an essential marker of an infection. Thus, it is needed to control monthly the blood status of *Toxoplasma*-seronegative pregnant women, since fresh first infections need treatment. Within this context, it is needed to evaluate and interpret the antibody reactions:

- *Toxoplasma* antibodies are noted with the help of the IIFT test system already 11 days after the infection and reach their highest levels after 3–4 weeks (like those in SAF tests).
- Occurrence of significant IgG levels, absence of IgM antibodies, and KBR titers of $\geq$1:10 indicate an acute toxoplasmosis.

Attention: Variations of the antibody titers may be based on physiological reactions and on the methods of analysis. Thus, repetitions of the tests are strongly recommended.

7.11 Therapy

7.11.1 Congenital Toxoplasmosis

The treatment is recommended not only in cases of existing symptoms but also in a persistent asymptomatic congenital toxoplasmosis (detected accidentally in serotests) in order to avoid later toxoplasmosis symptoms:

- **Pyrimethamine:** 1 mg/kg body weight every 2 days (in cases of severe organ infections: 2 mg for 3 days) combined with sulfadiazine (250 mg/kg body weight daily). In addition, the application of 5 mg folic acid for 2 days and control of the blood composition and amount of thrombocytes are recommended.
  Duration of chemotherapy: In cases of asymptomatic infections: 6 months; in cases of defined clinical symptoms: 12 months.
- **Spiramycin** (100 mg/kg body weight daily in two to three portions) is recommended in the case that the above-described treatment is not tolerated. In cases of clear CNS symptoms and/or chorioretinitis inclusive macular damages, it is recommended to give additionally **prednisolone** (1–2 mg/kg bodyweight) until inflammation symptoms decrease. **Important:** Always check the package insert of the product before use.

7.11.2 Postnatal Toxoplasmosis in the Case of Immunocompetent Persons

Low-grade symptoms and non-complicated lymphadenopathy do not warrant treatment, which, however, is recommended in cases of encephalitis, myocarditis,

chorioretinitis, etc. or in cases with strong persistent general symptoms. The **standard therapy** is the following: **Pyrimethamine:** Adults: 2 × 100 mg on day 1 (children 2 mg/kg body weight), followed by daily 20–50 mg (children 1 mg/kg bodyweight) combined with **sulfadiazine** 4 × 500–1000 mg daily (children 50–100 mg/kg body weight) and in addition folic acid (10 mg daily only, blood control is needed). **Important:** Discuss with physician the recent status!

7.11.3 Length of Treatment

2–6 weeks (in cases of chorioretinitis 4 weeks), since blindness might occur. Always discuss with the physician.

7.11.4 Progress of Control

The success of treatment must be constantly controlled by the physician.

7.11.5 Toxoplasmosis During Pregnancy

Therapeutic approaches should be done only in clearly documented cases of infection. The beginning is reasonable at the 20th week of pregnancy, applying pyrimethamine (50 mg on the first day, followed by 25 mg daily). It should be given with standard sulfadiazine and folic acid under strict blood status control. Treatment should be done in 3–4 always 1-week-long cycles interrupted by 4–6-week-long intervals until the birth of the baby. Before the 20th week and in cases that pyrimethamine is not accepted, spiramycin might be applicated (3 g = 9 mio I.E.) daily—divided into 3–4 doses until birth. **The checking of the actual treatment status should always be done to avoid old, no longer valid recommendations!**

7.11.6 Toxoplasmosis in the Case of Immunocompromised Persons

If by computer tomography typical symptoms have been detected (e.g., encephalitis, hypodense regions, and hollows inside the brain), therapy should be started as soon as possible. **Treatment** should be done by administration of **pyrimethamine** (first day 200 mg, followed by 75 mg (25–100 mg) daily plus **sulfadiazine** 4 g (2–6) daily in four divided doses. These compounds are administered for at least 3 weeks—depending on the severity of clinical symptoms. In the case of **sulfonamide intolerance**, pyrimethamine should be combined with **clindamycin** (4600 mg daily). **Atovaquone** (4740 mg daily) and azithromycin/pyrimethamine have been tested in pilot studies and have shown high efficacy. Due to the high rates of possible recurrence after a successful treatment, it is needed to add a so-called **secondary prophylaxis**. This can be done by ingestion of 25–50 mg pyrimethamine plus 2–4 g

sulfadiazine per day or by pyrimethamine alone (50–75 mg daily). Less effective is the ingestion of dapsone, cotrimoxazole, or clindamycin. The combination **epiroprim** and **dapsone** showed in animals a very good efficacy with respect to the elimination of *Toxoplasma gondii* stages and showed at the same time good effects against bacterial infections.

7.12 *Toxoplasma* Infections of Animals Which Are Potential Vectors for Human Infections

7.12.1 Final Hosts Cats

Diagnosis is done by demonstration of the typically unsporulated oocysts in fresh feces (Fig. 7.2) or sporulated ones (Fig. 7.3) in feces, which had been already situated for several days outside of the body.

7.12.2 Intermediate Hosts

Search for presence of cysts in muscle probes of animals before using it in home cooking (e.g. in pork meat). Also, a broad spectrum of serological tests show indications of persistent infections. However, it remains often doubtful whether an infection is acute or persisting since long time. Complete cooking of meat will inactivate potential infectious parasites.

Note: In some countries, toxoplasmosis of cats has to be announced to the veterinarian authorities!

7.12.3 Pathway of Infection of Cats

(1) Oral uptake of sporulated oocysts within feces of other cats
(2) Ingestion of mice containing muscle cysts of *T. gondii*

7.12.4 Prophylaxis

1. Do not feed raw meat to cats.
2. Prohibit entrance of cats into stables of farmed animals.
3. In households and farms: Clean regularly defecation places of cats.
4. Sheep might be protected by vaccines (e.g., OvilisToxovax®).
5. Humans: **Important:** Pregnant women without antibodies against *T. gondii* should avoid contacts with cats and their feces and they should not eat raw meat (especially that of pigs). Furthermore, they should be tested at monthly intervals for potentially rising antibodies.

7.12.5 Incubation Period

The occurring of symptoms of disease depends on the number of ingested oocysts or stages in raw meat. For example, in the case of pigs: mostly a few up to 7 days.

7.12.6 Prepatent Period

Cats excrete oocysts:

(a) In the case of oral uptake of sporulated oocysts; 21–24 days
(b) In the case of having ingested pseudocysts within meat of an infected intermediate host (e.g., mice): 9–11 days.
(c) In the case of feeding of mature muscle cysts: 3–5 days.

7.12.7 Patency

1–15 days depending on the ingested amounts of infectious stages.

7.12.8 Therapy

Application of **toltrazuril** (Baycox®): A permanent administration of 5–10 mg/kg bodyweight suppresses the excretion of oocysts by cats and thus can be used in households with a pregnant woman without antibodies against *T. gondii* (Rommel et al. 2006).

In cases of an acute toxoplasmosis of dogs and cats, the administration of **clindamycin** or **sulfadiazine** plus **trimethoprim** stops severe symptoms.

Attention: Pyrimethamine (Daraprim®) cannot be used, since it induces teratogenic effects in doses needed to eliminate the *Toxoplasma* stages.

7.13 Importance of Human Toxoplasmosis in South America

The countries on the South American continent are the regions with the highest burden rates of congenital toxoplasmosis and are known to harbor most pathogenic genotypes known around the globe (Table 7.1). In total 136 genotypes have been proven to occur there endangering the health and (rather often) life (Strang et al. 2020). The related data can be checked in different databases: For example, check the CAPES portal, which offers access to, for example, PubMed, Web of Science, Science Direct (Elsevier), SpringerLink, Taylor & Francis Online, or Embase.

Although in general 90% of the infections with *Toxoplasma gondii* remain asymptomatic, the remaining ones often lead to severe damages like adenopathies, macula popular erythema, hepatosplenomegalic reactions, fever, and myalgias (see Table 7.1).

Table 7.1 Selected published data of *Toxoplasma gondii* seroprevalence rates in South American countries, surrounding ones, and Europe (Pappas et al. 2009; Pleyer et al. 2019)

Countries, authors	Test region	Numbers of samples taken from pregnant women	Seroprevalence in % (95% confidence intervals)
Argentina Rickard et al. 1999; Marguez et Etcheverry 2003)	Buenos Aires	6,502,421	49.6–57.2
Brazil Porto et al. 2008	Recife	503	73.9–81.1
Brazil Lago et al. 2009	Rio Grande do Sul	2421	65.1–68.9
Brazil Reis et al. 2006; Varella et al. 2003	Porto Allegre	10,468 1261	60.2–62.0 57.1–62.5
Brazil Spalding et al. 2005	Rio Grande do Sul	2126	72.7–76.3
Brazil Olbrich Neto and Meira 2004	Sao Paulo	478	55.6–64.4
Brazil Rey and Ramalho 1999	Fortaleza	186	64.8–77.8
Colombia Rosso et al. 2008	Cali	955	60.3–66.7
Colombia Barrera et al. 2002	Bogota	637	43.1–50.9
Costa Rica Zapata et al. 2005	Central Valley	243 non-pregnant women 20–40 years	49.2–60.8
Cuba Sanchez-Gutierrez et al. 2003	Havanna + Pina del Rio	1210	59.1–64.5
Ecuador Velásquez Serra 2020	Pinchincha Guayas El Oro	1,405,683 250	71.4 73 16
Grenada Asthana et al. 2006	Nationwide	534	52.8–61.2
Mexico Alvarado-Esquivel et al. 2006	Durango	343	3.6–8.6
Trinidad and Tobago Ramsewak et al. 2008	Two-thirds of hospitals	450	38.3–47.5
Venezuela Triolo-Mieses and Traviezo-Valles 2006	Lara state	446	33.5–42.5
United States Jones et al. 2007	Nationwide childbearing age	6000	10.2–11.8
Germany Pleyer et al. 2019	Nationwide	Not given	Age dependent: Young (18–28 years) 20 old (70–79 years) 77
Norway	Nationwide	Not given	7–10
United Kingdom	Nationwide	Not given	44
France	Nationwide	Not given	50

Table 7.2 Comparison of symptoms of toxoplasmosis occurring in persons living either along the Amazon river in French Guiana or in other regions of this country published by Blaizot et al. (2019) (shortened). Rather similar results had been obtained in other countries of South America

Patients	11 confirmed Amazonian cases	94 acute cases overall French Guiana
Sex (male, female)	M 6, F 5	M 35, F 59
Age (months)	8–71	4–210
Ethnic groups	Caucasian 42.9% Amerindian 42.9% Maroon 14.2%	Amerindian 21.4% Maroon 28.6% Remnant?
Risk factors: Environment	Forest 45.5% Semiurban 36.4% Urban 18.2%	Forest and semiurban 51.2% Urban 48.8%
Type of symptoms	Fever 100% Lymphadenopathy 63.6% Hepatomegaly 54.5% Splenomegaly 54.5% Cutaneous signs 54.5% Digestive signs 27.2% Flu-like symptoms 27.2% Respiratory disorders 27.2% Shock 18.2% Death 0%	Fever 100% Lymphadenopathy 70.3% Hepatomegaly 65.8% Splenomegaly 35% Cutaneous signs 11.9% Digestive signs 38.1% Flu-like symptoms 4.8% Respiratory disorders 28.6% Septic shock 19% Death 7%
Biological characteristics at hospital admission	Anemia 67.7% High AST 45.5% Lymphocytosis 36.4% Neutrophilia 27.3% Thrombocytopenia 9%	Anemia 64.3% High AST 69.2% Lymphocytosis 48.6% Neutrophilia 40.3% Thrombocytopenia 0%
Fundoscopy	Normal when performed 36.4%	Performed in 69% of children: Abnormal 17.2%
Treatment of persons	PMT/SFD 45.5% TMP/SMX 45.5% SFD/TMP/SMX 9%	PMT/SFD 85.4% TMP/SMX 7.4% Spiramycin or TMP/sulfadoxine 7.4%
Time to apyrexia (days)	Median 5 d (1–16)	Median 5 d (1–14)

AST: Aspartate aminotransferase
PMT/SFD: Pyrimethamine (1 mg/kg/d) and sulfadiazine 100 mg/d
TMP/SMX: Trimethoprim 40–85 mg/kg/d and sulfamethoxazole 8–10 mg/kg/d

The South American strains of *Toxoplasma gondii* are apparently much more pathogenic than most of the rest of the world (Flegr et al. 2014; Rostami et al. 2020; Bigna et al. 2020). For example, the occurring infection symptoms are quite different in Europe, the USA, and the countries of South America (Tables 7.1 and 7.2). In the latter countries, the seroprevalences are similar and very high, so that it is suggested that in South America other strains of *T. gondii* have been spread. They have

Table 7.3 Comparison of human diseases in combination with toxoplasmosis in South America and Europe

Diseases	South America	Europe	Source
Retinochoroiditis	Severe cases: Brazil 47%	Severe cases 14%	Sauer et al. 2011
Intercranial lesions	Severe cases: 53%	Severe cases 9%	Sauer et al. 2011

probably existed before Europeans entered this continent. This seems to support that retinochoroiditis and intracranial lesions due to toxoplasmosis are much more common than in Europe (Table 7.3). The final severeness of an infection, however, depends finally on the health status of the infected persons, weakening accompanying diseases, and the available food in the related environment (Velásquez Serra et al. 2020).

References and Further Reading

Adomako-Ankomah Y, Wier GM, Boyle JP (2012) Beyond the genome: recent advances in *Toxoplasma gondii* functional genomics. Parasite Immunol 34(2–3):80–89

Aguirre AA, Longcore T, Barbieri M, Dabritz H, Hill D, Klein PN, Lepczyk C, Lilly EL, McLeod R, Milcarsky J, Murphy CE, Su C, Van Wormer E, Yolken R, Sizemore GC (2019) The one health approach to toxoplasmosis: epidemiology, control and prevention strategies. EcoHealth 16:378–390

Ajzenberg D, Bañuls AL, Su C et al (2004) Genetic diversity, clonality and sexuality in *Toxoplasma gondii*. Int J Parasitol 34:1185–1196

Alban L, Häsler B, van Schaik G, Ruegg S (2020) Risk-based surveillance for meat-borne parasites. Exp Parasitol 208:107808

Alday PH, Doggett JS (2017) Drugs in development for toxoplasmosis: advances, challenges, and current status. Drug Des Devel Ther 11:273–293

Alvarado-Esquivel C, Sifuentes-Alvarez A, Narro-Duarte SG, Estrada-Martinez S, Diaz-Garcia JH, Liesenfeld O, Martinez-Garcia SA, Canales-Molina A (2006) Seroepidemiology of *Toxoplasma gondii* infection in pregnant women in a public hospital in northern Mexico. BMC Infect Dis 6: 113

Ambroise-Thomas P, Petersen E (2000) Congenital toxoplasmosis. Scientific background, clinical management and control. Springer, Paris, pp 271–275

Asthana SP, Macpherson CN, Weiss SH, Stephens R, Denny TN, Sharma RN, Dubey JP (2006) Seroprevalence of *Toxoplasma gondii* in pregnant women and cats in Grenada, West Indies. J Parasitol 92:644–645

Baril L, Ancelle T, Goulet V, Thulliez P, Tirard-Fleury V, Carme B (1999) Risk factors for *Toxoplasma* infection in pregnancy: a case-control study in France. Scand J Infect Dis 31(3): 305–309

Barrera AM, Castiblanco P, Gomez JE, Lopez MC, Ruiz A, Moncada L, Reyes P, Corredor A (2002) Toxoplasmosis adquirida durante el embarazo, en el Instituto Materno Infantil en Bogota. Rev Salud Publica 4:286–293

Basavaraju A (2016) Toxoplasmosis in HIV infection: an overview. Trop Parasitol 6:129–135

Benenson MW, Takafuji ET, Lemon SM, Greenup RL, Sulzer AJ (1982) Oocyst-transmitted toxoplasmosis associated with ingestion of contaminated water. N Engl J Med 307:666–669

Bertranpetit E, Jombart T, Paradis E, Pena H, Dubey J, Su C, Mercier A, Devillard S, Ajzenberg D (2017) Phylogeography of *Toxoplasma gondii* points to a South American origin. Infect Genet Evol 48:150–155

Bigna JJ, Tochie JN, Tounouga DN, Bekolo AO, Ymele NS, Youda EL, Sime PS, Nansseu JR (2020) Global, regional, and country seroprevalence of *Toxoplasma gondii* in pregnant women: a systematic review, modelling and meta-analysis. Sci Rep 10(1):12102

Blaizot R, Nabet C, Blanchet D, Martin E, Mercier A, Dardé ML, Elenga N, Demar M (2019) Pediatric Amazonian toxoplasmosis caused by atypical strains in French Guiana, 2002–2017. Pediatr Infect Dis J 38(3):e39–e42

Bonametti AM, Passos JN, Koga da Silva EM, Macedo ZS (1997) Probable transmission of acute toxoplasmosis through breast feeding. J Trop Pediatr 43(2):116–120

Boyer KM, Holfels E, Roizen N, Swisher C, Mack D, Remington J, Withers S, Meier P, McLeod R, Toxoplasmosis Study Group (2005) Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. Am J Obstet Gynecol 192(2):564–571

Cañón-Franco WA, López-Orozco N, Gómez-Marín JE, Dubey JP (2014) An overview of seventy years of research (1944–2014) on toxoplasmosis in Colombia, South America. Parasite Vectors 7:427

Carme B, Demar-Pierre M (2006) Toxoplasmosis in French Guiana. A typical (neo-)tropical features of a cosmopolitan parasitosis. Med Trop (Mars) 66:495–503

Carme B, Bissuel F, Ajzenberg D et al (2002a) Severe acquired toxoplasmosis in immunocompetent adult patients in French Guiana. J Clin Microbiol 40:4037–4044

Carme B, Aznar C, Motard A et al (2002b) Serologic survey of *Toxoplasma gondii* in noncarnivorous free-ranging neotropical mammals in French Guiana. Vector Borne Zoonotic Dis 2:11–17

Carme B, Demar M, Ajzenberg D et al (2009) Severe acquired toxoplasmosis caused by wild cycle of *Toxoplasma gondii*, French Guiana. Emerg Infect Dis 15:656–658

Cenci-Goga BT, Rossitto PV, Sechi P, McCrindle CM, Cullor JS (2011) *Toxoplasma* in animals, food, and humans: an old parasite of new concern. Foodborne Pathog Dis 8:751–762

Chiari Cde A, Neves DP (1984) Human toxoplasmosis acquired by ingestion of goat's milk. Mem Inst Oswaldo Cruz 79(3):337–340

Christoph J, Kattner E, Seitz HM, Reiter-Owona I (2004) Strategien zur Diagnostik und Behandlung der pränatalen *Toxoplasma*-Infektion. Z Geburtshilfe Neonatol 208:10–16

Connolly MP, Goodwin E, Schey C, Zummo J (2017) Toxoplasmic encephalitis relapse rates with pyrimethamine-based therapy: systematic review and meta-analysis. Pathog Glob Health 111(1):31–44

Crouch EEV, Mittel LD, Southard TL, Cerqueira-Cézar CK, Murata FHA, Kwok OCH, Su C, Dubey JP (2019) Littermate cats rescued from a shelter succumbed to acute, primary toxoplasmosis associated with TOXO DB genotype #4, generally circulating in wildlife. Parasitol Int 72: 101942

da Costa MA, Pinto-Ferreira F, de Almeida RPA, Martins FDC, Pires AL, Mareze M, Mitsuka-Breganó R, Freire RL, da Rocha Moreira RV, Borges JM, Navarro IT (2020) Artisan fresh cheese from raw cow's milk as a possible route of transmission in a toxoplasmosis outbreak, in Brazil. Zoonoses Public Health 67:122–129

da Silva RC, Langoni H (2009) *Toxoplasma gondii*: host-parasite interaction and behavior manipulation. Parasitol Res 105(4):893–898

Dard C, Marty P, Brenier-Pinchart MP, Garnaud C, Fricker-Hidalgo H, Pelloux H, Pomares C (2018) Management of toxoplasmosis in transplant recipients: an update. Expert Rev Anti-Infect Ther 16(6):447–460

Davidson MG (2000) Toxoplasmosis. Vet Clin North Am Small Anim Pract 30:1051–1062

De La Fuente Villar BB, Neves ES, Louro VC, Lessa JF, Rocha DN, Gomes LHF, Junior SCG, Pereira JP Jr, Moreira MEL, Guida LDC (2020) Toxoplasmosis in pregnancy: a clinical,

diagnostic, and epidemiological study in a referral hospital in Rio de Janeiro, Brazil. Braz J Infect Dis 24:517–523

de Quadros RM, da Rocha GC, Romagna G, de Oliveira JP, Ribeiro DM, Marques SM (2015) *Toxoplasma gondii* seropositivity and risk factors in pregnant women followed up by the family health strategy. Rev Soc Bras Med Trop 48(3):338–342

Demar M, Ajzenberg D, Maubon D et al (2007) Fatal outbreak of human toxoplasmosis along the Maroni River: epidemiological, clinical, and parasitological aspects. Clin Infect Dis 45:e88–e95

Demar M, Hommel D, Djossou F et al (2012) Acute toxoplasmosis in immunocompetent patients hospitalized in an intensive care unit in French Guiana. Clin Microbiol Infect 18:E221–E231

Desmettre T (2020) Toxoplasmosis and behavioural changes. J Fr Ophtalmol 43(3):e89–e93

Diesel AA, Zachia SA, Müller ALL, Perez AV, Uberti FAF, Magalhães JAA (2019) Follow-up of toxoplasmosis during pregnancy: ten-year experience in a university hospital in southern Brazil. Rev Bras Ginecol Obstet 41:539–547

Dubey JP (2009) Toxoplasmosis of animals and humans. Parasites and vectors. CRC Press, Boca Raton

Dubey JP, Miller NL, Frenkel JK (1970) *Toxoplasma gondii* life cycle in cats. J Am Vet Med Assoc 157(11):1767–1770

Dubey JP, Gomez-Marin JE, Bedoya A, Lora F, Vianna MC, Hill D, Kwok OC, Shen SK, Marcet PL, Lehmann T (2005) Genetic and biologic characteristics of *Toxoplasma gondii* isolates in free-range chickens from Colombia, South America. Vet Parasitol 134:67–72

Dubey JP, Lago EG, Gennari SM, Su C, Jones JL (2012) Toxoplasmosis in humans and animals in Brazil: high prevalence, high burden of disease, and epidemiology. Parasitology 139:1375–1424

Dubremetz JF (2007) Rhoptries are major players in *Toxoplasma gondii* invasion and host cell interaction. Cell Microbiol 9:841–848

Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG (2018) Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. Clin Microbiol Rev 31(4): e00057–e00017

Edelhofer R, Prossinger H (2010) Infection with *Toxoplasma gondii* during pregnancy: seroepidemiological studies in Austria. Zoonoses Public Health 57(1):18–26

El Bissati K, Levigne P, Lykins J, Adlaoui EB, Barkat A, Berraho A, Laboudi M, El Mansouri B, Ibrahimi A, Rhajaoui M, Quinn F, Murugesan M, Seghrouchni F, Gómez-Marín JE, Peyron F, McLeod R (2018) Global initiative for congenital toxoplasmosis: an observational and international comparative clinical analysis. Emerg Microbes Infect 7(1):165

Ferguson DJ (2009) *Toxoplasma gondii*: 1908–2008, homage to Nicolle, Manceaux and Splendore. Mem Inst Oswaldo Cruz 104:133–148

Flegr J, Prandota J, Sovičková M, Israili ZH (2014) Toxoplasmosis–a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PLoS One 9(3): e90203

Frenkel JK (2000) Biology of *Toxoplasma gondii*. In: Ambroise-Thomas P, Petersen E (eds) Congenital toxoplasmosis. Scientific background, clinical management and control. Springer, Paris

Frenkel JK, Dubey JP, Miller NL (1970) *Toxoplasma gondii* fecal stages identified as coccidian oocysts. Science 167:893–896

Garweg JG (2016) Ocular toxoplasmosis: an update. Klin Monatsbl Augenheilkd 233:534–539

Gilbert RE, Freeman K, Lago EG, Bahia-Oliveira LM, Tan HK, Wallon M, Buffolano W, Stanford MR, Petersen E, European Multicentre Study on Congenital Toxoplasmosis (EMSCOT) (2008) Ocular sequelae of congenital toxoplasmosis in Brazil compared with Europe. PLoS Negl Trop Dis 2(8):e277

Gómez Marín JE, Zuluaga JD, Pechené Campo EJ, Triviño J, de-la- Torre A (2018) Polymerase chain reaction (PCR) in ocular and ganglionar toxoplasmosis and the effect of therapeutics for prevention of ocular involvement in South American setting. Acta Trop 184:83–87

Gómez-Marin JE, de-la-Torre A, Angel-Muller E, Rubio J, Arenas J, Osorio E, Nuñez L, Pinzon L, Mendez-Cordoba LC, Bustos A, de-la-Hoz I, Silva P, Beltran M, Chacon L, Marrugo M, Manjarres C, Baquero H, Lora F, Torres E, Zuluaga OE, Estrada M, Moscote L, Silva MT, Rivera R, Molina A, Najera S, Sanabria A, Ramirez ML, Alarcon C, Restrepo N, Falla A, Rodriguez T, Castaño G (2011) First Colombian multicentric newborn screening for congenital toxoplasmosis. PLoS Negl Trop Dis 5(5):e1195

Gontijo da Silva M, Clare Vinaud M, de Castro AM (2015) Prevalence of toxoplasmosis in pregnant women and vertical transmission of *Toxoplasma gondii* in patients from basic units of health from Gurupi, Tocantins, Brazil, from 2012 to 2014. PLoS One 10(11):e0141700

Gross U (ed) (1996) Toxoplasma gondii. Springer, Berlin, Heidelberg, New York

Grossklaus D, Baumgarten HJC (1967) The survival period of *Toxoplasma* stages in meat of pigs. Fleischwirtschaft 47:1372–1378

Halonen SK, Weiss LM (2013) Toxoplasmosis. Handb Clin Neurol 114:125–145

Hartmann K, Addie D, Belák S, Boucraut-Baralon C, Egberink H, Frymus T, Gruffydd-Jones T, Hosie MJ, Lloret A, Lutz H, Marsilio F, Möstl K, Pennisi MG, Radford AD, Thiry E, Truyen U, Horzinek MC (2013) *Toxoplasma gondii* infection in cats: ABCD guidelines on prevention and management. J Feline Med Surg 15:631–637

Heukelbach J, Meyer-Cirkel V, Moura RC, Gomide M, Queiroz JA, Saweljew P, Liesenfeld O (2007) Waterborne toxoplasmosis, northeastern Brazil. Emerg Infect Dis 13(2):287–289

Hill DE, Dubey JP (2016) *Toxoplasma gondii* as a parasite in food: analysis and control. Microbiol. Spectrum 4(4):PFS-0011-2015

Hill DE, Chirukandoth S, Dubey JP (2005) Biology and epidemiology of *Toxoplasma gondii* in man and animals. Anim Health Res Rev 6:41–61

Jamra LM, Martins MC, Vieira Mde P (1991) Effect of table salt on *Toxoplasma gondii*. Rev Inst Med Trop Sao Paulo 33(5):359–363

Janssen P, Piekarski G, Korte W (1970) Abortion in women with latent *Toxoplasma* infections. Klin Wochenschr 48:25–30

Jones JL, Dubey JP (2012) Food borne toxoplasmosis. Clin Inf Dis 55:845–851

Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M (2007) *Toxoplasma gondii* infection in the United States, 1999–2004, decline from the prior decade. Am J Trop Med Hyg 77:405–410

Kaye A (2011) Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants. J Pediatr Health Care 25:355–264

Khan K, Khan W (2018) Congenital toxoplasmosis: an overview of the neurological and ocular manifestations. Parasitol Int 67:715–721

Kim K, Weiss LM (2008) *Toxoplasma*: the next 100 years. Microbes Infect 10:978–984

Lago EG, Conrado GS, Piccoli CS, Carvalho RL, Bender AL (2009) *Toxoplasma gondii* antibody profile in HIV-infected pregnant women and the risk of congenital toxoplasmosis. Eur J Clin Microbiol Infect Dis 28:345–351

Lambooij MS, Veldwijk J, van Gils P, Mangen MJ, Over E, Suijkerbuijk A, Polder J, de Wit GA, Opsteegh M (2019) Consumers' preferences for freezing of meat to prevent toxoplasmosis- a stated preference approach. Meat Sci 149:1–8

Luna JC, Zamora A, Hernández-Arango N, Muñoz-Sánchez D, Pinzón MI, Cortés-Vecino JA, Lora-Suarez F, Gómez-Marín JE (2019) Food safety assessment and risk for toxoplasmosis in school restaurants in Armenia, Colombia. Parasitol Res 118:3449–3457

Mandelbrot L, Kieffer F, Sitta R, Laurichesse-Delmas H, Winer N, Mesnard L, Berrebi A, Le Bouar G, Bory JP, Cordier AG, Ville Y, Perrotin F, Jouannic JM, Biquard F, d'Ercole C, Houfflin-Debarge V, Villena I, Thiébaut R, TOXOGEST Study Group (2018) Prenatal therapy with pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission of toxoplasmosis: a multicenter, randomized trial. Am J Obstet Gynecol 219(4):386.e1–386.e9

Marquez MDLA, Etcheverry IS (2003) Seroprevalence of toxoplasmosis in pregnant women in La Plata area. Acta Bioquim Clin Latinoam 37:413–415

Mehlhorn H (2016a) Animal parasites. Springer International, Switzerland

Mehlhorn H (2016b) Human parasites. Springer International, Switzerland

Mehlhorn H (ed) (2016c) Encyclopedia of parasitology. 4th ed., Springer Berlin, Heidelberg
Mehlhorn H, Klimpel S (eds) (2019) Parasite and disease spread by major rivers on earth. Past and future perspectives. Springer, Berlin, New York
Mehlhorn T (2018) Analyse der Immunantwort gegen intrazelluläre Pathogene in der GBP2-defizienten Mauslinie. Doktor dissertation, Heinrich Heine University, Düsseldorf
Mirza Alizadeh A, Jazaeri S, Shemshadi B, Hashempour-Baltork F, Sarlak Z, Pilevar Z, Hosseini H (2018) A review on inactivation methods of *Toxoplasma gondii* in foods. Pathog Glob Health 112(6):306–319
Montoya JG, Remington JS (2008) Management of *Toxoplasma gondii* infection during pregnancy. Clin Infect Dis 47(4):554–566
Moura IPDS, Ferreira IP, Pontes AN, Bichara CNC (2019) Toxoplasmosis knowledge and preventive behavior among pregnant women in the city of Imperatriz, Maranhao, Brazil. Cien Saude Colet 24:3933–3946
Murillo-León M, Müller UB, Zimmermann I, Singh S, Widdershooven P, Campos C, Alvarez C, Könen-Waisman S, Lukes N, Ruzsics Z, Howard JC, Schwemmle M, Steinfeldt T (2019) Molecular mechanism for the control of virulent *Toxoplasma gondii* infections in wild-derived mice. Nat Commun 10(1):1233
Navarro IT, Vidotto O, Giraldi N, Mitsuka R (1992) Resistance of *Toxoplasma gondii* to sodium chloride and condiments in pork sausage. Bol Oficina Sanit Panam 112(2):138–143
Ngoungou EB, Bhalla D, Nzoghe A, Dardé ML, Preux PM (2015) Toxoplasmosis and epilepsy—systematic review and meta analysis. PLoS Negl Trop Dis 9(2):e0003525
Nicolle C, Manceaux G (1908) Sur une infection a corps de Leishman (ou organismvoirsins) du gondi. C R Acad Sci 147:736
Nicolle C, Manceaux G (1909) Sur une protozoaire nouveau du gondi. C R Acad Sci 148:369
Olbrich Neto J, Meira DA (2004) Seroprevalence of HTLV-I/II, HIV, syphilis and toxoplasmosis among pregnant women seen at Botucatu–Sao Paulo–Brazil: risk factors for HTLV-I/II infection. Rev Soc Bras Med Trop 37:28–32
Oliveira GMS, Simões JM, Schaer RE, Freire SM, Nascimento RJM, Pinheiro AMCM, Carvalho SMS, Mariano APM, Carvalho RC, Munhoz AD (2019) Frequency and factors associated with *Toxoplasma gondii* infection in pregnant women and their pets in Ilheus, Bahia, Brazil. Rev Soc Bras Med Trop 52:e20190250
Overdulve JP (1970) The identity of *Toxoplasma* Nicolle and Manceaux, 1909 with *Isospora* Schneider, 1881. Proc K Ned Akad Wet C 73(1):138–151
Pappas G, Roussos N, Falagas ME (2009) Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol 39:1385–1394
Pardini L, Bernstein M, Carral LA, Kaufer FJ, Dellarupe A, Gos ML, Campero LM, Moré G, Messina MT, Schneider MV, Freuler CB, Durlach RA, Unzaga JM, Venturini MC (2019) Congenital human toxoplasmosis caused by non-clonal *Toxoplasma gondii* genotypes in Argentina. Parasitol Int 68:48–52
Petersen E, Kijlstra A, Stanford M (2012) Epidemiology of ocular toxoplasmosis. Ocul Immunol Inflamm 20:68–75
Piekarski G, Witte HM (1970) The agents of toxoplasmosis: a specific parasite of cats. Umschau 11: 342–343
Pinto-Ferreira F, Caldart ET, Pasquali AKS, Mitsuka-Breganó R, Freire RL, Navarro IT (2019) Patterns of transmission and sources of infection in outbreaks of human toxoplasmosis. Emerg Infect Dis 25(12):2177–2182
Pleyer U, Gross U, Schlüter D, Wilking H, Seeber F (2019) Toxoplasmosis in Germany. Dtsch Arztebl Int 116:435–444
Porto AM, Amorim MM, Coelho IC, Santos LC (2008) Serologic profile of toxoplasmosis in pregnant women attended at a teaching-hospital in Recife. Rev Assoc Med Bras (1992) 54(3): 242–248

Rajapakse S, Weeratunga P, Rodrigo C, de Silva NL, Fernando SD (2017) Prophylaxis of human toxoplasmosis: a systematic review. Pathog Glob Health 111:333–342

Rajendran C, Su C, Dubey JP (2012) Molecular genotyping of *Toxoplasma gondii* from central and South America revealed high diversity within and between populations. Infect Genet Evol 12: 359–368

Ramanan P, Scherger S, Benamu E, Bajrovic V, Jackson W, Hage CA, Hakki M, Baddley JW, Abidi MZ (2020) Toxoplasmosis in non-cardiac solid organ transplant recipients: a case series and review of literature. Transpl Infect Dis 22(1):e13218

Ramsewak S, Gooding R, Ganta K, Seepersadsingh N, Adesiyun AA (2008) Seroprevalence and risk factors of *Toxoplasma gondii* infection among pregnant women in Trinidad and Tobago. Rev Panam Salud Publica 23:164–170

Reis MM, Tessaro MM, D'Azevedo PA (2006) Serologic profile of toxoplasmosis in pregnant women from a public hospital in Porto Alegre. Rev Bras Ginecol Obstet 28:158–164

Reiter-Owona I, Bialek R, Rockstroh JK, Seitz HM (1998) The probability of acquiring primary *Toxoplasma* infection in HIV-infected patients: results of an 8-year retrospective study. Infection 26(1):20–25

Rey LC, Ramalho IL (1999) Seroprevalence of toxoplasmosis in Fortaleza, Ceara, Brazil. Rev Inst Med Trop Sao Paulo 41:171–174

Rickard E, Costagliola M, Outen E, Cicero M, Garcia G, Dieguez N (1999) Toxoplasmosis antibody prevalence in pregnancy in Buenos Aires province, Argentina. Clin Microbiol Infect 5(Suppl 3):171

Robert-Gangneux F, Belaz S (2016) Molecular diagnosis of toxoplasmosis in immunocompromised patients. Curr Opin Infect Dis 29:330–339

Robert-Gangneux F, Dardé ML (2012) Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev 25:264–296

Rosso F, Les JT, Agudelo A, Villalobos C, Chaves JA, Tunubala GA, Messa A, Remington JS, Montoya JG (2008) Prevalence of infection with *Toxoplasma gondii* among pregnant women in Cali, Colombia, South America. Am J Trop Med Hyg 78:504–508

Rostami A, Riahi SM, Gamble HR, Fakhri Y, Nourollahpour Shiadeh M, Danesh M, Behniafar H, Paktinat S, Foroutan M, Mokdad AH, Hotez PJ, Gasser RB (2020) Global prevalence of latent toxoplasmosis in pregnant women: a systematic review and meta-analysis. Clin Microbiol Infect 26(6):673–683

Rudzinski M, Khoury M, Couto C, Ajzenberg D (2016) Reactivation of ocular toxoplasmosis in non-Hispanic persons, Misiones Province, Argentina. Emerg Infect Dis 22:912–913

Sabin AB (1942) Toxoplasmosis: a recently recognized disease of human beings. Adv Pediatr 1:1–60

Sabin AB, Feldman HA (1948) Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoon parasite (*Toxoplasma*). Science 108:660–663

Sabin AB, Olitski PK (1937) *Toxoplasma* and obligate intracellular parasitism. Science 85:336–338

Sanchez-Gutierrez A, Martin-Hernandez I, Garcia-Izquierdo SM (2003) Estudio de reactividad a *Toxoplasma gondii* en embarazadas de las provincias Ciudad de la Habana y Pinardel Rio, Cuba. Bioquimia 28:3–8

Sauer A, de la Torre A, Gomez-Marin J, Bourcier T, Garweg J, Speeg-Schatz C, Candolfi E (2011) Prevention of retinochoroiditis in congenital toxoplasmosis: Europe versus South America. Pediatr Infect Dis J 30:601–603

Schlaen A, Colombero D, Ormaechea S, Ladeveze E, Rudzinski C, Ingolotti M, Couto C, Rudzinski M (2019) Regional differences in the clinical manifestation of ocular toxoplasmosis between the center and northeast of Argentina. Ocul Immunol Inflamm 27:722–730

Schlüter D, Barragan A (2019) Advances and challenges in understanding cerebral toxoplasmosis. Front Immunol 10:242

Scholtyseck E, Mehlhorn H (1970) Ultrastructural study of characteristic organelles (paired organelles, micronemes, micropores) of sporozoa and related organisms. Z Parasitenkd (Parasitol Res) 34(2):97–127

Scholtyseck E, Mehlhorn H, Hammond DM (1972) Electron microscope studies of microgametogenesis in Coccidia and related groups. Z Parasitenkd (Parasitol Res) 38(2):95–131
Shuralev EA, Shamaev ND, Mukminov MN, Nagamune K, Taniguchi Y, Saito T, Kitoh K, Arleevskaya MI, Fedotova AY, Abdulmanova DR, Aleksandrova NM, Efimova MA, Yarullin AI, Valeeva AR, Khaertynov KS, Takashima Y (2018) *Toxoplasma gondii* seroprevalence in goats, cats and humans in Russia. Parasitol Int 67(2):112–114
Sibley LD, Khan A, Ajioka JW, Rosenthal BM (2009) Genetic diversity of *toxoplasma gondii* in animals and humans. Philos Trans R Soc Lond Ser B Biol Sci 364(1530):2749–2761
Silva LA, Fernandes MD, Machado AS, Reis-Cunha JL, Bartholomeu DC, Almeida Vitor RW (2019) Efficacy of sulfadiazine and pyrimethamine for treatment of experimental toxoplasmosis with strains obtained from human cases of congenital disease in Brazil. Exp Parasitol 202:7–14
Soares JAS, Caldeira AP (2019) Congenital toxoplasmosis: the challenge of early diagnosis of a complex and neglected disease. Rev Soc Bras Med Trop 52:e20180228
Spalding SM, Amendoeira MR, Klein CH, Ribeiro LC (2005) Serological screening and toxoplasmosis exposure factors among pregnant women in south of Brazil. Rev Soc Bras Med Trop 38: 173–177
Splendore A (1908) Un buovo protozoa parassita de conigli incontrato nelle lessioni anatomiche d' une mallattia che ricorda in molti punti il Kala-azar dell' uoma. Rev Soc Sci Sao Paulo 3:109–112
Strang AGGF, Ferrari RG, do Rosário DK, Nishi L, Evangelista FF, Santana PL, de Souza AH, Mantelo FM, Guilherme ALF (2020) The congenital toxoplasmosis burden in Brazil: systematic review and meta-analysis. Acta Trop 211:105608
Tenter AM (2009) *Toxoplasma gondii* in animals used for human consumption. Mem Inst Oswaldo Cruz 104:364–369
Tenter AM, Heckeroth AR, Weiss LM (2000) *Toxoplasma gondii*: from animals to humans. Int J Parasitol 30(12–13):1217–1258
Torgerson PR, Mastroiacovo P (2013) The global burden of congenital toxoplasmosis: a systematic review. Bull World Health Organ 91(7):501–508
Torrey EF, Yolken RH (2007) Schizophrenia and toxoplasmosis. Schizophr Bull 33(3):727–728
Triolo-Mieses M, Traviezo-Valles L (2006) Serological prevalence of *Toxoplasma gondii* antibodies in pregnancy in Palavecino municipality. Lara State, Venezuela. Kasmera 34:7–13
Varella IM, Wagner MB, Darela AC, Nunes LM, Muller RW (2003) Seroprevalence of toxoplasmosis in pregnant women. J Pediatr 79:69–74
Velásquez Serra GC, Piloso Urgiles LI, Guerrero Cabredo BP, Chico Caballero MJ, Zambrano SL, Yaguar Gutierrez EM, Barrera Reyes CG (2020) Current situation of congenital toxoplasmosis in Ecuador. J Community Health 45(1):170–175
Wallace MR, Rossetti RJ, Olson PE (1993) Cats and toxoplasmosis risk in HIV-infected adults. JAMA 269(1):76–77
Wallochnik J (2011) Parasites: unwished guests in human bodies. Ueberreuter Publisher, Vienna
Wei HX, Wei SS, Lindsay DS, Peng HJ (2015) A systematic review and meta-analysis of the efficacy of anti-*Toxoplasma gondii* medicines in humans. PLoS One 10(9):e0138204
Wolf A, Cowen D (1937) Granulomatous encephalomyelitis due to an encephalitozoon (encephalitic ancephalomyelitis): a new protozoan disease of man. Bull Neurol Inst NY 6:306–335
Wolf A, Cowen D, Paige B (1939) Human toxoplasmosis: occurrence in infants as encephalomyelitis verification by transmission to animals. Science 89:226–227
Wyrosdick HM, Schaefer JJ (2015) *Toxoplasma gondii*: history and diagnostic test development. Anim Health Res Rev 16(2):150–162
Zapata M, Reyes L, Holst I (2005) Decreased prevalence of *toxoplasma gondii* antibodies in adults form the Central Valley in Costa Rica. Parasitol Latinoam 60:32–37
Zhang K, Lin G, Han Y, Li J (2016) Serological diagnosis of toxoplasmosis and standardization. Clin Chim Acta 461:83–89

Tunga Spp. and Tungiasis in Latin America

8

Jorg Heukelbach, Tatiani Vitor Harvey,
and Cláudia Maria Lins Calheiros

Abstract

The fleas of the genus *Tunga* (Jarocki, 1838; family Tungidae) are ectoparasites of the order Siphonaptera. There are in total 14 *Tunga* species known, 12 of them occurring in Latin America. In this chapter, we present *Tunga* spp. described from South America. The fleas parasitize humans as well as domestic and sylvatic mammalian animals, but there are only two zoonotic species known to parasitize both animals and humans: *Tunga penetrans* and *Tunga trimamillata*. In general, knowledge on the life cycle, distribution, hosts, and pathology is very scant, with the exception of *T. penetrans* (L., 1758). Tungiasis is described in animals and humans, including the life cycle, epidemiology, and clinical aspects. We discuss integrated tungiasis control approaches, within the realm of One Health.

Keywords

Tunga penetrans · *Tunga trimamillata* · *Tunga terasma* · *Tunga terasma* · *Tunga bondari*

J. Heukelbach (✉)
Departamento de Saúde Comunitária, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil
e-mail: heukelbach@ufc.br

T. V. Harvey
College of Veterinary Medicine and Biomedical Sciences, Texas A & M University, College Station, TX, USA

C. M. L. Calheiros
Institute of Biological Sciences and Health (ICBS), Universidade Federal de Alagoas, Maceió, Brazil

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_8

8.1 *Tunga* Spp.

The genus *Tunga* (family Tungidae, order Siphonaptera; Jarocki, 1838) includes 14 species. *Tunga* spp. are the smallest fleas known—only about 1 mm in length—and show a very particular behavior, which differs from the other Siphonaptera: the females penetrate the skin of their hosts, enlarge massively, forming by hypertrophy of abdominal segments a so-called neosome, and produce eggs which are expulsed during parasitic life. The neosome contains the eggs and varies in form and size, according to the species (Linardi et al. 2014; Linardi and de Avelar 2014).

Tunga spp. are distributed mainly throughout Latin America—12 of the 14 known species occur in this region. With the exception of *Tunga penetrans* which has established itself in sub-Saharan Africa after introduction from South America, these 12 species are restricted to the American continent (Linardi and de Avelar 2014).

According to morphological characteristics and host preferences, the genus *Tunga* is divided into two groups: the so-called caecata group and the penetrans group (Smit 1962). Currently, there are seven known species of the caecata group, all infesting rodents: *Tunga caecata* and *Tunga bossii*, described from Brazil; *Tunga caecigena* and *Tunga callida*, found in China; *Tunga libis* encountered in Ecuador; *Tunga bonneti* described from Chile; and *Tunga monositus* from Mexico. The penetrans group consists of another seven distinct species infesting edentates, humans, and domestic animals: *Tunga penetrans*, *Tunga bondari*, *Tunga travassosi*, *Tunga terasma*, *Tunga trimamillata*, *Tunga hexalobulata*, and *Tunga perforans*, all encountered in South America.

In this chapter, we describe the parasite species of the penetrans group, as this group parasitizes primarily domestic animals, edentates, and humans. Table 8.1 presents these species, their host preferences, and geographic distribution. Three species have been described to infest domestic animals: *T. penetrans*, *T. trimamillata*, and *T. hexalobulata*. Human infestations have been described by *T. penetrans* and *T. trimamillata*. *T. penetrans* is known all over the continent, whereas the other species seem to have a more restricted geographic distribution. In general, data on distribution are scarce, with the exception of *T. penetrans*. Figure 8.1 presents the geographic distribution of *Tunga* spp. in Latin America, according to current knowledge available. It can be assumed that in fact several species are considerably more widespread on the continent.

8.1.1 *Tunga penetrans*

The so-called sand flea *T. penetrans* originally occurred only on the American continent, but has spread to the African continent, with trading routes during colonial times. Nowadays, the parasite is autochthonous on the American continent from southern Mexico to northern Argentina (excluding Chile), in the Caribbean, and in sub-Saharan Africa.

Table 8.1 *Tunga* spp.—hosts and distribution of the penetrans group in Latin America

Species	Hosts	Geographic distribution	Autochthonous human cases
T. penetrans	Primates Artiodactyla Rodentia Carnívora Cingulata Perissodactyla Pilosa	Latin America (from Southern Mexico to Northern Argentina), excluding Chile	Latin America (from Southern Mexico to Northern Argentina), excluding Chile
T. trimamillata	Primates Artiodactyla Rodentia	Ecuador, Peru, Brazil	Ecuador, Peru[a]
T. bondari	Pilosa: Tamandua	Brazil	–
T. travasossi	Cingulata: Dasypus	Brazil	–
T terasma	Cingulata: Dasypus, Cabassous, Euphrates, Priodontes	Brazil, Argentina	–
T. hexalobulata	Artiodactyla: Bos	Brazil	–
T. perforans	Cingulata: Oasypus	Argentina	–

[a]Most probably also in other Latin American countries

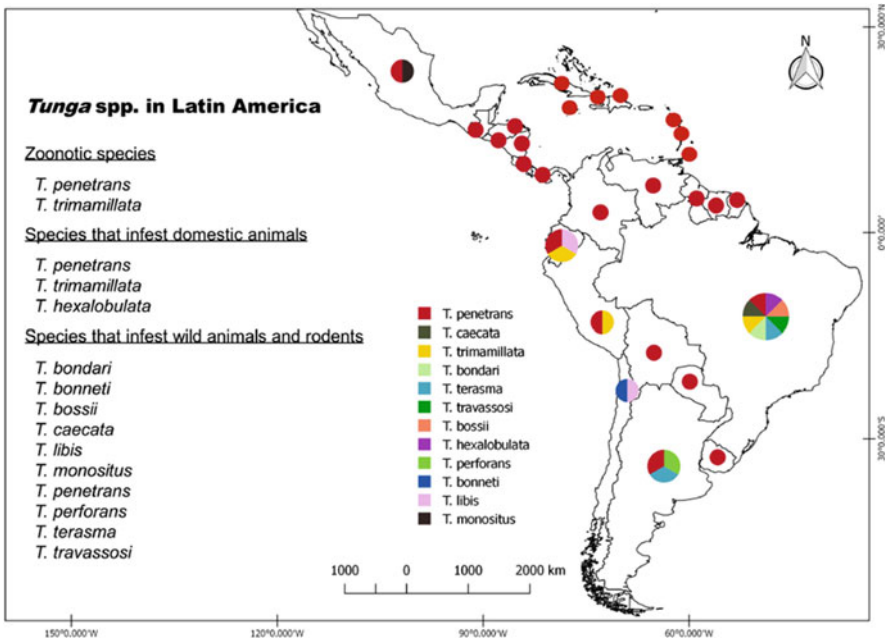


Fig. 8.1 Geographic distribution of *Tunga* spp. in Latin America

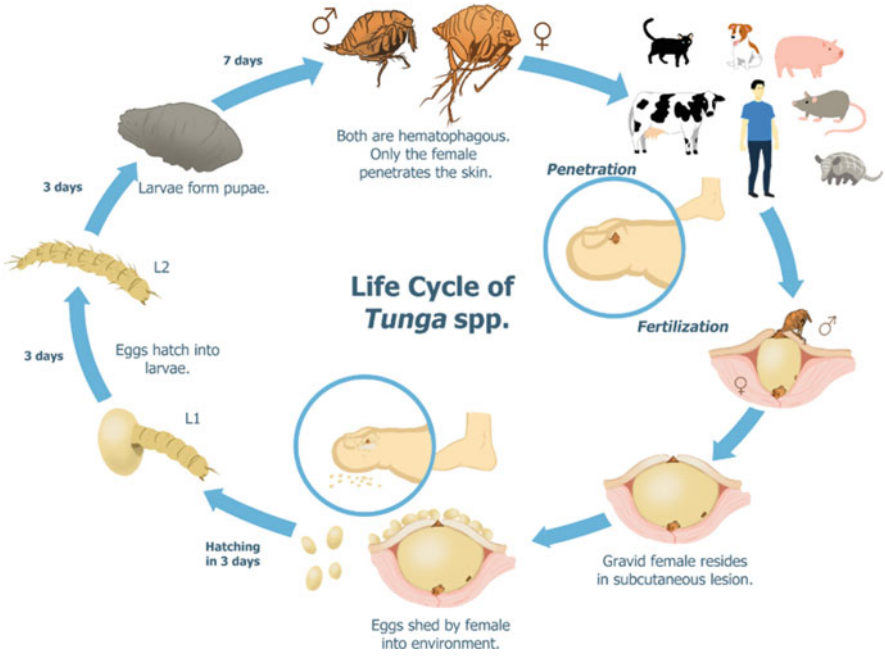


Fig. 8.2 Biological cycle of *Tunga* spp.

The life cycle of *T. penetrans* is depicted in Fig. 8.2. Eggs are expelled from lesions, most commonly on the human feet or pads of animals and develop into larvae. There are only two larval stages, unlike the majority of known flea species, which usually have three stages. In the soil, under favorable temperature and humidity conditions, first-stage (L1) larvae eclode from the fertilized eggs, about two to three days after being expelled. Some days later, L1 larvae differentiate under laboratory conditions into second-stage (L2) larvae. The larvae feed on organic debris found in the soil, and on their own carcass.

T. penetrans larvae and pupae are most commonly found inside human dwellings, especially if there is no solid floor, and in the sandy soil near houses and habitats of domestic animals (Linardi et al. 2010). About 9 days after egg excretion, the larvae differentiate into pupae, which become adult fleas around the 16th day, ready to penetrate skin of their host. Copulation seems to occur not only in the environment (Hicks 1930), but also after complete penetration of the female flea into the host's epidermis (Geigy and Suter 1960).

Both sexes of *T. penetrans* are obligate hematophagous. Only the female penetrates permanently, by introducing the head, thorax, and part of the abdomen into the host's tissues. For the continuation of the life cycle, the female flea needs to penetrate the epidermis of the host obligatorily and permanently. The male only seeks out the host to feed on blood and to mate with the female, and then leaves. The penetrated female flea undergoes through different stages of development, ending up

Fig. 8.3 Male and female adult *T. penetrans*

with considerable enlargement of her abdomen, forming a neosome: the flea grows from 1 mm in length to about 1 cm in diameter and begins to eliminate the eggs into the environment.

Six to seven days after penetration, when there are about 200 eggs in its abdomen, the flea begins to eliminate them into the environment. During its life in the host, the female can eliminate thousands of eggs. We counted a total of 2765 eggs eliminated by a single flea during a 46-day period (personal observation). After all the eggs are expelled, the flea dies, and eventually the remains are eliminated. Finally, a small scar limited to the epidermis remains, which disappears with time.

The pupae can survive for a prolonged time in the environment and after a stimulus, such as the vibration caused by a person walking in the sand, hatch within seconds, and then attack the host. Thus, houses left unattended for a prolonged time may remain infested, even in the absence of an animal reservoir that can maintain the cycle. After entering abandoned houses, within few moments hundreds of attacking fleas may appear (personal observation).

Morphologically, the adult flea has developed mouthparts, with long, serrated laciniae, adapted to penetrate the host. The eyes are pigmented, and the thorax is reduced in relation to the abdominal segment I (Fig. 8.3). As with other Siphonaptera, the eggs are ellipsoidal and whitish, measuring 0.4 mm on average. The larvae are eucephalic, vermiform, apodal, and whitish, with a chewing-type mouth apparatus. The L1 larvae, which measure about 1 mm in length, have a dorsal structure on the head intended for breaking eggs during hatching, called an egg-breaker. The pre-pupa stage is originated by the folding of the L2, which measures about 3 mm long, and subsequent joining of the cephalic and anal parts (Fig. 8.4). The pupae are encased, with sand particle adhesion on the outside, and internally coated by a delicate cuticle; they are initially whitish, and later turn brownish, measuring about 1 mm in length, much smaller than *Ctenocephalides* pupae.

Fig. 8.4 *T. Penetrans* egg, L1 and L2, and pupa

8.1.2 *Tunga trimamillata*

T. trimamillata infests humans and domestic animals (cows, sheep, pigs, goats). In bovines, deformation of nails has been observed, causing difficulty in walking. As with infestation with *T. penetrans*, secondary bacterial infection is common, often leading to ulcerations. The species has been described from Ecuador, Peru, and Brazil (Fioravanti et al. 2003; Pampiglione et al. 2003; Linardi et al. 2013), but may occur also in other Latin American countries. Many epidemiological studies on tungiasis do not differ between *T. penetrans* and *T. trimamillata*, and tungiasis may have been claimed falsely as *T. penetrans* infestation, instead of *T. trimamillata* (Linardi et al. 2013). Thus, *T. trimamillata* may be more widely dispersed than described. In contrast to *T. penetrans* which forms a globular neosome, the neosome of *T. trimamillata* is conical and larger. Infestations with *T. trimamillata* have been described to be more painful than those with *T. penetrans* (Linardi et al. 2013; Fioravanti et al. 2006).

8.1.3 *Tunga terasma*

T. terasma's first description dates back from 1937, by Jordan who described the penetrated female parasite in the southern naked-tailed armadillo *Cabassous unicinctus*. Since then, the parasite has been described to parasitize different armadillo species in Brazil: *Cabassous unicinctus*, *Euphractus sexcinctus*, and *Priodontes maximus* (Linardi et al. 2000). During a survey on leprosy mycobacteria in Brazil, Antunes et al. (2006) identified penetrated and hypertrophied *T. terasma* females on the abdomen of four nine-banded armadillos (*Dasypus novemcinctus*). Recently, *T. terasma* was also recorded from Argentinian armadillos (Ezquiaga et al. 2015). However, clinical and pathological data and information on life cycle, variety of host animals, and geographical distribution are virtually nonexistent.

8.1.4 *Tunga travassosi*

T. travassosi has been described parasitizing different species of armadillos in Brazil, and seemed to have been very common in these host animals in the 1920s

and 1930s (da Fonseca 1936; Pinto and Dreyfus 1927). However, this species is only known by its neosome, and there are no recent data on *T. travassosi* available (Linardi and de Avelar 2014).

8.1.5 *Tunga bondari*

T. bondari was described in an anteater in 1932 by Wagner (1932). The species is only known by its hypertrophied and penetrated female neosome, and there are no current data on any aspects related to this flea species.

8.1.6 *Tunga perforans*

T. perforans was described recently as a new species parasitizing Argentinian armadillos (Ezquiaga et al. 2015). No additional data on distribution and host animals are available.

8.1.7 *Tunga hexalobulata*

T. hexalobulata has been described in 2013 parasitizing the coronary band of cattle in Brazil (De Avelar et al. 2013). The hypertrophied female's neosome has six anterior humps and is smaller than those of the other Tunga species. There are no additional data available on other host animals, on the life cycle, or on the geographical distribution of the parasite.

8.2 Tungiasis in Domestic Animals

Tungiasis in domestic and wild animals and synanthropic rodents has been reported from Latin America, the Caribbean, sub-Saharan Africa, and Asia. Latin America concentrates 12 species that affect animals, unlike sub-Saharan Africa, where the infestation is caused particularly by *T. penetrans*, and in Asia, where only infestations by *T. callida* and *T. caecigena* have been reported (Linardi and de Avelar 2014; Ezquiaga et al. 2015). Three *Tunga* species infest domestic animals: *T. penetrans*, *T. trimamillata*, and *T. hexalobulata*.

Infestations by *T. penetrans* in domestic animals have been reported all over the African continent, such as Cameroon, the Democratic Republic of Congo, Ethiopia, Kenya, Nigeria, São Tome and Príncipe, Tanzania, and Uganda (Cooper 1967, 1976; Verhulst 1976; Njeumi et al. 2002; Ugbomoiko et al. 2008; Mutebi et al. 2015; Pampiglione et al. 1998; Nair et al. 2013). In Latin America, infestations occur throughout the continent, such as Argentina, Ecuador, Peru, and Brazil (Fig. 8.1) (De Avelar et al. 2013; Marin et al. 2015; Harvey et al. 2021; Pampiglione et al. 2009).

Fig. 8.5 Flea infestation in a resident (**a**) and a dog (**b**) from endemic Brazilian communities

Tunga spp. infest the skin of farm animals, such as pigs, bovines, goats, and sheep, also occurring in dogs (Fig. 8.5b), cats, guinea pigs, horses, donkeys, and llamas. The infestation spectrum of *T. penetrans* is broad, encompassing hosts belonging to eight different mammalian orders, such as Artiodactyla, Carnivora, Cingulata, Perissodactyla, Pilosa, Primates, Proboscidea, and Rodentia, including 11 domestic species (Table 8.1) (Linardi and de Avelar 2014). The main animal reservoirs of this species are pigs and dogs, besides rodents (Ugbomoiko et al. 2008; Mutebi et al. 2016a; Harvey et al. 2019). High prevalence rates in swine and canine populations are recorded particularly from resource-poor communities. *T. trimamillata* was found in cattle (*Bos taurus*), swine, sheep, and goat in Ecuador and Peru, and in cattle (*Bos taurus* and *Bos indicus*) and capybara in Brazil. *T. hexalobulata* has been reported only in Brazilian cattle (*Bos indicus*) (Linardi and de Avelar 2014).

Infestations in wild animals are caused by species of both the penetrans and caecata groups. Penetrans group infestations include *T. bondari* (anteater), *T. terasma*, and *T. travassosi* (armadillo) in Brazil; *T. perforans* (armadillo) in Argentina; and *T. penetrans*, which infests anteaters, armadillos, tapirs, pacas, agoutis, capuchins, monkeys, vicuñas, warblers, panthers, and wild rodents in Latin America, and porcupines and red river hogs in Africa. Species of the caecata group infest wild and synanthropic rodents mainly in Latin America, with the exception of *T. callida* and *T. caecigena*, which occur in China and Japan (Linardi and de Avelar 2014; Ezquiaga et al. 2015; Schott et al. 2020).

The clinical signs resulting from acute inflammation of the skin surrounding the neosomes vary in the degree of severity, according to the parasite burden, as well as the presence of secondary bacterial infections. Intense and continuous reinfestations cause severe disease, which can result in prostration, behavioral changes, lameness,

self-mutilation, severe anemia, septicemia, deformities, loss of digits, and even lead to death.

Routinely, the diagnosis of tungiasis is clinical and based on the detection of typical lesions; epidermal changes such as hyperkeratosis can make it difficult to identify lesions. Infestations usually occur in the less hairy and more vascular areas of the animals' paws. In ruminants and horses, sand fleas preferentially penetrate the coronary band and the interdigital spaces; in pigs, the coronary band and sole, especially in the forelegs; and in dogs and cats, the paw pads and the periungual area. Ectopic injuries are frequent and reported in other areas of the limbs, in addition to muzzle, nose pad, tail, abdomen, mammary glands, perineal area, scrotal sac, and foreskin (Harvey et al. 2021; Mutebi et al. 2016a, b, 2017; Heukelbach et al. 2004; Ribeiro et al. 2007).

Tungiasis can lead to a loss of profitability for meat and leather producers. Intense and chronic infestations in the paws can result in reduced food consumption and, consequently, interfere with body weight gain, in addition to causing the depreciation of the quality of the skin and leather of ruminants. Severe infestations in nursing sows have resulted in mastitis and agalactia, which can delay piglet development, as well as lead to death of the offspring. Severe scrotal injuries can interfere with the fertility potential of breeding males (Ribeiro et al. 2007; Mutebi et al. 2017).

Treatment options for tungiasis in domestic animals are limited, and registered drugs are not available for farm animals. A formulation containing 50% permethrin (pyrethroid) and 10% imidacloprid (neonicotinoid) showed 97.5% effectiveness after 14 days of treatment, possibly being suitable for pets (Klimpel et al. 2005). The silicone oil dimethicone, which kills embedded parasites by physical means, also appears as an option for the treatment of animals, but further studies are needed before its recommendation for use (Thielecke et al. 2014; Nordin et al. 2017).

8.3 Tungiasis in Humans

The first written reports of human tungiasis were made in the early colonial period. As early as 1525, tungiasis was described in Haiti, when Spanish conquistadores were frequently affected by the disease. At the same period, a German, who lived for several years with the Tupinambá Indians in southeastern Brazil, described tungiasis in indigenous communities, reporting biological, taxonomic, epidemiological, and semiological aspects (Heukelbach et al. 2001; Heukelbach 2005). Human infestations have been described for *T. penetrans* and *T. trimamillata*.

Tungiasis occurs in rural and urban areas, such as slums of big cities, and fishing communities. Prevalence may be high in these settings, and as a consequence of a high parasite load (Fig. 8.5a), complications are common, such as bacterial superinfection possibly leading to tetanus, ulceration, and deformation of digits and toes (Heukelbach 2005; Feldmeier et al. 2014). Children are usually more commonly affected, with prevalence reaching up to 80%.

The diagnosis of tungiasis is clinical and usually made by visual inspection, considering the typical topographic location and the natural history of the disease. A

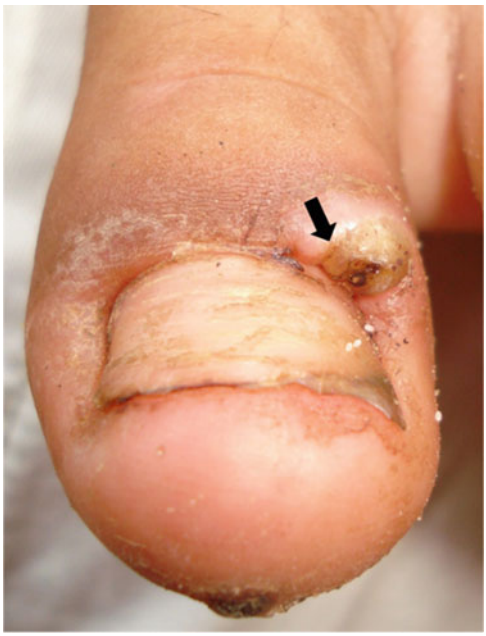


Fig. 8.6 Typical tungiasis lesion: a convex white lesion of about 1 cm with a central black spot, representing the last abdominal segments of the flea

mature penetrated female flea appears as a convex white lesion of about one centimeter with a central black spot, representing the last abdominal segments of the flea (Fig. 8.6). Local inflammation, hyperkeratosis, and desquamation of the skin around the mature lesion can commonly be observed. Eggs can often be seen around the lesion. Typically, tungiasis affects the periungual area of the toes, the heels, as well as the sides and soles of the feet. Penetrated fleas can be found on almost any part of the body, such as the hands, elbows, buttocks, legs, and anogenital region.

Infestation with one or a few fleas usually does not cause significant pathology if the lesion is removed under suitable and hygienic conditions. Itching and pain are commonly present. The disease is self-limited, lasting four to six weeks. However, in endemic areas constant and massive infestation occurs, and affected individuals may accumulate a few dozen or hundreds of penetrated fleas. In these cases, superinfection with pathogenic bacteria is present without exception. Most commonly, superinfection is caused by *Staphylococcus aureus* and streptococci, but other aerobic and anaerobic bacteria have also been isolated (Feldmeier et al. 2002). The superinfected lesions lead to the formation of pustules, suppuration, and ulceration. Severe infestation leads to chronic inflammation, cracks, difficulty in walking, deformity, and loss of toenails.

The occurrence of severe infestation is associated with precarious housing conditions, such as sandy floors inside houses, with the presence of animals on the compound, access to water and hygienic conditions, and low education and socioeconomic level. The male gender is usually more commonly affected. Behavior such as the type of common resting places and the non-use or irregular use of closed shoes

Fig. 8.7 Inadequate extraction of a *Tunga* sp. neosome

are associated with tungiasis (Heukelbach 2005; Feldmeier et al. 2014; Muehlen et al. 2006; Ugbomoiko et al. 2007; Elson et al. 2019b).

Treatment consists of surgical extraction of the penetrated parasites under sterile conditions, and the application of a topical antibiotic. The lesion in the epidermis should be carefully widened, starting at the central point of the lesion, with a sterile needle or similar instrument, to allow extraction of the entire flea without breaking it. In socio-economically disadvantaged areas, hygiene precautions are generally not applied, people use thorns or other instruments without appropriate disinfection (Fig. 8.7), and severe inflammation and bacterial superinfection may occur as a result of inadequate extraction. The tetanus immune status of the affected individual needs to be checked. In case of insufficient immune protection, vaccination is indicated.

Locally produced plant products are commonly used in affected communities, such as coconut oil, neem seed oil, cork bush, black monkey orange velvet leaf, potassium permanganate, or Sodom apple (Elson et al. 2017, 2019a). While especially coconut oil and neem seed oil are promising compounds, some of these plants are toxic, and in most cases, the efficacy has not been assessed systematically. Different types of other hazardous treatments are sometimes applied, such as insecticides for household use, motor oil, or kerosene (Winter et al. 2009).

Some randomized controlled trials have shown the efficacy of dimethicones, which are synthetic silicone oils (Miller et al. 2020). The topical use of dimethicone is safe in humans (Thielecke et al. 2014; Nordin et al. 2017; Miller et al. 2020; Heukelbach et al. 2008), but its high inflammability may pose logistical and safety challenges in communities where open fire cooking is common.

A repellent based on coconut oil, also containing jojoba, aloe vera, and panthenol (Zanzarin®), reduced the attack rate of sand fleas by more than 90%, and resolved tungiasis-associated morbidity in Brazil (Buckendahl et al. 2010; Feldmeier et al. 2006), and another study from Madagascar confirmed these impressive findings (Thielecke et al. 2013).

8.4 Control of Tungiasis Considering One Health

According to the World Health Organization (WHO), One Health is defined as "an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes." In fact, to effectively control tungiasis and to reduce the occurrence of severe disease, the associated determinants need to be considered as a whole. Several disciplines should be involved and work hand in hand, such as medicine, and veterinary, biological, agricultural, urban planning/architecture, and social sciences (Heukelbach 2020). Effective and sustainable control can only be achieved if policy makers and the healthcare sector create synergies and develop control programs to eliminate tungiasis as a public health problem. However, some politicians continue with their silo thinking, and the implementation of disciplinary approaches may be a major challenge in political practice (Gaviria 2021).

In addition, tungiasis is often not seen as an important condition, neither by the populations living in endemic areas (Fig. 8.8) nor by decision makers or health personnel, and there are usually no specifically dedicated disease control programs (Heukelbach et al. 2001; Winter et al. 2009; Heukelbach and Feldmeier 2004). Due to the absence of state and national tungiasis control programs, interventions will have to rely on commitment by non-governmental organizations, on motivation from single health professionals, and on collaboration with community leaders and with the entire community.

Fig. 8.8 Characteristics of Brazilian endemic communities

Table 8.2 Determinants leading to tungiasis and severe disease

People and Society	Poverty and social inequity
	Inadequate housing and Irving conditions
	Poor access to education
	Conflicts and wars, migration
	Increased agglomeration of people and animals
	Cultural aspects and individual behavior
	Gender
	Stigma and ostracism
	Inadequate health-care seeking behavior
	Inadequate treatment practices
	No specific professional training
Governance and Health Systems	Weak and vulnerable health systems
	Poor access of the population to the health system
	Missing prevention programs, no surveillance
	Health not a political priority
	Little research on poverty-related diseases
	Missing regional networks
	Traditional sector and silo thinking
	Underdeveloped and inadequate urban planning
Animal Health	Pets and farm animals as reservoirs
	Stray dogs as reservoirs
	Wild animals as reservoirs
	Rats and mice In urban settlements
	Destruction and reduction of natural habitats
Environment and Climate Change	More pronounced and prolonged dry seasons
	increasing contact of people in rural and urban settlements with wild animals
	Inadequate waste management practices
	Development of off-host stages in the environment

Tungiasis and severe tungiasis—caused by *T. penetrans* most commonly and to an unknown extent by *T. trimamillata*—are determined by a variety of factors, including those related to people and society, animal health, governance and health systems, and environment and climate change, as detailed in Table 8.2. There are domestic and sylvatic animal reservoirs; off-host stages develop at certain breeding sites in the community and even within houses; there is a strong link to poverty, poor living conditions, and hygiene; and individual behavior such as resting places and walking barefooted is important for transmission dynamics (Feldmeier et al. 2014; Heukelbach et al. 2002). Risk factor studies have shown that socioeconomic factors, male gender, age <15 years and the older age groups, sandy floor inside houses, no regular use of footwear, and presence of animals in the surroundings are usually associated with a higher risk of human tungiasis (Muehlen et al. 2006; Elson et al.

2019b; Obebe and Aluko 2020; Nsanzimana et al. 2019; Girma et al. 2018; Wafula et al. 2016).

A recent report has shown that a low-cost interdisciplinary community-based approach has been effective for the control of tungiasis in Nigeria (Heukelbach et al. 2021). In Kenya, tungiasis control also counted on cooperation with local communities; a local NGO intensively cooperated with communities and policy makers (Elson et al. 2017). In different communities, interventions may be adapted to the local conditions. In rural Madagascar, the attack rate could be reduced to zero by application of a plant-based repellent based on coconut oil; studies from Brazil also reported very high efficacy of this repellent (Buckendahl et al. 2010; Feldmeier et al. 2006). The dimethicone product is also known as a very effective treatment against head lice (Heukelbach et al. 2008, 2009). In a fishing community in Brazil, effective control was achieved by treatment of affected individuals and insecticide spraying of premises, but the effect did not last for a long time (Pilger et al. 2008). Treatment of individuals with a product made from neem and coconut oil, in-house floor spraying with neem solution, and propagation of the use of closed shoes effectively controlled human tungiasis in the Kenyan study (Elson et al. 2017). In some communities, people will most probably not change their behavior in relation to the use of closed shoes, as these are considered valuable assets (Feldmeier et al. 2014), while in other regions the provision of shoes may be an effective means to reduce the transmission pressure, especially in schoolchildren.

Regardless of the approach in a specific setting, it is important to think out of the box, and to join hands with other disease control programs, particularly neglected tropical diseases. For example, control should consider the reduction of disease burden and suffering in animals. This will also have positive effects on transmission in the community, and there will positive spillover effects regarding other zoonotic diseases. Reduction of the number of free-roaming pigs in rural communities will also have a positive effect not only on tungiasis but possibly also on the occurrence of cysticercosis in a rural community. Control of rats in low socioeconomic urban settings will further reduce the risk of leptospirosis and of rodent-borne viral diseases transmitted by rats (Mwabonimana et al. 2020; Boey et al. 2019). On the contrary, after widespread prohibition of free-roaming pigs due to cysticercosis risk in many Brazilian communities during the past few decades, reduction of tungiasis has been observed commonly, as seen with the reduction of tungiasis after anti-rat campaigns aimed at the reduction of transmission of leptospirosis in urban slums (personal observation).

Topical compounds such as dimethicones may also be used in the community for mass treatment against other diseases, such as pediculosis and possibly scabies. The reduction of the stray dog population and deworming of dogs will improve both animal health and human health. The application of an effective repellent to the feet may have positive effects on other diseases such as hookworms and hookworm-related cutaneous larva migrans, which you get by direct contact of bare skin with dog and cat feces (see Chap. 12). As severe tungiasis may be a port of entry for tetanus bacteria, tetanus vaccination should be considered in settings where severe

infestations occur to reduce the incidence of tetanus at high-risk areas (Feldmeier et al. 2002; Tonge 1989).

Increasing urbanization and improved housing conditions have contributed to a general reduction of the occurrence of tungiasis in recent decades (Heukelbach et al. 2021). However, it is still a highly prevalent disease in populations living in areas of extreme poverty. One Health intervention measures are needed to reduce the attack rate in high-risk communities. Interventions may not eradicate the disease, but may reduce the parasite load of highly infested individuals, thereby preventing severe pathology. Clearly, more research, political commitment, advocacy, and priority setting toward poverty-related diseases are needed, including increased financing and integration with other programs aiming at the elimination of neglected tropical diseases as a public health problem.

References

Antunes JM, Demoner Lde C, Martins IV, Zanini MS, Deps PD, Pujol-Luz JR (2006) Record of *Dasypus novemcinctus* (Mammalia: Xenarthra) parasited by *Tunga terasma* (Siphonaptera: Tungidae) in Alegre, State of Espirito Santo, Brazil. Rev Bras Parasitol Vet 15(4):206–207

Boey K, Shiokawa K, Rajeev S (2019) Leptospira infection in rats: a literature review of global prevalence and distribution. PLoS Neglect Trop Dis 13(8):e0007499. https://doi.org/10.1371/journal.pntd.0007499

Buckendahl J, Heukelbach J, Ariza L, Kehr JD, Seidenschwang M, Feldmeier H (2010) Control of tungiasis through intermittent application of a plant-based repellent: an intervention study in a resource-poor community in Brazil. PLoS Neglect Trop Dis 4(11):e879. https://doi.org/10.1371/journal.pntd.0000879

Cooper JE (1967) An outbreak of *Tunga penetrans* in a pig herd. Veter Rec 80(11):365–366

Cooper JE (1976) *Tunga penetrans* infestation in pigs. Vet Rec 98(23):472

da Fonseca F (1936) Sobre o macho de Tunga trvassossi Pinto et Dreyfus, 1927, e o parasitismo de *Euphractes sexcintus* L. por *Tunga penetrans* (L., 1758) (siph., tungidae). Revista de Entomologia 6(3–4):421–424

De Avelar DM, Facury Filho EJ, Linardi PM (2013) A new species of Tunga (Siphonaptera: Tungidae) parasitizing cattle from Brazil. J Med Entomol 50(4):679–684. https://doi.org/10.1603/me12221

Elson L, Wright K, Swift J, Feldmeier H (2017) Control of tungiasis in absence of a roadmap: grassroots and global approaches. Trop Med Infect Dis 2(3). https://doi.org/10.3390/tropicalmed2030033

Elson L, Randu K, Feldmeier H, Fillinger U (2019a) Efficacy of a mixture of neem seed oil (*Azadirachta indica*) and coconut oil (*Cocos nucifera*) for topical treatment of tungiasis. A randomized controlled, proof-of-principle study. PLoS Neglect Trop Dis 13(11):e0007822. https://doi.org/10.1371/journal.pntd.0007822

Elson L, Wiese S, Feldmeier H, Fillinger U (2019b) Prevalence, intensity and risk factors of tungiasis in Kilifi County, Kenya II: results from a school-based observational study. PLoS Neglect Trop Dis 13(5):e0007326. https://doi.org/10.1371/journal.pntd.0007326

Ezquiaga MC, Linardi PM, De Avelar DM, Lareschi M (2015) A new species of *Tunga* perforating the osteoderms of its armadillo host in Argentina and redescription of the male of *Tunga terasma*. Med Vet Entomol 29(2):196–204. https://doi.org/10.1111/mve.12106

Feldmeier H, Heukelbach J, Eisele M, Sousa AQ, Barbosa LM, Carvalho CB (2002) Bacterial superinfection in human tungiasis. Trop Med Int Health 7(7):559–564. https://doi.org/10.1046/j.1365-3156.2002.00904.x

Feldmeier H, Kehr JD, Heukelbach J (2006) A plant-based repellent protects against *Tunga penetrans* infestation and sand flea disease. Acta Trop 99(2–3):126–136. https://doi.org/10.1016/j.actatropica.2006.05.013

Feldmeier H, Heukelbach J, Ugbomoiko US, Sentongo E, Mbabazi P, von Samson-Himmelstjerna G et al (2014) Tungiasis—a neglected disease with many challenges for global public health. PLoS Neglect Trop Dis 8(10):e3133. https://doi.org/10.1371/journal.pntd.0003133

Fioravanti ML, Pampiglione S, Trentini M (2003) A second species of *Tunga* (Insecta, Siphonaptera) infecting man: *Tunga trimamillata*. Parasite 10(3):282–283

Fioravanti MI, Gustinelli A, Onore G, Pampiglione S, Trentini M (2006) Presence of *Tunga trimamillata* (Insecta, Siphonaptera) in Peru. Parasite 13(1):85–86

Gaviria A (2021) My experience with one health: between realism and optimism. One Health Implement Res 1:14–16. https://doi.org/10.20517/ohir.2020.001

Geigy R, Suter P (1960) Zur Copulation der Flöhe. Revue Suisse de Zoologie 67:206–210

Girma M, Astatkie A, Asnake S (2018) Prevalence and risk factors of tungiasis among children of Wensho district, southern Ethiopia. BMC Infect Dis 18(1):456. https://doi.org/10.1186/s12879-018-3373-5

Harvey TV, Heukelbach J, Assuncao MS, Fernandes TM, da Rocha C, Carlos RSA (2019) Seasonal variation and persistence of tungiasis infestation in dogs in an endemic community, Bahia State (Brazil): longitudinal study. Parasitol Res 118(6):1711–1718. https://doi.org/10.1007/s00436-019-06314-w

Harvey TV, Dos Santos FZ, Dos Santos KC, de Jesus AV, Guedes PEB, da Paixao SA et al (2021) Clinical and macroscopic morphological features of canine tungiasis. Parasitol Res 120(3):807–818. https://doi.org/10.1007/s00436-020-07013-7

Heukelbach J (2005) Tungiasis. Rev Inst Med Trop Sao Paulo. 47(6):307–313. https://doi.org/10.1590/s0036-46652005000600001

Heukelbach J (2020) One Health & Implementation Research: improving health for all. One Health Implement Res 1(1):1–3. https://doi.org/10.20517/ohir.2020.01

Heukelbach J, Feldmeier H (2004) Ectoparasites—the underestimated realm. Lancet. 363(9412):889–891. https://doi.org/10.1016/S0140-6736(04)15738-3

Heukelbach J, de Oliveira FA, Hesse G, Feldmeier H (2001) Tungiasis: a neglected health problem of poor communities. Trop Med Int Health 6(4):267–272. https://doi.org/10.1046/j.1365-3156.2001.00716.x

Heukelbach J, Mencke N, Feldmeier H (2002) Editorial: Cutaneous larva migrans and tungiasis: the challenge to control zoonotic ectoparasitoses associated with poverty. Trop Med Int Health 7(11):907–910

Heukelbach J, Costa AM, Wilcke T, Mencke N, Feldmeier H (2004) The animal reservoir of *Tunga penetrans* in severely affected communities of north-east Brazil. Med Vet Entomol 18(4):329–335. https://doi.org/10.1111/j.0269-283X.2004.00532.x

Heukelbach J, Pilger D, Oliveira FA, Khakban A, Ariza L, Feldmeier H (2008) A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial. BMC Infect Dis 8:115. 1471-2334-8-115 [pii]. https://doi.org/10.1186/1471-2334-8-115

Heukelbach J, Asenov A, Liesenfeld O, Mirmohammadsadegh A, Oliveira FA (2009) A new two-phase dimeticone pediculicide shows high efficacy in a comparative bioassay. BMC Dermatol 9:12. https://doi.org/10.1186/1471-5945-9-12

Heukelbach J, Ariza L, Adegbola RQ, Ugbomoiko US (2021) Sustainable control of tungiasis in rural Nigeria: a case for one health. One Health Implement Res 1:4–13. https://doi.org/10.20517/ohir.2021.01

Hicks EP (1930) The early stages of the jigger, *Tunga penetrans*. Ann Trop Med Parasitol 24:575–586

Klimpel S, Mehlhorn H, Heukelbach J, Feldmeier H, Mencke N (2005) Field trial of the efficacy of a combination of imidacloprid and permethrin against *Tunga penetrans* (sand flea, jigger flea) in dogs in Brazil. Parasitol Res 97(Suppl 1):S113–S1S9

Linardi PM, de Avelar DM (2014) Neosomes of tungid fleas on wild and domestic animals. Parasitol Res 113(10):3517–3533. https://doi.org/10.1007/s00436-014-4081-8

Linardi PM, Linardi PM, Guimaraes LR (2000) Família tungidae. Sifonápteros do Brasil. S□o Paulo: Museu de Zoologia da Universidade de S□o Paulo, pp 48–53

Linardi PM, Calheiros CM, Campelo-Junior EB, Duarte EM, Heukelbach J, Feldmeier H (2010) Occurrence of the off-host life stages of *Tunga penetrans* (Siphonaptera) in various environments in Brazil. Ann Trop Med Parasitol 104(4):337–345. https://doi.org/10.1179/136485910X12743554759902

Linardi PM, De Avelar DM, Filho EJ (2013) Establishment of *Tunga trimamillata* (Siphonaptera: Tungidae) in Brazil. Parasitol Res 112(9):3239–3242. https://doi.org/10.1007/s00436-013-3501-5

Linardi PM, Beaucournu JC, de Avelar DM, Belaz S (2014) Notes on the genus *Tunga* (Siphonaptera: Tungidae) II—neosomes, morphology, classification, and other taxonomic notes. Parasite 21:68. https://doi.org/10.1051/parasite/2014067

Marin RE, Houston R, Omanska-Klusek A, Alcaraz A, Garcia JP, Uzal FA (2015) Pathology and diagnosis of proliferative and ulcerative dermatitis associated with *Tunga penetrans* infestation in cattle. J Vet Diagn Invest 27(1):80–85. https://doi.org/10.1177/1040638714559597

Miller H, Trujillo-Trujillo J, Mutebi F, Feldmeier H (2020) Efficacy and safety of dimeticones in the treatment of epidermal parasitic skin diseases with special emphasis on tungiasis: an evidence-based critical review. Braz J Infect Dis 24(2):170–177. https://doi.org/10.1016/j.bjid.2020.01.004

Muehlen M, Feldmeier H, Wilcke T, Winter B, Heukelbach J (2006) Identifying risk factors for tungiasis and heavy infestation in a resource-poor community in Northeast Brazil. Trans R Soc Trop Med Hyg 100:371–380

Mutebi F, Krucken J, Feldmeier H, Waiswa C, Mencke N, Sentongo E et al (2015) Animal reservoirs of zoonotic tungiasis in endemic rural villages of Uganda. PLoS Neglect Trop Dis 9(10):e0004126. https://doi.org/10.1371/journal.pntd.0004126

Mutebi F, Krucken J, Feldmeier H, Waiswa C, Mencke N, von Samson-Himmelstjerna G (2016a) Tungiasis-associated morbidity in pigs and dogs in endemic villages of Uganda. Parasit Vectors 9:44. https://doi.org/10.1186/s13071-016-1320-0

Mutebi F, Krucken J, Mencke N, Feldmeier H, von Samson-Himmelstjerna G, Waiswa C (2016b) Two severe cases of tungiasis in goat kids in Uganda. J Insect Sci 16. https://doi.org/10.1093/jisesa/iew016

Mutebi F, Krucken J, Feldmeier H, Waiswa C, Mencke N, Eneku W et al (2017) High intensity of *Tunga penetrans* infection causing severe disease among pigs in Busoga, South Eastern Uganda. BMC Vet Res 13(1):206. https://doi.org/10.1186/s12917-017-1127-z

Mwabonimana MF, Inyagwa CM, Bebe BO, Shakala EK, King'ori AM (2020) Porcine cysticercosis control in Western Kenya: the interlink of management practices in pig farms and meat inspection practice at slaughter slabs. Vet Med Int 2020:7935656. https://doi.org/10.1155/2020/7935656

Nair SP, Tsehayneh K, Lemma ZT, Kassim M, Ramaswamy V (2013) Transmission dynamics of tungiasis in Ethiopia. World Res J Med Sci 1(1):7–9

Njeumi F, Nsangou C, Ndjend AG, Koga, Ostanello F, Pampiglione S (2002) *Tunga penetrans* au Cameroun. Revue Méd Vét 153(3):176–180

Nordin P, Thielecke M, Ngomi N, Mudanga GM, Krantz I, Feldmeier H (2017) Treatment of tungiasis with a two-component dimeticone: a comparison between moistening the whole foot and directly targeting the embedded sand fleas. Trop Med Health 45:6. https://doi.org/10.1186/s41182-017-0046-9

Nsanzimana J, Karanja S, Kayongo M, Nyirimanzi N, Umuhoza H, Murangwa A et al (2019) Factors associated with tungiasis among primary school children: a cross-sectional study in a rural district in Rwanda. BMC Public Health 19(1):1192. https://doi.org/10.1186/s12889-019-7481-y

Obebe OO, Aluko OO (2020) Epidemiology of tungiasis in sub-saharan Africa: a systematic review and meta-analysis. Pathog Glob Health:1–10. https://doi.org/10.1080/20477724.2020.1813489

Pampiglione S, Trentini M, Gentili FM, Mendes JLX, Pampiglione C, Rivasi F (1998) *Tunga penetrans* (Insecta: Siphonaptera) in pigs in São Tomé (Equatorial Africa): epidemiological, clinical, morphological and histopathological aspects. Rev Elev Med Vet Pays Trop 51:201–205

Pampiglione S, Trentini M, Fioravanti ML, Onore G, Rivasi F (2003) Additional description of a new species of Tunga (Siphonaptera) from Ecuador. Parasite 10(1):9–15

Pampiglione S, Fioravanti ML, Gustinelli A, Onore G, Mantovani B, Luchetti A et al (2009) Sand flea (*Tunga* spp.) infections in humans and domestic animals: state of the art. Med Vet Entomol 23(3):172–186. https://doi.org/10.1111/j.1365-2915.2009.00807.x

Pilger D, Schwalfenberg S, Heukelbach J, Witt L, Mencke N, Khakban A et al (2008) Controlling tungiasis in an impoverished community: an intervention study. PLoS Neglect Trop Dis 2(10): e324. https://doi.org/10.1371/journal.pntd.0000324

Pinto C, Dreyfus A (1927) *Tunga travassosi* n. sp., parasita de *Tatusia novemcinctus* do Brasil. Boletim Biológico (SPaulo) 9:174–178

Ribeiro JCVC, Coelho SC, Ruas JRM, Lana AMQ, Carvalho AU, Facury Filho EJ et al (2007) Infestação de *Tunga penetrans* siphonaptera: Tungidae em cascos de vacas leiteiras F1 Holandês-Zebu. Arquivo Brasileiro de Medicina Veterinária e Zootecnia 59:520–522

Schott D, Ribeiro PR, de Souza VK, Surita LE, de Amorim DB, Bianchi MV et al (2020) Clinical and pathological aspects of first report of *Tunga penetrans* infestation on southern brown howler monkey (*Alouatta guariba clamitans*) in Rio Grande do Sul, Brazil. J Med Primatol 49(6): 315–321. https://doi.org/10.1111/jmp.12491

Smit FGAM (1962) A new sand-flea from Ecuador. Entomologist 95:89–93

Thielecke M, Raharimanga V, Rogier C, Stauss-Grabo M, Richard V, Feldmeier H (2013) Prevention of tungiasis and tungiasis-associated morbidity using the plant-based repellent zanzarin: a randomized, controlled field study in rural Madagascar. PLoS Neglect Trop Dis 7(9):e2426. https://doi.org/10.1371/journal.pntd.0002426

Thielecke M, Nordin P, Ngomi N, Feldmeier H (2014) Treatment of Tungiasis with dimeticone: a proof-of-principle study in rural Kenya. PLoS Neglect Trop Dis 8(7):e3058. https://doi.org/10.1371/journal.pntd.0003058

Tonge BL (1989) Tetanus from chigger flea sores. J Trop Pediatr 35:94

Ugbomoiko US, Ariza L, Ofoezie IE, Heukelbach J (2007) Risk factors for tungiasis in Nigeria: identification of targets for effective intervention. PLoS Neglect Trop Dis 1(3):e87. https://doi.org/10.1371/journal.pntd.0000087

Ugbomoiko US, Ariza L, Heukelbach J (2008) Pigs are the most important animal reservoir for *Tunga penetrans* (jigger flea) in rural Nigeria. Trop Doct 38(4):226–227. https://doi.org/10.1258/td.2007.070352

Verhulst A (1976) *Tunga penetrans* (*Sarcopsylla penetrans*) as a cause of agalactia in sows in the Republic of Zaire. Vet Rec 98(19):384

Wafula ST, Ssemugabo C, Namuhani N, Musoke D, Ssempebwa J, Halage AA (2016) Prevalence and risk factors associated with tungiasis in Mayuge district, Eastern Uganda. Pan Afr Med J 24: 77. https://doi.org/10.11604/pamj.2016.24.77.8916

Wagner J (1932) Tunga bondari, eine neue Art der Sandflõhe. Novitates Zoologicae 38:248–249

Winter B, Oliveira FA, Wilcke T, Heukelbach J, Feldmeier H (2009) Tungiasis-related knowledge and treatment practices in two endemic communities in northeast Brazil. J Infect Dev Ctries 3(6):458–466. https://doi.org/10.3855/jidc.418

Human Myiasis on the South American Continent

9

Heinz Mehlhorn

Abstract

Humans and their animals are worldwide attacked by different groups of flies. The adults which may transfer various types of agents of diseases and their larvae even may enter the body of humans thus inducing eventually severe or even lethal diseases called myiasis. These parasites occur worldwide and thus also can be found often in large numbers in warm regions of the South American continent. Some common and important species are the targets of the present chapter.

Keywords

Myiasis · Fly induced diseases · Fly attacks · Treatment

9.1 Definition of Myiasis

The term **myiasis** is based on the old Greek term *myia* (fly, mosquito) and describes today a disease due to infestations by fly (= dipterous) larvae, which have entered the skin or organs of humans and/or animals and feed there ingesting dead and/or living cells/tissues Hall and Smith (1995); Goddard 2003; Mehlhorn 2016a, b; Singh and Singh 2015). All over the South American continent many fly species occur, wherefrom the larvae enter the skin of humans and many animals (Table 9.1). There are defined three different stages: **(1) papular protrusion**, **(2) furuncular protrusion**, **(3) protuberant protrusion** (Ragi et al. 2021). The term **pseudomyiasis** describes the apathogenic passage of fly larvae passaging the gastrointestinal tract of humans and animals (Fig 9.1).

H. Mehlhorn (✉)
Department of Parasitology, Heinrich Heine University, Duesseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_9

Table 9.1 Some skin-penetrating dipteran flies based on investigations of Francesconi and Lupi (2012)

Family	Subfamily	Genera/species
Muscidae	Muscinae	*Muscina* sp., *Musca domestica*
Fanniidae	Fanninae	*Fannia scalaris*, *Fannia canicularis*
Oestridae	Oestrinae	*Oestrus* sp.
Hypodermatidae	Hypodermaninae	*Hypoderma* species: *H. bovis*, *H. lineatum*
Gasterophilidae	Gasterophilinae	*Gasterophilus* sp.
Cuterobridae	Cuterobrinae	*Cuterebra* sp., *Dermatobia hominis*
Calliphoridae	Luciliinae	*Lucilia* sp.
	Calliphorinae	*Calliphora* sp.
Calliphoridae	Calliphorinae	*Cordylobia anthropophaga*
Calliphoridae	Calliphorinae	*Cochliomyia hominivorax*
Calliphoridae	Calliphorinae	*Cochliomyia macellaria*
Sarcophagidae	Sarcophaginae	*Sarcophaga* sp., *Wohlfartia* sp.

Explanations of Signs:

1. Black diamonds: characterize obligate parasites of vertebrates (Calliphoridae).
2. White diamonds: obligate endoparasites of vertebrates (Oestridae).
3. Black circles: facultative primary myiasis species.
4. White circles: facultative secondary myiasis species.
5. White squares: obligate parasites of invertebrates, for example, earthworms (Calliphoridae, Sarcophagidae).

9.2 Main Types of Myiasis According to Hall and Smith (1995)

9.2.1 Cutaneous Myiasis

9.2.1.1 Wound and Traumatic Myiasis

The larvae enter wounds either obligatorily (o) or facultatively (f):

- Calliphoridae (o, f)
- Fanniidae (f)
- Muscidae (f)
- Phoridae (f)
- Sarcophagidae (o, f).

9.2.1.2 Bloodsucking (Sanguinivorous) Myiasis

The larvae attach to the skin of hosts and start biting and sucking:

Involved families are:

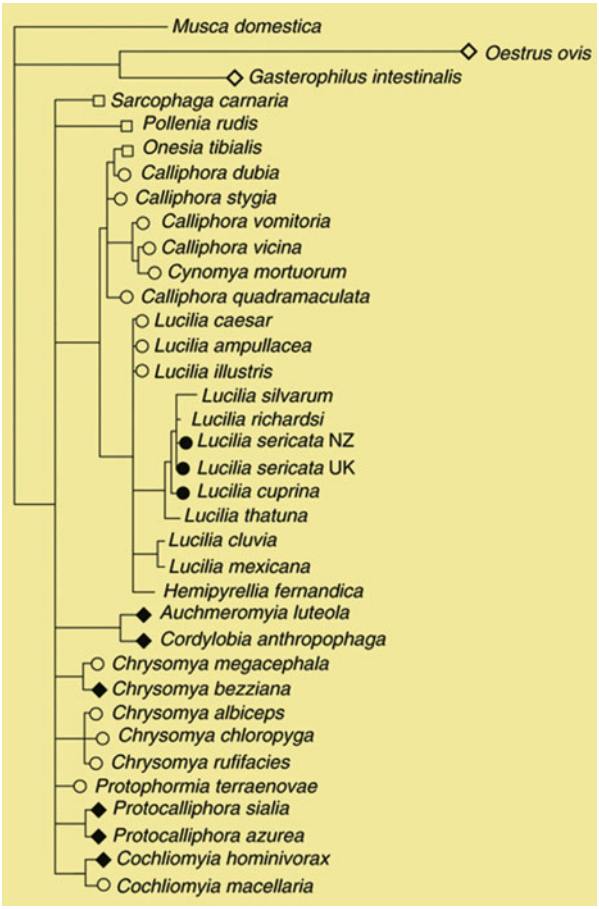


Fig. 9.1 Relations of some important fly species inducing potentially different types of myiasis in humans and vertebrate animals on different continents (according to several international authors, see references)

– *Auchmeromyia* (Calliphoridae) (o)
– Tabanidae (f)
– Therevidae (f)

9.2.1.3 Furuncular Myiasis

The larvae of this species penetrate deeper into the skin and induce during growth typical boil-like, mostly larger swellings:

– *Cordylobia* sp. (o)
– *Dermatobia* (o)
– *Wohlfahrtia* sp. (o)

9.2.1.4 Creeping Myiasis

The larvae enter the skin of humans, wander around, but do not finish their development in humans (= no pupa formation):

- Oestridae (e.g., *Hypoderma*) (o)
- Gasterophilidae (o)

9.2.2 Body Cavity Myiasis

The females deposit—depending on the species—their eggs either into the nose, sinuses, or pharynx. The larvae belong to the following families:

- Calliphoridae (o, f)
- Muscidae (f)
- Oestridae (f)
- Phoridae (f)
- Sarcophagidae (o, f)

9.2.3 Accidental Myiasis

9.2.3.1 Intestinal (Enteric, Rectal) Myiasis

This type is given, when eggs or larvae had been ingested within food. Involved species belong to the families of Calliphoridae, Fanniidae, Muscidae, Sarcophagidae, Sepsidae, and Tipulidae (f).

9.2.3.2 Urogenital Myiasis

Occurs due to smell attraction of adult female flies and their of laying eggs onto human tissues or clothes, from where the larvae become able to enter related human systems (f). Common and other involved species belong to the families of Calliphoridae, Fanniidae, Muscidae, Sarcophagidae.

Abbreviations: o = obligate parasitosis; f = facultative parasitosis.

9.3 Biology

The first stage larvae of some cyclorrhapha flies parasitize as stationary agents of disease in the skin, eyes, and/or other organs of humans and animals in their surroundings inducing clinical symptoms described by the Greek term **myiasis**. While the females of most of the typical and medically relevant fly species deposit their eggs immediately onto their selected vertebrate host (mammals and humans), the females of *Dermatobia hominis* attach them to the body of females of adult blood-feeding insects, which transport them to their hosts. This peculiar activity helps them to spread their eggs to a broader spectrum of hosts, since the females of

bloodsucking mosquitoes attack many different hosts in a variety of biotopes. The different adult specimens may in addition be worldwide spread by tourists or when being attached at containers/material being transported from the tropics to countries with moderate temperatures.

9.4 Important Species in South America

9.4.1 *Dermatobia hominis*

(a) **Trivial name:** Human **bot fly** or locally also called "**torsala**" fly, **berne**, **tropical warble fly,** or **vermacaque** belonging to the family Calliphoridae. In some regions of South America it is also called **berne** or **torsalo** (Fig. 9.2).
(b) **Hosts:** Humans, vertebrate animals (wild, domestic; for example, cattle, sheep, pigs, horses, dogs, cats, and even birds).
(c) **Geographic distribution:** Mexico, Central, and South America.
(d) **Appearance:** Adults: characteristic is their blueish body reaching a length of 15–17 mm. Their head and legs appear yellowish to brown and is equipped with a plumose arista (= a bristle-like branch of the two antennae). The whitish larvae reach a length of 2 cm and a width of 1 cm and they are provided with two hooks at the anterior end being followed by 6 rows of hooks surrounding the anterior half of the body (Fig. 9.3). Two spiracles are situated at the terminal end of the larval stages, which take up oxygen being distributed inside the body via a chitin channel system.
(e) **Biology/Development:** The life cycle of *D. hominis* is rather unique, since the fertilized adult females fix their eggs at the body of bloodsucking flies or mosquitoes by help of a quickly drying glue. As soon as these vectors feed on humans or on other potential warm-blooded hosts, the bot fly larvae leave (= hatch from) this vector and penetrate into the skin of the new host and feed

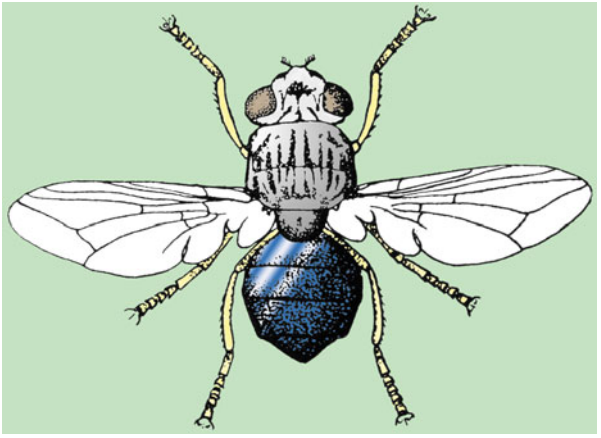


Fig. 9.2 Diagrammatic representation of an adult *Dermatobia hominis* fly

Fig. 9.3 Light micrograph of a second stage larva of *Dermatobia hominis*. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

inside a subdermal cavity (furuncle) of this host for 3 up to 6 weeks breathing air via a hole of this furuncle-like protrusion, which is often misdiagnosed as a so-called "staphylococcal boil." When having reached the full development, the larva emerges from the skin cavity via an opening, drops down to the ground during the night, and becomes a chitin-surrounded rather stiff pupa. When laying about 1 month on the ground the adult stages (♀ or ♂) emerge from their pupal cocoon and start the flying period of their life cycle. Worldwide exist at least 50 insect species, wherefrom the adult females attach their larvae at hosts and thus become spread over large regions endangering the health of humans and animals.

D. hominis attacks besides humans as well as animals (especially cattle) in tropical and subtropical regions of Central and South America. This activity increases their chances for local spreading, when these bloodsuckers seek their hosts and note the change of temperature on the vertebrate (phoretic) host (including humans). When the eggs are deposited on the skin of humans, the larvae note the change of temperature and penetrate immediately into the skin of the new host, stay in a subdermal cavity for 6–9 weeks and grow up via three instar larvae. The final larval stage drops down to the soil and pupates there. Finally the adult males and females emerge from the pupa shell and reach about 15 mm in length. Worldwide there exist at least up to 50 insect species, wherefrom the adults of which act as transporters of the larvae of *Dermatobia hominis* (Oestridae). This species—also described as human bot fly—is widely spread from Mexico down to Central and South American countries. Besides humans, many vertebrates (cattle, sheep, swine, horses, cats, dogs, and even birds) become infected and suffer from the same symptoms of disease as humans. The posterior margins of segment 11 are not equipped with dorsal spines.

Symptoms: Furuncular and urogenital myiasis.

9.4.2 Cuterebra Sp.

Eighty-five percent of human cases are cutaneous infections, main hosts are rodents (squirrels, rabbits), while humans are occasionally infected. The larva in human skin appears like a warble-like dermal tumor and thus is often misdiagnosed. Thus it is also misdiagnosed as boils or larva migrans.

9.4.3 Oestrus Ovis (Nose Bot Flies)

Greek: *oistros* = penetrating fly. Adults are ~1 cm long, females are about 1.3 cm long and throw their 500–600 larvae towards the nose and eyes of sheep and (!) humans (Fig. 9.4). The females, which do not feed, deposit the first stage larvae into the nostrils of their hosts (including humans). In humans also eyes, mouth, and outer ear have found to be filled—especially people working with sheep and goats. For example, there are reports that up to 50 larvae have been removed from the conjunctival sac of a single patient. However, larvae do not survive the first stage in man, but induce inflammations. In the nose of animals, the larva 3 is developed, drops down to soil, where the mature stage is reached within 2–4 weeks.

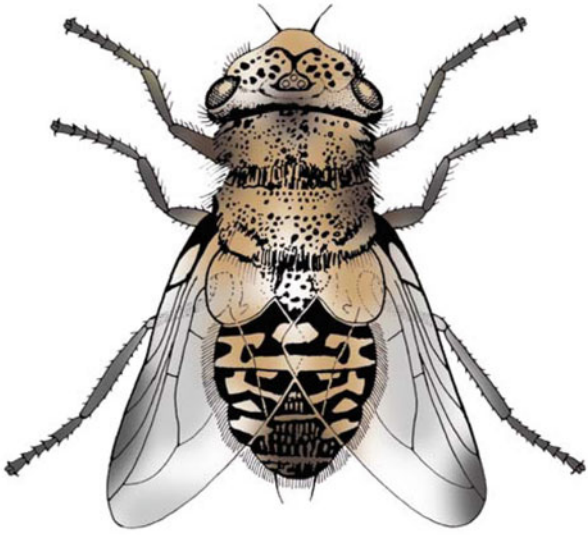


Fig. 9.4 Diagrammatic representation of an adult *Oestrus ovis* fly

9.4.4 Cochliomyia Hominivorax

(a) **Trivial names: (1) coquerel** (especially in Argentina, Brazil, Chile), **(2) New World screwworm fly** (named honoring the Brazilian scientist Coquerel in the year 1858).
(b) **Hosts:** Humans, wild and domestic mammals.
(c) **Geographic distribution:** It occurs in Central and South America—especially in Brazil the larvae induce the so-called **primary myiasis** in wild and domestic animals as well as in humans. Formerly and occasionally in recent times, it was reimported to the Caribbean Islands and to regions of the USA and Southern Mexico, where their numbers have been decreasing due to eradication programs using the sterile male release technique.
(d) **Appearance:** Adult stages of *C. hominivorax* appear bluish-green, are medium-sized (mm in length), have a yellowish-orange face, and are characterized by three longitudinal stripes along the thorax plate (Goddard 2003). Fully grown-up larvae reach a length of 2 cm, appear pinkish, and are typically characterized by rings with prominent spines around their body.
(e) **Biology/development:** The fertilized adult females of *C. hominivorax* are attracted by skin wounds of humans along the borders of which they deposit up to 500 eggs during different touch-downs. Around 12–15 h later the larvae (Fig. 9.5) hatch from the egg and enter the living tissue but leave air access to their posterior peritremes (= the plate with the breathing openings). The larvae may travel through living tissues and thus do not remain subdermal like the tumbu fly. After having fed for 4–7 days, the final larvae leave the skin and drop down to the ground, where they pupate within 7–10 days before the male or female adult hatches from the pupa skin. The whole developmental cycle takes about 20–24 days under optimum conditions. Thus in endemic regions masses of such females may attack (mainly during daylight) humans and their domestic animals year-round. Since the females lay mostly batches of eggs, often large numbers of maggots might be found in a wound thus endangering the health of humans considerably.

Fig. 9.5 Light micrograph of a larva of *Cochliomyia hominivorax*

(f) **Diseases:** Adult flies may transmit massive amounts of agents of diseases, which may and do kill persons and considerable amounts of animals every year. Thus a quick removal of the larvae is needed and cleaning of the wounds from bacteria and fungi is highly needed.
(g) **Treatment:** The control of screwworm fly myiasis of humans is mainly based on mechanical removal of the penetrated larvae under local anesthetics. However, special sites like spots in ears, nose, etc. require surgery. Infected dogs had been successfully treated using ivermectin and sarolaner, which both showed in addition high expulsion rates (Oliveira et al. 2019). Muñoz et al. (2020) recommended the use of cephalexin (20 mg/kg twice a day orally for 15 days)—sites like spots in the ears, nose, etc. require surgery under local anesthesia.

Attention: Screwworm flies lay eggs in large batches, which may comprise 10–100 in a single wound and thus the larvae increase the severeness of this infection.

9.4.5 Cochliomyia Macellaria

This species is also called "**secondary screwworm."** It is a carrion-breeding species, which has reached high importance in the field of medical and veterinary diseases as well as in forensic investigations. It occurs mainly in South America, but has also been described in parks of Southern Canada and all over down the USA. The adults fly in anthropized environments and also enter human dwellings. Usually the adults feed decomposing organic material and also human feces. Thus they may become transmitter of enteric pathogens such as, for example, *Salmonella* species. This species, which is characterized by the absence of dorsal spines at the margin of segment, is also considered as a **secondary screwworm** (Masiero et al. 2020), which induces a **facultative myiasis** when feeding on necrotic tissues. Thus they may be used in larval therapy. Thereby they are rather safe, because the larvae feed exclusively on injured integument and enter only dead bodies in contrast to other species (Oliveira et al. 2019).

According to measurements of Alvarez Garcia et al. (2017) their eggs measure ~1 mm in length, the larva 1 about 3 mm in length, the larva 2 about 7 mm, the larva 3 about 144 and the pupae reach 9 mm in length and about 3 mm in width.

The time of development takes in males about 20–30 days and 21–30 days in females. Cleaned and surface sterile larvae from laboratory productions are very useful to eliminate bacteria and viruses from inflamed wounds of humans (Masiero et al. 2020; Alvarez Garcia et al. 2017). Although the females in their adult stage live only for about 3 weeks, they produce up to 680 eggs, and thus in cases of large amounts they endanger the health of humans and farm animals to a high degree. Their status of developments has also reached significant importance in the forensic determination of the date of death of humans and animals, especially in cases of doubtful diseases.

9.4.6 *Chrysomya* Species

On the South American continent several *Chrysomya* species have been described (e.g., *C. albiceps*, *C. putoria*, *C. rufifacies*, *C. megacephala*) (Grella et al. 2015). Their bodies appear uniformly green to violet-blue.

9.4.7 Lucilia Eximia

This species belongs to the group of so-called green bottle flies and induces a so-called facultative **wound myiasis** as is done by the cosmopolitan species *Lucilia sericata* (Figs. 9.6, 9.7, and 9.8).

9.4.8 *Wohlfartia* Species

These species attack many hosts besides humans, who after infestations may suffer from a so-called **furuncular myiasis** due to boil-like skin protrusions. They belong to the group of flesh flies. The females are larviparous deponing first stage larvae instead of eggs.

9.4.9 *Cordylobia anthropophaga*

Single specimens of this species have been discovered in Latin American regions in persons coming back from Africa (Suárez et al. 2018)—thus their spreading and propagation should be underway. The penetrated larvae induce a boil-like swelling = a so-called furuncular myiasis.

Fig. 9.6 Light micrograph of an adult *Lucilia* fly

Fig. 9.7 Light micrograph of a *Lucilia* larva

Fig. 9.8 Light micrograph of pupae of *Lucilia* sp.

9.4.10 *Sarcophaga haemorrhoidales* (Syn *S. cruentata*)

This is one of the most common species being involved in human myiasis. It is spread worldwide except for parts of Australasia (Fig. 9.9).

9.5 Treatment of Human Myiasis

9.5.1 Mechanical Removal

The larvae of the different species can be removed from their "bore hollow" by squeezing, during which the abdominal region of the larva will appear and thus can be removed by use of a forceps. However, in most cases, bacterial superinfections occur, which must be treated by application of antibiotics after removal of the larva.

Fig. 9.9 Macrophoto of an adult *Sarcophaga* fly and a pupa. Typical are the dorsal stripes. Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

9.5.2 Chemical Control Measurements

It is important to keep the number of flies low inside and close to human dwellings. The method of choice is the use of products that block the larval development by spraying growth inhibitors on potential fly breeding sites (e.g., cyromazine, diflubenzuron, methoprene among several others, which have to be used in combination). So-called glueing catcher products are especially helpful to decrease the number of flies and other aggressive insects in homes in addition to the use of nets in front of windows.

9.5.3 Sterile Male Insect Technique

In the year 1957 started in South America a program to sterilize male flies based on the successful action in North and Central America (Wyss 2000) followed by a program rearing mass production and sterilization of males being set free thus decreasing the production of fertile eggs and progeny by females (Concha et al. 2016). However, due to the large amounts of untreated males, the amount of females bearing the stages remain still high and treatment phases must go on consequently as well as self-protection activities (e.g., use of repellents and body covers, etc.).

9.5.4 Use of Living Larvae to Clean Infected Wounds

As shown above (e.g., Masiero et al. 2020; Mehlhorn 2016a, b) a broad spectrum of flies deposit their eggs/larvae on wounds of animals and humans in order to feed thereon considerable amounts of tissues. During feeding, they induce massive amounts of inflammations by spreading bacteria, which often have developed resistances against common antibiotics. Thus efforts had been done to produce clean fly larvae, which are placed onto contaminated wounds. They start feeding there, which leads to elimination of bacteria from the wound surface (Masiero et al. 2020). However, the permanent movements of the feeding larvae are not very agreeable, so that it was looked for further methods.

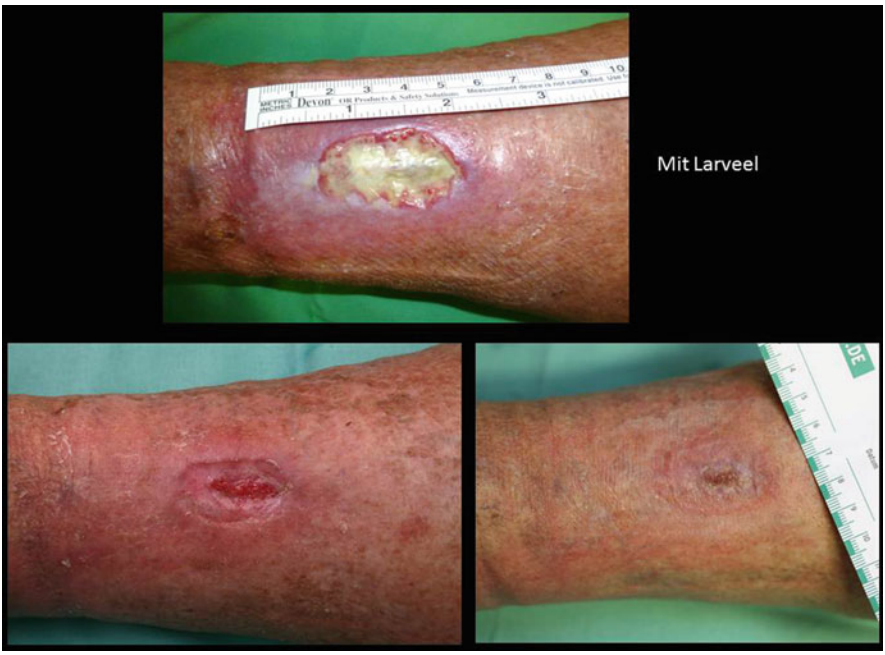


Fig. 9.10 Macrophoto of a wound at the beginning of treatment with Larveel® (above) and healing stages (below) starting from the left. The cleaning of the wound can also be done by living larvae, which, however, takes much longer and induces at bad feeling at all

9.5.5 Larveel®—A Powder Obtained from Fly Maggots to Heal Non-healing Wounds

The university spin-off company Alpha-Biocare GmbH (Neuss, Germany) has developed an ultrafine, sterile powder obtained from laboratory-grown, sterile fly maggots of the fly *Lucilia sericata* (trade name Larveel®). If this powder is diluted in sterile water and dropped onto non-healing wounds of humans and animals, a rather thin film layer is formed on the wounds. If these wounds become covered using a sterile plastic wound cover, the Larveel® layer with the bacteria becomes fixed at the plaster and thus the agents of disease become removed from the wound. This process is repeated every 3 days, the wound starts closing from the periphery and is finally fully closed (Fig. 9.10).

9.5.6 Manual Removal of Fly Larvae from Skin

The manual removal of such larvae from the skin is difficult, since they stick mostly rather deep in the skin of humans and animals. Furthermore, the surface of the larvae is equipped with numerous, retrograde orientated hooks, which fix them in the skin. Therefore it is recommended to proceed as follows in cases of furuncular myiasis:

1. One method is to cover the opening of the furuncular protrusion with a layer of paraffine in order to inhibit the entrance of oxygen into the larva-containing hollow. As consequence of the lack of oxygen, the larva will move to the opening and thus can be taken and removed by help of a forceps.
2. Another (somewhat rustical) method is to cover the larva-containing opening by a piece of bacon, so that the larva lacks oxygen and will enter the bacon, from where it can be removed mechanically without problems.
3. A third method of larval removal is to fill the cavity of the hollow with oil. This also will lead to the fact that the larva leaves the hollow and thus can be easily removed by help of a forceps.

9.5.7 Prevention

To avoid invasion of adult flies that could depone eggs on bodies or special place, it is recommended to clean sites where females could depone their eggs. This could be done by placing fly nets before windows, cleaning tables contaminated by food, establishing electric fly killers, etc.

9.5.8 Chemical Elimination

Specialists could spray products onto walls that contain registered chemicals like cyfluthrin, fenfluthrin, propoxur, pyrethrum, etc.

References

Alvarez Garcia DM, Pérez-Hérazo A, Amat E (2017) Life history of *Cochliomyia macellaria* (Fabricius, 1775) (Diptera, Calliphoridae), a blowfly of medical and forensic importance. Neotrop Entomol 46:606–612

Concha C, Palavesam A, Guerrero FD, Sagel A, Li F, Osborne JA, Hernandez Y, Pardo T, Quintero G, Vasquez M, Keller GP, Phillips PL, Welch JB, McMillan WO, Skoda SR, Scott MJ (2016) A transgenic male-only strain of the New World screwworm for an improved control program using the sterile insect technique. BMC Biol 14(1):72

das Neves JH, Carvalho N, Amarante AF (2015) *Dermatobia hominis*: potential risk of resistance to macrocyclic lactones. Vet Parasitol 212:483–486

Francesconi F, Lupi O (2012) Myiasis. Clin Microbiol Rev 25:79–105

Goddard J (2003) Physician's guide to arthropods of medical importance, 4th edn. CRC Press, Boca Raton, London, New York

Grella MD, Savino AG, Paulo DF, Mendes FM, Azeredo-Espin AM, Queiroz MM, Thyssen PJ, Linhares AX (2015) Phenotypic polymorphism of *Chrysomya albiceps* (Wiedemann) (Diptera: Calliphoridae) may lead to species misidentification. Acta Trop 141(Pt A):60–72

Hall MJR, Smith KGV (1995) Diptera causing myiasis in man. In: Lane RP, Crosskey RW (eds) Medical insects and arachnids. Chapman & Hall, London

Masiero FS, Aguiar ESV, Pereira DIB, Thyssen PJ (2020) First report on the use of larvae of *Cochliomyia macellaria* (Diptera: Calliphoridae) for wound treatment in veterinary practice. J Med Entomol 57:965–968

Mehlhorn H (ed) (2016c) Encyclopedia of parasitology, vol 3 volumes, 4th edn. Springer, Berlin, Heidelberg, New York
Muñoz AAF, Caceres AFB, León JCP (2020) First report of myiasis in dogs caused by *Cochliomyia hominivorax* (Coquerel 1858) in Colombia. Vet Parasitol Reg Stud Reports 19:100356
Oliveira PC, Almeida GPS, Cardoso JD, Tavares RB, Fernandes JI, Correia TR, Verocai GG, Scott FB (2019) Efficacy of sarolaner on the treatment of myiasis caused by *Cochliomyia hominivorax* (Diptera: Calliphoridae) in dogs. Vet Parasitol 276:108966
Singh A, Singh Z (2015) Incidence of myiasis among humans-a review. Parasitol Res 114:3183–3199
Suárez JA, Ying A, Orillac LA, Cedeño I, Sosa N (2018) First case of furuncular myiasis due to *Cordylobia anthropophaga* in a Latin American resident returning from Central African Republic. Braz J Infect Dis 22:70–73
Wyss JH (2000) Screwworm eradication in the Americas. Ann N Y Acad Sci 916:186–193

Further Reading

Abdel-Hafeez EH, Mohamed RM, Belal US, Atiya AM, Takamoto M, Aosai F (2015) Human wound myiasis caused by *Phormia regina* and *Sarcophaga haemorrhoidalis* in Minia governorate. Egypt Parasitol Res 114(10):3703–3709
Abdo EN, Sette-Dias AC, Comunian CR, Dutra CE, Aguiar EG (2006) Oral myiasis: a case report. Med Oral Patol Oral Cir Bucal 11(2):E130–E131
Abraham LS, Azulay-Abulafia L, Aguiar Dde P, Torres F, Argenziano G (2011) Dermoscopy features for the diagnosis of furuncular myiasis. An Bras Dermatol 86:160–162
Alexander JO (1984) Arthropods and human skin. Springer, Berlin. chapter 8
Alvarez Garcia DM, Pérez-Hérazo A, Amat E (2019) Spatial and temporal variation of the blowflies community (Diptera: Calliphoridae) from an urban area in northern South America. J Med Entomol 56:464–471
Amendt J, Campobasso CP, Gaudry E, Reiter C, LeBlanc HN, Hall MJ (2007) Best practice in forensic entomology—standards and guidelines. Int J Legal Med 121:90–104
Avni-Magen N, Eshar D, Friedman M, Kirmayer D, Letschert L, Gati I, Kaufman E, Paz A, Lavy E (2018) Retrospective evaluation of a novel sustained-release ivermectin varnish for treatment of wound myiasis in zoo-housed animals. J Zoo Wildl Med 49:201–205
Badenhorst R, Villet MH (2018) The uses of *Chrysomya megacephala* (Fabricius, 1794) (Diptera: Calliphoridae) in forensic entomology. Forensic Sci Res 3:2–15
Bangsgaard R, Holst B, Krogh E, Heegaard S (2000) Palpebral myiasis in a Danish traveler caused by the human bot-fly (*Dermatobia hominis*). Acta Ophthalmol Scand 78:487–489
Batista-da-Silva JA, Moya-Borja GE, Queiroz MM (2011) Factors of susceptibility of human myiasis caused by the new world screwworm, *Cochliomyia hominivorax* in Sao Goncalo, Rio de Janeiro, Brazil. J Insect Sci 11:1–7
Bauer A, Bauer AM, Tomberlin JK (2020) Impact of diet moisture on the development of the forensically important blow fly *Cochliomyia macellaria* (Fabricius) (Diptera: Calliphoridae). Forensic Sci Int 312:110333
Baumgartner DL (1993) Review of *Chrysomya rufifacies* (Diptera: Calliphoridae). J Med Entomol 30:338–352
Bedini S, Guarino S, Echeverria MC, Flamini G, Ascrizzi R, Loni A, Conti B (2020) *Allium sativum*, *Rosmarinus officinalis*, and *Salvia officinalis* essential oils: a spiced shield against blowflies. Insects 11(3):143
Bernardes Filho F, Martins G, Barbará EF, Paiva ML, Coelho Filho RL, Nery JA (2014) Dermoscopy as an auxiliary tool for the diagnosis of furuncular myiasis. An Bras Dermatol 89:663–665

Biale H, Geden CJ, Chiel E (2017) Effects of pyriproxifen on wild populations of the house fly, *Musca domestica*, and compatibility with its principal parasitoids. Pest Manag Sci 73:2456–2464

Blaizot R, Vanhecke C, Le Gall P, Duvignaud A, Receveur MC, Malvy D (2018) Furuncular myiasis for the Western dermatologist: treatment in outpatient consultation. Int J Dermatol 57: 227–230

Boatright SA, Tomberlin JK (2010) Effects of temperature and tissue type on the development of *Cochliomyia macellaria* (Diptera: Calliphoridae). J Med Entomol 47:917–923

Boggild AK, Keystone JS, Kain KC (2002) Furuncular myiasis: a simple and rapid method for extraction of intact *Dermatobia hominis* larvae. Clin Infect Dis 35:336–338

Bongiorno MR, Pistone G, Aricò M (2007) Myiasis with *Dermatobia hominis* in a Sicilian traveller returning from Peru. Travel Med Infect Dis 5:196–198

Bowles VM, Meeusen EN, Young AR, Andrews AE, Nash AD, Brandon MR (1996) Vaccination of sheep against larvae of the sheep blowfly (*Lucilia cuprina*). Vaccine 14:1347–1352

Braverman I, Dano I, Saah D, Gapany B (1994) Aural myiasis caused by flesh fly larva, *Sarcophaga haemorrhoidalis*. J Otolaryngol 23:204–205

Brewer TF, Wilson ME, Gonzalez E, Felsenstein D (1993) Bacon therapy and furuncular myiasis. JAMA 270:2087–2088

Brundage A, Bros S, Honda JY (2011) Seasonal and habitat abundance and distribution of some forensically important blow flies (Diptera: Calliphoridae) in Central California. Forensic Sci Int 212:115–120

Byrd JH, Butler JF (1998) Effects of temperature on *Sarcophaga haemorrhoidalis* (Diptera: Sarcophagidae) development. J Med Entomol 35:694–698

CABI (2018) *Cochliomyia hominivorax*. In: Invasive species compendium. Available from: www.cabi.org/isc/datasheet/11753

Calvo LM, Suárez MM, Apolinario RM, Martín AM (2005) Larvae in the external auditory canal and nasal fossae of an alcoholic patient. Enferm Infecc Microbiol Clin 23:323–324

Calvopina M, Ortiz-Prado E, Castañeda B, Cueva I, Rodriguez-Hidalgo R, Cooper PJ (2020) Human myiasis in Ecuador. PLoS Negl Trop Dis 14(2):e0007858

Cardoso SV, Ramadinha RR (2007) Evaluation of myiasis treatment in dogs using nitenpyram. Rev Bras Cien Vet 14:139–142

Carvalho CJB, Cad M-P (2008) Key to the adults of the most common forensic species of Diptera in South America. Revista Brasileira de Entomologia 52:390–340

Clyti E, Nacher M, Merrien L, El Guedj M, Roussel M, Sainte-Marie D, Couppié P (2007) Myiasis owing to *Dermatobia hominis* in a HIV-infected subject: treatment by topical ivermectin. Int J Dermatol 46:52–54

Correia TR, Scott FB, Verocai GG, Souza CP, Fernandes JI, Melo RM, Vieira VP, Ribeiro FA (2010) Larvicidal efficacy of nitenpyram on the treatment of myiasis caused by *Cochliomyia hominivorax* (Diptera: Calliphoridae) in dogs. Vet Parasitol 173:169–172

Costa-Júnior LM, Chaves DP, Brito DRB, Santos VAFD, Costa-Júnior HN, Barros ATM (2019) A review on the occurrence of *Cochliomyia hominivorax* (Diptera: Calliphoridae) in Brazil. Rev Bras Parasitol Vet 28:548–562

da Silva BB, Borges US, Pimentel IC (2005) Human vaginal myiasis caused by *Cochliomyia hominivorax*. Int J Gynaecol Obstet 89:152–153

da Silva BF, Bassetto CC, do Amarante AF (2012) Epidemiology of *Oestrus ovis* (Diptera: Oestridae) in sheep in Botucatu, state of Sao Paulo. Rev Bras Parasitol Vet 21:386–390

Deak G, Ionică AM, Nădășan-Cozma G, Mihalca AD (2020) *Dermatobia hominis* in a dog imported from Brazil to Romania. Parasit Vectors 13(1):386

Delshad E, Rubin AI, Almeida L, Niedt GW (2008) *Cuterebra* cutaneous myiasis: case report and world literature review. Int J Dermatol 47:363–366

Di Tullio F, Mandel VD, Miglietta R, Pellacani G (2019) Cutaneous myiasis in a traveler returning from Argentina. Dermatol Ther 32(5):e12996

Dufek MI, Oscherov EB, Damborsky MP, Mulieri PR (2019) Calliphoridae (Diptera) in human-transformed and wild habitats: diversity and seasonal fluctuations in the humid Chaco ecoregion of South America. J Med Entomol 56:725–736

Dunphy L, Sood V (2019) *Dermatobia hominis* 'the human botfly' presenting as a scalp lesion. BMJ Case Rep 12(3):e228310

Failoc-Rojas VE, Molina-Ayasta C, Salazar-Zuloeta J, Samamé A, Silva-Díaz H (2018) Case report: Myiasis due to *Cochliomyia hominivorax* and *Dermatobia hominis*: clinical and pathological differences between two species in northern Peru. Am J Trop Med Hyg 98:150–153

Farias LABG, Teixeira MJ, Pires Neto RDJ (2020) Palpebral myiasis due *Cochliomyia macellaria* in an alcoholic patient. Rev Soc Bras Med Trop 54:e20200168

Faridnia R, Soosaraei M, Kalani H, Fakhar M, Jokelainen P, Zolfaghari Emameh R, Banimostafavi ES, Ziaei Hezarjaribi H (2019) Human urogenital myiasis: a systematic review of reported cases from 1975 to 2017. Eur J Obstet Gynecol Reprod Biol 235:57–61

Fonseca-Muñoz A, Pérez-Pacheco R, Ortega-Morales BO, Reyes-Estebanez M, Vásquez-López A, Chan-Bacab M, Ruiz-Vega J, Granados-Echegoyen CA (2019) Bactericidal activity of *Chrysomya rufifacies* and *Cochliomyia macellaria* (Diptera: Calliphoridae) larval excretions-secretions against *Staphylococcus aureus* (Bacillales: Staphylococcaceae). J Med Entomol 56: 1598–1604

Franca-Rodriguez ME, de Calistro TC, Freyre A, Toyos R (1977) *Fannia* sp., vector de *Dermatobia hominis* encontrado en Uruguay. AnFac Quim Urug 1977:103–110

Fresia P, Silver M, Mastrangelo T, De Azeredo-Espin AM, Lyra ML (2014) Applying spatial analysis of genetic and environmental data to predict connection corridors to the New World screwworm populations in South America. Acta Trop 138(Suppl):S34–S41

Gaci R, Delord M, Parola P, Brouqui P, Lagier JC (2015) Extended perineal *Dermatobia hominis* myiasis in a traveler returning from South America. JAMA Dermatol 151:1389–1390

Garbeloto E, de Souza-Trinidade B, Alvez-Canal F (2013) Genital and breast myiasis: case series. J Trop Med Parasitol 36:98–104

García-Cubillana de la Cruz JM, Mingo Regúlez J, Blanco Villero JM, Iravedra Gutiérrez JA (2009) A slow developing abscess. Dermatobia hominis. An Pediatr (Barc) 71:175–176

Gassel M, Wolf C, Noack S, Williams H, Ilg T (2014) The novel isoxazoline ectoparasiticide fluralaner: selective inhibition of arthropod γ-aminobutyric acid- and L-glutamate-gated chloride channels and insecticidal/acaricidal activity. Insect Biochem Mol Biol 45:111–124

Gazi U, Taylan-Ozkan A, Mumcuoglu KY (2020) The effect of *Lucilia sericata* larval excretion/secretion (ES) products on cellular responses in wound healing. Vet Entomol. https://doi.org/10.1111/mve.12497

González Fernández D, Valdés Pineda F, Gómez de Castro C, Vázquez-López F (2015) Furuncular myiasis due to *Dermatobia hominis*. Med Clin (Barc) 144:50

Graczyk TK, Knight R, Gilman RH, Cranfield MR (2001) The role of non-biting flies in the epidemiology of human infectious diseases. Microbes Infect 3:231–235

Grube E (1860) Beschreibung einer Oestridenlarve aus der Haut des Menschen (Description of an oestrid larva in the skin of humans). Arch Naturgesch 26:9–16

Gunn A, Bird J (2011) The ability of the blowflies *Calliphora vomitoria* (Linnaeus), *Calliphora vicina* (rob-Desvoidy) and *Lucilia sericata* (Meigen) (Diptera: Calliphoridae) and the muscid flies *Muscina stabulans* (Fallén) and *Muscina prolapsa* (Harris) (Diptera: Muscidae) to colonise buried remains. Forensic Sci Int 207:198–204

Hale AJ, Mathison B, Pritt B, Collins K (2019) Endemic bot fly larvae infection in northern New York state. IDCases 16:e00531

Han HS, Sharma R, Jeffery J, Noli C (2017) *Chrysomya bezziana* (Diptera: Calliphoridae) infestation: case report of three dogs in Malaysia treated with spinosad/milbemycin. Vet Dermatol 28(2):239–e62

Haruki K, Hayashi T, Kobayashi M, Katagiri T, Sakurai Y, Kitajima T (2005) Myiasis with *Dermatobia hominis* in a traveler returning from Costa Rica: review of 33 cases imported from South America to Japan. J Travel Med 12:285–288

Hassan MU, Khan MN, Abubakar M, Waheed HM, Iqbal Z, Hussain M (2010) Bovine hypodermosis—a global aspect. Trop Anim Health Prod 42:1615–1625
Hochedez P, Caumes E (2008) Common skin infections in travelers. J Travel Med 15:252–262
Hohenstein EJ, Buechner SA (2004) Cutaneous myiasis due to *Dermatobia hominis*. Dermatology 208:268–270
Hope FW (1840) On insects and their larvae occasionally found in the human body. Trans R Entomol Soc London 2:256–272
Ireland S, Turner B (2006) The effects of larval crowding and food type on the size and development of the blowfly, *Calliphora vomitoria*. Forensic Sci Int 159:175–181
James MT (1947) Screwworm fly *Chrysomya beziana*. USDA Misc Publ 631
Jellinek T, Nothdurft HD, Rieder N, Löscher T (1995) Cutaneous myiasis. Int J Dermatol 34:624–626
Jervis-Bardy J, Fitzpatrick N, Masood A, Crossland G, Patel H (2015) Myiasis of the ear: a review with entomological aspects for the otolaryngologist. Ann Otol Rhinol Laryngol 124:345–350
Khoobdel M, Sobati H, Dehghan O, Akbarzadeh K, Radi E (2019) Natural host preferences of parasitoid wasps (hymenoptera: Pteromalidae) on synanthropic flies. Eur J Transl Myol 29(2): 8197
Kovaleva A, Climent PC, Bécares CV, Martín Azaña MJ, Irishina N, Goy EI (2013) Urogenital myiasis by *Cordylobia anthropophaga*. J Pediatr Adolesc Gynecol 26(6):e123–e125
Krönert C, Wollina U (2009) Painful, slow developing abscesses. Furuncular miyasis due to double skin infestation by *Dermatobia hominis*. J Dermatol Case Rep 3:24–26
Kuşcu F, Özsoy KM, Ulu A, Kurtaran B, Kömür S, İnal AS, Taşova Y, Aksu HSZ (2017) Furuncular myiasis caused by *Dermatobia hominis* in a traveler returning from the Amazon jungle. Turkiye Parazitol Derg 41:173–176
Landehag J, Skogen A, Åsbakk K, Kan B (2017) Human myiasis caused by the reindeer warble fly, *Hypoderma tarandi*, case series from Norway, 2011 to 2016. Euro Surveill 22(29):30576
Li XY, Pape T, Zhang D (2019) Taxonomic review of *Gasterophilus* (Oestridae, Gasterophilinae) of the world, with updated nomenclature, keys, biological notes, and distributions. Zookeys 891: 119–156
Lia RP, Rehbein S, Giannelli A, Fankhauser B, Otranto D (2019) Longrange® (eprinomectin 5% w/v extended-release injection) efficacy against *Hypoderma lineatum* in an endemic area in southern Italy. Parasit Vectors 12(1):231
Lindsay SW, Lindsay TC, Duprez J, Hall MJ, Kwambana BA, Jawara M, Nurudeen IU, Sallah N, Wyatt N, D'Alessandro U, Pinder M, Antonio M (2012) *Chrysomya putoria*, a putative vector of diarrheal diseases. PLoS Negl Trop Dis 6(11):e1895
Logar J, Marinic-Fiser N (2000) Cutaneous myiasis caused by *Hypoderma lineatum*. Wiener Klin Wschr 120:619–621
Lopes-Costa PV, dos Santos AR, Pereira-Filho JD, da Silva BB (2008) Myiasis in the uterine cavity of an elderly woman with a complete uterine prolapse. Trans R Soc Trop Med Hyg 102:1058–1060
López Millán C, Olea MS, Dantur Juri MJ (2015) Unusual presence of *Ornidia robusta* (Diptera: Syrphidae) causing pig myiasis in Argentina. Parasitol Res 114:4731–4735
Ly P, Aizenberg A, Martin T, Lopez M, Arturo Saldaña M, Hughes GL, Cabada MM (2018) Intestinal myiasis caused by *Sarcophaga* spp. in Cusco, Peru: a case report and review of the literature. Case Rep Infect Dis 2018:3685439
MacInnis AE, Higley LG (2020) Competition among three forensically important blow fly species (Diptera: Calliphoridae): *Phormia regina*, *Lucilia sericata*, and *Chrysomya rufifacies*. Environ Entomol 49:1473–1479
Maier H, Hönigsmann H (2004) Furuncular myiasis caused by *Dermatobia hominis*, the human botfly. J Am Acad Dermatol 50(2 Suppl):S26–S30
Marquez AT, Mattos MD, Nascimento SB (2007) Myiasis associated with some socioeconomic factors in five urban areas of the state of Rio de Janeiro. Rev Soc Bras Med Trop 40:175–180

Martínez-Hernández F, Vega-Memije ME, Villalobos G, Perez-Rojas D, Asz-Sigall D, Rivas N, Alejandre R, Maravilla P, Valdovinos MR (2019) Myiasis caused by *Dermatobia hominis* in Mexico: morphological and molecular identification using the cytochrome oxidase I gene. Rev Inst Med Trop Sao Paulo 61:e45

Martínez-Rojano H, Noguez JC, Huerta H (2018) Nosocomial myiasis caused by *Lucilia sericata* (Diptera: Calliphoridae) and neonatal myiasis by *Sarcophaga* spp. (Diptera: Sarcophagidae) in Mexico. Case Rep Infect Dis 2018:5067569

Massey RL, Rodriguez G (2002) Human scrotal myiasis due to *Dermatobia hominis*. Urol Nurs 22: 1397–1398

McGarry JW (2014) Tropical myiases: neglected and well travelled. Lancet Infect Dis 14:672–674

McGraw TA, Turiansky GW (2008) Cutaneous myiasis. J Am Acad Dermatol 58(907–926):quiz 927-929

Mehlhorn H (2016a) Animal parasites: Diagnosis, treatment, prevention. Springer International, Switzerland

Mehlhorn H (2016b) Human parasites: diagnosis, treatment, prevention. Springer International, Switzerland

Meira LMR, Barbosa TM, Jales JT, Santos AN, Gama RA (2020) Insects associated to crime scenes in the northeast of Brazil: consolidation of collaboration between entomologists and criminal investigation institutes. J Med Entomol 57:1012–1020

Menghi CI, Gatta CL, Oliva A (2010) Otomyiasis by *Cochliomyia hominivorax* in two children from the outskirts of Buenos Aires, Argentina. Rev Argent Microbiol 42:176–178

Missotten GS, Kalpoe JS, Bollemeijer JG, Schalij-Delfos NE (2008) Myiasis of the upper eyelid. J AAPOS 12:516–517

Moya-Borja GE, Muniz RA, Sanavria A, Goncalves LC, Rew RS (1993) Therapeutic and persistent efficacy of doramectin against *Dermatobia hominis* in cattle. Vet Parasitol 49:85–93

Mulieri PR, Patitucci LD (2019) Using ecological niche models to describe the geographical distribution of the myiasis-causing *Cochliomyia hominivorax* (Diptera: Calliphoridae) in southern South America. Parasitol Res 118:1077–1086

Murali A, Kannan R, Srinivasan N, Kumar JS (2010) Intestinal Myiasis: all worms in the stool are not worms! Infect Dis Clin Pract 18:65–66

Nascimento EMF, Oliveira JB, Paes MJ, Lobo AP, Silva ALA, Júnior ERS, Leal JLF, Moya Borja GE (2005) Miíases humanas por *Cochliomyia hominivorax* (Coquerel, 1858) (Diptera, Calliphoridae) em hospitais públicos na cidade do Recife, Pernambuco, Brasil. Entomol y Vectores 12:37–51

Nassu MP, Thyssen PJ (2015) Evaluation of larval density Cochliomyia macellaria F. (Diptera: Calliphoridae) for therapeutic use in the recovery of tegumentar injuries. Parasitol Res 114: 3255–3260

Navajas A, Cardenal I, Piñan MA, Ortiz A, Astigarraga I, Fdez-Teijeiro A (1998) Hypereosinophilia due to myiasis. Acta Haematol 99(1):27–30

Neel WW, Urbina O, Viale E, de Alba J (1955) Combate del torsalo *Dermatobia hominis* (L. Jr.) por medio de insecticidas en Turrialba, Costa Rica. Turrialba 5(4):139–146

Niederegger S, Wartenberg N, Spiess R, Mall G (2013) Influence of food substrates on the development of the blowflies *Calliphora vicina* and *Calliphora vomitoria* (Diptera, Calliphoridae). Parasitol Res 112:2847–2853

Olea MS, Centeno N, Aybar CA, Ortega ES, Galante GB, Olea L, Juri MJ (2014) First report of myiasis caused by *Cochliomyia hominivorax* (Diptera: Calliphoridae) in a diabetic foot ulcer patient in Argentina. Korean J Parasitol 52:89–92

Olsen J, Nejsum P, Jemec GBE (2017) *Dermatobia hominis* misdiagnosed as abscesses in a traveler returning from Brazil to Denmark. Acta Dermatovenerol Alp Pannonica Adriat 26:43–44

Olumide YM (1994) Cutaneous myiasis: a simple and effective technique for extraction of *Dermatobia hominis* larva. Int J Dermatol 33:148–149

Paloschi GC, Ramos CI, de Souza AP (1991) Vetores de ovos de *Dermatobia hominisno* planalto catarinense. Pesqui Agropeu Brasil 26:1872–1883

Panadero-Fontán R, Otranto D (2015) Arthropods affecting the human eye. Vet Parasitol 208:84–93

Panu F, Cabras G, Contini C, Onnis D (2000) Human auricolar myiasis caused by *Wohlfartia magnifica* (Schiner) (Diptera: Sarcophagidae): first case found in Sardinia. J Laryngol Otol 114: 450–452

Paquette C, Garant D, Savage J, Réale D, Bergeron P (2020) Individual and environmental determinants of *Cuterebra* bot fly parasitism in the eastern chipmunk (*Tamias striatus*). Oecologia 193:359–370

Pascoal G, Oliveira FQ, Siqueira RR, Lopes MG, Martins Neto MP, Gamonal AC (2016) Excision of furuncular myiasis larvae using a punch: a simple, practical and aesthetic method. An Bras Dermatol 91:358–361

Passos MR, Varella RQ, Tavares RR, Barreto NA, Santos CC, Pinheiro VM, Bravo RS, Morelhi MH (2002) Vulvar myiasis during pregnancy. Infect Dis Obstet Gynecol 10:153–158

Passos MR, Ferreira DC, Arze WN, Silva JC, Passos FD, Curvelo JA (2008) Penile myiasis as a differential diagnosis for genital ulcer: a case report. Braz J Infect Dis 12(2):155–157

Pezzi M, Bonacci T, Leis M, Mamolini E, Marchetti MG, Krčmar S, Chicca M, Del Zingaro CNF, Faucheux MJ, Scapoli C (2019) Myiasis in domestic cats: a global review. Parasit Vectors 12(1):372

Philippi RA (1861) Beschreibung einer neuen Fliegenart, deren Larven in der Nase und Stirnhöhle einer frau gelebt haben (description of a new fly species, the larvae of which lived inside the nose and frontal sinus of a woman) (German). Z Ges Naturwiss (Halle, Germany) 17:161–175

Puente S, Otranto D, Panadero R, Herrero MD, Rivas P, Ramírez-Olivencia G, Mariscal C Jr, Perteguer MJ, Díez-Baños P, Gárate T (2010) First diagnosis of an imported human myiasis caused by *Hypoderma sinense* (Diptera: Oestridae), detected in a European traveler returning from India. J Travel Med 17(6):419–423

Quintanilla-Cedillo MR, León-Ureña H, Contreras-Ruiz J, Arenas R (2005) The value of Doppler ultrasound in diagnosis in 25 cases of furunculoid myiasis. Int J Dermatol 44:34–37

Ragi SD, Kapila R, Schwartz RA (2021) The botfly, a tropical menace: a distinctive myiasis caused *by Dermatobia hominis*. Am J Clin Dermatol 22:81–88

Rodríguez-Hidalgo R, Tapia-Chiriboga A, Arciniegas S, Vanwambeke SO, Benítez-Ortiz W (2019) Epidemiological analysis of the New World screwworm (*Cochliomyia hominivorax*) in Ecuador. Transbound Emerg Dis 66:968–977

Rogers EKB, Franklin D, Voss SC (2021) Dietary effects on the development of *Calliphora dubia* and *Chrysomya rufifacies* (Diptera: Calliphoridae): implications for postmortem interval. J Med Entomol 58:79–87

Rossi MA, Zucoloto S (1973) Fatal cerebral myiasis caused by the tropical warble fly, *Dermatobia hominis*. Am J Trop Med Hyg 22:267–269

Rutland BE, Byl KM, Hydeskov HB, Miniter B, Johnson CA (2017) Systemic manifestations of *Cuterebra* infection in dogs and cats: 42 cases (2000-2014). Am Vet Med Assoc 251:1432–1438

Sancho E (1988) Human botfly. Parasitol Today 4:242–246

Sanford MR, Whitworth TL, Phatak DR (2014) Human wound colonization by *Lucilia eximia* and *Chrysomya rufifacies* (Diptera: Calliphoridae): myiasis, perimortem, or postmortem colonization? J Med Entomol 51:716–719

Schwartz E, Gur H (2002) *Dermatobia hominis* myiasis: an emerging disease among travellers to the Amazon basin of Bolivia. J Travel Med 9:97–99

Singh TS, Rana D (1989) Urogenital myiasis caused by *Megaselia scalaris* (Diptera: Phoridae): case report. J Med Entomol 26:228–229

Sivelli P, Vinciguerra R, Tondini L, Cavalli E, Galli A, Chelazzi P, Donati S, Bartalena L, Grossi P, Azzolini C (2015) Eyelid myiasis caused by *Cordylobia anthropophaga*. Ocul Immunol Inflamm 23:259–260

Smith SM (2015) Treating infestations of the human botfly, *Dermatobia hominis*. Lancet Infect Dis 15:512

Solomon M, Lachish T, Schwartz E (2016) Cutaneous myiasis. Curr Infect Dis Rep 18(9):28
Tamir J, Haik J, Orenstein A, Schwartz E (2003) *Dermatobia hominis* myiasis among travelers returning from South America. J Am Acad Dermatol 48:630–632
Tay SY, Ramasamy BR, Watson DA, Montoya M (2018) Treatment of nasal myiasis with ivermectin irrigation. BMJ Case Rep 2018:bcr2017224142
Thyssen PJ, Nassu MP, Costella AM, Costella ML (2012) Record of oral myiasis by *Cochliomyia hominivorax* (Diptera: Calliphoridae): case evidencing negligence in the treatment of incapable. Parasitol Res 111:957–959
Tsuda S, Nagaji J, Kurose K, Miyasato M, Sasai Y, Yoneda Y (1996) Furuncular cutaneous myiasis caused by *Dermatobia hominis* larvae following travel to Brazil. Int J Dermatol 35:121–123
Udgaonkar US, Dharamsi R, Kulkarni SA, Shah SR, Patil SS, Bhosale AL, Gadgil SA, Mohite RS (2012) Intestinal myiasis. Indian J Med Microbiol 30:332–337
Vijay K, Kalapos P, Makkar A, Engbrecht B, Agarwal A (2013) Human botfly (*Dermatobia hominis*) larva in a child's scalp mimicking osteomyelitis. Emerg Radiol 20:81–83
Villalobos G, Vega-Memije ME, Maravilla P, Martinez-Hernandez F (2016) Myiasis caused by *Dermatobia hominis*: countries with increased risk for travelers going to neotropic areas. Int J Dermatol 55:1060–1068
Villamil-Gómez WE, Cardona-Ospina JA, Prado-Ojeda JS, Hernández-Prado H, Figueroa M, Causil-Morales PN, Pérez-Reyes K, Palechor-Ocampo LA, Rodríguez-Morales AJ (2019) Pin-site myiasis caused by screwworm fly in nonhealed wound, Colombia. Emerg Infect Dis 25:379–380
Wakamatsu TH, Pierre-Filho PT (2006) Ophthalmomyiasis externa caused by *Dermatobia hominis*: a successful treatment with oral ivermectin. Eye 20:1088
Wells JD, Kurahash H (1994) *Chrysomya megacephala* (Fabricius) (Diptera: Calliphoridae) development: rate, variation, and the implications for forensic entomology. Jpn J Sanit Zool 45:303–309
West JK (2013) Simple and effective field extraction of human botfly, *Dermatobia hominis*, using a venom extractor. Wilderness Environ Med 24:17–22
Wohlfahrt D, Woolf MS, Singh B (2020) A survey of bacteria associated with various life stages of primary colonizers: *Lucilia sericata* and *Phormia regina*. Sci Justice 60:173–179
Yazar S, Ozcan H, Dinçer S, Sahin I (2002) Vulvar myiasis. Yonsei Med J 43:553–555
Zhang B, Huang H, Wang H, Zhang D, Chu H, Ma X, Ge Y, Ente M, Li K (2018) Genetic diversity of common *Gasterophilus* spp. from distinct habitats in China. Parasit Vectors:11:474
Zhou X, Kambalame DM, Zhou S, Guo X, Xia D, Yang Y, Wu R, Luo J, Jia F, Yuen M, Xu Y, Dai G, Li L, Xie T, Puthiyakunnon S, Wei W, Xie L, Liang S, Feng Y, Huang S, Hu Y, Mo Q, Mai R, Zhang X, Spradbery P, Zhou X (2019) Human *Chrysomya bezziana* myiasis: a systematic review. PLoS Negl Trop Dis 13(10):e0007391
Zumpt F (1963) The problem of intestinal myiasis in humans. S Afr Med J 37:305–307
Zumpt F (1965) Myiasis in man and animals in the old world. Butterworths, London

Schistosomiasis Control: Present Situation and Perspectives

10

Carlos Graeff-Teixeira and Otávio Sarmento Pieri

Abstract

Schistosomiasis mansoni is an infectious disease of poverty that affects over 2 million people in communities deprived of proper sanitation and safe water supply in Latin America; it is endemic in Brazil, which accounts for 90% of the cases, and Venezuela. This chapter shows that, although infection indices have progressively decreased in the last decades, elimination of this disease as a public health problem, pledged for 2030, will only be achieved with strong interdisciplinary and intersectoral efforts under the One Health approach targeted to the Sustained Development Goals.

Keywords

Schistosoma mansoni · Infection · Disease · Morbidity · Zoonosis · History · Distribution · Control guidelines · Prevalence · Diagnosis · Treatment · Snail control · Health education

C. Graeff-Teixeira (✉)
Department of Pathology, Infectious Diseases Unit, CCS, Federal University of Espirito Santo, Vitória, Brazil
e-mail: carlos.teixeira@ufes.br

O. S. Pieri
Laboratory of Environmental and Health Education, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, Brazil
e-mail: opieri@ioc.fiocruz.br

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_10

10.1 Parasite, Infection, and Disease

Schistosoma mansoni is a trematode flatworm living inside venous vessels in the portal-mesenteric systems. Oviposition occurs especially at sigmoid-rectal venous distal branches and eggs shall reach feces after a challenging migration facing inflammatory response, the physical barriers of a counter-current blood flow and the thickness of intestinal wall tissues (Colley et al. 2014). It is estimated that approximately only one-third of eggs reach the intestinal lumen and are released with feces in the environment (Cheever et al. 1994). Sanitation with proper handling of human excreta breaks the transmission cycle and it is a fundamental control measure (Sarvel et al. 2011).

Miracidia are ciliated multicellular larvae, and they hatch if eggs reach fresh water, but not saline water. They are infective to snails from *Biomphalaria* genus, especially *B. glabrata*, and their mobility and infectivity are highly dependent on temperature and water density. Miracidia usually survive for less than 1 day. If they penetrate the snail tegument, the parasite asexually reproduces with several generations of stages called sporocysts. Cercaria is the ultimate stage of development in snails and the infective stage for vertebrate hosts, that is released continuously by snails for weeks. The release is especially triggered by light, which explains the higher risk of infection from 10 a.m. to 4 p.m. (Nguyen et al. 2020).

Human infection is a consequence of skin exposure to cercaria-containing environmental water. The larvae lose their bifurcated tail and migrate through the skin and venous vessels to mature into worms inside portal-mesenteric venous system.

At any stage, most infected individuals are asymptomatic. Three main clinical manifestations may occur at the acute phase: (1) cercarial dermatitis; (2) febrile illness; (3) neuroschistosomiasis, only after oviposition begins. At each isolated cercaria penetration site, a localized dermatitis may manifest as pruritic papules with spontaneous remission after 7 days, popularly known as "swimmers' itch," with its typical distribution in skin areas submersed in contaminated waters. Cercaria from many other trematode species may similarly produce papular dermatitis. Another clinical manifestation within the acute phase may result from systemic hypersensitivity reaction to migrating worms and/or initial oviposition (few initial weeks/months). Sudden onset of a febrile illness, malaise, weakness, myalgia, non-productive cough, followed by unspecific abdominal symptoms and accompanied by blood eosinophilia. Chest imaging may disclose patchy scattered infiltrates suggestive of schistosomula migrating in the lungs. Patients usually spontaneously recover after 2–10 weeks. This "toxemic" febrile disease was named "Katayama's Fever," a more common and severe clinical manifestation of *Schistosoma japonicum* infections in Asia. These allergic reactions are usually more common and more severe within populations from non-endemic areas, either visiting endemic areas or after a recent introduction/re-emergence of the infection.

While pathogenesis is dominated by hypersensitivity reactions in acute phase, the chronic pathology is centered in eggs trapped in tissues with the granulomatous reaction and a dysfunctional fibrotic resolution. Clinical forms occurring in the chronic phase of schistosomiasis mainly affect intestines and the liver. Compromise

of liver and spleen may evolve to the classical hepatosplenic schistosomiasis with periportal fibrosis, leading eventually to portal hypertension and liver failure (Andrade and Bina 1983). Three main clinical syndromes are recognized in chronic schistosomiasis: (1) intestinal; (2) hepato-intestinal; (3) hepatosplenic (Brasil 2014).

Intestinal schistosomiasis is characterized by unspecific general symptoms (malaise, weakness, dizziness, headaches) diarrhea and dysenteric episodes (sometimes with blood in feces) and abdominal pain may indicate an affected large intestine. Colons may be painful at palpation. It is hard to rule out hepatic involvement and many authors avoid consideration of an isolated intestinal involvement.

Liver is enlarged and palpable in the right abdominal quadrant, with hard consistency and also a prominent left lobe, besides the manifestations of intestinal lesions in hepato-intestinal schistosomiasis. But liver function markers are normal and there is no jaundice.

Two key findings for definition of **hepatosplenic schistosomiasis** (HSS) are (1) periportal thickening due to fibrosis (Symmers pipe stem fibrosis); (2) portal hypertension and secondary spleen enlargement (Lambertucci 2014). Abdominal palpation shall be accompanied by ultrasound examination for a proper evaluation. It is important to differentiate other causes of hepatosplenomegaly, like visceral leishmaniasis, malaria, lymphoma, leukemia, infectious mononucleosis. Integrity of hepatic functions is a major criterion to classify HSS either as compensated or decompensated (e.g., hypoalbuminemia, hyperbilirubinemia). Patients gradually develop portal hypertension and start presenting bleeding from secondary gastro-esophageal varices, one main cause of death in schistosomiasis (Barbosa et al. 2016). Compensated HSS may exceptionally occur without portal hypertension, generally in children, who may also show growth retardation. Decompensated HSS is characterized by severe degradation of hepatic functions alongside the widespread deposition of fibrotic tissue in portal spaces, with reduction in size of the organ. Ascites, jaundice, and encephalopathy are three important consequences of hepatic failure.

HSS and other clinical forms may complicate after association with (1) many other organs affected by schistosomiasis: like lungs and kidney (glomerulonephritis); (2) other liver diseases: chronic active hepatitis, viral hepatitis B and C, non-infectious cirrhosis, portal thrombosis; (3) pseudo-neoplasic, tumoral inflammatory lesions; (4) co-morbidities: chronic *Salmonella* bacteremia, other enterobacteria bacteremia, soft tissues and liver abscesses, and immunosuppressive conditions (drugs, AIDS, HTLV) (Brasil 2014).

Transverse myelitis due to granulomatous reaction to eggs trapped in spinal venous plexus may produce lower limbs paralysis and anal/bladder sphincter dysfunctions. Neuroschistosomiasis is a severe complication arising at either acute or chronic phase of the infection and not necessarily associated with heavy egg burdens (Lambertucci et al. 2007; Ferrari et al. 2008).

With *S. mansoni* infection it is not expected a frequent presence of eggs and lesions in the genito-urinary tract, usually seen in Africa with *S. haematobium* infections. But genito-urinary schistosomiasis is a topic of interest for a raised awareness and proper screening of lesions affecting female and male reproductive

organs, what can lead to infertility and an increased risk for transmission of sexually transmitted diseases (Sturt et al. 2020).

Although it is true that classical severe morbidity depends on the number of eggs trapped in tissues and the chronicity of infection, there is evidence for a more subtle but debilitating and persistent disease, even with low egg numbers. The evidence coming from two robust metanalysis studies leads to the understanding that the highest burden of disease is produced by this "generalized morbidity" rather than the well-known "site specific morbidity" (King et al. 2005; King and Dangerfield-Cha 2008). Anemia, chronic abdominal pain, diarrhea, exercise intolerance, undernutrition, and growth stunting have been associated with a chronic inflammatory disease in infected individuals that recover after praziquantel treatment (King and Dangerfield-Cha 2008). Cognitive deficits are also improved with better control of schistosomiasis and other chronic parasitic infections, like soil-transmitted helminthiasis (Yuan et al. 2005).

10.2 One Health Approach: Zoonotic Schistosomiasis

Unlike *S. japonicum* infections from Asia (Zou et al. 2020), animals other than humans do not have an important role in maintaining the *S. mansoni* cycle in nature, but rodents may contribute to maintenance of the latter species, both in Africa and in Central and South America (Gentile et al. 2006; Catalano et al. 2018; Hewitt and Willingham 2019). Susceptibility to experimental infection and in semi-natural conditions, as well as several surveys demonstrating high prevalence estimates, have been reported mostly from Brazil and the Caribbean Island of Guadeloupe (Table 10.1) (Kawazoe and Pinto 1983; Théron et al. 1992; Gentile et al. 2006). There are indications that a zoonotic cycle can support the transmission of *S. mansoni* in late stages of control when prevalence and intensity in humans are expected to reach very low numbers. But this is an issue open for further investigations, especially in low endemicity areas.

Infection in the black rat, *Rattus rattus*, was followed for 8 years in Guadeloupe, French West Indies, with prevalence estimates from 28% (sample: 72 animals) to 61% (sample: 66) and an overall prevalence of 40% (243/611 animals) (Théron et al. 1992). *Rattus norvegicus* was also found with infection in Guadeloupe, but it was a small sample and these animals are apparently less adapted to the parasite as indicated by lack of egg elimination in feces (Alarcón-de-Noya et al. 1997).

Animals other than rodents are either apparently not involved in the maintenance of the cycle in the Americas or have a role yet to be investigated. No infection was detected in 15 monkeys examined in Saint Lucia (Jordan 1985). *S. mansoni* infection was reported from Saint Kitts, in five to seven West African Green monkeys, *Chlorocebus aethiops* (Cameron 1928), but a later survey in 2015 did not detect any infection in 94 monkeys (Hewitt and Willingham 2019). Other apparently incidental isolated findings came from Suriname: a single squirrel monkey and a great anteater, *Myrmecophaga tridactyla* presenting eggs with a lateral-spine in the intestines (Swellengrebel and Rijpstra 1965; Rijpstra and Swellengrebel 1962).

Table 10.1 Rodent species infected with *Schistosoma mansoni* in the Caribbean Region and South America: selected examples of evaluation of natural infection and higher prevalences from 1975 to 2019

Country/ Locality	Prevalence	N examined	Taxon	References
Brasil				
Maranhão,	64%	225	*Holochilus sciureus*	Silva-Souza et al. (2019)
São Bento				
Maranhão,	28.7%	101	*Holochilus sciureus*	Miranda et al. (2015)
São Bento				
Rio de Janeiro,	46.1% (avg)[a]	9 (avg)	*Nectomys squamipes*	Gentile et al. (2006)
Sumidoro	71.1% (avg)	9 (avg)	*Nectomys squamipes*	
Rio de Janeiro,	56.5%	23	*Nectomys squamipes*	Silva et al. (1992)
Sumidoro			*Akodon arviculoides*	
Bahia, Planalto	47%	48	*Nectomys*	Silva and Andrade (1989)
da Conquista				
Minas Gerais,	2.7%	111	*Zygodontomys lasiurus*	Carvalho et al. (1975)
Belo Horizonte	39.3%	28	*Holochilus brasiliensis*	
	75%	8	*Nectomys squamipes*	
Guadaloupe (French West Indies)				
	59%	73	*Rattus rattus*	Alarcón-de-Noya et al. (1997)
	40%	611	*Rattus rattus*	Théron et al. (1992)

[a]Avg: average

Bovine species can hold productive infections as demonstrated both from experimental infections and surveys looking for natural infections (Modena et al. 2008).

10.3 Brief Story and Occurrence of Schistosomiasis in the Americas

S. mansoni was most probably introduced in the New World with the slave traffic from West Africa for almost 300 years beginning in mid-sixteenth century. DNA sequencing data and analysis provided several indications supporting this hypothesis, although evidences are not considered as strong as those produced with studies on the origins of *Plasmodium falciparum*, *Fasciola hepatica,* and *Onchocerca volvulus* occurring in the New World (see extensive review by Morgan et al. 2005).

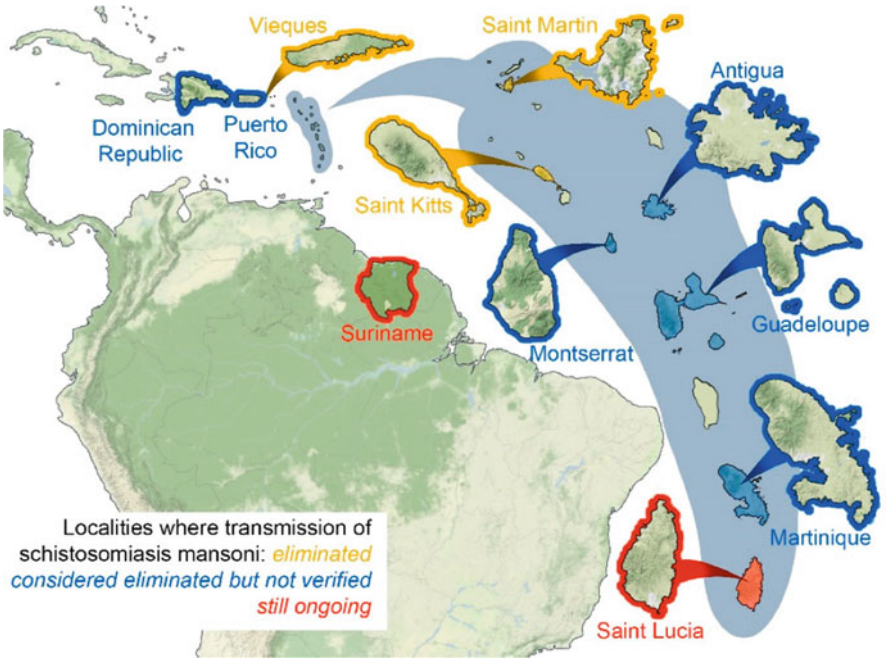


Fig. 10.1 Countries and territories in the Caribbean region with a history of schistosomiasis mansoni endemicity and their current transmission status. (Hewitt and Willingham 2019—https://www.mdpi.com/2414-6366/4/1/24/htm, Attribution 4.0 International CC BY 4.0)

South America and the Caribbean region are at the center of the early history of schistosomiasis mansoni discoveries. In 1902, Sir Patrick Manson published a short case report of an Englishman presenting lateral-spined eggs in stools, that lived since 1887 in Antigua, Anguilla, and finally in Saint Kitts (Manson 1902). Five years later, the new species was proposed by Sambon as *Schistosoma mansoni* in honor of Manson, after examination of a poorly conserved male worm (Katz 2008b). A full description and definitive differentiation between *S.haematobium* and the new species was made possible with examination of 24 worms performed by Manoel Pirajá da Silva, in Salvador, Brazil, 4 years after his first findings in 1904 of lateral-spined eggs in Brazilian patients (Katz 2008b). In Venezuela, the first patient was diagnosed in Caracas and the report was published in 1906 by Vicente Raúl Soto (Noya et al. 2015).

Schistosomiasis occurs in 10 countries or territories in the Caribbean region (Fig. 10.1) and South America (WHO 2013) (Fig. 10.1). Most of the people at risk of infection and hot spots for transmission are situated in the Latin-American largest country: 9 out of 10 individuals at risk for acquiring schistosomiasis live in Brazil (PAHO 2016). Two countries, Brazil and Venezuela (Fig. 10.2), concentrate on the populations requiring chemotherapy (WHO 2013).

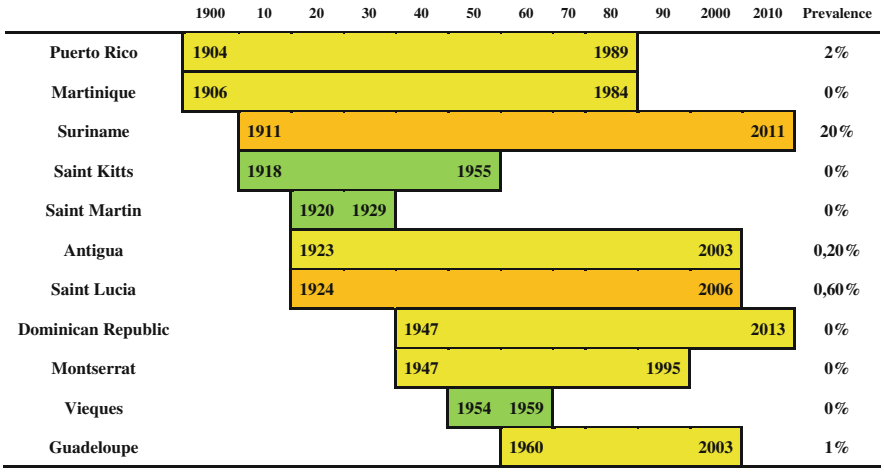
Fig. 10.2 Status of schistosomiasis transmission in Latin-American countries (blue). Only Brazil and Venezuela have areas requiring periodic chemotherapy (red)

Brazil hosted 91 population surveys from 1952 to 2010, including a national survey in 2011–2014 (Katz 2018). All other countries are required to update their prevalence and intensity data, after 50–20 years without published reports (Zoni et al. 2016) (Table 10.1). Countries and territories have been classified as requiring: (1) preventive chemotherapy: Brazil and Venezuela; (2) updated surveys: Saint Lucia and Suriname, with possibility of transmission remaining; (3) verification to confirm transmission interruption: Antigua-Barbado, Dominican Republic, Guadeloupe, Martinique, Monserrat, Puerto Rico (WHO 2013). In Saint Kitts, Saint Martin, and Vieques, transmission is considered eliminated (Hewitt and Willingham 2019) (Tables 10.2 and 10.3).

Table 10.2 Countries in the Caribbean region and South America with a history of schistosomiasis transmission and time period for the last survey in human populations, modified from Zoni and collaborators, 2016

Country	Time period
Martinique	1970
Guadaloupe	1969–1973
Monserrat	1978
Dominican Republic	1994
Suriname	1995
Saint Lucia	1996
Puerto Rico	1999
Venezuela	1998–2000

Table 10.3 Countries and territories in the Caribbean region and South America with occurrence of *Schistosoma mansoni* transmission



Years of first report and last survey on human populations. Green: countries where transmission has been interrupted. Yellow: countries where surveys are needed to access the possibility of remaining transmission. Orange: countries that require chemotherapy. Adapted from Hewitt and Willingham (2019)

10.4 Guidelines, Control Efforts in the World and in the Americas

Since the 1950s, the World Health Organization has established a series of guidelines for schistosomiasis control on a global scale (WHO 2020). Scientific research has provided the advancement of knowledge, redefining goals, and strategies. Revised and new control recommendations were progressively adjusted by the WHO Expert Committees, based on the accumulated experience in endemic countries, including Brazil. Successive WHO guidelines recommended changes in control priorities, from emphasis in transmission control until the early 1980s to

morbidity control after mid-1980s. As pointed out by Katz (2008a), the significant drop in the incidence and prevalence of hepatosplenic forms due to treatment of infection carriers as shown by several Brazilian studies, was pivotal for this change in emphasis. As a result, control measures mainly based on snail control were replaced by selective chemotherapy until the end of the 1990s and, since the early 2000s, mass drug administration (MDA) targeted at the most vulnerable groups. Other control measures, although recommended, have not had as much priority over the decades (Barbosa et al. 2008).

In 2009, resolution CD49.R19 of the Directing Council of the Pan American Health Organization (PAHO 2009) urged Member States to drastically reduce schistosomiasis prevalence and parasite load in high transmission areas to less than 10% prevalence as measured by quantitative egg counts (with available cost-effective interventions). The proposed strategy, as recommended by WHO (2002, 2006), was MDA for at least 75% of the school-age children (SAC) living in at-risk areas, improvements of excreta disposal systems, access to safe water, and educational actions. However, the Brazilian Government's representatives strongly opposed to the MDA scheme, as it would represent a step backward for the Region. It was argued that studies conducted in Brazil had shown that MDA effect on infection indicators was transitory; instead, countries should focus on strengthening capacity for diagnosis and treatment of infection carriers at the primary care level and on improving environmental sanitation (PAHO 2009).

From 2010, WHO began publishing yearly estimates of population requiring MDA and number of people given praziquantel based on information provided at district or secondary administrative level for each endemic country (WHO 2012b). To estimate the population requiring preventive chemotherapy for schistosomiasis annually, available national population data were adjusted using the annually reported growth rate. For Brazil, the strategy recommended by WHO has been annual MDA of SAC attending the initial and the final schooling years as the country was considered low risk; thus, 1.5 million of SAC (33% of the at-risk SAC in the country) were required to undergo MDA regardless their individual infection status (https://www.who.int/neglected_diseases/preventive_chemotherapy/sch/en/). In contrast, the strategy recommended by the Brazilian MoH has been periodic active search surveys in the endemic area followed by different treatment schemes according to the prevalence level (Brasil 2014). As a result, the annual report provided by the Brazilian MoH for the WHO/PCT databank does not contain the required information on the number of SAC treated, which misleadingly reduces the number of people treated and the national coverage (Table 10.4).

According to WHO, the yearly national coverage of treatment for schistosomiasis in Brazil has been negligible whereas it has been more than 70% according to the MoH (Table 10.4). It can be calculated from the SISPCE database (2006–2016) that an annual average of 1.6 million people from the endemic area were targeted for testing, of which 1.2 million were assayed by the Kato-Katz method; the annual egg-positive rate during that period averaged 6.4%. As pointed out by Cabello et al. (2016), the MoH emphasis on community-based surveys followed by treatment of the infection carriers of all age groups at the primary health care level aims to attend

Table 10.4 Schistosomiasis (SCH) implementation data by year for Brazil according to WHO and to the MoH

WHO implementation data (PCT databank)*							MoH implementation data (SISPCE databank)**					
year	SAC population requiring PC for SCH	Population requiring PC for SCH	Reported number of people treated	Age group	Reported number of SAC treated	National coverage	Population targeted for SCH testing	Population tested for SCH	Age group	Egg-positives	Population treated	Treatment coverage
2006			154,394	SAC / Adults	97,815	0.37%	2,777,845	2,151,816	All	118,355	111,502	94.2%
2007			123,905	SAC / Adults	21,551	0.29%	2,524,219	1,935,224	All	103,083	94,908	92.1%
2008			76,306	SAC / Adults		0.18%	1,899,626	1,430,505	All	75,493	69,726	92.4%
2009			30,397	All	6,091	0.07%	1,989,948	1,475,659	All	76,719	70,677	92.1%
2010	1,460,250	1,460,250	39,866	All	41	2.73%	1,853,199	1,385,929	All	69,418	61,819	89.1%
2011	1,472,340	1,472,340	26,677	Adults		1.81%	1,713,574	1,270,559	All	59,940	52,230	87.1%
2012	1,485,112	1,485,112	27,178	All		1.83%	1,223,159	895,532	All	38,823	29,600	76.2%
2013	1,497,865	1,497,865					1,115,305	798,568	All	37,038	28,316	76.5%
2014	1,510,363	1,510,363					1,134,909	820,678	All	33,357	26,200	78.5%
2015	1,523,333	1,523,333					983,096	709,169	All	22,434	16,707	74.5%
2016	1,535,838	1,535,838	16,054	SAC / Adults	3,643	0.20%	499,082	353,540	All	12,009	8,582	71.5%
2017	1,549,046	1,552,328	3,897	SAC / Adults	615	0.25%	NV	NV	NV	NV	NV	NV
2018	1,550,386	1,556,890	9,756	SAC / Adults	3,252	0.63%	NA	NA	NA	NA	NA	NA
2019	1,550,386	1,556,890					NA	NA	NA	NA	NA	NA

*https://www.who.int/neglected_diseases/preventive_chemotherapy/sch/en/
** http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinan/pce/cnv/pcebr.def

NV – Not validated
NA – Not available

The PCT databank convenes information on mass administration of praziquantel among school-age children (SAC) as required by WHO; the SISPCE databank records information on selective administration of praziquantel among all ages as required by the MoH

Brazil's epidemiological peculiarities and to comply with public health policies and principles pertaining the country's Unified Health System (SUS).

10.5 Morbidity and Mortality Trends

Decreasing infection intensity, prevalence, and mortality estimates, as well as decreasing occurrence of severe hepatosplenic clinical forms, have been reported in the last four decades, in most endemic areas in Brazil, Venezuela, and the Caribbean region following the reduction in prevalence and intensity of infections (Zoni et al. 2016; Hofstede et al. 2014). Several systematic analyses of secondary data (Amaral et al. 2006; Martins-Melo et al. 2014) and also from the experience of several research groups and anatomo-pathological services from Brazil have described a decreasing trend (Andrade 1998). Hospitalizations because of schistosomiasis also show a reducing trend (Fig. 10.3) (Amaral et al. 2006). While spontaneous morbidity and mortality reduction may occur (Katz and Brener 1966) chemotherapy of human populations has had a fundamental role in the successful control of schistosomiasis (Hofstede et al. 2014). Parasite-killing drugs may at least partially revert liver fibrosis and spleen compromise in hepatosplenic clinical forms (Bina and Prata 1983). Several other factors contribute to the current decreasing trend: urbanization, improved socio-economic conditions, increased supply of

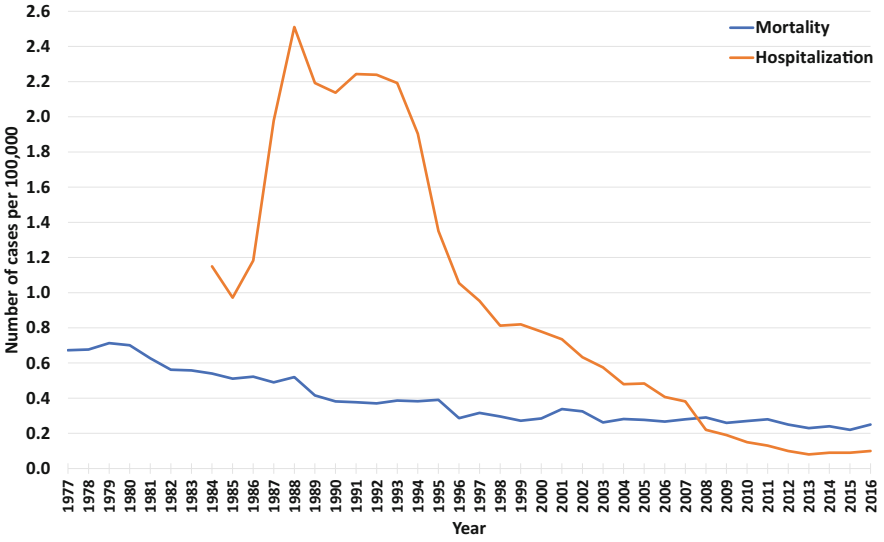


Fig. 10.3 Decreasing trends of mortality (1977–2016) and hospitalization (1984–2016) for schistosomiasis in Brazil, as recorded by the Ministry of Health. Sources: Mortality Information System (SIM) and Hospital Information System (SIH)

qualified health services and political priority for nation-wide control programs with integrated actions on the environment, water and sanitation, health education, and snail control (Andrade 1998; Amaral et al. 2006; Hofstede et al. 2014; Barbosa et al. 2016). Reduction in morbidity is usually less dramatic, but more persistent. Prevalence reduction can be more striking, but less persistent, especially because of reinfection, demonstrating the need for integrated, sustained, long-term control programs (Coura et al. 1992). In some settings, like in Venezuela, Puerto Rico, and Saint Kitts, changing farming practices and environmental conditions, both pre-existent and resulting from control actions, were key drivers for successful reductions in transmission (Hewitt and Willingham 2019).

The north-eastern Brazilian State of Pernambuco and other hot spots in Minas Gerais and Bahia are exceptions to this general decreasing trend with a remaining high number of severe hepatosplenic forms and deaths (Barbosa et al. 2016; Zoni et al. 2016; Martins-Melo et al. 2018). Exceptions like Pernambuco remind us the focal occurrence of schistosomiasis with its remaining transmission hot spots, as well as the conjunction of factors favoring persistence and expansion of transmission, including the lack of a sustained and integrated approach as proposed by WHO (Barbosa et al. 2016; WHO 2013). Important to note that four low endemic areas: Venezuela, Puerto Rico, Suriname, and Dominican Republic, lack published surveys in human populations since 1990s (Zoni et al. 2016). There are indications that

schistosomiasis is re-emerging in Venezuela after discontinuation of a very successful control program initiated in 1940s (Noya et al. 2015).

Neuroschistosomiasis was usually not included in the category of "severe clinical forms," what has been partially corrected in recent years with a growing awareness of its severity, especially considering its egg burden independent association and occurrence with lightly infected individuals (Ferrari et al. 2008). While in most areas the classical severe forms, especially **hepatosplenic schistosomiasis**, are gradually disappearing (Andrade 1998), neuroschistosomiasis remains a most probably underdiagnosed condition as we advance to late stages of morbidity and transmission elimination (Lambertucci et al. 2007).

10.6 Control Situation: Reducing Intensity and Prevalence Towards Elimination as a Public Health Problem

As a signatory to resolution WHA65.21 on the elimination of schistosomiasis, the Brazilian government has committed to attain WHO goals for morbidity control by 2020 and elimination as a public health problem by 2025 (WHO 2012a; PAHO 2014), later postponed to 2030 (WHO 2020). As shown in Fig. 10.4, this would involve progressively lowering endemicity by initially focusing on morbidity to reduce the intensity of infection, then on prevalence to reduce the number of cases; subsequently, focus would be on transmission to reduce the risk of infection, and finally on surveillance to validate elimination. The currently recommended indicator for the target of morbidity control is 5% prevalence of heavy-intensity infections, whereas for elimination as public health problem it is 1% prevalence of heavy-intensity infections (PAHO 2014; WHO 2020). For schistosomiasis mansoni, these indicators are estimated by carrying out regular stool surveys in sentinel sites and

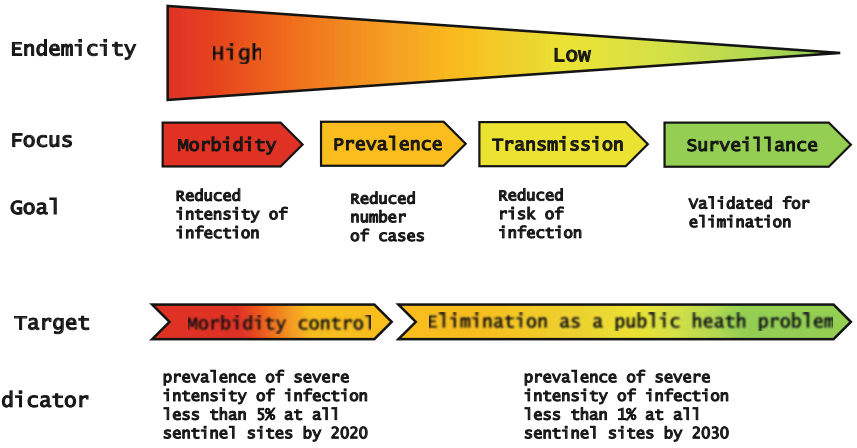


Fig. 10.4 Steps towards the elimination of schistosomiasis as a public health problem. Modified from Bergquist et al. (2009)

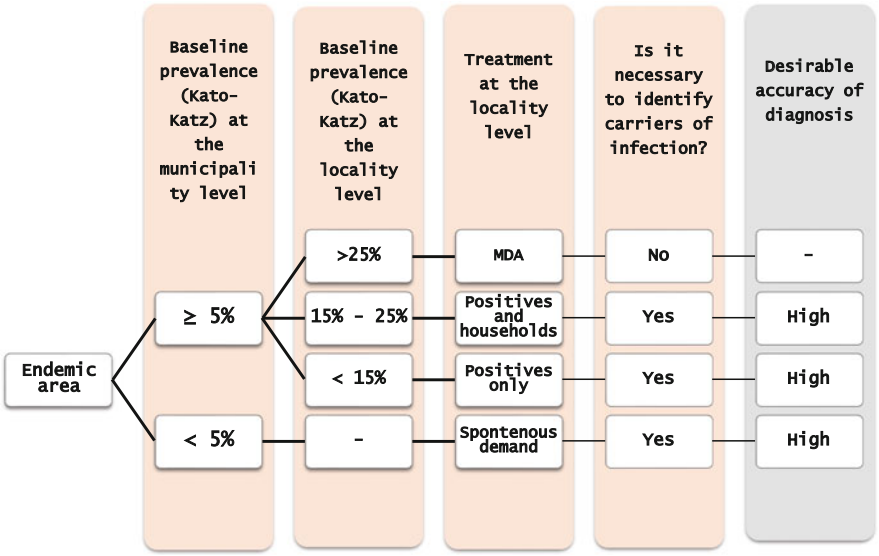


Fig. 10.5 Diagnosis and treatment scheme recommended by the Brazilian Ministry of Health for elimination of schistosomiasis as a public health problem

egg counting by the Kato-Katz method (two slides from one stool sample). Thus, the prevalence of heavy-intensity infections is expressed as the proportion (%) of subjects with 400 eggs per gram of stool (epg) or more among all subjects examined and is calculated as follows: [(number of subjects with epg $\geq$ 400) $\div$ (number of subjects examined) $\times$ 100] (WHO 2011).

The main strategy proposed by WHO for reducing morbidity and transmission of schistosomiasis towards its elimination is through preventive chemotherapy, the regular distribution of praziquantel to population groups at risk according to prevalence classes estimated from baseline stool survey (one Kato-Katz sample, two slides) among school-aged children (Crompton and WHO 2006; Gabrielli et al. 2011; WHO 2011; 2013). For Brazil, WHO has recommended the distribution of praziquantel to all school-age children twice during their schooling years (e.g., once on entry and once on exit), as most endemic municipalities are considered at low risk; this is equivalent to mass drug administration (MDA) of one-third of school-age population annually (WHO 2012b). As a result, the number of individuals requiring preventive chemotherapy for schistosomiasis in Brazil every year has been estimated by WHO at 1.5 million.

The current MoH guideline for schistosomiasis elimination in Brazil, launched in 2012 to attend resolution WHA65.21 (Brasil 2014), prescribes community-wide stool surveys (one Kato-Katz sample, two slides) at regular intervals in endemic municipalities with baseline prevalence at 5% or above. As shown in Fig. 10.5, MDA is proposed only to persons over 5 years of age from localities with baseline prevalence above 25%. From that value down to 15% it is necessary to identify the

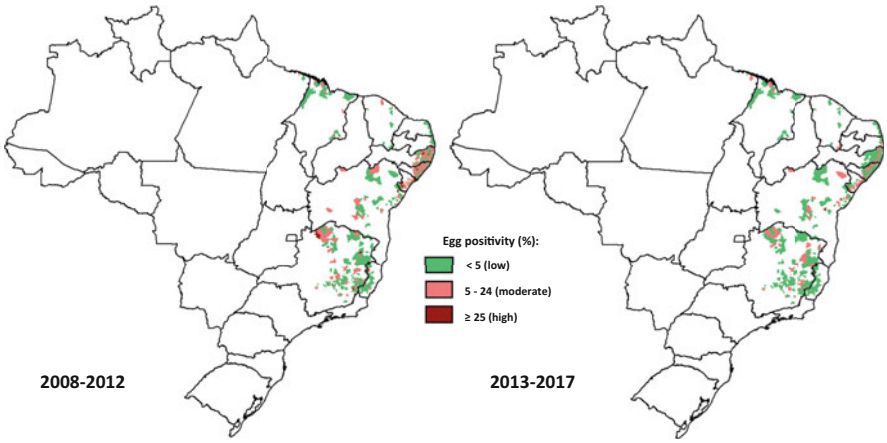


Fig. 10.6 Geographical distribution of schistosomiasis mansoni in Brazil by prevalence class in two periods of 5 years (2008–2012 and 2013–2017) according to SISPCE (System for the Schistosomiasis Control Program)

infection carriers in the locality and treat them together with their households; below 15%, only the infection carriers in the locality are required to be treated. Endemic municipalities with baseline prevalence below 5% are not screened and treatment is subjected to spontaneous demand at the local health units.

According to the Information System for the Schistosomiasis Control Program (SISPCE 2021), in the 5 years (2008–2012) prior to the implementation of the new MoH guideline 901 endemic municipalities had been surveyed, totaling 6.5 million Kato-Katz tests, 320,393 (5%) of which positives; a total of 284,052 treatments had been administered, averaging 56,810 per year. In the first 5 years (2013–2017) under the new MoH guideline, 2.7 million Kato-Katz tests were performed in 623 endemic municipalities, yielding 105,187 (3.9%) positives, and 79,905 treatments were administered, averaging 15,981 per year. It is noteworthy that the number of municipalities of the endemic area in the spontaneous demand category (prevalence less than 5%) increased from 69.5% (626 out of 901) in the 2008–2012 period to 77.0% (480 out of 623) in the 2013–2017 period. Thus, as shown in Fig. 10.6, the endemic municipalities requiring active search (either for selective chemotherapy or MDA) were already minority in the former period and decreased even more in the latter. It is also of interest that the number of exams with more than 400 epg was 21,184 in the 2008–2012 period and 5,965 in the 2013–2017 period, yielding a prevalence of heavy-intensity infections of 0.32% and 0.22%, respectively.

It is clear from the data available in the SISPCE (2021) that both intensity and prevalence of schistosomiasis infection in Brazil have been falling to levels compatible with achieving elimination as a public health problem by 2030. It is unfortunate that this accomplishment is not reflected in WHO/PCT databank where annual coverage of preventive chemotherapy is calculated on the assumption that one-third of the at risk school-age population (1.5 million) should be subjected to

MDA every year (WHO 2012b, 2021). As pointed out by Favre et al. (2015), Brazil's public health policies and epidemiological characteristics advocate community-wide interventions against schistosomiasis within the Family Health Strategy (FHS), conducted at the primary health care level and framed by the Unified Health System (SUS). This involves early identification of infection carriers and timely treatment of all at-risk age groups rather than only school-aged children. Implementation of genuine preventive measures such as environmental sanitation and safe water supply backed by community mobilization and health education is also of paramount importance. So far, emphasis on diagnosis and treatment has been disproportionately greater than on the other intervention measures.

As shown in Fig. 10.5, the diagnostic method currently used by the MoH (Kato-Katz) is useful in monitoring *S. mansoni* infection in sentinel sites but not in detecting infected individuals for treatment, particularly in low endemicity areas. As the target shifts from morbidity control towards elimination as public health problems, the effectiveness of community interventions will require highly accurate diagnostic methods which may not be available by 2030. Therefore, a One Health approach will be needed to incorporate initiatives such as WASH (health promotion, improved water supply, sanitation, and hygiene) to effectively combat schistosomiasis and other diseases of poverty (Zhou 2012).

10.7 Control Situation in Brazil: Snails and Environmental Interventions Including Sanitation and Water

Until the mid-1970s, the fight against schistosomiasis as recommended by WHO was focused on the control of transmission due to the lack of effective and safe drugs. In Brazil, the strategy was chiefly through the reduction of populations of intermediate host snails (*Biomphalaria glabrata*, *B. straminea*, and *B. tenagophila*) by periodically applying molluscicide in the potential transmission sites (Brasil 2008). However, results from the few studies carried out under field conditions with the only molluscicide approved for large-scale use (niclosamide) in schistosomiasis control campaigns were disappointing; the effect on snail populations was transitory and not cost-effective, the impact on non-target organisms was significant, whereas the influence on human infection was negligible (Barbosa et al. 2008). With the advent of oxamniquine, a more effective and safer drug, the MoH initiated a partly successful large-scale program for controlling transmission in highly endemic areas focused on chemotherapy and, to a lesser extent, niclosamide application (Machado 1982). In the mid-1980s, the focus of control recommended by the WHO shifted from transmission to morbidity, aimed at reducing infection intensity and preventing severe forms of the disease (Katz 1998). As a result, the Brazilian Schistosomiasis Control Program (PCE) further intensified chemotherapy by replacing oxamniquine with a much cheaper drug (praziquantel), and progressively reduced the use of niclosamide, the cost of which had become prohibitive (Barbosa et al. 2008). Other products with molluscicide proprieties, including those of plant origin, as well as alternative methods using predators, competitors, parasites, or

pathogens (biological control) have been sought for snail control (Brasil 2008; Coelho and Caldeira 2016). However, so far none has been submitted to the MoH and the regulatory agencies for approval.

In the mid-2000s, the MoH assigned a group of specialists from various academic institutions, as well as from governmental agencies involved in environmental regulation, to participate in the elaboration of directives for surveillance and control of epidemiologically important molluscs in Brazil. Since then, it has been established that snail control, whether by chemical, biological, or physical methods, must comply with the concerning environmental legislation; public health organs may be exempted from authorization by the environmental agencies provided the action is part of a government program. At present, the PCE recommends snail control with niclosamide only in special situations, such as when there is a localized outbreak of acute cases or when high prevalence (>25%) estimated by routine Kato-Katz method (one stool sample with two slides) persists even with the periodic treatment of the population (Brasil 2014); in this situation, molluscicide application is recommended shortly before chemotherapy and again a few weeks later (WHO 2017). However, as pointed out by Coelho and Caldeira (2016), routine Kato-Katz method is likely to underestimate prevalence levels in some endemic areas, which may require reassessment of the need for snail control using more robust egg-finding methods.

MoH directives for schistosomiasis surveillance and control strongly recommends the elimination of host snail populations by physical or environmental measures e.g., draining or filling in the breeding sites, whenever technically recommended and acceptable by the community in highly endemic areas. Rectification, lining, and channeling of water courses are recommended as long lasting but relatively expensive measures of environmental control; low-cost measures, such as regularly cleaning and removing aquatic vegetation, may suffice in some cases (Brasil 2014).

The MoH also provides a set of engineering interventions through the National Health Foundation (FUNASA) for promoting sanitary solutions aimed at disease prevention and control within the Unified Health System (SUS), primarily in municipalities with less than 50,000 inhabitants and in rural areas. This includes allocation of resources for environmental sanitation and safe water supply measures that are selected by epidemiological and technical criteria and implemented through agreement with the local and municipal Health Councils to warrant community involvement (Brasil 2014; Funasa 2020). As pointed out on Sect. 10.6, sanitation and water supply may ensure the reduction of various infectious diseases of poverty, whereas chemotherapy and snail control are disease-specific (Fig. 10.7).

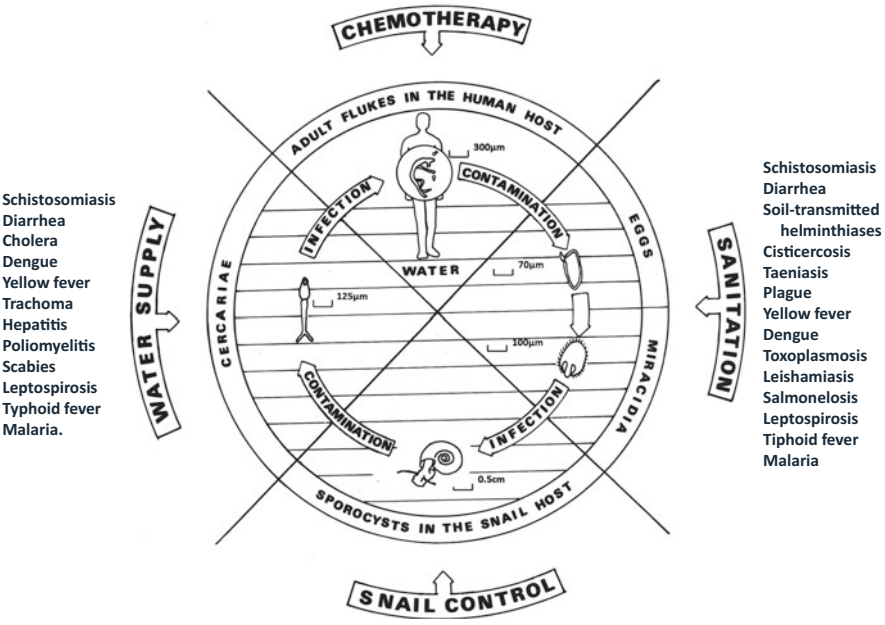


Fig. 10.7 Life cycle of *Schistosoma mansoni* and control interventions. Sanitation and water supply are recommended by the Brazilian Ministry of Health against various infectious diseases of poverty besides schistosomiasis (FUNASA 2020)

10.8 Strategies of Health Education and Insertion in Basic Care, Integration with Control of Other Infectious Diseases of Poverty

It was pointed out in Sect. 10.6 that health education is sought as a key component for schistosomiasis prevention at the primary health care level within Brazil's Unified Health System (SUS). However, educational actions must be contextualized to the realities of the target population or group to promote higher participation in control campaigns and better knowledge about the disease (Favre et al. 2021). The MoH directives for schistosomiasis surveillance and control (Brasil 2014) include recommendations and operational guidance on educational strategies that are useful not only to combat schistosomiasis but other infectious diseases of poverty as well. The main recommendations for the health educator under this One Health approach are:

- **Participate** in the negotiations for the allocation of resources, together with the local health and education groups, community associations, and other stakeholders, before the implementation of educational actions.
- **Stimulate** the integration of the various participants (decision-makers, health professionals, teachers, community leaders, and the target population) in the implementation of educational actions.

- **Ensure** the participation and involvement of the community in the continuity and sustainability of all phases of disease control.
- **Promote** reflections on socio-economic and cultural factors that affect health and condition the well-being of the population.
- **Help** people understand that their own behavior can be a facilitating factor in disease transmission.
- **Apply** new approaches or teaching strategies, such as relating content in an interdisciplinary way, emphasizing the participation of pupils and teachers in the school environment and the population in communal spaces, and valuing the construction of knowledge through experience.
- **Consider** that the educational process is not only for the acquisition of skills, but a construction of affective relationships, appreciation of oneself, respect for others and eco-social responsibility.
- **Encourage** the empowerment of health and education professionals involved in health programs to improve the work environment, which will have repercussions on control programs.

The MoH directives also include recommendations for developing educational materials based on previous investigation of the knowledge, attitudes, behaviors, and beliefs of the population, in order to establish appropriate level of language and information content. Suitable language and attractive designs (including color images, if financially feasible) would favor motivation and the building of knowledge among children and teenagers. Educational materials should avoid technical language and content, which may be offered in supplementary texts for people who wish to obtain more detailed knowledge. Stylized pictures that may lead to misrepresentations or may be pedagogically inappropriate should also be avoided. If there are drawings, include real images of the parasites, providing measurements or scales, to show what they are like. The ideal is to set up a laboratory demonstration at school or in the health service, providing slides with the parasites for microscopic observation, which is highly motivating and educational (Fig. 10.8**).**

The MoH directives additionally highlight the importance of stimulating the target population by various means, so that information is accessed by different senses (vision, hearing, touch), using literary texts, music, drawings, dramatization, and modeling. The use of television clippings, videos, or other media with characters that people identify with in scenes of everyday life is also stressed, considering that individuals benefit more from concrete experiences and pedagogical means and strategies that integrate cognitive and affective aspects.

An initiative aiming to provide digital materials for teachers and pupils of basic education in Brazil was recently implemented strictly following MoH recommendations (http://www.xistose.com/). It promotes discussion and knowledge building on schistosomiasis and other infectious diseases of poverty through virtual meetings, in which popular and scientific knowledge can be shared. It stimulates dialogue that leads to a reflection of the relations between health and socio-economic and cultural development, public policies, and citizenship. The purpose is to start a

Fig. 10.8 Observing *Schistosoma mansoni* eggs on a Kato-Katz slide under a microscope as part of educational actions in the school environment

process of sensitization and transformation of concepts of disease and health in a participatory way (Fig. 10.9).

Another initiative following the MoH recommendations on health education is a booklet specifically targeted at education and health professionals working in basic care (Brasil 2018). It provides guidance on how to carry out proper educational actions with the aim of contributing to the elimination of schistosomiasis as a public health problem in Brazil. It advises the health and education workers in basic care to recover the history of the disease in endemic localities, verify the risks and factors related to transmission and update the prevalence estimates before undergoing community interventions. Finally, it stresses that the process of effectively implementing control strategies requires commitment from the different governmental spheres, active participation of the communities, and availability of human and financial resources.

10.9 Development and Evaluation of Diagnostic Methods

Detection of eggs in fecal thick-smears using the Kato-Katz method has been the main stem for population screening for many decades (WHO 1985). But it lacks sensitivity as infection intensities decrease in late stages of transmission control. Methods for the detection of antibodies and nucleic acids have been developed and extensively applied, especially in Venezuela and Brazil (Alarcón-de-Noya et al.

Fig. 10.9 Internet site providing digital materials on schistosomiasis and other infectious diseases of poverty for teachers and pupils of basic education in Brazil (http://www.xistose.com/)

2007; Gomes et al. 2013; Hofstede et al. 2014). In recent years, antigen detection (POC-CCA, point-of-care circulating cathodic antigen) in urine has been proposed as a substitute for KK smears, but there is also growing concern because of recent demonstration of lack of reproducibility between batches of the immunochromatographic kits and increased false-positive results in non-endemic populations in Brazil (Graeff-Teixeira et al. 2021a). So there is still need for accurate, cost-effective, and easy-to-perform tests, especially for use in low endemicity areas and at late stages of transmission control, as well as tools to certify transmission interruption. The needed testing must also have the proper standardization and performance evaluation (Banoo et al. 2006; Graeff-Teixeira et al. 2021b). Two sensitive egg detection methods were standardized and evaluated in Brazil: Saline Gradient (SG) and Helmintex (HTX). Isolation of eggs from stools is based on density gradient (SG, Coelho et al. 2009) and the coupling with paramagnetic beads and magnetic behavior of eggs+beads (HTX, Teixeira et al. 2007). SG and HTX contribute as reference methods to improve performance evaluation of molecular methods, especially for low endemicity settings, but not as routine screening method (Lindholz et al. 2018; Silva-Moraes et al. 2019).

An important component of the successful Venezuelan experience controlling schistosomiasis was the development and evaluation of diagnostic tools to overcome the limitations of sensitivity with parasitological methods (Alarcón-de-Noya et al.

2007). In the years 1950s the Circumoval Precipitin Test (COPT) was developed consisting in visualization at the microscope of antibodies recognizing antigens released by embryonated eggs from *S. mansoni*. COPT has been considered as a reference method with high sensitivity (92–100%) and specificity (96–100%) and with a good correlation with activity of infection. But it is also a labor intensive and expensive method requiring the maintenance of the parasite cycle in the laboratory as source of fresh, live eggs. It also requires a large amount (100 uL) of serum. Serology using egg soluble antigen (SEA) depleted or not (SEA-ELISA) from carbohydrate molecules after treatment with Sodium-Metaperiodate (SMP-SEA-ELISA) was widely used in Venezuela as a screening procedure with 99% sensitivity and 97% specificity (Noya et al. 2002). Worsening political and socio-economic situation in Venezuela in recent years prevents the adequate continuous assessment of residual transmission in that country that probably is in a late stage suitable for transmission interruption certification in many areas. In a rural community ("Los Toros," 50 km from Valencia, north-central Venezuela) prevalence estimated by SMP-SEA-ELISA was 31.5% after a survey of 92% of its 122 inhabitants (Ferrer et al. 2020).

10.10 Development in Treatment, Pediatric Formulation of Praziquantel

The control of schistosomiasis in Brazil was implemented at the national level in the mid-1970s by the MoH, focussing its activities on wide-scale treatment with oxamniquine; this drug, manufactured by Pfizer™ under the trade name Mansil®, had two formulations: capsule with 250 mg of the active ingredient and 50 mg/ml solution in flasks with 15 or 240 ml for pediatric use. It was the only drug used in control campaigns until the late 1990s (Katz 1998, 2008a). The MoH recommended dose was 20 mg/kg for children from 2 years (or 10 kg of body weight) up to 15 years (or 60 kg of body weight) and 15 mg/kg for the remaining age groups. Children weighing between 10 and 20 kg received only the pediatric formulation, whereas those between 21 and 35 kg also could be given capsules (Brasil 2014); thus, the recommended dosage ranged from 4 ml (for children with 10–11 kg) to 15 ml (children with 34–35 kg) of the pediatric formulation, and from two capsules (for children with 21–23 kg) to five capsules (for children with 55–60 kg) (Table 10.5).

In the late 1990s, the MoH started using 600 mg praziquantel tablets manufactured by Farmanguinhos/Fiocruz for a fraction of the cost of oxamniquine; the recommended dose is 60 mg/kg for children from 2 years (or 10 kg of body weight) up to 15 years (or 60 kg of body weight) and 50 mg/kg for the remaining age groups (Table 10.5). However, the pediatric formulation of oxamniquine continued to be used by the MoH in preference to praziquantel among children weighing 10–35 kg until its acquisition was discontinued in the early 2000s. Since then, control campaigns in Brazil have faced two issues with administering praziquantel: firstly, the bitter taste and the large size of the tablets make it usually necessary to

Table 10.5 Dosage table of oxamniquine (50 mg/ml solution and 250 mg capsule), 600 mg praziquantel racemate (rac-PZQ) tablets and 150 mg levo-praziquantel oral dispersive tablets (L-PZQ ODT) for children with 10–60 kg of body weight (approximately 2–15 years old)

Oxamniquine (20mg/kg) *			Rac-PZQ (600mg/kg) *		L-PZQ ODT (50mg/kg)	
Body weight (kg)	50mg/ml solution (ml)	250-mg capsules	Body weight (kg)	600-mg tablets	Body weight (kg)	150-mg tablets
10 – 11	4	-	10 – 12	1	11 - 13	4
12 – 13	5	-	13 – 16	1½	14 – 16	5
14 – 16	6	-	17 – 20	2	17 – 19	6
17 – 18	7	-	21 – 25	2½	20 – 22	7
19 – 20	8	-	26 – 30	3	23 – 25	8
21 – 23	9	2	31 – 35	3½	26 – 28	9
24 – 25	10	2	36 – 40	4	29 – 31	10
26 – 27	11	2	41 – 45	4½	32 – 34	11
28 – 29	12	2	46 – 50	5	35 – 37	12
30 – 31	13	2	51 – 55	5½	38 – 40	13
32 – 33	14	3	56 – 60	6	41 – 43	14
34 – 35	15	3			44 – 46	15
36 – 43	-	3			47 – 49	16
44 – 54	-	4			50 – 52	17
55 – 60	-	5			53 – 55	18
Use of pediatric formulation: Preferred Extended					56 – 58	19
* Body-weight classes recommended by the Ministry of Health (Brasil 2014)					59 – 60	20

Preferred age range for pediatric formulations: 2–6 years (10–35 kg); extended age range: 7–15 years (26–60 kg)

crush and mix them with some candy or juice for children to accept medication; secondly, the tablets are supplied without any score making it difficult to break them in half to adjust the amount of drug to the body weight (Table 10.5).

The only currently available formulation for pediatric use is a syrup formulation of Epiquantel® with 600 mg/5 ml of praziquantel, manufactured by the Egyptian International Pharmaceutical Industries Company (EIPICO) in Africa. However, it has shown cost-benefit and production issues (Stothard et al. 2013) and a significantly lower efficacy for *S. mansoni* than for *S. haematobium* (Garba et al. 2013). WHO (2010) recommended the use of crushed tablets until a suitable pediatric formulation be made available. Thus, a proper validation study of the Epiquantel® syrup formulation is required before it can be considered for use in Brazil.

In 2012, a public-private partnership was created to develop, register, and provide access to a child-appropriate praziquantel formulation. This partnership, named Pediatric Praziquantel (PEDPZQ) Consortium, congregates pharmaceutical companies, research institutions, and universities from Europe and the following endemic countries: Kenya, Ivory Coast, and Brazil. (https://www.pediatricpraziquantelconsortium.org/). A key component of PEDPZQ Consortium is the involvement of external experts on pediatric formulations, epidemiology, worm control, or regulatory affairs from scientific and government communities (Hussaarts et al. 2017). As a result of this multidisciplinary and intersectoral approach, an orodispersible tablet (ODT) formulation was developed, containing only the L- (levo) enantiomer that, together with the D- (dextro) enantiomer, makes up the 1:1 racemate of the commercial preparation. The 150 mg orodispersible tablets of L-praziquantel (ODT L-PZQ) were chosen because only the L-enantiomer has antischistosomal activity, and the D-enantiomer is responsible for most of the adverse effects and bitter taste of the racemate (Reinhard-Rupp and Klohe 2017). The 150 mg tablet size allows adequate 50 mg/kg dosing for the preferred age range (up to 6 years of age) as pointed out by Olliaro et al. (2013) and can also be considered for the extended age range (up to 15 years or 60 kg of body weight) (Table 10.5).

It was pointed out on Sect. 10.4 that most endemic localities in Brazil are at low risk. This makes them eligible for active search followed by treatment of the infection carriers if prevalence (one Kato-Katz sample, two slides) is less than 15%, as recommended by the MoH (Brasil 2014). Thus, the proportion of recipients of the pediatric formulation estimated for Brazil may differ from that estimated for endemic countries where MDA is the treatment scheme of choice. Fig. 10.10 shows the age distribution among infection carriers of a representative locality in the endemic area of Brazil (Lindholz et al. 2018). The Kato-Katz prevalence was 12% (55 positives of 461 tested), making it necessary for the largest possible number of infection carriers to be identified for treatment. By using a highly sensitive method based on egg detection (Helmintex®) in combination to Kato-Katz 187 positives were identified. As a result, only 6% would be recipients of the pediatric formulation in the preferred age range (2–6 years), in contrast with an estimated 10% for areas of MDA (Reinhard-Rupp and Klohe 2017); however, extending the use of the pediatric formulation to the age group of 7–15 years age would reach 35% of the eligible population. At present, a clinical trial phase III on the safety and efficacy of ODT L-PZQ is in the final stage in Kenya and Ivory Coast, which will allow deciding between the doses of 50 and 60 mg/kg (https://clinicaltrials.gov/ct2/show/record/

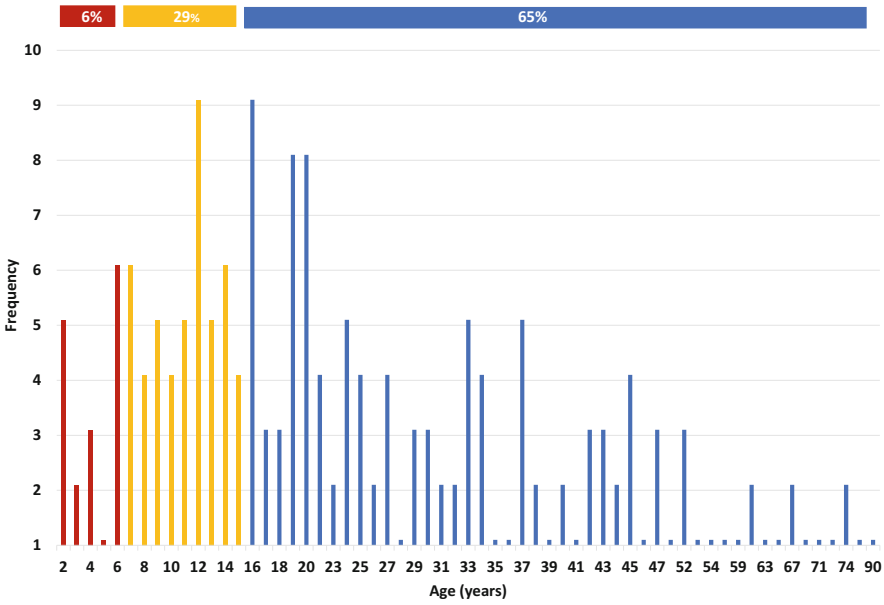


Fig. 10.10 Proportion of recipients of the pediatric formulation of praziquantel in an endemic community of schistosomiasis in Brazil. Preferred ages: 2–6 years; extended ages: 7–15 years. Dataset from Lindholz et al. (2018) available at http://journals.plos.org/plosntds/article/asset?unique & id=info:doi/10.1371/journal.pntd.0006274.s002

NCT03845140). An implementation of the Access and Distribution Plan in priority African countries is planned by the PEDPZQ Consortium for 2023. However, further studies are needed before the ODT L-PZQ is incorporated into the routine of control campaigns in Brazil.

10.11 Perspectives and Concluding Remarks

Complexity of hosts-environment-parasite interactions and their dynamics explains the apparent paradox of increasing uncertainties as we reach advanced stages of control, both in South America, the Caribbean region and other continents. Several important issues are emerging and requiring researchers' and policy-makers' attention: (1) the role of animals other than humans in maintaining the transmission; (2) the need for several high-performance diagnostic tools and their combined application in diverse settings; (3) the heterogeneity on distribution of infection intensities with transmission hot spots; (4) the challenge for engagement of multiple stakeholders, including communities living in endemic areas; (5) very basic needs and improvements in life conditions, including safe water and sanitation.

It was pointed out in Sect. 10.6 that the MoH commitment to reach schistosomiasis elimination by 2020 remains unattended, even though a special guideline was established in 2012 to accomplish it. The new road map launched by WHO (2020)

Fig. 10.11 Targets for Sustainable Development Goal 6 directly relevant to elimination of schistosomiasis and other neglected tropical diseases (Fitzpatrick and Engels 2016)

identified critical gaps and defined actions required at the global level to reach it by 2030 and urged endemic countries to attend the relevant targets of the Sustainable Development Goals (SDG). SDG 6 (clean water and sanitation) is directly relevant to schistosomiasis and other neglected tropical diseases, particularly targets 6.1 and 6.2 (Fitzpatrick and Engels 2016). Other SDGs are also of relevance, such as SDG 1 (no poverty), SDG 2 (zero hunger), SDG 4 (quality education), and SDG 13 (climate action), although indirectly (Fig. 10.11).

The new WHO road map also requests further intersectoral collaboration to address issues related to diagnostics, monitoring and evaluation, access to and logistics for medicines and medical products, capacity strengthening, advocacy, and funding (WHO 2020). This request attends the "One Health—One World" approach recommended by the Special Program for Research and Training in Infectious Diseases of Poverty (TDR), which may be characterized as follows (Zhou 2012): (1) urgency in intersectoral collaboration; (2) priority for interdisciplinary research; (3) greater collaboration between research institutions and government agencies, including public-private partnerships; (4) incorporation of an eco-epidemiological approach in disciplines of Public Health, Medicine, Social Sciences, Veterinary Sciences, and Agricultural Sciences.

In conclusion, the current MoH guideline already comprises the One Health strategy as it recommends an interdisciplinary and intersectoral strategy for community interventions involving, but not limited to, active search and timely treatment of

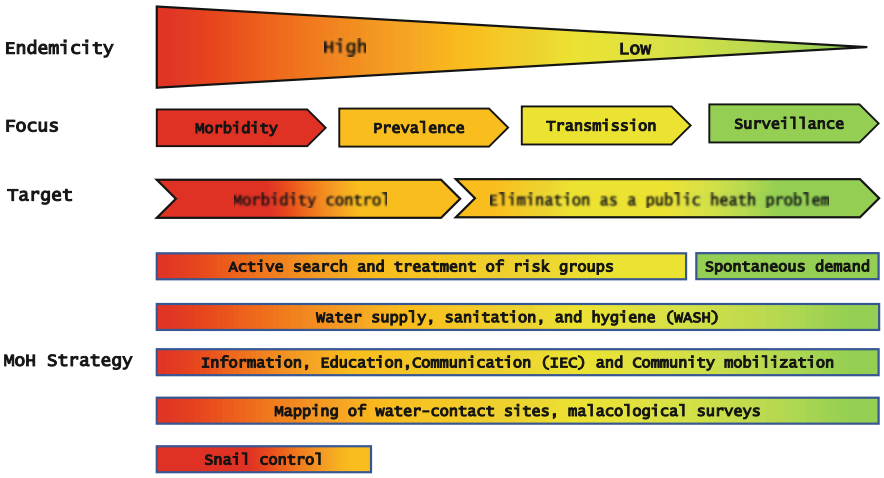


Fig. 10.12 Ministry of Health (MoH) interdisciplinary and intersectoral strategy for morbidity control and elimination of schistosomiasis as a public health problem (Brasil 2014)

risk groups (Fig. 10.12). As pointed out in Sect. 10.5, improved living conditions of the at-risk populations due to priority public policies implemented from the early 2000s to the mid-2010s may have contributed substantially to a sustained, decreasing trend in prevalence and intensity of infection as well as morbidity and mortality of schistosomiasis in Brazil. Although the future for this political priority is currently uncertain, crucial components of the MoH strategy, namely, provision of safe water supply, sanitation, and hygiene (WASH), should receive much more attention from government agencies than has been given recently because they have been formally endorsed as targets in the 2030 Agenda for SDG 6. Other components of the MoH strategy, such as IEC (information, education, and communication), community mobilization, mapping of water-contact sites and malacological surveys and control, will also require strong interdisciplinary and intersectoral efforts under the One Health approach to achieve schistosomiasis elimination in due time.

References

Alarcón-de-Noya B, Pointier JP, Colmenares C et al (1997) Natural *Schistosoma mansoni* infection in wild rats from Guadeloupe: parasitological and immunological aspects. Acta Trop 68:11–21

Alarcón-de-Noya B, Ruiz R, Losada S et al (2007) Detection of schistosomiasis cases in low-transmission areas based on coprologic and serologic criteria. Venezuelan Exp Acta Trop 103(1):41–49

Amaral RS, Tauil PL, Lima DD, Engels D (2006) An analysis of the impact of the Schistosomiasis Control Programme in Brazil. Mem Inst Oswaldo Cruz 101(Suppl 1):79–85

Andrade ZA (1998) The situation of hepatosplenic schistosomiasis in Brazil today. Mem Inst Oswaldo Cruz 93(Suppl 1):313–316

Andrade ZA, Bina JC (1983) A patologia da forma hepato-esplênica da esquistossomose mansoni em sua forma avançada—estudo de 232 necrópsias completas. Mem Inst Oswaldo Cruz 78(3): 285–305

Banoo S, Bell D, Bossuyt P et al (The TDR Diagnostics Evaluation Expert Panel) (2006) Evaluation of diagnostic tests for infectious diseases: general principles. Nat Rev Microbiol 4:S21–S31

Barbosa CS, Favre TC, Amaral RS, Pieri OS (2008) Epidemiology and control of schistosomiasis mansoni. In: Carvalho OS, Coelho PMZ, Lenzi HL (eds) *Schistosoma mansoni* and schistosomiasis: a multidisciplinary vision. FIOCRUZ, Rio de Janeiro, pp 964–1008

Barbosa CS, Gomes ECS, Campos JV et al (2016) Morbidity of mansoni schistosomiasis in Pernambuco-Brazil: analysis on the temporal evolution of deaths, hospital admissions and severe clinical forms (1999–2014). Acta Trop 164:10–16

Bergquist R, Johansen MV, Utzinger J (2009) Diagnostic dilemmas in helminthology: what tools to use and when? Trends Parasitol 25:151–156

Bina JC, Prata A (1983) Regression of hepatosplenomegaly by specific treatment of schistosomiasis. Rev Soc Bras Med Trop 16(4):213–218

Brasil (2008) [Surveillance and Control of Molluscs with Epidemiological Importance: technical directives: Schistosomiasis Control and Surveillance Program (PCE)]. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica, 2nd edn. Ministério da Saúde, Brasília, p 178

Brasil (2014) [Surveillance of schistosomiasis mansoni: technical guideline], 4th edn. MS/SVS/DVDT, Brasília: Ministério da Saúde. 144 p. http://bvsms.saude.gov.br/bvs/publicacoes/vigilancia esquistossome mansoni diretrizes tecnicas.pdf Accessed 01/03/2021

Brasil (2018) [Health education for schistosomiasis control]. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. Brasília: Ministério da Saúde, 40 p. http://bvsms.saude.gov.br/bvs/publicacoes/educacao_saude_controle_esquistossomose.pdf Accessed 01/03/2021

Cabello R, Beck L, Massara CL et al (2016) *Schistosoma mansoni* infection and related knowledge among schoolchildren in an endemic area of Minas Gerais, Brazil, prior to educational actions. Acta Trop 164:208–215

Cameron TWM (1928) A New Definitive Host for *Schistosoma mansoni*. J Helminthol 6(4): 219–222

Carvalho OS, Milward-Andrade R, Cortês MBN (1975) Roedores silvestres na epidemiologia da esquistossomose mansônica no Lago da Pampulha, Belo Horizonte, Minas Gerais (Brasil). Rev Soc Bras Med Trop 9(1):26:35

Catalano S, Sène M, Diouf ND et al (2018) Rodents as natural hosts of zoonotic *Schistosoma* species and hybrids: an epidemiological and evolutionary perspective from West Africa. J Infect Dis 218:429–433

Cheever AW, Macedonia JG, Mosimann JE, Cheever EA (1994) Kinetics of egg production and egg excretion by *Schistosoma mansoni* and *S. japonicum* in mice infected with a single pair of worms. Am J Trop Med Hyg 50(3):281–295

Coelho P, Caldeira RL (2016) Critical analysis of molluscicide application in schistosomiasis control programs in Brazil. Infect Dis Poverty 5:57

Coelho PM, Jurberg AD, Oliveira AA, Katz N (2009) Use of a saline gradient for the diagnosis of schistosomiasis. Mem Inst Oswaldo Cruz 104:720–723

Colley DG, Bustinduy AL, Secor WE, King CH (2014) Human schistosomiasis. Lancet 383:2253–2264

Coura JR, Conceição J, Santos ML et al (1992) Cross-sectional and evolutive studies of schistosomiasis mansoni in untreated and mass treated endemic areas in the southeast and northeast of Brazil. Mem Inst Oswaldo Cruz 87(Suppl 4):175–182

Crompton DWT, World Health Organization (2006) Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. World Health Organization https://apps.who.int/iris/handle/10665/43545. Accessed 21/01/2021

Favre TC, Pereira AP, Beck LC et al (2015) School-based and community-based actions for scaling-up diagnosis and treatment of schistosomiasis toward its elimination in an endemic area of Brazil. Acta Trop 149:155–162

Favre TC, Massara CL, Beck L et al (2021) Adherence to diagnosis followed by selective treatment of schistosomiasis mansoni and related knowledge among schoolchildren in an endemic area of Minas Gerais, Brazil, prior to and after the implementation of educational actions. Parasite Epidemiol Control 13:e00208

Ferrari TC, Moreira PR, Cunha AS (2008) Clinical characterization of neuroschistosomiasis due to *Schistosoma mansoni* and its treatment. Acta Trop 108:89–97

Ferrer E, Villegas B, Mughini-Gras L et al (2020) Diagnostic performance of parasitological, immunological, and molecular tests for the diagnosis of *Schistosoma mansoni* infection in a community of low transmission in Venezuela. Acta Trop 204:105360

Fitzpatrick C, Engels D (2016) Leaving no one behind: a neglected tropical disease indicator and tracers for the sustainable development goals. Int Health 8(Suppl 1):15–18

FUNASA (2020) [Sanitation for Health Promotion] http://www.funasa.gov.br/web/guest/saneamento-para-promocao-da-saude?inheritRedirect=true Accessed 21/01/2021.

Gabrielli AF, Montresor A, Chitsulo L et al (2011) Preventive chemotherapy in human helminthiasis: theoretical and operational aspects. Trans R Soc Trop Med Hyg 105(12):683–693

Garba A, Lamine MS, Djibo A et al (2013) Safety and efficacy of praziquantel syrup (Epiquantel™) against *Schistosoma haematobium* and *Schistosoma mansoni* in preschool-aged children in Niger. Acta Trop 128:318–325

Gentile R, Costa-Neto SF, Gonçalves MML et al (2006) An ecological field study of the water-rat *Nectomys squamipes* as a wild reservoir indicator of *Schistosoma mansoni* transmission in an endemic area. Mem Inst Oswaldo Cruz 101(Suppl. 1):111–117

Gomes LI, Enk MJ, Rabello A (2013) Diagnosing schistosomiasis: where are we? Rev Soc Bras Med Trop 47(1):3–11

Graeff-Teixeira C, Favero V, Pascoal VF et al (2021a) Low specificity of point-of-care circulating cathodic antigen (POC–CCA) diagnostic test in a non-endemic area for schistosomiasis mansoni in Brazil. Acta Trop 217:105863

Graeff-Teixeira C, Favero V, Souza RP et al (2021b) Use of *Schistosoma mansoni* soluble egg antigen (SEA) for antibody detection and diagnosis of schistosomiasis: the need for improved accuracy evaluations of diagnostic tools. Acta Trop 215:105800

Hewitt R, Willingham AL (2019) Status of Schistosomiasis Elimination in the Caribbean Region. Trop Med Infect Dis 4(1):24

Hofstede SN, Tami A, van Liere GA et al (2014) Long-term effect of mass chemotherapy, transmission and risk factors for *Schistosoma mansoni* infection in very low endemic communities of Venezuela. Acta Trop 140:68–76

Hussaarts L, van der Weijde K, Dome P et al (2017) Product development programs for neglected tropical diseases: a crucial role for expert meetings. PLoS Negl Trop Dis 11:e0005183

Jordan P (1985) Schistosomiasis: the St. Cambridge University Press, Cambridge, UK, Lucia Project, p 442

Katz N (1998) Schistosomiasis control in Brazil. Mem Inst Oswaldo Cruz 93(Suppl 1):33–35

Katz N (2008a) Clinical therapy in schistosomiasis mansoni. In: Carvalho OS, Coelho PMZ, Lenzi HL (eds) *Schistosoma mansoni* and schistosomiasis: a multidisciplinary vision. FIOCRUZ, Rio de Janeiro, pp 964–1008

Katz N (2008b) The discovery of schistosomiasis mansoni in Brazil. Acta Trop 101:67–71

Katz N (2018) [National survey of prevalence of schistosomiasis mansoni and soil-transmitted helminthiases]. René Rachou Institute-FIOCRUZ, Belo Horizonte. http://www2.datasus.gov.br/datasus/index.php?area=0208 Accessed May 12th, 2021.

Katz N, Brener Z (1966) Evolucão clínica de 112 casos de esquistossomose mansoni observados após dez anos de permanência em focos endêmicos de Minas Gerais. Rev Inst Med Trop S Paulo 8:139–142

Kawazoe U, Pinto ACM (1983) Importância epidemiológica de alguns animais silvestres na esquistossomose mansônica. Rev Saúde públ S Paulo 17:345–366

King CH, Dangerfield-Cha M (2008) The unacknowledged impact of chronic schistosomiasis. Chronic Illn 4:65–79

King CH, Dickman K, Tisch DJ (2005) Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet 365:1561–1569

Lambertucci JR (2014) Revisiting the concept of hepatosplenic schistosomiasis and its challenges using traditional and new tools. Rev Soc Bras Med Trop 47(2):130–136

Lambertucci JR, Silva LC, Amaral RS (2007) Guidelines for the diagnosis and treatment of schistosomal myeloradiculopathy. Rev Soc Bras Med Trop 40:574–581

Lindholz CG, Favero V, Verissimo CM et al (2018) Study of diagnostic accuracy of Helmintex, Kato-Katz, and POC-CCA methods for diagnosing intestinal schistosomiasis in Candeal, a low intensity transmission area in northeastern Brazil. PLoS Negl Trop Dis 12:e0006274

Machado PA (1982) The Brazilian program for schistosomiasis control, 1975–1979. Am J Trop Med Hyg 31:76–86

Manson P (1902) Report of a case of bilharzia from the West Indies. Br Med J 2:1894

Martins-Melo FR, Pinheiro MC, Ramos NA et al (2014) Trends in schistosomiasis-related mortality in Brazil, 2000–2011. Int J Parasitol 44:1055–1062

Martins-Melo FR, Carneiro M, Ramos NA (2018) The burden of Neglected Tropical Diseases in Brazil, 1990–2016: a subnational analysis from the Global Burden of Disease Study 2016. PLoS Negl Trop Dis 12:e0006559

Miranda GS, Rodrigues JGM, Lira MGS et al (2015) Monitoring positivity for *Schistosoma mansoni* in rodents *Holochilus* sp. naturally infected. Ciência Animal Brasileira 16(3):456–463

Modena CM, Lima WD, Coelho PMZ (2008) Wild and domesticated animals as reservoirs of Schistosomiasis mansoni in Brazil. Acta Trop 108(2–3):242–244

Morgan JAT, Dejong RJ, Adeoye GO et al (2005) Origin and diversification of the human parasite *Schistosoma mansoni*. Mol Ecol 14:3889–3902

Nguyen K, Gemmel B, Rohr J (2020) Effects of temperature and viscosity on miracidial and cercarial movement of *Schistosoma mansoni*: ramifications for disease transmission. Int J Parasitol 50(2):153–159

Noya O, Alarcón-de-Noya B, Losada S et al (2002) Laboratory diagnosis of schistosomiasis in areas of low transmission. A review of a line of research. Mem Inst Oswaldo Cruz 97(Suppl: I):167–169

Noya O, Katz N, Pointier JP et al (2015) Schistosomiasis in America. In: Franco-Paredes C, Santos-Preciado J (eds) Neglected Tropical Diseases—Latin America and the Caribbean. Neglected Tropical Diseases. Springer, Vienna. https://doi.org/10.1007/978-3-7091-1422-3_2 Accessed May 12th, 2021

Olliaro PL, Vaillant M, Hayes DJ et al (2013) Practical dosing of praziquantel for schistosomiasis in preschool-aged children. Tropical Med Int Health 18:1085–1089

Pan American Health Organization (2009) 49th Directing Council—Final Report, 61st Session of the Regional Committee, Washington, DC, USA https://iris.paho.org/bitstream/handle/10665.2/34484/CD49-PFR-e.pdf?sequence=1&isAllowed=y Accessed 21/01/2021

Pan American Health Organization (2014) PAHO/WHO Schistosomiasis Regional Meeting. Defining a road map toward verification of elimination of schistosomiasis transmission in Latin America and the Caribbean by 2020. https://www.paho.org/en/documents/pahowho-schistosomiasis-regional-meeting-defining-road-map-toward-verification-0 Accessed May 12th, 2021

Pan American Health Organization (2016). Neglected infectious diseases in the Americas: success stories and innovation to reach the neediest. https://iris.paho.org/handle/10665.2/31250 Accessed May 12th, 2021

Reinhard-Rupp J, Klohe K (2017) Developing a comprehensive response for treatment of children under 6 years of age with schistosomiasis: research and development of a pediatric formulation of praziquantel. Infect Dis Poverty 6:122

Rijpstra AC, Swellengrebel NH (1962) Lateral-spined schistosome ova in a great anteater, *Myrmecophaga tridactyla* L. (Edentata), from Surinam. Trop Geogr Med 14:279–283

Sarvel AK, Oliveira AA, Silva AR et al (2011) Evaluation of a 25-year-program for the control of schistosomiasis mansoni in an endemic area in Brazil. PLoS Negl Trop Dis 5(3):e990

Silva RR, Machado-Silva JR, Faerstein NF et al (1992) Natural infection of wild rodents by *Schistosoma mansoni*—pathological aspects. Mem Inst Oswaldo Cruz 87(Supl:1):271–276

Silva TMC, Andrade ZA (1989) Infecção natural de roedores silvestres pelo *Schistosoma mansoni*. Mem Inst Oswaldo Cruz 82(2):227–235

Silva-Moraes V, Shollenberger LM, Siqueira LMV et al (2019) Diagnosis of *Schistosoma mansoni* infections: what are the choices in Brazilian low-endemic areas? Mem Inst Oswaldo Cruz 114: e180478

Silva-Souza N, Silva APC, Oliveira RM et al (2019) Parasitological and histological aspects of *Holochilus sciureus* naturally infected by *Schistosoma mansoni*. Braz J Vet Parasitol 28(4): 769–772

SISPCE (2021) [Schistosomiasis Control Program (PCE): health information]. http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinan/pce/cnv/pcebr.def Accessed 21/01/2021

Stothard JR, Sousa-Figueiredo JC, Betson M et al (2013) Schistosomiasis in African infants and preschool children: let them now be treated! Trends Parasitol 29:197–205

Sturt AS, Webb EL, Francis SC et al (2020) Beyond the barrier: Female Genital Schistosomiasis as a potential risk factor for HIV-1 acquisition. Acta Trop 209:105524

Swellengrebel NH, Rijpstra AC (1965) Lateral-spined schistosome ova in the intestine of a squirrel monkey from Surinam. Trop Geogr Med 17:80–84

Teixeira CF, Neuhauss E, Ben R et al (2007) Detection of *Schistosoma mansoni* eggs in feces through their interaction with paramagnetic beads in a magnetic field. PLoS Negl Trop Dis 1: e73

Théron A, Pointier JP, Morand S et al (1992) Long-term dynamics of natural populations of *Schistosoma mansoni* among *Rattus rattus* in patchy environment. Parasitology 104(2):291–298

World Health Organization (1985) The control of schistosomiasis. WHO, Geneva. Technical Report Series 728. https://www.who.int/publications/i/item/WHO-TRS-728 Accessed 14/05/2021

World Health Organization (2002) Prevention and Control of Schistosomiasis and Soil-transmitted Helminthiasis: Report of a WHO Expert Committee. WHO Technical Report Series 912, WHO, Geneva. https://apps.who.int/iris/bitstream/handle/10665/42588/WHO_TRS_912.pdf?sequence=1&isAllowed=y Accessed 21/01/2021

World Health Organization (2006) Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers. WHO, Geneva http://apps.who.int/iris/bitstream/handle/10665/43545/9241547103_eng.pdf?sequence=1 Accessed 21/01/2021

World Health Organization (2010) Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-aged children. World Health Organization https://www.who.int/schistosomiasis/resources/9789241501880/en/ Accessed 21/01/2021

World Health Organization (2011) Helminth control in school-age children: a guide for managers of control programmes, 2nd ed. World Health Organization. https://apps.who.int/iris/handle/10665/44671

World Health Organization (2012a) Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation: executive summary. World Health Organization. https://apps.who.int/iris/handle/10665/70809 Accessed 21/01/2021

World Health Organization (2012b) Schistosomiasis: population requiring preventive chemotherapy and number of people treated in 2010. Weekly Epidemiological Record, No 4, 87, 37–44. https://www.who.int/wer/2012/wer8704.pdf?ua=1 Accessed 21/01/2021

World Health Organization (2013) Schistosomiasis: Progress Report 2001–2011 and Strategic Plan 2012–2020. WHO, Geneva http://apps.who.int/iris/handle/10665/78074 Accessed 21/01/2021

World Health Organization (2017) Field use of molluscicides in schistosomiasis control programmes: an operational manual for programme managers. Geneva. https://apps.who.int/iris/bitstream/handle/10665/254641/9789241511995-eng.pdf?sequence=1&isAllowed=y Accessed 21/01/2021

World Health Organization (2020) Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. World Health Organization. https://apps.who.int/iris/handle/10665/332094 Accessed 21/01/2021

World Health Organization (2021) Neglected Tropical Diseases PCT databank. Schistosomiasis. https://www.who.int/neglected_diseases/preventive_chemotherapy/sch/en/ Accessed 13/01/2021

Yuan LP, Manderson L, Ren MY et al (2005) School-based interventions to enhance knowledge and improve case management of schistosomiasis: a case study from Hunan, China. Acta Trop 96:248–254

Zhou XN (2012) Prioritizing research for "One health—One world". Infect Dis Poverty 1:1

Zoni AC, Catala L, Ault SK (2016) Schistosomiasis prevalence and intensity of infection in Latin America and the Caribbean Countries, 1942–2014: a systematic review in the context of a regional elimination goal. PLoS Negl Trop Dis 10:e0004493

Zou H-Y, Yu Q-F, Qiu C et al (2020) Meta-analyses of *Schistosoma japonicum* infections in wild rodents across China over time indicates a potential challenge to the 2030 elimination targets. PLoS Negl Trop Dis 14(9):e0008652

Hookworms in South America: A Constant Threat Especially to Children

11

Heinz Mehlhorn

Abstract

Hookworms (= bloodsucking nematodes) belong to the group of the most common and extremely dangerous worms worldwide. They attack humans as well as animals, especially in so-called developing countries in warm climates as in South America. Especially people living in regions with a low-graded health system are still today highly endangered and suffer from large numbers of death cases ranging from young kids to old persons.

The present chapter gives insights into the life cycle of these worms, their morphology, their life cycle, prevention methods, and treatment changes in times of progressing drug resistances. Thus it is time to ameliorate the hygienic systems in these countries by the help of the One Health program and by information targeted to a broad spectrum of endangered people how to avoid infections.

Keywords

Hookworms · *Necator americanus* · *Ancylostoma* species · Human health program by WHO · Hygienic ameliorations

11.1 Topics

1. **Name of Agent of Disease:** Greek: *ankylos* = bended, hook-like; *stoma* = mouth; *duodenalis* = living in the intestinal region of the duodenum; *necator* = killer; *americanus* = American; group: old and new world hookworms, which belong to the worm group of nematodes.

H. Mehlhorn (✉)
Department of Parasitology, Heinrich Heine University, Duesseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_11

2. **Geographic Distribution:** In South America two helminth species are the most common ones attacking humans: *Ancylostoma duodenale* and *Necator americanus*. In addition further species like *Ancylostoma caninum*, *A. tubaeforme*, *A. braziliensis*, *A. ceylanicum* attack many countries of South American mainly animals, but apparently also humans in large (Logan et al. 2020). However, mostly they do not reach the adult stage in humans and stick as larvae somewhere in the skin. The danger in many rural regions is very high (Logan et al. 2020). There had been found soil being infested close to human dwellings in ranges of up to 87.5%, although in general, the numbers decrease slowly.
3. **Life Cycle (**Fig. 11.1**):** The whitish appearing adults of the species *Ancylostoma duodenale*, *A. braziliensis,* and *Necator americanus* measure about 10–12 mm in length and are constantly fixed at the intestinal wall of humans and other vertebrate hosts and suck their blood as well as that of many rather unspecific hosts. By the help of their typical cutting plates inside the mouth (Figs. 11.2 and 11.3) they destroy the intestinal wall and its blood vessels and thus they become able to suck permanently considerable amounts of blood, which get lost for their hosts and thus they induce a significant weakening. This often very significant loss of blood supports the upgrading of other infections often leading to death, especially in the case of weak children or persons being hit by further diseases.

The **hookworm infection of humans** and warm-blooded animals (Fig. 11.1) starts when free-living larvae 3 penetrate their skin and stripe off their second larval sheath. After an obligatory passage of a heart-lung-trachea-esophagus passage, the larvae reach within 3-7 days the inner side of the intestine, where they become attached, grow up by bloodsucking, and reach maturity within 4-6 weeks. Then couples are formed whereby both male and female in copula attach themselves at the intestinal wall and start sucking blood (Fig. 11.1). This blood is not only used to cover the needed amounts of food, but they use additionally the oxygen contained in the blood of their hosts. This special behavior leads to the fact that infected humans and animals discharge considerable amounts of blood in their feces and thus become hit by **anemia**, which is especially very dangerous for children and malnourished persons. On the other side, the female worms become able to produce enormous amounts of eggs: for example, females of *Necator americanus* (Fig. 11.4) excrete up to 15,000 eggs per day, which are thin-walled like those excreted by *Ancylostoma* species (9000–10,000 eggs per day). The eggs (Fig. 11.5) are thin-walled, measure 60 × 40 μm, and contain only two to eight cells just after deposition. Under agreeable warm and humid outside conditions (like those in the tropics) the first, so-called rhabditiform larva develops within (only) 2 days and leaves the egg. This quick development makes it necessary for diagnosis to examine mainly fresh feces in order to avoid laboratory-borne infections (!). Early investigations also avoid finding and misinterpretation of other nematodes such as those of the genera *Trichostrongylus* or *Ternidens,* etc.

After hatching of the larva 1 from the egg (Fig. 11.5) outside of the body, larvae 2 and 3 develop under striping off their surface cuticle (Fig. 11.1, stages 5–8). The

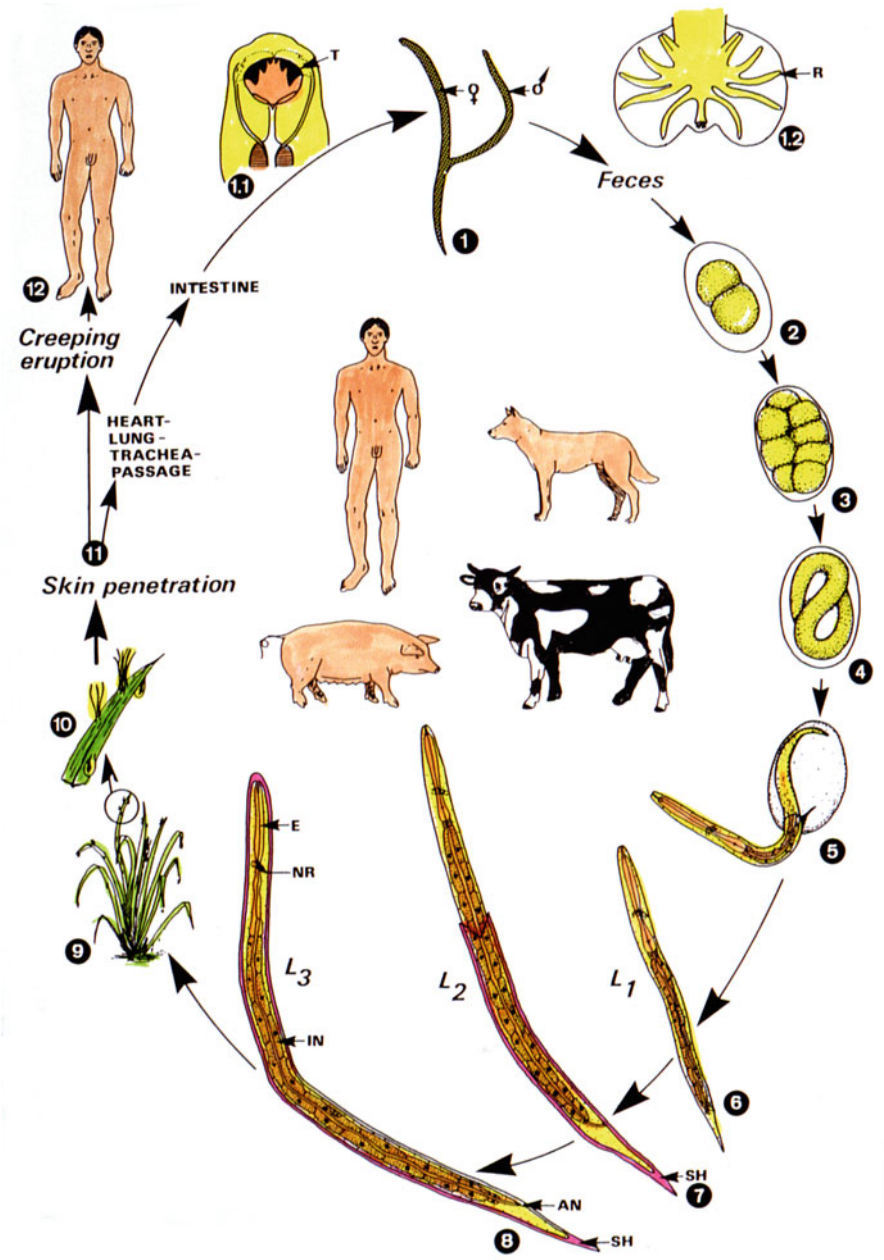


Fig. 11.1 Hookworms of humans and animals: Diagrammatic representation of the life cycle of hookworms of the genera *Ancylostoma duodenale*, *A. caninum*, *A. braziliense*, *Necator americanus* ***1*** The adults inhabit in a copula position the small intestine of their hosts, attaching themselves by means of their buccal cavity to the mucous layer and sucking blood using their species-specific teeth (***1.1***). By help of their copulatory bursa (fortified with specific rays; ***1.2***) the males are attached to the female vulva (location varies according to species) thus giving rise to the typical Y-shaped copulatory aspects. ***2–4*** Eggs are excreted unembryonated and develop the L_1 on the soil. ***5–8*** The

third stage larva is the so-called **filariform stage**, which reaches a length of 500–650 μm and is still enclosed within the cuticle sheath of the second-stage larva and thus is named **"sheathed larva,"** which may penetrate into the human or animal skin. As soon as this larva has entered the host body and penetrated into one of its blood vessels, it starts a heart-lung-trachea- esophagus passage (but drifts occasionally also into other organs). The larva 3 (in general) reaches the intestine within 3–8 days, where it grows up to maturity within 4–6 weeks.

Besides the larvae of *A. duodenale* (Fig. 11.6) and *Necator americanus* there exist on the soil other ones which mainly penetrate animals, but they may also enter the skin of humans, but they do not reach maturity and remain stuck somewhere in the skin or in organs of the penetrated hosts (humans). Especially the larvae of *Ancylostoma braziliense* remain mainly in the skin of humans producing swellings described as "larva migrans" or "creeping eruption" (Fig. 11.7).

4. Symptoms of Disease: The most important problem in cases of an infection with *Ancylostoma* and *Necator* hookworms (Figs. 11.2, 11.3, 11.4, and 11.5) is posed by the constant loss of blood by sucking of eventually very high numbers of worms in a human body—especially in the case of children, who are not nourished sufficiently. Thus disability-adjusted life years (DALYs) measuring the overall disease burden of a person have been counted in the last years at 3.2 million, which represents about one half of the DALYs counted worldwide for soil-transmitted helminth infections. Especially malnourished children and pregnant women are highly endangered in South American countries—especially in overcrowded towns with low rates of personal income.

The **blood loss**, which even goes on for a while due to blocking of blood clots after detachment of satisfied worms is one of the most important reasons to increase morbidity by **high-graded anemia**. Sucking hookworms also induce ulcers and eventually large inflammation reactions due to the mechanical damages during the blood sucking phase. The malaise (anemia) due to the bloodsucking is even increased due to the fact that poor families cannot buy sufficient food for infested

Fig. 11.1 (continued) L_1, which is called a rhabditiform larva (due to its esophagus), escapes from the eggshell and feeds on organic material. Then it undergoes the first molt by completely shedding its cuticle and replacing it by a thicker new one. After a time spent feeding, the L_2 (still in a rhabditiform shape) molts and is now the infectious filariform L_3. The second-stage cuticle may be retained (***8***) as a loose-fitting sheath or it may be lost earlier (***7***). ***9–10*** The L_3 stages live in the upper few millimeters of soil, migrate to the surface, and are often found in groups of thousands on the soil or on plants (moving synchronously). ***11*** Infection of final hosts occurs when L_3 contacts the skin and burrows into it. After a heart-lung-trachea passage, the L_3 larvae reach the intestine, molt twice, and become sexually mature (In some species the transplacental transmission of L_3 or the transmission within mother's milk is possible). ***12*** If a human becomes invaded by an L_3 larva of a species or strain that normally matures in animals (e.g., *A. caninum, A. braziliense*) the larvae may migrate for months within the cutaneous layers, leading to a disease called "creeping eruption." *AN* anus, *E* esophagus, *IN* intestine, *NR* nerve ring, *R* rays of bursa copulatrix, *SH* sheath (originating from the molted cuticle of the preceding larval stage), *T* tooth (here each equipped with three peaks). Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016a)

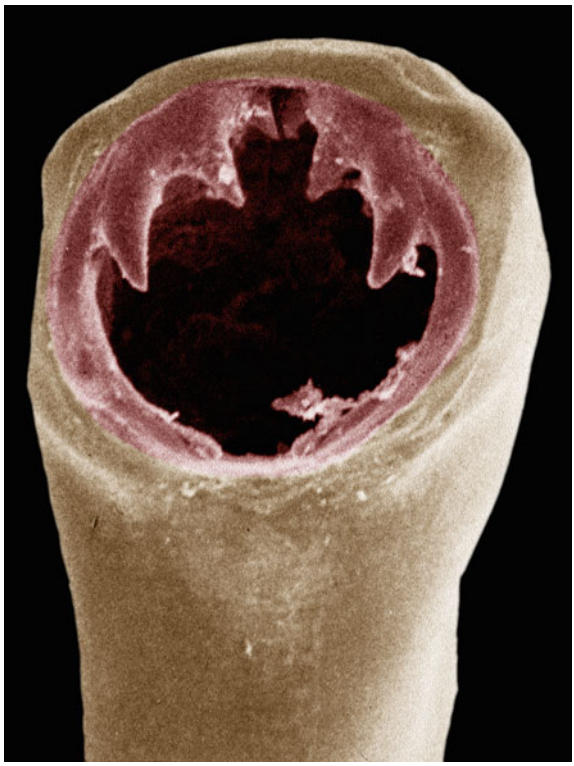


Fig. 11.2 Scanning electron micrograph of the mouth region of an adult hookworm of the species *Ancylostoma duodenale* showing two lateral cutting plates each bearing two teeth

family members. Especially pregnant women are highly endangered by blood loss due to sucking of several worms at the same time (Fig. 11.8).

11.2 Phases of Disease

– Skin Penetration Phase:

Itching and formation of papulae at the penetration sites of the larva 3.

– Lung Passage:

Symptoms are induced like bronchitis, lymph node swellings and lung and trachea inflammations.

– Acute Disease:

In cases of high mass infections, hemoglobin becomes massively decreased. Reddish and even black stools are excreted and fever as well as high-grade eosinophilia occur.

– Chronic Phase of Disease:

This phase is very dangerous, since worms live up to 20 years. Thus, there is a constant blood loss which leads to a considerable weakness of the patient. Further symptoms are abdominal pain, slight fever, obstipation, occult bloody stool,

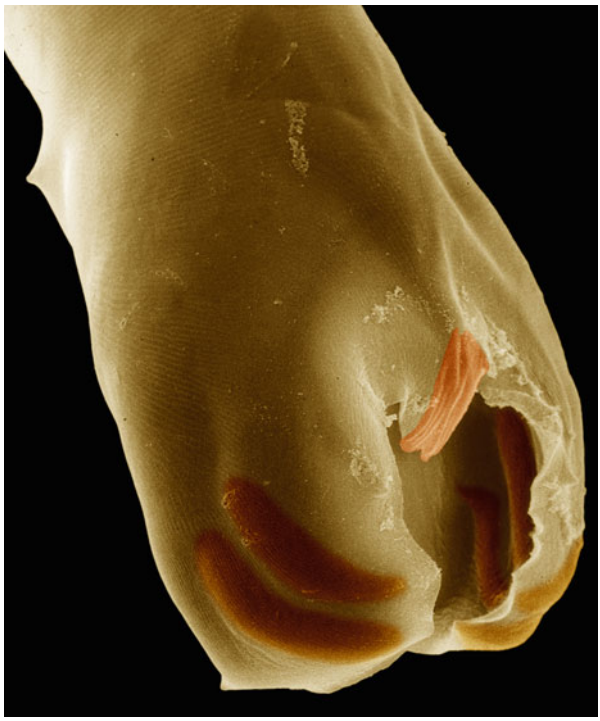


Fig. 11.3 Scanning electron micrograph of the hind region of an adult male hookworm of the genus *Ancylostoma duodenale* showing the so-called "bursa copulatrix," which is used to enclose the female sexual opening during copulation (see Fig. 1.1)

Fig. 11.4 Scanning electron micrograph of an adult hookworm of the species *Necator americanus*, the mouth of which is equipped with two cutting plates, which is used as a criterion for a significant diagnosis.
Figs. 2–4: Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016b)

increasing anemia with consequences such as cachexia, heart and circulation problems, which in high-graded infections may lead finally to death.

At least 100,000 people die worldwide per year due to heavy infections with these hookworms. Especially children are in general severely hit, since they are often

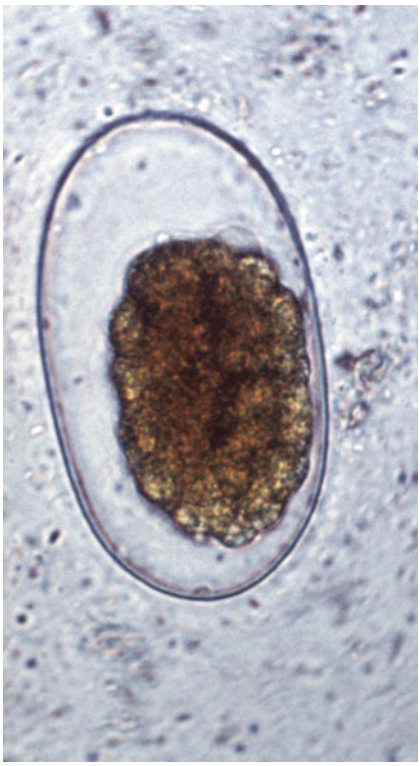


Fig. 11.5 Light micrograph of an egg of a hookworm showing dividing cells to form finally a larva

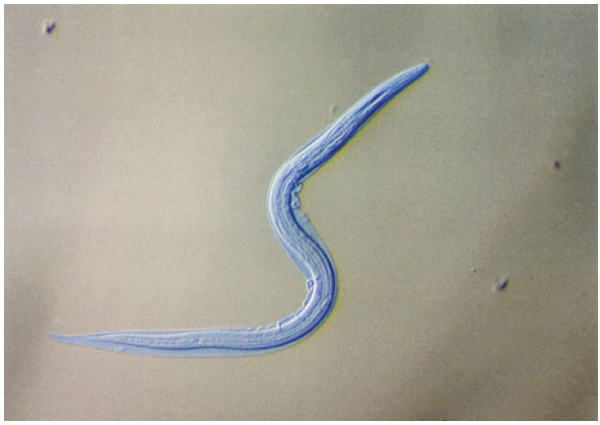


Fig. 11.6 Light micrograph of a so-called rhabditiform larva, which has left the egg

double infections with other parasites, viruses and/or bacteria, when they play on contaminated soil.

- Pregnancy: This phase is associated with lower eosinophil counts and lower eosinophil response to hookworms—especially during the second and third

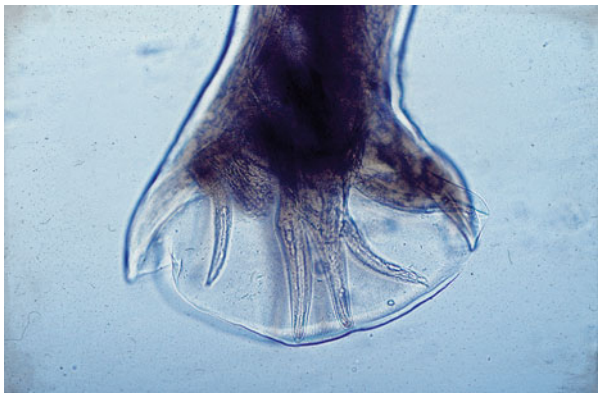


Fig. 11.7 Light micrograph of the terminal end of an adult female hookworm, which is able to clutch the sexual opening of the female thus leading to the typical Y-like aspect of the couple as shown in **Fig. 1.1**

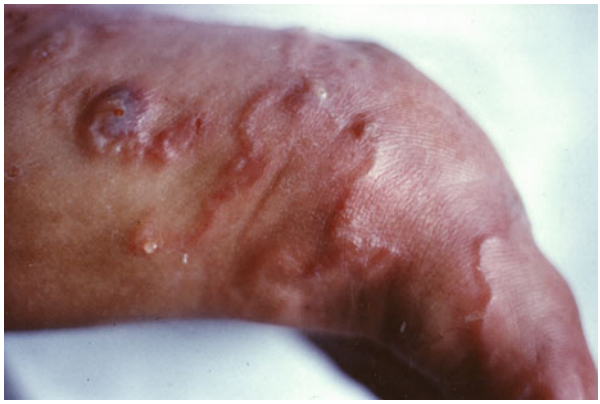


Fig. 11.8 Macrophoto of a human arm into which has been entered by hookworm larvae which wander around. This aspect is mainly seen in cases of infection of species, which in general do not parasitize as adults in the intestine of humans. Figs. 5–8: Reprinted by permission from Springer Nature: Springer International Publishing (Mehlhorn 2016a)

trimester. Both hookworm and pregnancy are associated with a higher erythrocyte sedimentation rate (ESR) (Anderson et al., 2020).

5. Pathway of Infection: The infection of humans and animals occurs by the following procedure shown in Fig. 11.1: The infection occurs by the penetration of the larva 3, which has been developed via two molts on the soil and penetrates thereafter into the skin of a host (naked feet of humans, animals). Due to the lack of a development of immunity, repeated infections are possible as well as self-infections. Recent studies (Furtado et al., 2020a, b) showed that house dust might transport eggs of *Necator americanus* (and probably others) from outside into human dwellings, which increases the risk of infection.

6. Diagnosis: Microscopical demonstration of eggs inside the feces by the help of concentration methods such as sedimentation, like M.I.F.C. (merthiolate iodine formol concentration) or S.A.F. (sodium acetate formalin concentration). Fresh excreted eggs of the hookworms can be distinguished from eggs of the worms belonging to the genera *Trichostrongylus* and *Ternidens* (e.g., *T. deminutus*) by the fact that they only contain two to eight embryonic cells, while the eggs of the two other genera contain at least 32, 64 or even more cells.

7. Prophylaxis: Wearing of firm shoes in endemic regions, avoidance of contact to human feces. Regions with high amounts of human cases must build open-air toilets in order to avoid infections due to larvae 3 in human cases. Fruits collected from soil should be washed before eating, since they might have contact to worm-containing feces. **Attention:** Working in laboratory with hookworm eggs must consider the fact that larvae hatch very quick: thus, tables and vessels must be intensively cleaned.

8. Incubation Period: A few hours after penetration of the larva 3 the signs of dermatitis may already become observed, while it takes about 2 weeks after the percutaneous infection that intestinal symptoms start to increase.

9. Prepatent Period: 5–6 weeks.

10. Patency: Up to 20 years.

11. Three Therapy Recommendations by WHO:

1. **Preventive chemotherapy (deworming)**, should be done using annual or biannual[a] single-doses of albendazole (400 mg) or **mebendazole (500 mg)**[b]. This is recommended as a public health intervention for all young children (12-23 months of age), preschool (24-59 months of age) and school-age children living in areas where the baseline prevalence of any soil-transmitted infection is 20% or higher among children, in order to reduce the worm burden of soil-transmitted helminth infections (*strong recommendation, low-quality evidence*).

   [a] **Biannual administration** is recommended where the baseline prevalence is over 50%.

   [b] **A half-dose of albendazole (i.e., 200 mg) is recommended for children younger than 24 months of age.**

2. **Preventive chemotherapy (deworming)**, using annual or biannual[a] single-dose **albendazole** (400 mg) or **mebendazole** (500 mg), is recommended as a public health intervention for all non-pregnant adolescent girls (10–19 years of age) and non-pregnant women of reproductive age (15–49 years of age) living in areas where the baseline prevalence of any soil-transmitted helminth infection is 20% or higher among non-pregnant adolescent girls and non-pregnant women of reproductive age, in order to reduce the worm burden of soil-transmitted helminth infection (*strong recommendation, moderate-quality evidence*).

   [a] **Biannual administration** is recommended where the baseline prevalence is over 50%.

3. **Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg)**, is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (1) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and (2) anemia is a severe public health problem, with a prevalence of 40% or higher among pregnant women[a], in order to reduce the worm burden of hookworm and *T. trichiura* infection (*conditional recommendation, moderate-quality evidence*).

Table 11.1 Characteristics of the so-called human hookworms *Ancylostoma duodenale* and *Necator americanus*

Charcteristics	*Ancylostoma duodenale*	*Necator americanus*
Mouth opening	4 teeth (= 2 plates each with two points	2 cutting plates
Terminal end of females	With a terminal point	Without a terminal point
Appearance of the two spiculae of males	Always separated, not fused	Often fused at the tips, equipped with crocs

[a] For the most recent estimates of the prevalence of anaemia, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS).

4. Benzimidazole resistance has been shown in Brazil in *Necator americanus* as well as *Ascaris lumbricoides* (Zuccherato et al., 2018) (Table 11.1).

References

Anderson AS, Trumble BC, Hové C, Kraft TS, Kaplan H, Gurven M, Blackwell AD (2020) Old friends and friendly fire: pregnancy, hookworm infection, and anemia among tropical horticulturalists. Am J Hum Biol 32(2):e23337

Furtado LFV, Dos Santos TR, de Oliveira VNGM, Rabelo ÉML (2020a) Genotypic profile of benzimidazole resistance associated with SNP F167Y in the beta-tubulin gene of *Necator americanus* helminths obtained from Brazilian populations. Infect Genet Evol 86:104594

Furtado LFV, Dias LTO, Rodrigues TO, Silva VJD, Oliveira VNGM, Rabelo ÉML (2020b) Egg genotyping reveals the possibility of patent *Ancylostoma caninum* infection in human intestine. Sci Rep 10(1):3006

Logan J, Pearson MS, Manda SS, Choi YJ, Field M, Eichenberger RM, Mulvenna J, Nagaraj SH, Fujiwara RT, Gazzinelli-Guimaraes P, Bueno L, Mati V, Bethony JM, Mitreva M, Sotillo J, Loukas A (2020) Comprehensive analysis of the secreted proteome of adult *Necator americanus* hookworms. PLoS Negl Trop Dis 14(5):e0008237

Mehlhorn H (2016a) Animal parasites. Springer International, Switzerland

Mehlhorn H (2016b) Human parasites. Springer International, Switzerland

Zuccherato LW, Furtado LF, Medeiros CDS, Pinheiro CDS, Rabelo ÉM (2018) PCR-RFLP screening of polymorphisms associated with benzimidazole resistance in *Necator americanus* and *Ascaris lumbricoides* from different geographical regions in Brazil. PLoS Negl Trop Dis 2018 Sep 17;12(9):e0006766

Further Reading

Albonico M, Stoltzfus RJ, Savioli L, Tielsch JM, Chwaya HM, Ercole E, Cancrini G (1998) Epidemiological evidence for a differential effect of hookworm species, *Ancylostoma duodenale* or *Necator americanus*, on iron status of children. Int J Epidemiol 27:530–537

Bartsch SM, Hotez PJ, Asti L, Zapf KM, Bottazzi ME, Diemert DJ, Lee BY (2016) The global economic and health burden of human hookworm infection. PLoS Negl Trop Dis 10(9): e0004922

Brooker S, Jardim-Botelho A, Quinnell RJ, Geiger SM, Caldas IR, Fleming F, Hotez PJ, Correa-Oliveira R, Rodrigues LC, Bethony JM (2007) Age-related changes in hookworm infection,

anaemia and iron deficiency in an area of high *Necator americanus* hookworm transmission in south-eastern Brazil. Trans R Soc Trop Med Hyg 101(2):146–154

Chammartin F, Scholte RG, Guimarães LH, Tanner M, Utzinger J, Vounatsou P (2013) Soil-transmitted helminth infection in South America: a systematic review and geostatistical meta-analysis. Lancet Infect Dis 13(6):507–518

Coello RD, Pazmiño BJ, Reyes EO, Rodríguez EX, Rodas EI, Rodas KA, Dávila AX, Rodas JP, Cedeño PP (2019) A case of cutaneous larva migrans in a child from Vinces, Ecuador. Am J Case Rep 20:1402–1406

Crompton DW (2000) The public health importance of hookworm disease. Parasitology 121 (Suppl):S39–S50

Darling ST, Smillie WG (1921) Studies on hookworm infection in Brazil. Rockefeller Inst Med Res, New York, Monograph, p 14

de Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L (2003) Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 19(12):547–551

Jackson A, Heukelbach J, Calheiros CM, Soares Vde L, Harms G, Feldmeier H (2006) A study in a community in Brazil in which cutaneous larva migrans is endemic. Clin Infect Dis 43(2):e13–e18

Leon IF, Strothmann AL, Islabão CL, Jeske S, Villela MM (2020) Geohelminths in the soil of the Laguna dos Patos in Rio Grande do Sul state. Brazil Braz J Biol 80(4):839–843

Lima FS, Silva T, Carvalho ACF et al (2017) Contaminocao ambiental por ovos de *Ancylostoma* spp. e *Toxocara* spp. Em areas des sais pracas publicas do municipio de Valenca, Estada Rio de Janeiro. Acta Biomed Bras 8:35–42

London D, Hruschka D (2014) Helminths and human ancestral immune ecology: what is the evidence for high helminth loads among foragers? Am J Hum Biol 26(2):124–129

Loukas A, Hotez PJ, Diemert D, Yazdanbakhsh M, McCarthy JS, Correa-Oliveira R, Croese J, Bethony JM (2016) Hookworm infection. Nat Rev Dis Primers 2:16088

Lucio-Forster A, Liotta JL, Yaros JP, Briggs KR, Mohammed HO, Bowman DD (2012) Morphological differentiation of eggs of *Ancylostoma caninum*, *Ancylostoma tubaeforme*, and *Ancylostoma braziliense* from dogs and cats in the United States. J Parasitol 98(5):1041–1044

Mehlhorn H (2016c) Encyclopedia of parasitology, 4th edn. Springer, Berlin

Mejia R, Seco-Hidalgo V, Garcia-Ramon D, Calderón E, Lopez A, Cooper PJ (2020) Detection of enteric parasite DNA in household and bed dust samples: potential for infection transmission. Parasit Vectors 13(1):141

Miranda RR, Tennessen JA, Blouin MS, Rabelo EM (2008) Mitochondrial DNA variation of the dog hookworm *Ancylostoma caninum* in Brazilian populations. Vet Parasitol 151(1):61–67

Papaiakovou M, Pilotte N, Grant JR, Traub RJ, Llewellyn S, McCarthy JS, Krolewiecki AJ, Cimino R, Mejia R, Williams SA (2017) A novel, species-specific, real-time PCR assay for the detection of the emerging zoonotic parasite *Ancylostoma ceylanicum* in human stool. PLoS Negl Trop Dis 11(7):e0005734

Pullan RL, Smith JL, Jasrasaria R, Brooker SJ (2014) Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 7:37

Rabelo ÉML, Miranda RRC, Furtado LFV, Redondo RAF, Tennessen JA, Blouin MS (2017) Development of new microsatellites for the hookworm *Ancylostoma caninum* and analysis of genetic diversity in Brazilian populations. Infect Genet Evol 51:24–27

Silva GSD, Ferreira FC, Romera DM, Soares VE, Bonuti MR (2020) Larva migrans in Votuporanga, Sao Paulo, Brazil: where does the danger hide? Rev Bras Parasitol Vet 29(3): e004920

WHO (2017) Guideline: preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups. isbn:978-92-4-155011-6

One Health Approach to Control Human and Zoonotic Hookworm Infections

12

Jorg Heukelbach

Abstract

Human hookworm infection is linked to a variety of factors, such as poverty, inadequate living conditions, absence of adequate sanitary facilities, cultural habits, and ineffective prevention programs/health systems. Zoonotic hookworm infection, leading to cutaneous larva migrans in humans, is related to the presence of animals (dogs and cats) serving as reservoirs. Climate and soil structure are also important determinants for larval development in the environment, and consequently for both human and animal hookworm infections. Health systems usually focus on individual medicalization, leading eventually to antiparasitic overuse and development of drug resistances. Given the reduced sustainability and effectiveness of the community interventions observed over the last decades, there is a need for more comprehensive approaches. In this chapter, we discuss the One Health Approach as a multidisciplinary measure to control hookworm disease. Integrated control programs would reduce transmission sustainably, for example, by combining mass drug administration aiming at the entire population rather than only schoolchildren or other defined target groups, and expansion of sanitary improvement programs. Once available, widespread application of a hookworm vaccine will be an additional tool to further boost control efforts. Health professionals involved in specific control programs should integrate into an interdisciplinary manner differing disciplines and departments. Existing overlapping disease control programs should be integrated, to achieve sustainable and cost-effective control on the long run, of both human and animal hookworm infection, and hookworm-related cutaneous larva migrans, in addition to other neglected tropical diseases.

J. Heukelbach (✉)
Departamento de Saúde Comunitária, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil
e-mail: heukelbach@ufc.br

H. Mehlhorn, J. Heukelbach (eds.), *Infectious Tropical Diseases and One Health in Latin America*, Parasitology Research Monographs 16,
https://doi.org/10.1007/978-3-030-99712-0_12

Keywords

One health approach · Hookworms · Animal hookworms · Cutaneous larva migrans

12.1 Human Hookworm Infection and Cutaneous Larva Migrans

About 470 million people are estimated to be infected with hookworms worldwide. In Latin America, the predominant human hookworm species is *Necator americanus.* The parasites may survive for many years in the human intestine, and chronic disease can cause cognitive deficits, growth retardation, as well as reduced school and work performance. Continuous intestinal blood loss may lead to iron-deficiency anemia. Despite intensive mass drug administration efforts during the past decades, the disease burden continues being high, both in low and middle-income settings (Loukas et al. 2016). In fact, due to the tremendous burden, human hookworm infection has been considered the most important neglected tropical disease (Haldeman et al. 2020).

On the other hand, infestation with animal hookworm larvae, mainly from dogs and cats, leads to a self-limiting condition in humans: hookworm-related cutaneous larva migrans. The adult hookworms living in the intestine of dogs and cats expel eggs, which hatch in the excreted animal feces and develop into infective larvae in the environment. Similar to human hookworms, the animal hookworm larvae penetrate into the upper layer of the epidermis, after the host's direct contact with the contaminated feces. If this new host is a dog or a cat, the larvae migrate further into the lymphatic and blood systems, finally reaching the intestine, and cause animal hookworm disease. If the host is a human being, larvae will penetrate into the skin, but will not be able to penetrate the basal membrane, and migrate within the epidermis, without completing their life cycle. Larvae may survive for months in the epidermis, and while creeping around cause unbearable itching (Heukelbach and Feldmeier 2008). The prevalences of hookworm infections in dogs are usually high in both urban and rural areas, and soil samples from public parks, streets, playgrounds, and beaches are often contaminated with dog and cat feces containing animal hookworm larvae (Heukelbach and Feldmeier 2008). In tropical regions, especially in resource-poor communities, people often walk barefooted. Walking barefooted and inadequate housing have been described as risk factors for cutaneous larva migrans in these settings (Heukelbach et al. 2008). Humans usually are also infested while sitting on the floor or at the beach where animals have deposited their feces.

Anthelminthic drugs against human and animal hookworm infections are usually effective, but in endemic areas reinfection is common, and control strategies should include improved water quality, sanitation, and hygiene (Loukas et al. 2016).

12.2 Hookworm Control and One Health

Already in the nineteenth century, the German physician Rudolf Virchow recognized the link between humans and animals within the realm of infectious diseases and formed the term zoonosis. Later, in the twentieth century, medical disciplines were more and more specialized, with increasing separation and silo thinking. This is partly a result of specific human and animal disease management, and individualized treatment (Rushton et al. 2018).

Human hookworm disease control programs are usually based on regular mass administration of anthelminthic drugs every 6–12 months (mostly albendazole or mebendazole), to school-aged children in endemic regions. These widespread deworming programs are targeted at soil-transmitted helminth infections in general, but usually have a focus on specific target groups. Annual deworming with albendazole or mebendazole has been discussed to be less effective for hookworms than for other soil-transmitted helminth infections, and in fact prevalences did not decrease considerably on the long run, even after 20 years of mass-treatment programs (Loukas et al. 2016). There are growing concerns about drug resistance, and a need for long-term interventions, given the long lifespan of adult worms in the human intestine. Vaccines currently under development may prevent moderate and severe infections, leading to more sustainable control than being achieved via mass drug administration programs (Haldeman et al. 2020).

Given the reduced sustainability and effectiveness of the interventions observed over the last decades, there is a need for more comprehensive multidisciplinary approaches. Integrated control programs would reduce transmission sustainably, for example, by combining mass drug administration aiming at the entire population rather than only schoolchildren or other defined target groups, and expansion of sanitary improvement programs. Once available, widespread application of a hookworm vaccine will an additional tool to further boost control efforts. These approaches should consider the multi-faceted characteristics of hookworm transmission dynamics and integrate several disciplines.

Hookworm infection is clearly linked to poverty, inadequate living conditions, absence of adequate sanitary facilities and sewage systems, cultural habits and human behavior, poor health systems, and ineffective prevention programs. In addition, zoonotic hookworm infection, leading to cutaneous larva migrans in humans, is related to the presence of animals (dogs and cats) serving as reservoirs. Climate and soil structure are other important determinants for larval development outside the host, and consequently both human and animal hookworm infections.

Similar to other neglected tropical diseases, the determinants leading to human and animal hookworm infections and respective diseases are linked with each other, and related to a variety of factors, including the human health, animal health, and the environment (Heukelbach 2021). Despite increasing advocacy for integrated approaches during the recent years, human, animal, and environmental health are still today often highly separated into different sectors, within guidelines, policy frameworks, management structures, and governance (Kock et al. 2018). In addition, classical health systems are based on individual medicalization, leading eventually

to antibiotic and anthelminthic overuse and development of antimicrobial resistances. A paradigm shift towards to a fully integrated One Health approach covering a broad array of disciplines and considering humans, animals, and plants is needed, to overcome the current and future public health problems (Kock et al. 2018).

The integrated and sustainable control of hookworm infection requires not only mass drug administration, but also sanitary improvements (Water—Sanitation and Hygiene [WASH] programs). Integrated WASH interventions including improved sanitary facilities and sewage management, access to clean water, promotion of handwashing, health education, and use of shoes will also prevent infections with other soil-transmitted helminths, diarrhea and other diseases. While there is some evidence that shoe wearing reduces the chance of hookworm infection, the effectiveness of shoes has been discussed, and depending on the cultural context, compliance to shoe use may be low. WASH activities should be embedded in community engagement and awareness campaigns. These measures would increase the general health situation of the population, and it seems obvious that WASH programs will be an important tool for soil-transmitted control efforts in general, but its effectiveness for reduction of human hookworm infection is still a matter of debate, and the results of available studies are mixed (Haldeman et al. 2020).

Effective control measures of both human hookworm infection and cutaneous larva migrans will necessarily include infection control not only in humans, but also in dogs and cats. Clearly, mass drug interventions will have an effect on transmission dynamics of human hookworm infection, but not on cutaneous larva migrans. This can only be achieved by systematic anthelminthic treatment of dogs and cats, reduction of the free-ranging and stray dog population, and environmental measures. However, in resource-poor settings and in areas with a deficient public veterinary health system and a high number of stray dogs, this is a difficult endeavor, and the community will have to be involved in addition to public health professionals and veterinarians. Despite the lack of interdisciplinary thinking, a control program based on communication campaigns, community involvement, and treatment of animals has been effective in an endemic area in South Africa (McCrindle et al. 1996).

One Health is a multidisciplinary approach considering all these different factors, areas, and interactions, to effectively and sustainably control diseases (Heukelbach 2021). Ideally, a group of diseases should be targeted in collaboration with differing disease control programs, as control measures and treatments often overlap. Treatments of choice for severe cutaneous larva migrans are oral ivermectin and albendazole. Singular lesions can easily be treated with topical thiabendazole (Heukelbach and Hengge 2009). Interestingly, ivermectin is also effective against human hookworm disease, other soil-transmitted helminths, lice infestations, and scabies. In addition, ivermectin has been used extensively for the control of lymphatic filariasis and onchocerciasis. Interventions, for example, based on mass-drug administration with ivermectin and additional focus on animal diseases will also reduce an array of other parasitic diseases.

In conclusion, health professionals involved in specific control programs should think out of the box, and integrate into an interdisciplinary manner differing

disciplines and departments. The differing somehow overlapping disease control programs should be integrated, to achieve sustainable and cost-effective control on the long run, of both human and animal hookworm infection, and hookworm-related cutaneous larva migrans, in addition to other neglected tropical diseases.

References

Haldeman MS, Nolan MS, Ng'habi KRN (2020) Human hookworm infection: is effective control possible? A review of hookworm control efforts and future directions. Acta Trop 201:105214. https://doi.org/10.1016/j.actatropica.2019.105214

Heukelbach J (2021) One health & implementation research: improving health for all. One Health Implement Res 1(1):1–3. https://doi.org/10.20517/ohir.2020.01

Heukelbach J, Feldmeier H (2008) Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. Lancet Infect Dis 8(5):302–309. https://doi.org/10.1016/S1473-3099(08)70098-7

Heukelbach J, Hengge UR (2009) Bed bugs, leeches and hookworm larvae in the skin. Clin Dermatol 27(3):285–290. S0738-081X(08)00220-4 [pii]. https://doi.org/10.1016/j.clindermatol.2008.10.008

Heukelbach J, Jackson A, Ariza L, Feldmeier H (2008) Prevalence and risk factors of hookworm-related cutaneous larva migrans in a rural community in Brazil. Ann Trop Med Parasitol 102(1):53–61. https://doi.org/10.1179/136485908X252205

Kock R, Queenan K, Garnier J, Nielsen LR, Buttigieg S, de Meneghi D et al (2018) Health solutions: theoretical foundations of the shift from sectoral to integrated systems. In: Rüegg SR, Häsler B, Zinsstag J (eds) Integrated approaches to health. Wageningen Academic Publishers, Wageningen, pp 22–37

Loukas A, Hotez PJ, Diemert D, Yazdanbakhsh M, McCarthy JS, Correa-Oliveira R et al (2016) Hookworm infection. Nat Rev Dis Primers 2:16088. https://doi.org/10.1038/nrdp.2016.88

McCrindle CM, Hay IT, Kirkpatrick RD, Odendaal JS, Calitz EM (1996) A primary health care approach to an outbreak of cutaneous larva migrans. J S Afr Vet Assoc 67(3):133–136

Rushton J, Nielsen LR, Cornelsen L, Queenan K, Rüegg SR, Häsler B (2018) Evaluation of integrated approaches to health with a focus on one health. In: Rüegg SR, Häsler B, Zinsstag J (eds) Integrated approaches to health. Wageningen Academic Publishers, Wageningen, pp 14–21