Oral Transmission of Chagas Disease

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Chagas disease is now an active disease in the urban centers of countries of nonendemicity and endemicity because of congenital and blood and/or organ transplantation transmissions and the reactivation of the chronic disease in smaller scale than vectorial transmission, reported as controlled in countries of endemicity. Oral transmission of Chagas disease has emerged in unpredictable situations in the Amazon region and, more rarely, in areas of nonendemicity where the domiciliary triatomine cycle was under control because of exposition of the food to infected triatomine and contaminated secretions of reservoir hosts. Oral transmission of Chagas disease is considered when >1 acute case of febrile disease without other causes is linked to a suspected food and should be confirmed by the presence of the parasite after direct microscopic examination of the blood or other biological fluid sample from the patient.

NEW TRENDS IN EPIDEMIOLOGY

Chagas disease, first described in 1909 by Carlos Justiniano Chagas, affects approximately 8 million infected persons in Mexico and Central and South America and causes 12 500 deaths annually; 41 200 new cases are reported annually (2006) [1]. A considerable contingent of the infected population has migrated from the rural areas to the urban centers of countries of endemicity, leading to the urbanization of Chagas disease in both countries of endemicity and countries of nonendemicity [2].

The etiologic agent of Chagas disease, *Trypanosoma cruzi*, is a protozoan parasite that acquires flagellate forms in the peripheral blood and biological fluids and nonflagellate (amastigote) forms in the tissues of infected animals and humans. The biological vectors are domestic and sylvatic insects of the subfamily Triatominae (Hemiptera, Family Reduviidae); the most frequent vectors are *Triatoma infestans*, *Triatoma brasiliensis*, *Panstrongylus megistus*, *Rhodnius prolixus*, and *Rhodnius pallescens*. Triatominae are found in a large area of the Americas [3], from the United States and Mexico in the north to Argentina and Chile in the south, and a wide range of mammals and nonmammal animals (marsupials, Chiroptera, Rodentia, Edentata, native primates) can serve as reservoir hosts.

Transmission occurs at the bite sites of blood-sucking triatomine bugs through the entry of parasite-laden feces containing the flagellate metacyclic forms that pass through the bite wound and mucous membranes/conjunctiva. Endemic to Latin America, Chagas disease has a great impact on morbidity and mortality affecting vulnerable individuals and is considered a neglected disease. The main control strategy in areas of endemicity is controlling vector activity. In Brazil and other Southern Cone, Andean, Central American, and Amazon Basin countries, coordinated multicenter programs have led to a 70% reduction in the number of new infections in South America because of the interruption of vectorial and blood transfusion transmissions [3, 4]. As a consequence, active infection in children has not been observed.

Only a few autochthonous cases have been reported in the United States, although the most important triatomine vectors were found in large areas: in the eastern United States (*Triatoma sanguisuga*), central Texas and also in Mexico (*Triatoma gerstaeckeri*), and Arizona and

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California (*Triatoma protacta* and *Triatoma rubida*) [5, 6]. An estimated 20% of the vectors in these areas are infected, and their defecation is delayed 10–20 minutes after feeding; thus, it occurs far from the bite site. This, combined with good housing conditions and hygienic and alimentary habits, might explain the small number of autochthonous cases in the United States.

Chagas disease is now an emerging disease associated with congenital, blood, and organ transplantation transmissions in developed countries, in which 1%–26% of immigrants are infected, depending on the country and/or the immigrants' nationality [2, 7, 8]. In the United States, approximately 300 000 individuals are estimated to be infected with *T. cruzi* [9].

In addition, physicians are not aware of the occurrence of reactivation of chronic Chagas disease in patients with immunosuppression or comorbidities, such as human immunodeficiency virus infection, or about the occurrence of congenital infection [10–13]. More recently, initiatives in countries of nonendemicity have been implemented to control the transmission of this disease by blood transfusion and transplantations of organs from infected donors from regions of endemicity.

In the context of great morbidity associated with vector-transmitted Chagas disease because of the prevalence of millions of chronic cases in Brazil and Latin America, orally transmitted acute Chagas disease has emerged as the principal form of transmission in the Amazon Basin and other regions where triatomine intradomiciliary and peridomestic control has been effective. Seven to 8 outbreaks (112 acute cases) occurred during 1965–2009 in areas outside Amazonia, where the triatomine were under control. In contrast, during 2000–2010, >1000 acute cases were reported in 138 outbreaks, mainly in the Brazilian Amazon (Figure 1*A*). Of these cases, 776 (71%) have been attributed to the ingestion of contaminated food and beverages (Figure 1*B*) [14].

OUTBREAKS OF ORAL TRANSMISSION AND SUSPECTED FOOD

Although the activity of the main vector of the disease has been controlled in some countries, complete control of transmission by the vector is almost impossible because of the zoonotic cycle of *T. cruzi*.

Oral transmission probably represents the principal route for contamination of vectors and animals [15] and for the transmission of acute human disease in the Amazon [14] and is supposed to have been the main mechanism of parasite dispersion among mammals since 1921 [15].

Outbreaks in humans attributed to oral transmission have been registered in rural and periurban areas of nonendemicity in South America (Table 1). In Brazil, these outbreaks have involved food, sugar cane juice, water, or soup contaminated with infected triatomine or their feces [17, 23, 25, 28–30]; or contaminated with infected secretions from the anal glands of marsupials [16, 18, 21]; açaí (*Euterpe oleracea*); or bacaba (*Oenocarpus bacaba*), a regional fruit, contaminated by triatominae [20, 24, 31, 32]. In Colombia and Venezuela, outbreaks have been related to guava, orange, or tangerine juices that were probably contaminated by triatomine [26, 27].

Considering that the majority of outbreak studies failed to identify infected vectors in patients' domiciles, the definition of oral, in contrast to vector, transmission is determined by epidemiological and clinical investigators.

DEFINITION AND CLINICAL AND LABORATORY ASPECTS OF ACUTE CHAGAS DISEASE

Clinical Aspects of Acute Chagas Disease Transmitted by Triatomine Bite

Chagas disease transmitted by a triatomine bite causes apparent acute disease in only 1 of 30 infected individuals, with fever and mononuclear phagocytic system involvement and bilateral palpebral and/or leg edema. Severe myocarditis and/or meningoencephalitis are reported in 5%–10% of cases, most of which are in newborns, breastfeeding infants, and older individuals. Up to 50% of patients present with unilateral palpebral edema, also known as Romaña's sign, as the first sign of infection or with the inoculation chagoma at the infection site [33]. Parasitemia is high in the first 4 weeks (detection of *T. cruzi* by direct microscopic examination of peripheral blood samples) and then decreases over the next 8 weeks. After 12 weeks, the parasite can only be detected by parasitological enrichment methods (in vitro xenodiagnosis and blood culture; 30%–50% positivity) or molecular methods (polymerase chain reaction [PCR], 45%–95% positivity) [34]. During the chronic phase, highly sensitive anti–*T. cruzi* immunoglobulin G (IgG) (enzyme-linked immunosorbent assay) is the gold standard for diagnosis (>95% positivity), but it cross-reacts with *Leishmania*. Immunoblotting using trypomastigote antigens represents the confirmatory method [35].

During the chronic phase, the following forms could occur: (1) an asymptomatic or indeterminate form (without digestive or cardiac involvement) in 60%–70% of the patients that lasts for the individual's entire life in the majority of the patients, (2) a cardiac form in 20%–30%, or (3) a digestive (megaesophagus and/or megacolon) or mixed form (cardiac plus digestive) in 5%–15%.

CLINICAL SYNDROMES

The incubation period is 3–22 days for oral transmission [18, 24, 29, 33], compared with 4–15 days for vectorial transmission and 30–112 days for blood transfusion transmission [33].

The clinical signs and symptoms of orally transmitted acute Chagas disease, although similar to those of acute Chagas disease

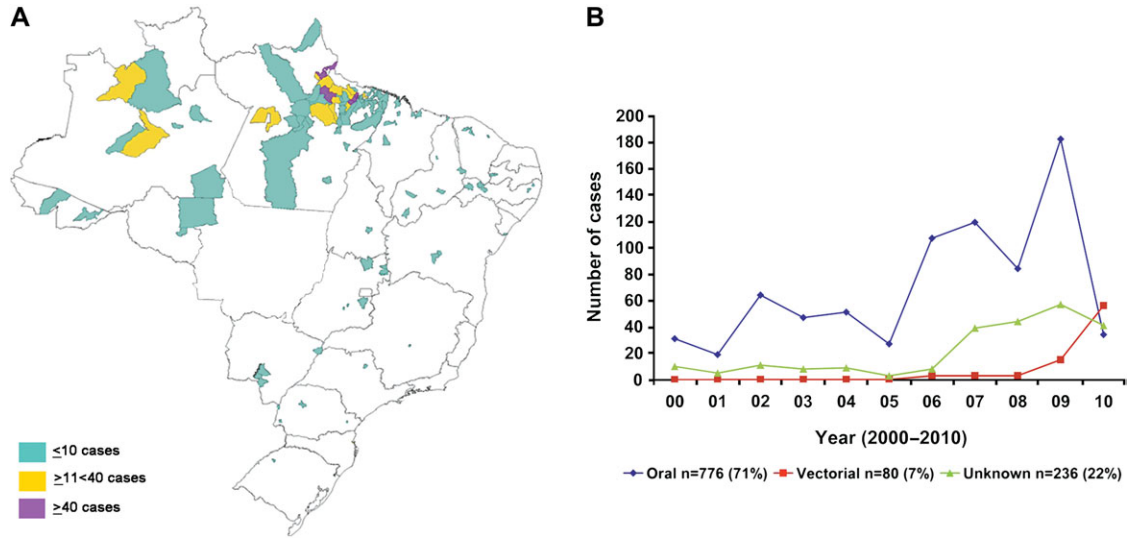

Figure 1. *A,* Acute Chagas disease in Brazil, by municipality, 2000–2010. *B,* Number of cases of acute Chagas disease in Brazil according to type of transmission, 2000–2010. Notification method changed since 2009; current estimated data are more reliable than previous data. Source: Health Ministry of Brazil, http://portal.saude.gov.br/portal/saude/profissional/visualizar_texto.cfm?idtxt=31454. Accessed 26 July 2011, adapted by Gerência Técnica em Doença de Chagas (3 August 2011) [14].

transmitted by vector bites, exhibit some peculiarities (Table 2) [19, 20, 23–31]: an undifferentiated febrile syndrome without chagoma, fever (temperature, 38°C–39°C), myalgia, headache, vomiting, arthralgia, and prostration; phagocytic mononuclear involvement, including splenomegaly, hepatomegaly, or adenopathy, similar to the typhoidic form of toxoplasmosis, typhus, or typhoid fever and infectious mononucleosis syndrome associated with lymphocytosis and atypical lymphocytes; icterohemorrhagic syndrome (hemorrhages [20, 25, 29], with epistaxis, hematemesis, melena, jaundice [20, 25, 26, 29], and, rarely, shock are more frequent in the oral route of transmission), differential diagnosis including dengue, hepatitis, hantaviral infection, or severe leptospirosis; focal findings (eg, signs of myocarditis, including pericarditis, pancarditis, pericardial effusion, cardiac tamponade, cardiomegaly, cardiac insufficiency, anasarca, pleural effusion, arrhythmias [19, 20, 23, 29], meningoencephalitis, and dermatitis) and differential diagnosis including other causes of myocarditis, toxic exanthema, viral hepatitis, and glomerulonephritis; and bilateral bipalpebral and/or leg edema that is not attributable to heart or kidney insufficiency (this symptom is valuable for differentiating this diagnosis from other febrile mononucleosis-like or typhoid-like syndromes).

No external signs of parasite entry are observed in the orally transmitted disease. A hemorrhage may reflect entry through the digestive mucosa, which is expressed by an intense inflammatory infiltrate with amastigotes [36]. Maculopapular or petechial exanthema, erythema nodosum, and cardiac manifestations, such as pericardial effusion, pleural effusion, and icterus, are more frequently seen with orally transmitted than vector-transmitted disease (Table 2).

LABORATORY DIAGNOSIS

Acute Chagas disease is confirmed by the following criteria:

- parasitological (the most reliable): to detect the presence of *T. cruzi* by direct microscopy after fresh analysis of the peripheral blood sample or other biological secretions (cephaloraquidian liquid); less sensitive than buffy coat, microhematocrit, and Strout methods;
- immunological (in combination with clinicoepidemiological criteria): to detect the presence of anti–*T. cruzi* immunoglobulin M (IgM), excluding false-positive antibodies (after absorption of rheumatoid factor) or 3 dilutions increased IgG antibody titer in a 21-day period [35, 37, 38];
- molecular (in combination with clinicoepidemiological criteria): to detect the presence of a positive PCR result for a patient without previous infection); and
- clinicoepidemiological (clinical signs of acute Chagas disease; a strong epidemiological link to an infection source and a confirmed positive case).

Patients with chronic Chagas disease with other febrile diseases may coexist with patients with acute cases in outbreaks. Thus, the presence of anti-parasite IgG antibodies or parasite DNA or positive parasitological enrichment methods is insufficient for establishing the diagnosis of acute Chagas disease, because

Table 1. Outbreaks of Orally Transmitted Acute Chagas Disease[a]: Location of Occurrence, Source of Contaminated Food, Infected Group, Triatomines and Reservoirs, Death, and Cause of Death

Study (First Author)	Region	Source of Contaminated Food	Infected Group[b]	Triatomines	Reservoirs	No. of Deaths/Total	Cause of Death
Silva, 1968 [16]	Teutônia-RS, rural	Shared meal	Students and worker of a rural school	2 km apart, 1 infected *Triatoma megistus*	Infected opossums (*Didelphis marsu pialis*)	6/17	Acute myocarditis (autopsies)
Shaw, 1969 [17]	Belém-Pará, urban	Shared meal	Members of family	NR	NR	1/4	Sudden death (epigastric/ retrosternal pain)
Shikanai-Yasuda, 1991 [18]	Catolé do Rocha-Paraíba, rural	Shared first sugarcane juice	Attendants of a party	3.2% infected triatomine: peri-domicilium	Infected opossums *(Didelphis albiventris*)	1/26[b], other febrile person died	1 case - myocarditis
Pinto, 2001 [19]	Abaetetuba-Pará, Amazon, Brazil, periurban	Shared açai paste/juice	Members of a family	NR	NR	0/13	NR
Pinto, 2008 [20]	Pará, Amazon, Brazil, urban/rural	Shared açai or regional fruits paste/juice	Members of families or attendants of parties	Triatomines peridomicilium	NR for outbreaks	?/181 NR for outbreaks	Myocarditis, digestive bleeding
Ministry of Health, Brazil, 2005 [21]	Navegantes, Catarina, highway	Shared sugarcane juice sold in a side road stand	Travelers drinking the same juice in a stand	Infected *Triatoma tibiamaculata*	Infected opossums	3/25	Heart failure; digestive bleeding
Beltrão, 2008 [22]	Breves e Bagre Pará, Amazon, urban	Shared food	Participants of common meals	Not found	NR	0/25	NR
Dias, 2008 [23]	Macaúbas-Bahia, Small town	Shared water or beverage	Members of a family	Infected *Triatoma sordida*	Infected opossums	2/7	Heart failure
Nobrega, 2009 [24]	Barcarena- Pará, urban	Shared açai paste/juice	Participants of a meeting	Not found 90 days later	NR	0/11	NR
Cavalcanti, 2009 [25]	Redenção-Ceará, rural	Shared soup with fresh herbs	Members of a family	*Triatoma brasiliensis*, *Panstrongylus lutzi* (noninfected after pesticides)	Infected marsupials and rodents (*Trypanosoma cruzi*)	0/8	NR
Hernandez, 2009 [26]	Lebrija, Santander Colômbia, rural and urban	Shared orange or tangerine juice?	Family and community	Noninfected *Panstrongylus geniculatus*	Noninfected marsupials (negative)	2/10	1 acute myocarditis
Noya, 2010 [27]	Caracas-Venezuela, urban	Shared guava juice	Students and workers of a school	Infected triatomine	Rodent	1/103[c]	Acute myocarditis
Bastos, 2010 [28]	Ibipitanga, Bahia, rural	Sugarcane juice	Familiar microepidemic	Infected individual *Triatoma sordida*	NR	0/6	NR

Abbreviation: NR, no report.

[a] Outbreaks occurred after ingestion of a determined food or beverage in a known location by members of a family or attendants of meetings.

[b] This patient was the wife of the patient who died of chagasic cardiopathy.

[c] Total number of cases unknown because of the low rates of positive polymerase chain reaction results and lack of information about absorption of rheumatoid factor for positive immunoglobulin M serology for most of the patients.

Table 2. Signs and Symptoms of Orally Transmitted Acute Chagas Disease

Reference, First Author (No. of Cases)	Fever, %	Myalgia, %	Leg Edema, %	Facial Edema, %	Abdominal Pain, %	Diarrhea, %	Skin Rash, %	Dyspnea, %	Palpitation, %	Hepatomegaly, %	Splenomegaly, %	Hemorrhagic Jaundice , %
Silva [16] (17)	86	28	43	57	NR[a]	NR	Yes	22	28	NR	NR	NR
Shaw [17] (4)	100	25	NR	NR	50	50	NR	25	25	50	NR	NR
Shikanai-Yasuda [18] (26)	100	100	84.6	92	NR	NR	34.6	3.8	3.8	34.6	34.6	NR
Pinto et al [19] (13)	100	53.9	76.9	NR	No	NR	23.1	30.8	46.2	No	7.7	NR
M. Health, Navegantes [28] (25)	100	89	40	NR	72	35	48	48	40	20	8	35(28)
Beltrão [21] (25)	96	76	NR	NR	64	NR	NR	52	NR	NR	NR	NR
Dias [22] (7)	71	43	14	71	85	NR	NR	71	43	14	NR	NR
Nobrega [23] (11)	100	82	82	100	46	NR	NR	64	64	NR	NR	46
Hernandez [25] (10)	80	10	30	70	50	30	NR	30	60	20	NR	20(10)
Pinto [20] (181)	100	85.6	57.5	59.1	45.3	6.6	29.8	56.9	NR	21	11	2.8
Cavalcanti [24] (8)	100	100	100	100	100	12	100	25	25	100	100	38 (38)

Abbreviation: NR, not reported.

results of PCR and IgG antibody testing are positive in chronic Chagas disease [34]. The percentage of positive serologic test results in the Brazilian states involved in outbreaks (but not in the same region) ranges from <0.001% to 5.4%.

An evaluation of acute Chagas disease must include chest radiography and echo-Doppler cardiography for patients with cardiac involvement. The main changes in electrocardiography include [19, 28] rhythmic disturbances (atrial arrhythmia and supraventricular or ventricular extrasystoles), conduction disturbances (atrioventricular blockade, right branch block, or anterosuperior division block), and voltage disturbances (low QRS, T alterations, and an increased PR interval).

DEFINITIONS OF ACUTE ORALLY TRANSMITTED CHAGAS DISEASE

After excluding other forms of transmission [39], a confirmed case (according to Pan American Health Organization 2009 guidelines) is defined as parasitological criteria (as described in laboratory diagnosis), epidemiological evidence of a food or drink as the source of the infection, and >1 case of acute Chagas disease without apparent chagoma (signals and symptoms as described before). A probable case is defined as parasitological criteria and >1 case of acute Chagas disease with clinical features and an epidemiological link to a confirmed case. A suspected case is defined as the signs and symptoms of >1 case of acute Chagas disease in the presence of immunological criteria.

Treatment

Treatment should be prescribed as soon as possible to improve the chance of survival and/or cure. Benznidazole (first choice) or nifurtimox were indicated for at least 60 days and should be monitored, because adverse effects might be present [33, 39].

Usually, signs and symptoms disappear in most of the treated patients soon after the treatment, but long-term follow up has not been reported [18–20]. Most electrocardiographic abnormalities and cardiac function normalized, but ventricular repolarization abnormalities persisted 6 months later in 50% in one study [28]. The main causes of death are shown in Table 1 and occurred in nontreated or recently treated patients. Deaths in older individuals were described in >1 outbreak [18, 20], and death from cardiac tamponate involved nontreated children.

EPIDEMIOLOGICAL SURVEYS AND RISK FACTORS FOR HUMAN INFECTION

Food and drink involved in the outbreak are possibly contaminated in multiple ways from the time of harvest until the moment of consumption (Table 1).

In the Paraiba outbreak [18], the presence of anal gland secretions from infected marsupials in manufacturing machines left

uncovered during the night was one of the hypotheses for this beverage contamination. Crushed triatomines with a low infection index represented a less probable alternative source of infection.

In the Santa Catarina outbreak [30], the typing of *T. cruzi* in the opossums (TCI) and triatomines (TCI and TCII) found in the neighborhood of the outbreak suggested that the latter was the source of the infection in humans (typed as TCII). In Bahia, contamination was attributed to triatomines, because their feces were found in the kitchen of patients' dwellings, and 50% of *T. cruzi* infections were observed in *Triatoma sordida* isolates collected in the neighborhood of the house [23].

Different degrees of environmental and biodiversity changes have been registered in the regions where the outbreaks occurred. Although intradomiciliary colonization did not occur in most of the Amazon, the role of açai as a food source and the presence of human activities close to the sylvatic cycle of triatomine and to wild animal reservoirs have been associated with the transmission of the disease beyond the wild habitats [28, 31, 40]. More than 50% of the triatomines found in the vicinity of the houses and villages were infected in some outbreaks registered in the Brazilian Amazon (Z3 and TCI clones) [31].

In other regions (Navegantes, Redenção, and Coari), the predominance of opossum is considered a marker of environmental changes and a source of blood for triatomines. Decreased biodiversity of small animals, imbalance between sylvatic triatomine, and wild animal cycles were associated with deforestation because of human colonization [40].

Substantial infection rates also reported in domestic animals need to be confirmed and, possibly, represent the final barrier before *T. cruzi* transmission reaches humans in the border of forests [40].

In Texas, the death of 3 dogs from chagasic cardiomyopathy was associated with widespread infestation of *T. gerstaeckeri* in the peridomestic environment [41]. In a large-scale study, a 3.6% *T. cruzi* infection rate has been described among dogs [42]. The high incidence of infection in triatomine vectors in the southeastern United States and Texas and in raccoons and opossums [43] and the potential increase in the species distribution area have been discussed as additional risk factors for the introduction of Chagas disease in the United States [41].

The dramatic increase in the outbreaks of orally transmitted Chagas disease seen in recent years could be partially attributed to the better recognition of this disease, active surveillance, previous underestimation of the disease, lack of good handling practices in food processing, and environmental changes, with increased rates of triatomine infection in ecotopes close to the houses.

THE PARASITE

The infection of mice via blood infected with trypomastigotes [15] and the experimental infection of rats, domestic animals, and opossums via milk, blood, or food infected with triatomines or their feces have been reported [44, 45]. The infectivity of triatomine metacyclic trypomastigotes in the mouse oral mucosa was observed with an inoculum of 1250 forms and has also been documented in 70%–100% of mice inoculated with 6–8 $\times$ 10^4 forms from triatomine excretions [46, 47]. The first case of orally transmitted human infection was documented in 1936 in a sick mother, whose milk was infected with *T. cruzi* and who transmitted the disease to her infant [48].

The invasion of metacyclic trypomastigotes in the gastric mucosal epithelium of mice relies on the parasite's stage-specific gp82 glycoprotein, which is relatively resistant to peptic digestion [49] and is decreased by specific antibody opsonization [50]. Another glycoprotein, gp90, seems to inhibit the cell invasion. Parasites with gp90 isoform susceptible to pepsin become invasive after contact with gastric juice, which explains the severity of the disease in some oral outbreaks [51].

Although the parasite was not naturally found in implicated foods, experimental in vitro data showed that it is able to survive in beverages, such as sugar cane juice up to 12 hours, with use of direct methods, and up to 24 hours, with use of experimental inoculation [52], and in açai or other regional fruits for many hours, supporting even extremes of pH and temperature, although extremely sensitive to dryness. Mice experimental infection showed that oral infectivity depends on the parasite invasion site (oral or gastric mucosa). One Colombian strain (biodeme type III), which has been reported in sylvatic hosts, was similarly infectious, regardless of gastric or intraperitoneal inoculation, whereas a Peruvian strain was less virulent when using gastric inoculation [53].

The severity of the disease depends on the number of parasites ingested and resistance of the parasites in the digestive mucosa, the regulation of invasion by local factors (gastric juices and glycoproteins), and the host's innate immune response. Protection by previous infection is not known in human disease, because in the outbreaks, the infected population was susceptible and the control population did not present with chronic disease [18, 20, 26]. In animal studies, it has been shown that a TH2 immune response at the mucosal level as well as a systemic TH1 immune response is able to induce protection against oral challenge, but only TH1 immune response protects against systemic challenge [54].

Most of the outbreaks occurred during the warm months from July through March, mainly from July through December, which may be attributable to an increased density of triatomines and the increased production of infected feces [14, 45]. An estimated 1°C increase in the temperature over the next few years, with repercussion in increased activity of triatomine vectors, and the lack of awareness about the disease are matters of concern for the future transmission of Chagas disease in the United States [6].

FUTURE CHALLENGES

In 2007, the Brazilian Health Ministry, with the aid of a group of experts, provided recommendations for controlling food contamination [55]: pasteurizing food and beverages, chemically treating white açai juice, implementing good handling practices in all phases of food processing after harvesting, developing techniques for inactivating and detecting the parasite in the food, and educating the involved population.

Additional measures include improving access to early diagnosis and treatment, performing surveillance in the Amazon region with use of Malaria and Febrile Syndrome Surveillance (ictero-hemorrhagic syndrome and other diseases transmitted by food), developing consistent epidemiological investigations, training human health resources for management of orally transmitted Chagas disease, producing protocols for treatment, developing a network of physicians for references and counterreferences for severe cases of acute Chagas disease, and maintaining vectorial control over *T. infestans* in the country.

Although many of these recommendations have been implemented, difficult access to rural areas, late diagnosis, detection of parasites in the food, their inactivation in the food handling at home, and implementation of good handling practices of food processing in Amazon and the country in general remain as challenges to control oral acute Chagas transmission in Brazil. Additional obstacles for successful control are represented by unpredictability of the outbreaks and uncontrolled increasing activity of sylvatic triatomines.

Notes

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