

# Large Urban Outbreak of Orally Acquired Acute Chagas Disease at a School in Caracas, Venezuela

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(See the editorial commentary by Miles, on pages 1282–1284.)

**Background.** *Trypanosoma cruzi* oral transmission is possible through food contamination by vector's feces. Little is known about the epidemiology and clinical features of microepidemics of orally acquired acute Chagas disease (CD).

**Methods.** A case-control, cohort-nested, epidemiological study was conducted during an outbreak of acute CD that affected a school community. Structured interviews were designed to identify symptoms and sources of infection. Electrocardiograms were obtained for all patients. Specific serum antibodies were assessed by immunoenzymatic and indirect hemagglutination tests. In some cases, parasitemia was tested directly or by culture, animal inoculation, and/or a polymerase chain reaction technique.

**Results.** Infection was confirmed in 103 of 1000 exposed individuals. Of those infected, 75% were symptomatic, 20.3% required hospitalization, 59% showed ECG abnormalities, parasitemia was documented in 44, and 1 child died. Clinical features differed from those seen in vectorial transmission. The infection rate was significantly higher among younger children. An epidemiological investigation incriminated contaminated fresh guava juice as the sole source of infection.

**Conclusions.** This outbreak was unique, because it affected a large, urban, predominantly young, middle-class, otherwise healthy population and resulted in an unprecedented public health emergency. Rapid diagnosis and treatment avoided higher lethality. Food-borne transmission of *T. cruzi* may occur more often than is currently recognized.

The burden of illness associated with Chagas disease (CD) remains the second highest among all of the endemic tropical diseases in Latin America and results in an annual loss of >2 million disability-associated life years (DALYs) [1, 2]. Although Chile, Uruguay, and Brazil have been certified as free of vectorial transmission by domiciliary *Triatoma infestans* [1], eradication

appears to be an impossible task because of the complexity of the zoonotic life cycle of its causative agent, *Trypanosoma cruzi*. In addition to vectorial transmission, other secondary mechanisms of infection include congenital, transfusional, organ transplantation-related, and oral transmission. A sparse number of outbreaks of orally acquired human CD have been reported from Brazil [3–7], Argentina [8], and Colombia [9].

Venezuela has a successful CD vector control program that is based on the improvement of rural housing and vector control [10, 11]. However, epidemiological data suggest a reemergence of the infection [12–14]. At the capital, Caracas, which is a densely populated cosmopolitan city surrounded by mountains covered by tropical forests, the local sylvatic triatomine vector, *Panstrongylus geniculatus*, has been recorded since 1920 [15]; it was reported inside the houses in 1986 [16] and captured in the wild or within households show-

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ing a high rate (76.1%) of *T. cruzi* infection [17]. However, vectorial transmission has not been reported in this city.

The current study describes the largest known outbreak of orally acquired CD to date in the American continent, which involved numerous children and personnel from an urban school in Caracas.

## METHODS

On 6 December 2007, trypomastigotes of *T. cruzi* were detected on peripheral blood smears from a 9-year-old student (index case), who was admitted to the Hospital Universitario de Caracas (Caracas, Venezuela) with a 3-week history of fever of unknown origin (FUO). Twenty persons from the patient's school were hospitalized with similar symptoms and were later found to have circulating trypomastigotes and/or serological test results positive for CD. The municipal health authorities were contacted at once, and they reported an unexpected simultaneous sharp increase in medical consultations and absenteeism among school personnel from 30 October through 25 November 2007.

The center involved (Unidad Educacional "Andrés Bello") is located in the Municipality of Chacao, in the eastern part of Caracas, with predominantly middle-class inhabitants. All of the food and beverages consumed by the students and personnel were supplied by the same caterer that supplied other municipal schools, with the exception of breakfast, which was prepared under unsupervised sanitary conditions, located in a distant slum on the western mountain slopes of the city. A multidisciplinary task force was summoned to analyze the epidemiological situation with the aim of controlling the outbreak [18]. A case-control, cohort-nested, epidemiological outbreak study was designed to assess the extent of the outbreak and to identify possible sources of infection. Cases were classified as "suspected" or "confirmed" in accordance with a consensus document prepared by the interdisciplinary group, based on World Health Organization recommendations [19]. A suspected case patient was any person with an epidemiological link to the institution involved from 10 October through 1 November 2007 who developed FUO of >5 days duration and other clinical manifestations. A confirmed case patient was any suspected case patient or asymptomatic person with the epidemiological link who, in addition, exhibited blood parasites or specific anti-*T. cruzi* antibodies by 2 different serological techniques: enzyme-linked immunosorbent assay (ELISA) and indirect hemagglutination (IH) or ELISA and Western blot (WB) tests.

The study population consisted of all students, teachers, workers from the school, external persons involved with the preparation or transportation of food consumed in the school, and any person considered to be a "school contact" potentially at risk. Blood samples for diagnosis were initially collected from

11 December through 14 December 2007, as an emergency intervention, with the aim of identifying infected persons and immediately starting antiparasitic treatment of any individual affected by a severe, potentially lethal, acute illness in the context of a large outbreak that occurred at a critical time of the year (3 days before a prolonged Christmas and new year vacation). During a second sampling that was performed 6 weeks later, 21 January through 25 January 2008, all participants undertook a detailed clinical and epidemiological questionnaire on CD risk factors (eg, exposure to vectors, transfusions, infected relatives, contact with animal reservoirs, and ingestion of food and/or beverages in the school). Case patients were compared with control subjects from the same cohort of exposed individuals.

The study was performed under the supervision of the Ethical Committee of the Tropical Medicine Institute. Informed written consent was obtained from each participant or from their legal guardians.

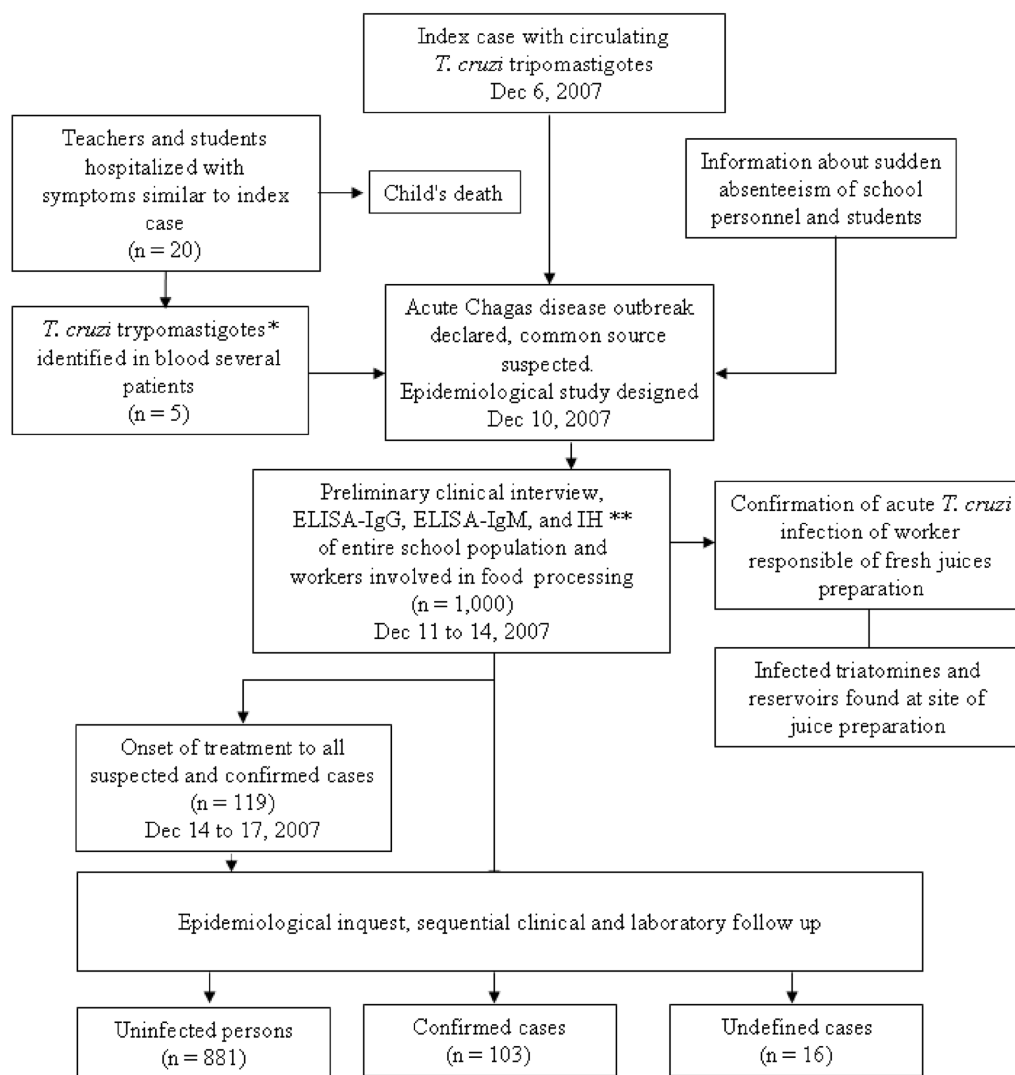
For the first 43 symptomatic patients, fresh and Giemsa-stained peripheral blood smears were reviewed for trypomastigotes. In addition, 2 mL of blood were cultured in biphasic medium and checked periodically over at least 3 months. Mice were inoculated intraperitoneally with 300  $\mu$ L of blood and examined each week [19].

All serum samples were screened for immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against a crude extract of *T. cruzi* epimastigotes [20] with use of an ELISA developed in house [21] and an IH test [22]. The immunodiagnosis of CD was based on the positivity of at least 2 specific serological tests [19]. Those samples with ELISA results positive for IgG and negative IH results were also tested with WB tests [23].

A representative number of 150 blood samples were randomly evaluated by a polymerase chain reaction (PCR). For the DNA extraction, 5 mL of blood was mixed with an equal volume of 6M guanidine HCl /0.2M EDTA (GE) [24]. The amplification reactions were targeted to the 330-base pair mini-circle fragment of the *T. cruzi* kinetoplastid DNA [25].

Conventional 12-lead electrocardiogram (ECG) recordings were obtained from confirmed or suspected case patients and treated with either benznidazole (Rochagan; Roche Laboratories) at a dosage of 6 mg/kg/day for 60 days or nifurtimox (Lampit; Bayer Laboratories) at a dosage of 8 mg/kg/day for 90 days [19, 26].

The dependent variable or main outcome was based on serological status. Epidemiological exposure was evaluated using  $\chi^2$  or the Student's *t* test depending on the binary or continuous independent distribution of the variable. Only variables significantly associated in the univariate regression were included in the multivariate regression, using  $P < .05$  as the entry criteria. The relationship between risk factors and final outcome (*T.*



**Figure 1.** Study profile and major outcomes of the epidemiological investigation of the outbreak of acute Chagas disease, Caracas, Venezuela, 2007. \*Parasitemia investigation by direct techniques. \*\*Parasitemia, Western blot, and polymerase chain reaction tests performed on a more limited group of exposed individuals (see Methods). ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IH, indirect hemagglutination; *T. cruzi*, *Trypanosoma cruzi*.

*cruzi* infection) was estimated by means of the paired odds ratio (OR), with 95% confidence intervals (CIs). Stata, version 6.0 for Windows (Stata), was used as the basic statistical software for all calculations.

## RESULTS

Figure 1 depicts the general outline of the study. Because the outbreak occurred in a well-off urban area of the city with no current vectorial transmission, a food-borne mechanism was presumed to be the cause. Date of exposure was estimated to occur between 10 October and 25 October 2007, based on previous reports of orally acquired infections with documented incubation periods of 5–20 days [5].

The demographic characteristics of the entire exposed pop-

ulation ( $n = 1000$ ) are shown in table 1. No statistically significant differences were found in the attack rates among the sexes. Although, as a whole, age was not associated with the main outcome, a more meticulous revision of age distribution of those infected revealed a bimodal distribution curve, with a reverse trend, in which the OR for CD decreased with age for children but increased with age for adults. As depicted in Tables 1 and 2, significantly different attack rates were observed among students and teachers in relation to their school attendance (morning vs afternoon shifts; 65 cases [17.9%] among 363 subjects vs 10 cases [2.6%] among 385 subjects; OR, 3.19 [95% CI, 2.1–4.8;  $P < .001$ ]). The difference between the attack rate among students of the morning shift (22.5%) and the attack rate among children of the afternoon shift (2.4%) was statis-

**Table 1. Demographic Characteristics and Rates of Infection of 1000 Individuals Exposed to Infection at a Public School Community of Caracas, Venezuela, Affected by a Large Outbreak of Orally Acquired Acute Chagas Disease in December 2007**

Variable	No. (%) of exposed individuals (n = 1000)	
	Study population	Infected subjects
<b>Age</b>		
≤18 years old	795 (79.5)	77 (9.6)
>18 years old	205 (20.5)	26 (12.6)
<b>Sex</b>		
Male	455 (45.1)	50 (10.9)
Female	545 (54.9)	53 (9.7)
<b>Students</b>		
Kindergarten	65 (8.7)	15 (23.1)
1st grade	63 (8.4)	13 (20.6)
2nd grade	54 (7.2)	7 (12.9)
3rd grade	61 (8.1)	9 (14.7)
4th grade	66 (8.8)	7 (10.6)
5th grade	92 (12.3)	9 (9.7)
6th grade	82 (10.9)	7 (8.5)
7th grade	96 (12.8)	6 (6.2)
8th grade	89 (11.9)	0 (0)
9th grade	79 (10.5)	4 (5.1)
Subtotal	747 (74.7)	77 (10.3)
<b>Nonstudents</b>		
Personnel	165 (16.5)	25 (15.2)
Food handlers	16 (1.6)	1 (6.2)
Other contact	72 (7.2)	0 (0)
Subtotal	253 (25.3)	26 (10.2)
<b>Shift</b>		
Morning	363 (36.3)	65 (17.9)
Afternoon	385 (38.5)	10 (2.6)
Both	252 (25.2)	28 (11.1)

tically significant ( $P < .05$ ). Although the absolute number of infected children was higher (77 of 103 infected subjects), the maximum infection rate (15.2%) was observed among the school employees. One of the 16 workers who were involved directly in the preparation or transportation of luncheons showed evidence of acute *T. cruzi* infection, with serological test results positive for specific IgM and IgG (Table 1).

A significant positive correlation was found between ingestion of guava juice and risk of infection (OR, 3.5 [95% CI, 1.85–6.7]) (Table 2). The epidemiological interviews revealed that, except for the guava juice, all other beverages were made in the early morning. The guava fruits, in contrast, were boiled the night before and left to cool inside a large uncovered pot before blending in the morning. Once in the school, the juice was delivered to the morning shift, first to school personnel, then to kindergarten students, and then to students in ascending grades. Some personnel and students of the afternoon shift customarily consumed any remaining juice.

Of those infected, 75% were symptomatic, 20.3% required hospitalization, and a 5-year-old child died of acute chagasic myocarditis. Most patients reported fever that lasted >7 days, abdominal pain, headache, dry cough, and myalgia; to a lesser degree, they reported diarrhea, facial edema, malaise, arthralgias, dyspnea, and tachycardia (Table 3). In the univariate regression analysis, the following symptoms showed a significant association with a higher risk of serologically confirmed infection: fever, arthralgias, skin lesions (rash, erythema nodosum, or facial edema), and cardiovascular abnormalities. However, on the multivariate analysis, only fever and cardiovascular abnormalities showed statistical significance.

In 61 (59%) of the 103 confirmed cases,  $\geq 1$  abnormality was noticed on the ECG recordings. T wave abnormalities were significantly more common among patients  $\leq 18$  years of age, whereas supraventricular arrhythmias and microvoltages were predominant among adults (Table 4), who more frequently developed severe clinical cardiological manifestations that required hospitalization.

Among 1000 persons evaluated, 103 individuals had anti-*T. cruzi* IgG antibodies by ELISA, and 90 (87.3%) were also IgM positive. The specific IH test was concordant in 99 (96.1%) of 103 individuals, whereas the remaining 4 individuals had positive WB results.

Because of logistic constraints, parasitemia could be assessed in only 43 patients by parasitological methods. Of these, 13 (30.2%) had positive fresh-stained blood smear results, in vitro culture, or mice inoculation.

Sixteen individuals with ELISA results positive for anti-*T. cruzi* IgG antibodies but negative IH results nevertheless received a full course of antiparasitic treatment. During follow-up, they became IgG seronegative while remaining persistently negative according to both IH and WB results. Five such patients developed clinical signs, as well as ECG abnormalities. Because these patients did not fulfill World Health Organization criteria for the CD diagnosis, they were considered to have undefined cases (Figure 1).

Samples of 150 persons were randomly chosen to be tested by specific PCR targeted at the *T. cruzi* kinetoplastid DNA. The reaction was positive in 35 (79.5%) of 44 serologically confirmed cases. All 106 seronegative individuals tested were also negative by PCR. A collateral survey performed at the site where the incriminated juice was processed revealed the presence of infected *P. geniculatus* and domestic rats.

As part of an ongoing cooperative study with the Instituto López Neyra in Granada, Spain, 3 parasite isolates obtained from patients, as well as from 1 infected triatomine captured at the juice preparation site, were typed using *T. cruzi* ribosomal and mini-exon gene markers. Preliminary results revealed a great genetic homogeneity, with all of the isolates belonging to the *T. cruzi* I lineage. Furthermore, homology analysis of the

**Table 2. Univariate and Multivariate Logistic Regression Analysis of Risk Factors Associated with *Trypanosoma cruzi* Transmission during an Outbreak of Orally Acquired Chagas Disease, Caracas, Venezuela, 2007**

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
<b>Age</b>				
≤18 Years	0.85 (0.79–0.91)	.01	0.7 (0.73–0.87)	.001
>18 Years	1.03 (1.0–1.07)	.02	1.03 (1.1–1.05)	.01
Worker vs student	1.3 (0.83–2.06)	.24	...	...
Shift (morning vs afternoon)	3.19 (2.1–4.8)	.001	4.7 (2.6–8.3)	.001
Any fresh beverage	2.17 (0.77–6.1)	.14	...	...
Guava juice	3.5 (1.85–6.7)	.001	3.2 (1.4–7.1)	.004
Passion fruit juice	0.95 (0.59–1.62)	.95	...	...
Melon juice	1.16 (0.76–1.7)	.47	...	...
Lemon-starch drink	1.03 (0.68–1.52)	.85	...	...
“Chicha”	0.77 (0.51–1.18)	.24	...	...
Oat meal drink	1.37 (0.9–2.0)	.13	...	...
Tamarind juice	0.6 (0.39–0.94)	.60	...	...
Mango juice	0.79 (0.5–1.1)	.26	...	...
Papaya juice	1.32 (0.8–2.0)	.19	...	...
Pineapple juice	0.72 (0.4–1.9)	.12	...	...

**NOTE.** CI, confidence interval; OR, odds ratio.

sequence of an amplified polymorphic mini-exon from *T. cruzi* RNA confirmed that all parasite isolates from the patients were identical, which was consistent with a common source of infection.

## DISCUSSION

Thanks to a coordinated program in the Southern Cone countries, the transmission of CD has been successfully interrupted in Uruguay and Chile, as well as in at least 8 of the 12 states of Brazil in which CD is endemic [19, 27]. However, the per-

sistence of numerous sylvatic foci and the wide distribution of vectors and reservoirs, together with a progressive reduction in the availability of the vector's natural source of blood (birds and mammals) in intervened forested areas, is driving originally wild triatomines to invade human dwellings [28, 29]. Once domiciliation has occurred, *P. geniculatus* may feed abundantly on domestic reservoirs, as well as on humans. As part of their nocturnal activity, vectors circulate widely inside the house and can thereby eventually contaminate unprotected food and beverages with their feces. There is also the possibility of trans-

**Table 3. Univariate and Multivariate Logistic Regression Analysis According to Symptoms and Serological Test Results for 1000 Individuals Exposed during an Outbreak of Orally Transmitted Acute Chagas Disease in Caracas, Venezuela, 2007**

Symptom	No. (%) of subjects (n = 1000)	Serological test results		Univariate analysis		Multivariate analysis	
		Percent positive/percent negative	P <sup>a</sup>	OR (95% CI)	P	OR (95% CI)	P
Fever	190 (19.0)	46.6/15.7	.001	4.6 (3.0–7.1)	.001	5.4 (3.9–9.6)	.001
Artralgias	18 (1.8)	6.6/1.2	.001	5.7 (2.1–15.4)	.001	3.3 (0.4–26.2)	.250
Skin lesions <sup>b</sup>	30 (3.0)	11.4/2.0	.001	6.2 (2.9–13.4)	.001	2.2 (0.7–6.9)	.140
Cardiovascular	4 (0.4)	1.9/0.2	.001	8.6 (1.2–62.0)	.030	4.3 (1.2–12.8)	.040
Gastrointestinal	84 (8.4)	11.4/8.0	.230	1.4 (0.7–2.8)	.240	...	...
Respiratory	49 (4.9)	7.6/4.5	.170	1.7 (0.7–3.7)	.170	...	...
Unspecific	26 (2.6)	4.7/2.3	.140	2.0 (0.7–2.8)	.150	...	...

**NOTE.** CI, confidence interval; OR, odds ratio.

<sup>a</sup> By  $\chi^2$  analysis.

<sup>b</sup> Rash, erythema nodosum, and facial edema.

**Table 4. Basal Electrocardiogram (ECG) Abnormalities by Age Group for 61 Infected Patients from an Outbreak of Orally Acquired Acute Chagas Disease in Caracas, Venezuela, 2007**

ECG abnormality	Age group		Total	P <sup>a</sup>
	≤18 Years (n = 48)	>18 Years (n = 13)		
ST abnormality	30	4	34	.028
T abnormality	39	1	40	<.001
Supraventricular arrhythmia	3	6	9	.002
Ventricular arrhythmia	2	0	2	.897
Microvoltage/decrease amplitud QRS	0	3	3	.007
QTc prolongation	2	0	2	.897
Fascicular block	3	2	5	.621
AV block	2	0	2	.897

<sup>a</sup> Yates corrected  $\chi^2$  analysis.

mission by food contamination with urine or anal secretions of infected marsupials [30].

The genetic homogeneity and lack of significant genetic intralinear polymorphism observed in all of the isolates thus far typed from the current outbreak is consistent with a common source of infection. Moreover, the confirmation of an acute infection in the woman responsible for the preparation of the juice lends further support to evidence that indicates short-term exposure, as do the logistic regression analysis results, which incriminated the guava juice as the possible source of contamination. We therefore postulate that, during the night, infected triatomines might have contaminated the unprotected pot where the guava juice was left before being blended in the early morning. Once the juice arrived at the school, it was first served to the teachers and afterwards served to the students, progressing from the lower to the higher grades of the morning shift. Any remaining juice was later shared by the teachers and students of the afternoon shift. This sequence of events could explain the relatively high attack rate observed among school personal (15.2%) and the significant decrease in the attack rate among students in the ninth grade (5.1%), compared with that among kindergarten students (23.1%). The significant difference in the attack rates found between students of the morning (22.5%) and afternoon shifts (2.4%) suggests that the concentration of the inoculum may have been different for both groups, perhaps reflecting a steady decrease in the survival of infecting metacyclic trypomastigotes [31].

Orally transmitted CD episodes have been described previously, all of which have been reported in South America [3–9, 32–34]. Distinctive epidemiological features included a lower number of infected persons (37 cases being the maximum number reported in any outbreak); relatively high lethality (up to 35.2%, with an average rate of 7.1%); a preponderance of cases occurring among adults; and occurrence in remote rural areas or in urban communities where fruits obtained from areas of

endemism, such as açai (*Euterpe oleracea*), piassava (*Leopoldina piçaba*), and sugar cane, were consumed. The present outbreak is unique in that it affected a large, predominantly young, healthy urban population and was associated with high rates of parasitemia and morbidity but a very low mortality rate (0.97%). The latter probably relates to prompt diagnosis and treatment. It is the first time that contaminated guava juice has been incriminated as the source of infection. Moreover, this represents a genuine urban oral CD outbreak, because the *T. cruzi* strain that was involved in the outbreak originated from an inner-city household, where peridomestic triatomines and rodent reservoirs allowed the maintenance of transmission.

One crucial problem was the overwhelming amount of clinical cases that required diagnostic confirmation. Serological testing with the ELISA was very useful for this purpose, and the assessment of both IgG and IgM anti-*T. cruzi* antibodies for all members of the exposed population enabled us to demonstrate the infection in the early phase. The concurrent onset of symptoms in most cases and the fact that specific IgM antibodies were demonstrated in a high percentage of cases (87.3%) further suggests that exposure to the infecting inoculum was recent [35] and singular or short-lived.

Of the 103 individuals in whom *T. cruzi* parasitemia was determined by parasitological methods and/or PCR, 44 (40.7%) had positive test results. This is probably one of the highest rates of parasitemia ever documented in any orally transmitted CD outbreak.

Although 75% of the infected individuals were symptomatic, the predominant clinical manifestations observed (fever, headache, and myalgias) are all highly unspecific. Indeed, dengue, mononucleosis, hepatitis, and intoxications were among the causes contemplated initially. Clinical findings such as facial edema, gingivitis, and dry cough are probably the consequence of the penetration of the parasite throughout the oral cavity, lips or pharyngeal mucosa. These latter manifestations, along

with other unexpected findings, such as erythema nodosum, anasarca, and lower limbs edema, are not described in vectorial transmission and even in prior reports of orally-acquired CD. They may be related to the host's immune inflammatory response conditioned by the genetics of each individual or by a high parasite load [36]. On the other hand, the findings of acute myocarditis were observed in an unusually high proportion (59%) of confirmed cases.

The diagnosis of acute CD requires a high index of suspicion by the clinician, especially when patients are seen away from the traditional areas of endemicity. In countries in which CD occurs, this condition must be considered in the differential diagnosis of FUO, because food-borne acute CD may occur more often than is currently recognized.

Progressive environmental changes that affect the ethology and ecology of potential *T. cruzi* reservoirs and vectors, together with an increase in human populations surrounded by inter-vened forests, have favored the urbanization and domiciliation of the cycle maintained by *P. geniculatus*, thus affecting the poor populations of the misery belts around most Latin American cities and middle-class populations, under the concept of the "edge-mediated effects" [37]. This new situation imposes necessary changes in the strategy of CD control programs, which until now have been limited to vector control activities in rural Latin American communities in areas of endemicity.

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