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Trypanosoma cruzi and Chagas' Disease in the United States

Caryn Bern,[1]* Sonia Kjos,[2] Michael J. Yabsley,[3] and Susan P. Montgomery[1]

Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia[1]; Marshfield Clinic Research Foundation, Marshfield, Wisconsin[2]; and Department of Population Health, College of Veterinary Medicine, University of Georgia, Athens, Georgia[3]

* Corresponding author. Mailing address: Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, 1600 Clifton Rd. N.E., Atlanta, GA 30333. Phone: (404) 718-4726. Fax: (404) 718-4816. E-mail: cxb9@cdc.gov.

INTRODUCTION

Chagas' disease is caused by the protozoan parasite *Trypanosoma cruzi* (234). World Health Organization disease burden estimates place Chagas' disease first among parasitic diseases in the Americas, accounting for nearly 5 times as many disability-adjusted life years lost as malaria (343). An estimated 8 million people are currently infected, and 20 to 30% of these will develop symptomatic, potentially life-threatening Chagas' disease (Table 1) (214). *T. cruzi* is carried in the guts of hematophagous triatomine bugs; transmission occurs when infected bug feces contaminate the bite site or intact mucous membranes. *T. cruzi* can also be transmitted through transfusion, through transplant, and congenitally (177, 234).

Historically, transmission and morbidity were concentrated in rural areas of Latin America where poor housing conditions favor vector infestation. However, in the last several decades, successful vector control programs have substantially decreased transmission in rural areas, and migration has brought infected individuals to cities both within and outside Latin America (87, 111, 196). Since 1991, several subregional initiatives have made major advances in decreasing vector infestation in human dwellings and extending screening of the blood supply for *T. cruzi* (87, 269). In 2007, control efforts in Latin America were formally joined by an initiative to address the "globalization" of Chagas' disease, recognizing the increasing presence of imported cases in Europe, North America, and Japan and the potential for local transmission through nonvectorial routes (344). The United States occupies an ambiguous position in this new initiative. While the United States has never participated in Latin American Chagas' disease control programs, it cannot be classified as an area where the disease is "not endemic" in the same sense as Europe or Japan. The southern tier of states from Georgia to California contains established enzootic cycles of *T. cruzi*, involving several triatomine vector species and mammalian hosts such as raccoons, opossums, and domestic dogs (26, 151, 345). Nevertheless, most *T. cruzi*-infected individuals in the United States are immigrants from areas of endemicity in Latin America (29).

This article will present an overview of clinical and epidemiological aspects of Chagas' disease, with a focus on data and issues specific to *T. cruzi* and Chagas' disease in the United States. Topics to be covered include vector biology and ecology, animal reservoirs, *T. cruzi* strain typing, human Chagas' disease, and future research needed for control of Chagas' disease in the United States.

TRYPANOSOMA CRUZI LIFE CYCLE AND TRANSMISSION

Life Cycle

Nearly all the salient features of the *T. cruzi* life cycle were described by Carlos Chagas, the scientist who discovered the organism, in 1909 (62). *T. cruzi* is a kinetoplastid protozoan which infects vertebrate and invertebrate hosts during defined stages in its life cycle (234, 292). The triatomine vector ingests circulating trypomastigotes when it takes a blood meal from an infected mammalian host. In the midgut of the vector, trypomastigotes transform through an intermediate form sometimes

TABLE 1. Countries where Chagas' disease is endemic and estimates of the seroprevalence and number of infected inhabitants

Region	Country where Chagas' disease is endemic[a]	Estimated seroprevalence (%)[b]	Estimated no. of infected individuals[b]
North America	United States	NDA	300,167[c]
	Mexico	1.03	1,100,000
Central America	Belize	0.74	2,000
	Costa Rica	0.53	23,000
	El Salvador	3.37	232,000
	Honduras	3.05	220,000
	Guatemala	1.98	250,000
	Nicaragua	1.14	58,600
	Panama	0.01	21,000
South America	Argentina	4.13	1,600,000
	Bolivia	6.75	620,000
	Brazil	1.02	1,900,000
	Chile	0.99	160,200
	Colombia	0.96	436,000
	Ecuador	1.74	230,000
	Guyana	1.29	18,000
	Suriname	NDA	NDA
	French Guiana	NDA	NDA
	Paraguay	2.54	150,000
	Peru	0.69	192,000
	Uruguay	0.66	21,700
	Venezuela	1.16	310,000

[a] Vector-borne *T. cruzi* transmission occurs, or occurred until recently, in parts of these countries.

[b] Disease burden estimates are for the year 2005, based on references 29 and 214. NDA, No data available.

[c] The number for the United States reflects the estimated number of infected immigrants from countries in Latin America where the disease is endemic. No estimate of the number of locally acquired infections is currently available.

called a spheromastigote to epimastigotes, the main replicating stage in the invertebrate host. Epimastigotes migrate to the hindgut and differentiate into infective metacyclic trypomastigotes, which are excreted with the feces of the vector. Metacyclic trypomastigotes enter through the bite wound or intact mucous membrane of the mammalian host and invade many types of nucleated cells through a lysosome-mediated mechanism (50). In the cytoplasm, trypomastigotes differentiate into the intracellular amastigote form, which replicates with a doubling time of about 12 h over a period of 4 to 5 days. At the end of this period, the amastigotes transform into trypomastigotes, the host cell ruptures, and the trypomastigotes are released into the circulation. The circulating parasites can then invade new cells and initiate new replicative cycles, and they are available to infect vectors that feed on the host. In the absence of successful antitrypanosomal treatment, the infection lasts for the lifetime of the mammalian host.

Transmission Routes

Vector-borne transmission. The vector-borne transmission route, occurring exclusively in the Americas, is still the predominant mechanism for new human infections. The feces of infected bugs contain metacyclic trypomastigotes that can enter the human body through the bite wound or through intact conjunctiva or other mucous membranes.

Congenital transmission. Between 1 and 10% of infants of *T. cruzi*-infected mothers are born with congenital Chagas' disease (14, 24, 289). Congenital transmission can occur from women themselves infected congenitally, perpetuating the disease in the absence of the vector (263). Factors reported to increase risk include higher maternal parasitemia level, less robust anti-*T. cruzi* immune responses, younger maternal age, HIV and, in an animal model, parasite strain (9, 32, 34, 107, 289).

Blood-borne transmission. Transfusional *T. cruzi* transmission was postulated in 1936 and first documented in 1952 (109, 307). The risk of *T. cruzi* transmission per infected unit transfused is estimated to be 10 to 25%; platelet transfusions are thought to pose a higher risk than other components such as packed red cells (31, 308). In 1991, the prevalence of *T. cruzi* infection in donated blood units ranged from 1 to 60% in Latin American cities (268). Since then, blood donation screening has become accepted as an important pillar of the Chagas' disease control initiatives (220, 269). Serological screening of blood components for *T. cruzi* is now compulsory in all but one of the countries in Latin America where the disease is endemic, and the prevalence of infection in screened donors has decreased substantially (196, 269). Nevertheless, Chagas' disease screening coverage by country was estimated to vary from 25% to 100% in 2002, and the risk of transmission, though much decreased, has not been eliminated (269). The residual risk in Latin America where screening has been implemented is estimated to be 1:200,000 units (269, 308).

Organ-derived transmission. Uninfected recipients who receive an organ from a *T. cruzi*-infected donor may develop acute *T. cruzi* infection. However, transmission is not universal; in a series of 16 uninfected recipients of kidneys from infected donors, only 3 (19%) acquired *T. cruzi* infection (238). Nineteen instances of transmission by organ transplantation have been documented in the literature (13 kidney, 1 kidney and pancreas, 3 liver, and 2 heart transplants) (16, 61, 66, 79, 99, 101, 157, 238, 279). The risk from heart transplantation is thought to be higher than that from kidney or liver transplantation (65). One case of transmission through unrelated cord blood transplantation has been reported (104).

Oral transmission. Recently, increasing attention has focused on the oral route of *T. cruzi* transmission; several outbreaks attributed to contaminated fruit or sugar cane juice have been reported from Brazil and Venezuela (28, 82, 208). Most outbreaks are small, often affecting family groups in the Amazon region, where the palm fruit açaí is a dietary staple that appears to be particularly vulnerable to contamination, perhaps from infected vectors living in the trees themselves (74, 208). The largest reported outbreak to date led to more than 100 infections among students and staff at a school in Caracas; locally prepared guava juice was implicated (82).

TRIATOMINE VECTOR BIOLOGY AND ECOLOGY

Background

The epidemiology of vector-borne *T. cruzi* is closely linked to the biological and ecological characteristics of local vectors and mammalian reservoir hosts. Triatomines of both sexes must take blood meals to develop through their nymphal stages to adults, and females require a blood meal to lay eggs. Thus, nymphs and adults of either sex may be infected with *T. cruzi*, but infection rates increase with increasing vector stage and age. Most domestic triatomine species feed nocturnally and are able to complete their blood meal without waking the host (169). The major Latin American vectors defecate during or immediately after taking a blood meal.

T. cruzi infection is transmitted to wild mammals by sylvatic triatomine species; these bugs often colonize the nests of rodent or marsupial reservoir hosts (169, 311). Sylvatic triatomine adults may fly into human dwellings because of attraction by light and cause sporadic human infections (74). Domestic transmission cycles occur where vectors have become adapted to living in human dwellings and nearby animal enclosures; domestic mammals such as dogs, cats, and guinea pigs play important roles as triatomine blood meal sources and *T. cruzi* reservoir hosts (69, 124, 131). Some triatomine species can infest both domestic and sylvatic sites and may play a bridging role (192).

There are more than 130 triatomine species in the Americas, many of which can be infected by and transmit *T. cruzi* (169, 311). However, a small number of highly domiciliated vectors are of disproportionate importance in the human epidemiology of disease (Table 2) (311). The domestic environment provides abundant blood meal sources, and poor quality housing with adobe or unfinished brick walls provides crevices and other diurnal hiding places for triatomines (170, 201). Thatch roofs provide an attractive habitat for some species (117). In communities where the disease is endemic, 25 to 100% of houses may be infested, and a house and its immediate surroundings may support large colonies of juvenile and adult bugs (170, 201, 230).

In areas of the Amazon where deforestation and human immigration have occurred, tree-dwelling sylvatic triatomine

TABLE 2. The major triatomine species that colonize the domestic and peridomestic environment and play an important role in the epidemiology of Chagas' disease in Latin America[a]

Vector species	Locations
Triatoma infestans	Argentina,[b] Brazil,[c] Chile,[c] Paraguay,[b] southern Peru, Uruguay[c]
Rhodnius prolixus	Colombia, El Salvador, Guatemala,[d] Honduras, southern Mexico, Nicaragua, Venezuela
Triatoma dimidiata	Belize, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, northern Peru, Venezuela
Panstrongylus megistus	Argentina, Brazil, Paraguay, Uruguay
Triatoma brasiliensis	Northeastern Brazil

[a] Data are from reference 311.
[b] *T. cruzi* transmission by *T. infestans* has been certified as interrupted in 6 provinces of Argentina and 1 department of Paraguay (220).
[c] *T. cruzi* transmission by *T. infestans* has been certified as interrupted throughout the country (220).
[d] *T. cruzi* transmission by *R. prolixus* has been certified as interrupted throughout the country (220).

populations have survived and rebounded by adapting to new vertebrate host species (2). These opportunistic vertebrates (opossums and rodents) are competent Chagas' disease reservoirs and are acclimated to living in close proximity to humans where remnant vegetation is located. The concentration of triatomines and vertebrate reservoirs in the peridomestic realm has lead to increased interactions between sylvatic triatomine species and humans in deforested areas of the Amazon and Panama and to an apparent increase in the incidence of Chagas' disease in humans (4, 244).

Triatomine Distribution in the United States

Eleven species of triatomine bugs have been reported from the United States: *Triatoma gerstaeckeri*, *T. incrassata*, *T. indictiva*, *T. lecticularia*, *T. neotomae*, *T. protracta*, *T. recurva*, *T. rubida*, *T. rubrofasciata*, *T. sanguisuga*, and *Paratriatoma hirsuta* (Fig. 1 and Table 3). Triatomines are present across the southern half of the country, distributed from the Pacific to Atlantic coasts (Fig. 2). One species (*T. rubrofasciata*) is found in Hawaii. A high degree of polymorphism has been noted in several species across their geographic ranges, particularly *T. protracta*, *T. rubida*, and *T. sanguisuga*, resulting in proposed subspecies classifications (249, 251, 254, 296). However, due to the recognition of morphological intermediates across some subspecies groups and the absence of supporting data (e.g., paired molecular and morphological studies), these subspecies have not been universally accepted as valid taxonomic groups (110, 169).

All U.S. species except *T. rubrofasciata* and *T. sanguisuga* have been collected in Mexico; the distribution of *T. sanguisuga* likely extends into northeastern Mexico as well (255). A review of the published literature from 1939 to 2010 resulted in reports of wild-caught triatomine bugs from 262 counties in 28 states. The greatest species diversity occurs in the southwest, particularly Texas, Arizona, and New Mexico. More specifically, high species diversity is concentrated in south-central Arizona and southwestern Texas, where up to five species have been recorded in a single county (Fig. 2). *T. cruzi*-infected specimens have been reported from 10 states, predominantly from counties in the Southwest (Fig. 3A). All species except *T. incrassata* and *P. hirsuta* have been found naturally infected with *T. cruzi* (Fig. 3B to L).

County-level maps (Fig. 2 and 3) reflect in part where collection efforts have been focused over the past 70 years. There is no evidence of a temporal or spatial trend in the published reports to suggest any recent migration of species into or within the United States. The county maps do not necessarily reflect triatomine population densities or provide a complete representation of their distributions. Rather, the maps more likely provide an indication of where the bugs have been considered a pest to humans or animals and where field efforts were concentrated as a consequence or where specimens were collected coincidentally by researchers studying other animal systems (i.e., reports based on museum specimens). Collection records are more comprehensive in the southwestern states and Florida, with sparse records in the southeastern states. Early discovery of the association of U.S. triatomine bugs with *Neotoma* species of woodrats may have aided field research in

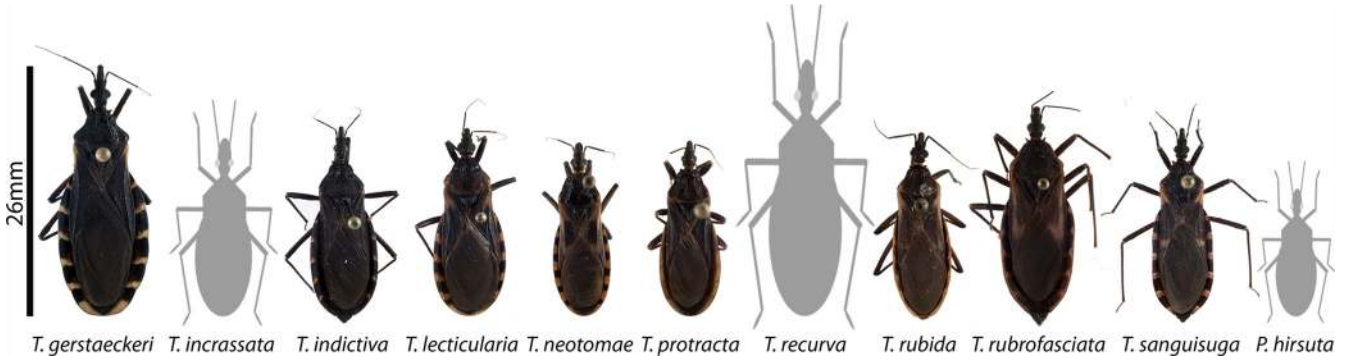

FIG. 1. Photographs of U.S. triatomine species, *Triatoma* and *Paratriatoma.* The image size relative to the scale bar represents the average length of each species. Photographs for *T. incrassata*, *T. recurva*, and *P. hirsuta* were unavailable. All photographs are by S. Kjos.

TABLE 3. Geographic location, *Trypanosoma cruzi* prevalence, human interaction, and sites of collection of *Triatoma* and *Paratriatoma* species in the United States

Species	State(s)	Total no. tested	No. (%) positive	Human bites/allergic reactions	Collection site(s)[a]	References
T. gerstaeckeri	NM, TX	1,800	1,038 (58)	+/+	B, C, D, H, L, LS, WR	26, 49, 94, 150, 160, 169, 195, 217, 228, 239, 259, 282, 296, 330–332, 341
T. incrassata	AZ	Not reported	Not reported	−/−	L	169, 255
T. indictiva	AZ, NM, TX	12	4 (33)	−/−	H, L, WR	150, 151, 229, 259, 296, 332, 341
T. lecticularia	FL, GA, MO, NM, OK, SC, TN, TX	282	144 (51)	+/−	D, H, L, T, WR	150, 169, 195, 218, 250, 256, 259, 282, 312, 332, 341
T. neotomae	TX	53	40 (76)	−/−	D, WR	49, 85, 94, 150, 282, 296
T. protracta	AZ, CA, CO, NM, NV, TX, UT	4,124	723 (18)	+/+	H, L, R, T, WR	95, 96, 135, 150, 152, 153, 159, 187, 203, 204, 217, 237, 243, 255, 256, 259, 273, 282, 285, 296, 304, 320–322, 326, 327, 329, 330, 332, 335, 336, 339–341
T. recurva	AZ	565	71 (13)	+/+	C, H, L, R, WR	95, 96, 152, 237, 255, 256, 296, 321, 325, 329, 330, 332, 335, 336, 339
T. rubida	AZ, CA, NM, TX	1,340	96 (7)	+/+	H, L, WR	95, 96, 150, 152, 153, 156, 237, 256, 259, 273, 282, 296, 321, 324, 329, 330, 332, 335, 336, 341
T. rubrofasciata	FL, HI	2	2 (100)	+/+	H, LS, WP	12, 169, 255, 296, 337
T. sanguisuga	AL, AR, FL, GA, IL, IN, KS, KY, LA, MD, MO, MS, NC, NJ, OH, OK, PA, SC, TN, TX, VA	1031	151 (15)	+/+	D, H, L, LS, T, WP, WR	27, 41, 49, 54, 77, 90, 94, 116, 120, 128, 134, 147, 150, 152, 169, 195, 212, 218, 228, 231, 239, 254, 259, 282, 286, 296, 332, 345, 347
P. hirsuta	AZ, CA, NV	66	0 (0)	+/−	H, L, WR	169, 251, 252, 255, 256, 296, 324, 333, 335, 336

[a] B, bird nest; C, cave; D, dog kennel; H, house; L, lights; LS, livestock pens; R, roadbed; RK, rocks; T, trees; WP, woodpile; WR, woodrat nest.

the southwestern states, because woodrat species in this region build easily identifiable, above-ground dens. The absence of records in some areas of the southeastern United States may reflect a paucity of field studies or published records in those locations rather than being an indication of true absence of the bug. The detection of *T. cruzi*-infected wild mammals in many of these areas suggests the presence of the vectors. Additionally, recent efforts to model the geographic distribution of U.S. species based on the land cover, climate, and host composition of known collection sites indicate favorable habitat suitability in many of these unsurveyed or underreported regions (26, 137, 158, 259). Characteristics of each species are summarized in Table 3 and described in detail in the sections that follow.

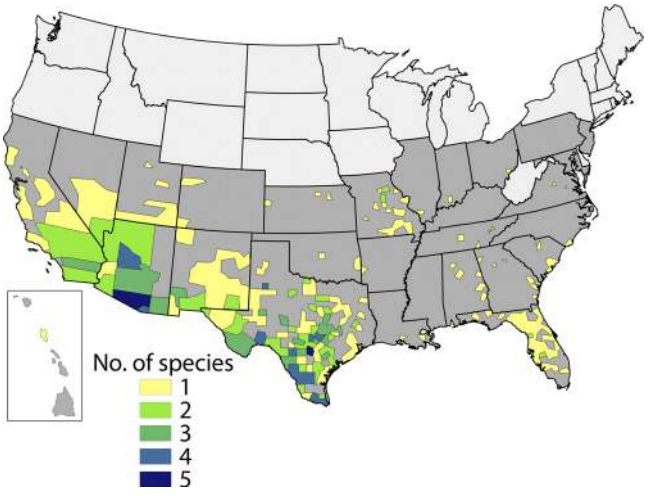

FIG. 2. Triatomine species diversity in the continental United States and Hawaii by county. States shaded gray have reported at least one species. The states of Kentucky, Maryland, Mississippi, New Jersey, and Pennsylvania have each reported one species but with no locality specified. References are provided in Table 3.

Description of U.S. Triatomine Species

***Triatoma gerstaeckeri* (Stål).** *T. gerstaeckeri* is one of the most frequently collected and tested species in the United States; 57.7% (1,038/1,800) of tested specimens were found to harbor *T. cruzi*. *T. cruzi*-infected specimens have been found in both Texas and New Mexico and in the majority of the counties where testing has been reported (Fig. 3B). Published reports from the 1930s to 1960s describe *T. gerstaeckeri* as a pest species of humans and livestock; the adult bugs were frequent invaders of rural houses in Texas, and reports of humans being bitten were common (217, 330, 332). Human encounters have been less frequently reported in recent decades (49, 151). Infected *T. gerstaeckeri* specimens were recently recovered from the residence of a child with acute Chagas' disease in southern Texas (151). In northeastern Mexico, this species is considered an important Chagas' disease vector due to its close association

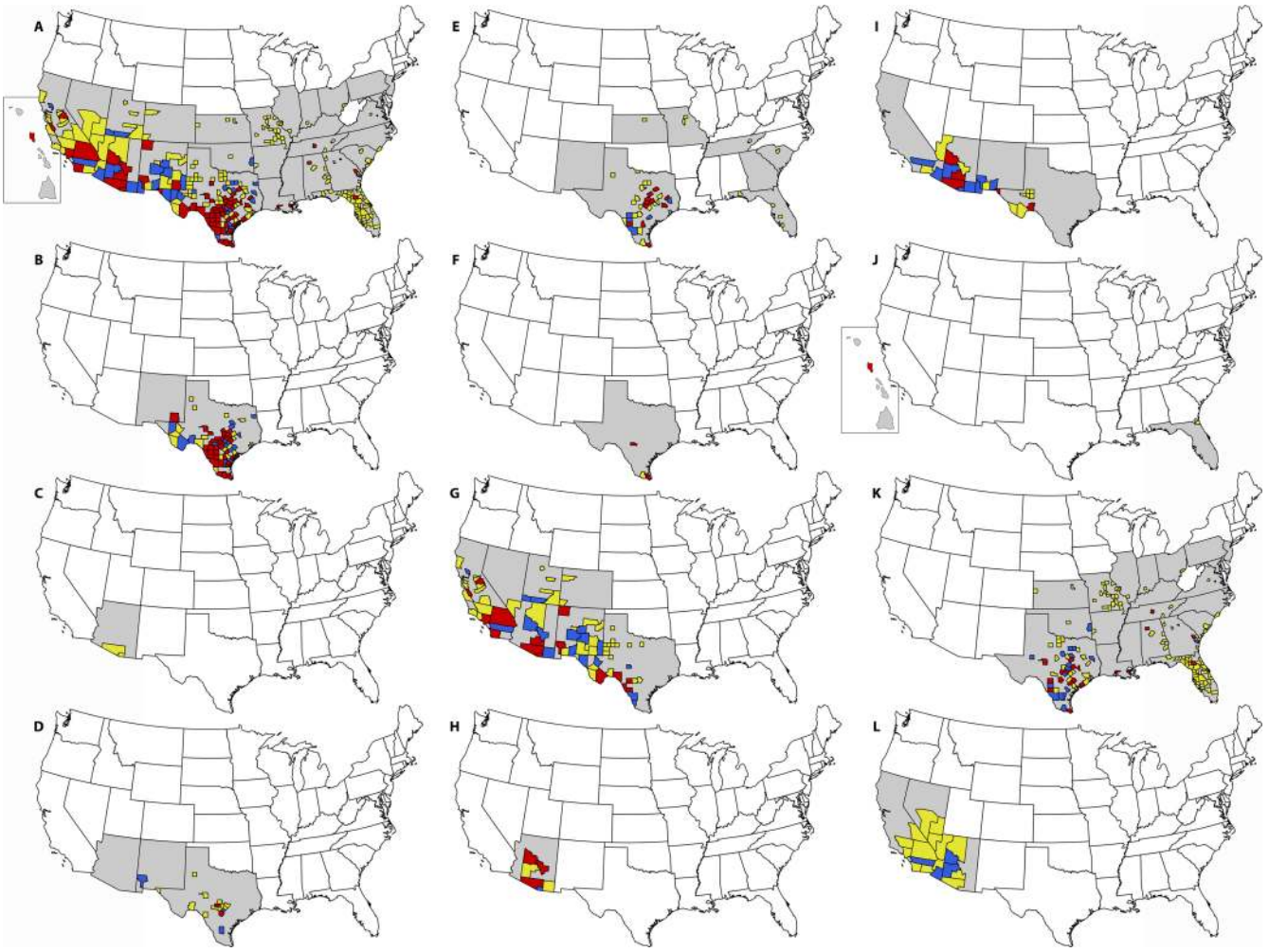

FIG. 3. Triatomine species geographic distribution by state (gray areas) and county and *Trypanosoma cruzi* infection status by county in the continental United States and Hawaii. (A) All species; (B) *Triatoma gerstaeckeri*; (C) *T. incrassata*; (D) *T. indictiva*; (E) *T. lecticularia*; (F) *T. neotomae*; (G) *T. protracta*; (H) *T. recurva*; (I) *T. rubida*; (J) *T. rubrofasciata*; (K) *T. sanguisuga*; (L) *Paratriatoma hirsuta.* Red, *T. cruzi*-positive specimens; blue, negative specimens; yellow, no testing reported. References are provided in Table 3.

with human dwellings (184, 288). U.S. *T. gerstaeckeri* data derive predominantly from Texas, where the bug has been found in a wide variety of habitats. The species was collected from a rock squirrel burrow in a cave in the southeastern corner of New Mexico (341).

***Triatoma incrassata* Usinger.** *T. incrassata* is somewhat similar to *T. protracta* in size and general appearance of legs and head, but it has a distinctive abdominal margin which is largely yellow on the dorsal surface and entirely yellow on the ventral surface. It has been collected at lights in the two southern Arizona counties of Santa Cruz and Pima (Fig. 3C) (169, 255). The major mammalian hosts and *T. cruzi* infection prevalence for this species are unknown.

***Triatoma indictiva* Neiva.** *T. indictiva* was considered a subspecies of *T. sanguisuga* in the past but is currently accorded full species status (110, 169, 296). This species is very similar in appearance to *T. sanguisuga*, with the exception of the uniformly black pronotum and narrower horizontal markings on the abdominal edge. The distributions of the two species overlap in the central regions of Texas, with *T. indictiva* continuing further west to Arizona and *T. sanguisuga* continuing east to the Atlantic coast (Fig. 3D and K). Reported collection of *T. indictiva* is much less frequent than that of *T. sanguisuga*. Additional collection sites for *T. indictiva* in New Mexico and Arizona were provided in a map by Lent and Wygodzinsky in 1979, but specific location designations were not given (169). Specimens were collected from woodrat nests in New Mexico and at lights in Texas (229, 332). *T. indictiva* has been found naturally infected with *T. cruzi* in specimens from Texas (151, 229).

***Triatoma lecticularia* (Stål).** *T. lecticularia* has a geographic distribution similar to that of *T. sanguisuga*, from the south-central United States east to the Atlantic coast (Fig. 3E). Its range probably includes Oklahoma, Arkansas, Louisiana, Mississippi, and Alabama based on similarities in ecological characteristics between these states and adjacent areas where it has been reported. Specimens of *T. lecticularia* from New Mexico have been reported, but specific location information was not provided (254, 296). *T. lecticularia* had been variously classified as a subspecies of as well as synonymized with *T. sanguisuga*

prior to Usinger's 1944 reclassification (296). Therefore, early reports of *T. lecticularia* and *T. sanguisuga* may be difficult to confirm without reviewing the actual specimens. Ryckman in 1984 contended that reports of *T. lecticularia* from Arizona and California are erroneous, presumably based on earlier taxonomic confusion and contemporary knowledge of the species distribution (254). *T. lecticularia* can be distinguished from *T. sanguisuga* and *T. indictiva* based on its shorter, domed head and uniform covering of all body surfaces with dark hairs. *T. lecticularia* has been collected from houses, dog kennels, woodrat nests, and rock squirrel burrows in hollow logs in Texas, from houses in South Carolina, and at lights in Missouri (151, 195, 256, 312, 345). In early reports, this species was described as a nuisance species, commonly found in well-constructed homes of central Texas (218). In 1940, Packchanian conducted experimental inoculation of the gut contents of a *T. cruzi*-infected *T. lecticularia* bug into the eye of a human subject in order to demonstrate the infectivity of a *T. cruzi* strain from Texas (216). Localized symptoms, fever, lymphadenopathy, and trypomastigotes visualized on blood films confirmed infection in this individual. The high *T. cruzi* infection prevalence (144/282; 51%) in *T. lecticularia* was derived primarily from specimens collected from woodrat nests in Texas (282, 332).

***Triatoma neotomae* Neiva.** In the United States, *T. neotomae* is known only from Texas, primarily the southern tip (Fig. 3F). The inclusion of other states in its range by some authors is most likely an error, as published records of *T. neotomae* outside Texas or northeastern Mexico could not be found. This species is similar in size to *T. protracta* but with distinctive yellow markings around the abdominal margin and basal half of wings, a glossy body surface, and a ventrally flattened abdomen. Also like *T. protracta*, this species is closely associated with *Neotoma* spp. of woodrats, for which it was named. It has been found almost exclusively in woodrat nests throughout its range, with a single report from a dog kennel in Cameron County, TX (151). The small sample size limits interpretation of this species' high cumulative *T. cruzi* infection prevalence (40/53; 76%); however, this is likely related to the high infection levels reported among woodrats in this region (49, 93, 219).

***Triatoma protracta* (Uhler).** *T. cruzi* was first reported in the United States from a *T. protracta* specimen collected in 1916 in a woodrat nest in San Diego County, CA (155). *T. cruzi* testing data are most abundant for this species, with an overall prevalence of 17.5% (723/4,124). Infected specimens have been reported from four of seven states across its range: California, Arizona, New Mexico, and Texas (Fig. 3G). *T. protracta* is closely associated with western woodrat species and is commonly found in nests throughout the bug's geographic distribution. Large aggregations of *T. protracta* were reported from roadbeds in southern California in an area where woodrat nests were removed as a consequence of highway construction (340). Attracted by lights, the displaced bugs frequently entered houses in the area and became a source of annoyance for residents. *T. protracta* has also been reported as frequently entering houses in other areas of California, New Mexico, and Arizona (187, 273, 304, 332, 336). First reported as a pest of humans in Yosemite Valley, CA, in the 1860s, *T. protracta* continues to be an important cause of severe allergic reactions in humans who are bitten (152, 198). This species was implicated in a human case of Chagas' disease in north-central California (203).

***Triatoma recurva* (Stål).** *T. recurva* naturally infected with *T. cruzi* has been found in the southern half of Arizona (Fig. 3H). A single report of *T. recurva* collected in western Texas has not been confirmed or replicated (138, 151). Early reports describe *T. recurva* as a pest of humans, primarily in the Alvardo Mine area of Yavapai County, AZ, where it was a common invader of houses and tents of mining employees (332, 336). Recent reports describe home invasions and hypersensitivity reactions due to bites that occurred in and around houses in Pima and Cochise Counties, AZ (152, 237). Although the species has been collected occasionally from woodrat nests, the woodrat is not considered the primary host of *T. recurva* (96, 255, 321). The preferred host for this species is unknown, but it has been observed in association with rodents, particularly rock squirrels, and feeds on reptiles and guinea pigs in laboratory settings (96, 255, 324, 334, 336). *T. recurva* is the largest of the U.S. species (average length, 29 mm) and has relatively hairless body surfaces, including the first two segments of the mouthparts. It is brown to black in appearance, with slender, long legs and head and an orange-yellow abdominal margin. Its body size, head and leg characteristics, and uniformly colored pronotum distinguish this species from others in its range.

***Triatoma rubida* (Uhler).** In the United States, *T. rubida* has been found from western Texas to southern California; *T. cruzi*-positive specimens have been reported from Arizona and Texas (Fig. 3I). The cumulative infection prevalence in the published literature is low (96/1,340; 7.2%). However, in a recent study, the gut contents of 65 (41%) of 158 *T. rubida* specimens collected in and around houses in Pima County, AZ, yielded positive results by *T. cruzi* PCR (237). Despite the presence of nymphal stages inside houses in this study, the authors remarked that the numbers were too low to conclude that colonization was established. In contrast, a study from Sonora, Mexico, reported that 68% of houses were colonized by *T. rubida*, suggesting that this species was domesticated in that region (221). Both the U.S. and Mexican study areas had experienced disruption of previously undisturbed environments considered suitable habitats for both triatomine and *T. cruzi* vertebrate hosts. Human bite encounters, including hypersensitivity reactions due to *T. rubida*, continue to be a public health issue in Arizona (152, 226, 237). This species has been frequently collected from woodrat nests throughout its range (96, 256, 321, 332, 336). It can be distinguished morphologically from other species in its range by the first antennal segment, which reaches or surpasses the tip of the head.

***Triatoma rubrofasciata* (DeGeer).** Described in 1733, *T. rubrofasciata* was the first species classified in the Triatominae subfamily and is the current type species for the *Triatoma* genus (270). It is the only triatomine species found in both the Eastern and Western Hemispheres and is frequently found in port cities in close association with the roof rat (*Rattus rattus*) (255). Molecular and morphometric data support the hypothesis that Old World triatomine species derive from *T. rubrofasciata* carried from North America with rats on sailing ships during the colonial period (136, 223, 270). In the United States, this species has been collected from houses in Florida and Hawaii and in chicken and pigeon coops and cat houses in

Hawaii. Specimens have been reported from Jacksonville, FL, and Honolulu, HI (Fig. 3J) (296, 337). Wood (in 1946) reported 2 specimens collected from Honolulu to be infected with *T. cruzi* based on morphological and motility characteristics (337). Allergic reactions to *T. rubrofasciata* bites have been reported in humans from Hawaii (12).

***Triatoma sanguisuga* (Leconte).** *T. sanguisuga* is one of the most widely distributed species in the United States, with its range spanning from Texas and Oklahoma eastward to the Atlantic coast (Fig. 3K). This species has been reported in Pennsylvania, New Jersey, Maryland, and Kentucky, but without specific location data (169, 254, 296). Although published records are lacking, its range probably includes West Virginia. Reports of *T. sanguisuga* from states west of Texas were likely mistaken due to taxonomic reclassification (see "*Triatoma indictiva* Neiva" above). In every state where testing has been conducted, *T. cruzi*-infected *T. sanguisuga* has been found, including Texas, Oklahoma, Louisiana, Alabama, Tennessee, Georgia, and Florida. It has been collected from diverse natural settings across its range, in association with many different vertebrate hosts, including woodrats, cottonrats, armadillos, raccoons, opossums, frogs, dogs, chickens, horses, and humans (120, 150, 212, 215, 332, 348). Human annoyance and allergic reactions to *T. sanguisuga* bites were reported as early as the mid-1800s in Georgia, Kansas, Oklahoma, and Florida and recently in Louisiana (116, 147, 152, 161, 215). This species was found inside the residences of human Chagas' disease patients in Tennessee and Louisiana and in the vicinity of the home of a *T. cruzi*-seropositive blood donor in Mississippi (54, 90, 134).

***Paratriatoma hirsuta* Barber.** *P. hirsuta* is known from the western United States, collected from arid regions of California, Nevada, and Arizona (Fig. 3L). Although it has been demonstrated to be a competent vector of *T. cruzi* in experimental settings, a naturally infected specimen has yet to be reported (321). It has been most frequently collected from woodrat nests in its range but has also been found in houses and other human dwellings in Yavapai County, AZ, and Riverside County, CA, and at lights in Palm Springs, CA (251, 296, 336). Ryckman (in 1981) described this species as having important public health significance due to allergic reactions caused by its bite (252). This is one of the smallest U.S. triatomine species (average length, 13 mm) and can be distinguished from *T. protracta*, which is similar in size and geographic distribution, by a pervasive covering of dark hairs on all body surfaces.

Human-Vector Interactions and *T. cruzi* Transmission Potential in the United States

Eight of the 11 species have been associated with human bites, and seven have been implicated in allergic reactions (Table 3). Allergic reactions occur in response to antigens delivered in the vector saliva during blood feeding and are unrelated to the *T. cruzi* infection status of the bug. Most allergic reactions are localized at the bite site, characterized by a large welt and intense itching (315). Severe reactions are generally systemic and may involve angiodema, urticaria, difficulty breathing, nausea, diarrhea, and/or anaphylaxis (152, 226). Although allergic reactions to triatomine bites have been reported from states throughout the southern United States, the incidence is highest in the southwestern states, with *T. protracta* and *T. rubida* most frequently implicated (106, 152, 204, 226, 237). The most common scenario involves invasion of an adult bug into a human dwelling, where it bites a sleeping individual.

Contemporary encounters between humans and triatomine bugs in the United States are often associated with destruction or invasion of vertebrate host habitats, compromised housing structures, or both. Disruption of host burrows (as described above for *T. protracta*) provokes the bugs to seek new refuges, and their innate attraction to lights often leads them to nearby human dwellings. Most triatomine species show flexibility in host and habitat requirements, which allows them to adapt to changing environments. A host preference for some species has been difficult to establish due to association with multiple vertebrate habitats and the ability of the insects to mature and reproduce successfully on multiple host species in laboratory settings. Although mammals are the only vertebrate reservoirs for *T. cruzi*, many triatomine species utilize other animal groups as blood hosts, including reptiles and amphibians (*T. gerstaeckeri*, *T. protracta*, *T. recurva*, *T. rubida*, and *T. sanguisuga*) and birds (*T. gerstaeckeri* and *T. sanguisuga*) (169, 228, 253, 338). A recent blood meal analysis study of Texas field specimens provides evidence of a broad host range for *T. gerstaeckeri* and *T. sanguisuga*. The DNAs from nine vertebrate species (woodrat, dog, cat, cow, pig, raccoon, skunk, armadillo, and human) were detected in *T. gerstaeckeri* gut specimens, and DNAs from three species (dog, avian, and human) were detected in *T. sanguisuga* gut specimens (149).

Because vector colonization of houses in the United States is rare, the risk of vector-borne transmission to humans is considered to be quite low. With the exception of the 2006 Louisiana case in which the residence was found to harbor triatomine colonies, vector-borne transmission to humans in the United States has been attributed to adult bugs invading houses (90, 134, 203). Expansion of human settlements into environments that support an active sylvatic disease cycle could result in an increase in adult invaders and, potentially, colonization events. Colonization of houses by triatomines is an important factor in vector-borne transmission because it increases the probability of encounters between humans and potentially infected vectors.

In addition to adaptability to domestic structures, triatomine feeding and defecation behaviors are important risk factors for vector-borne transmission and vary across species. The timing and placement of defecation after feeding greatly influence the risk of transmission via fecal contamination of the host bite site or other exposed tissues. A small number of studies have reported on these characteristics in U.S. species. In 1951 Wood reported the following average postfeeding defecation times (minutes) for the adults of four U.S. species: *T. protracta*, 30.6 ($n = 10$); *T. rubida*, 1.6 ($n = 5$); *T. recurva*, 75.7 ($n = 3$); and *P. hirusta*, 35.0 ($n = 2$) (327). In a similar study in 2007 using both nymphs and adults of three Mexican species (also present in the United States), Martinez-Ibarra et al. reported the following results: *T. protracta*, 6.7 ($n = 475$); *T. lecticularia*, 8.3 ($n = 368$); and *T. gerstaeckeri*, 11.5 ($n = 733$) (183). Likewise, Zeledon et al. (1970) reported the following results for nymphs and adults of three Latin American species: *R. prolixus*, 3.2

(n = 210); *T. infestans*, 3.5 (n = 210); and *T. dimidiata*, 11.3 (n = 210) (352). In 1970 Pippin reported the proportion of bugs defecating within 2 min postfeeding for adults of two U.S. and one Latin American species: *R. prolixus*, 74.6% (n = 169); *T. gerstaeckeri* 19.4% (n = 160); and *T. sanguisuga* 16.9% (n = 136) (228). Similarly, in 2009 Klotz et al. reported the proportion of bugs defecating before or directly after feeding for adults of two U.S. species: *T. rubida*, 45% (n = 40); and *T. protracta*, 19.4% (n = 31) (153). In that study, it was noted that none of the bugs of either species defecated on the host during the experiment. Although direct comparisons across studies is problematic due to variation in methods and conditions (e.g., temperature, blood host, and feeding apparatus), it appears that U.S. species in general exhibit greater postfeeding defecation delays than important Latin American vector species. Delayed defecation and a low frequency of domestic colonization contribute to a low probability of autochthonous U.S. human infection due to vector-borne transmission, which is the primary route of infection in areas of hyperendemicity in Latin America.

ANIMAL RESERVOIRS OF *TRYPANOSOMA CRUZI*

Background

Concurrent with the demonstration of *T. cruzi* in the first recognized human patient, Carlos Chagas observed the parasite in the blood of a domestic cat in the same household (62). Subsequently, Chagas went on to demonstrate *T. cruzi* in armadillos and primates, confirming the role of wildlife as reservoirs (63, 64). To date, over 100 mammalian species have been reported as natural hosts for *T. cruzi*, and all mammals are considered to be susceptible to infection. Birds are refractory to infection due to complement-mediated lysis and macrophage-induced killing of the parasites (146, 188). Although *T. cruzi* has a wide host range, the epidemiologically important reservoirs vary by geographic region due to the biology and ecology of the mammals and vectors and how these interactions translate to risk of human exposure. Opossums and armadillos are important reservoirs throughout the Americas, a finding consistent with genetic data suggesting that these two groups are the ancestral hosts for the two major ancestral lineages of *T. cruzi* (112, 349).

Transmission routes for wildlife and domestic animal species are similar to those for humans. Sylvatic animals become infected during feeding activity of vectors present in their burrows, dens, or temporary shelters. As in humans, infection occurs when bug feces containing the parasites enters a wound or mucous membrane. In addition, the insectivorous behavior of many animals (e.g., woodrats) increases the likelihood of infection via the ingestion of infected bugs (78, 241, 250). Transplacental transmission has been documented in laboratory mice and rats (15, 81, 127). Although not proven to occur in wildlife, this route likely contributes to maintenance of the parasite in the sylvatic cycle as well. Ingestion of infected meat was once considered a possible route of transmission, but a recent study with raccoons suggests that this is probably uncommon (241).

Wildlife Reservoirs of *T. cruzi* in the United States

In the United States, natural *T. cruzi* infection was first reported in the big-eared woodrat *Neotoma macrotis* (syn. *N. fuscepes macrotis*) in California (316). In the 1940s, natural infections were reported from house mice, southern plains woodrats (*N. micropus*), nine-banded armadillos (*Dasypus novemcinctus*), and Virginia opossums (*Didelphis virginiana*) in Texas and from brush mice (*Peromyscus boylii rowleyi*) and woodrats (*N. albigula*) in Arizona (219, 321). Early experimental infection trials with parasites from these hosts and *Triatoma* spp. indicated that laboratory rats, laboratory mice, guinea pigs, domestic dogs, rhesus macaques, opossums (*D. virginiana*), six species of *Peromyscus*, and four species of woodrats were susceptible (77, 154, 215, 217, 316, 321). In addition, an isolate from a naturally infected *Triatoma* species from Texas was shown to be infectious to a human (216). Subsequent surveys in the 1950s and 1960s documented infections in raccoons (*Procyon lotor*), Virginia opossums, striped skunks (*Mephitis mephitis*), and gray foxes (*Urocyon cinereoargenteus*) in the southeastern United States (185, 212, 305).

Currently, at least 24 species are recognized as natural wildlife hosts for *T. cruzi* in the United States (Table 4). Reported *T. cruzi* infection rates vary widely by host species and geographic area. However, the observed variation may be due in part to the use of different diagnostic assays with very different sensitivities. As in humans, the majority of infected animals are in the chronic phase of the infection; therefore, serological testing is more sensitive than methods that rely on detection of parasites (346). However, unlike serological tests, visualization of the parasites allows the examiner to distinguish *T. cruzi* from other *Trypanosoma* species (e.g., *T. neotomae*, *T. kansasensis*, *T. peromysci*, and *T. lewisi*-like sp.) reported from rodents based on morphology (186, 207, 294, 317, 328; M. J. Yabsley, unpublished data). If serology is used for screening, infections should be confirmed with a *T. cruzi*-specific assay. Some PCR assays will amplify other *Trypanosoma* and/or *Leishmania* species, and more specific methods may be necessary to confirm the infection as *T. cruzi*.

The primary reservoirs and transmission dynamics of *T. cruzi* differ between the eastern and western regions of the United States. The greatest vector diversity and density occur in the western United States (Fig. 2), where many triatomine species live in the nests of woodrats. In this region, woodrats are the most common reservoir; however, infection has also been demonstrated in other rodents, raccoons, skunks, and coyotes (Table 4; Fig. 4A and B). Rodents other than woodrats utilize habitats similar to those of woodrats (old woodrat nests, small caves, and holes in rock walls) where triatomines are found, while coyotes, raccoons, skunks, and opossums likely become infected when bugs feed on them in their dens or through ingestion of bugs. In the eastern United States, the prevalence of *T. cruzi* is highest in raccoons, opossums, armadillos, and skunks (Table 4; Fig. 4A and B). There are several woodrat species in the eastern United States, but densities are much lower than for woodrat species in the western United States, and nests are less evident because they utilize burrows instead of large above-ground constructed nests. Little is known about the prevalence of *T. cruzi* in eastern woodrat species. To date, only one survey for *T. cruzi* has been conducted, and none of 23

TABLE 4. Hosts of *Trypanosoma cruzi* in the United States[a]

Species	State(s)	Total no. tested	No. (%) positive	Assay type (sample or specific assay)	Reference(s)
Raccoon (*Procyon lotor*)	AL	35	5 (14)	Culture (heart and blood)	212
	AZ	5	1 (20)	Serology (IFA)	46
	FL	184	4 (2)	Blood smear	262, 284
	FL	33	4 (12)	Culture (blood)	262
	FL	70	38 (54)	Serology (IFA)	46
	FL, GA	608	9 (1.5)	Culture (kidney)	185
	GA	54	12 (22)	Culture (blood)	231
	GA	30	13 (43)	Culture (blood)	224
	GA	510	168 (33)	Serology (IFA)	46
	GA	10	5 (50)	Culture (blood)	262
	GA, SC	221	104 (47)	Serology (IFA)	345
	KY	44	17 (39)	Culture (blood)	118
			19 (43)	Serology (IFA)	
	MD	472	2 (0.4)	Culture (heart)	130
	MD	NK[b]	5	Culture (blood)	305
	MO	109	74 (68)	Serology (IFA)	46
	NC	20	3 (15)	Culture (blood)	144
	OK	8	5 (63)	Culture (blood)	141
	TN	3	2 (66)	Culture (blood)	134
	TN	706	206 (29)	Serology (IFA)	179
	TX	25	6 (24)	Culture (blood)	262
	TX	9	0	Serology (indirect hemagglutination)	49
	TX	19	4 (21)	Culture (blood)	M. Yabsley et al., unpublished
	VA	464	153 (33)	Serology (IFA)	129
Ringtail (*Bassariscus astutus*)	AZ	1	1 (100)	Serology (IFA)	46
Opossum (*Didelphis virginiana*)	AL	126	17 (14)	Culture (blood and heart)	212
	FL	27	14 (52)	Serology (IFA)	46
	GA	39	6 (15)	Culture (blood)	231
	GA	421	118 (28)	Serology (IFA)	46
	GA	29	3 (10)	PCR (liver)	222
	GA, FL	552	88 (16)	Culture (kidney)	185
	KY	48	0 (0)	Culture (blood)	118
			6 (13)	Serology (IFA)	
	MD	219	0 (0)	Culture (heart)	130
	NC	12	1 (8)	Culture (blood)	144
	OK	10	0	Culture (blood)	141
	LA	48	16 (33)	Culture (blood)	19
	TX	8	5 (63)	Culture (blood)	219
	TX	391	63 (16)	Blood smear	94
	VA	6	1 (17)	Serology (IFA)	46
Nine-banded armadillo (*Dasypus novemcinctus*)	LA	98	1 (1)	Culture (blood)	19
	LA	80	23 (29)	Culture (blood)	348
			30 (38)	Serology (direct agglutination)	
	TX	15	1 (7)	Culture (blood)	219
Striped skunk (*Mephitis mephitis*)	AZ	34	3 (9)	Serology (IFA)	46
	CA	1	1 (100)	Serology and histology	248
	GA, FL	306	3 (1)	Culture (kidney)	185
	GA	1	1 (100)	Serology (IFA)	46
	TX	3	2 (67)	Culture (blood)	Yabsley et al., unpublished
Gray fox (*Urocyon cinereoargenteus*)	GA, FL	118	2 (2)	Culture (kidney)	185
	GA	21	0	Serology (IFA)	46
	SC	26	2 (8)	Serology (IFA)	245
Bobcat (*Felis rufus*)	GA	62	2 (3)	Serology (IFA)	46
American badger (*Taxidea taxus*)	TX	8	2 (25)	Serology (indirect hemagglutination)	49
Coyote (*Canis rufus*)	GA	23	1 (4)	Serology (IFA)	46
	TX	134	19 (14)	Serology (IFA)	119

Continued on following page

TABLE 4—*Continued*

Species	State(s)	Total no. tested	No. (%) positive	Assay type (sample or specific assay)	Reference(s)
	VA	26	1 (4)	Serology (IFA)	46
Feral swine (*Sus scrofa*)	GA	110	0	Serology (IFA)	46
Southern plains woodrat (*Neotoma micropus*)	TX	30	5 (17)	Culture (blood)	49
	TX	100	31 (31)	Culture (blood)	219
	TX	159	42 (26)	PCR (liver)	227
	NM	NK	1	Xenodiagnosis	341
White-throated woodrat (*Neotoma albigula*)	AZ	NK	2	NK	328
	NM	NK	1	Xenodiagnosis	341
Big-eared woodrat (*Neotoma macrotis* = *N. fuscipes* subsp. *macrotis*)	CA	99	9 (9)	Xenodiagnosis and blood smear	318, 319, 328, 339
Brush mouse (*Peromyscus boylii rowleyi*)	AZ	NK	1	NK	328
Gilbert white-footed mouse (*Peromyscus truei gilberti*)	CA	NK	2	NK	328
Pinon mouse (*Peromyscus truei montipinoris*)	CA	NK	11	Xenodiagnosis	339
Western harvest mouse (*Reithrodontomys megalotis*)	CA	NK	1	Xenodiagnosis	323
Hispid pocket mouse (*Perognathus hispidus*)	TX	25	4 (16)	Culture (blood)	49
House mouse (*Mus musculus*)	TX	2	1 (5)	Culture (blood)	219
Mexican spiny pocket mouse (*Liomys irrorattus*)	TX	11	1 (9)	Culture (blood)	49
Grasshopper mouse (*Onychomys leucogaster*)	TX	9	1 (11)	Culture (blood)	49
CA ground squirrel (*Spermophilus beecheyi*)	CA	19	2 (11)	Culture (blood)	203
Mexican ground squirrel (*Spermophilus mexicanus*)	TX	1	1 (100)	Culture (blood)	Yabsley et al., unpublished
Whitetail antelope squirrel (*Ammospermophilus leucurus*)	NM	NK	3	Xenodiagnosis	339, 341
Hispid cotton rat (*Sigmodon hispidus*)	TX	1	1 (100)	Culture (blood)	Yabsley et al., unpublished

[a] Only selected negative results are shown if large numbers of a particular species were examined.
[b] NK, not known.

Neotoma floridana animals in Kansas were positive (294). Reports of wildlife infections are shown at the county level (when possible) in Fig. 4A and B.

Domestic and Exotic Animal Infections in the United States

In addition to indigenous wildlife reservoirs, domestic and exotic animals can become infected if they are present in an enzootic area and come in contact with infected bugs. Transmission routes are similar to those for wildlife, with ingestion of bugs likely being an important route.

Canine Chagas' disease. In Central and South America, domestic dogs are important reservoirs in the domestic cycle and can be used as sentinels for local transmission (123). A similar cycle has been recognized in the United States, but the importance of domestic dogs as *T. cruzi* infection reservoirs is not as well understood (26). *T. cruzi* infection in domestic dogs has been reported widely throughout the southern United States since 1972 (Fig. 4C) (18, 20, 23, 41, 105, 134, 150, 189, 205, 206, 239, 274, 287, 298, 312). Infection has been documented in at least 48 different breeds in the United States, with the sporting and working breeds accounting for the majority of cases, presumably due to greater exposure to infected vectors and mammalian tissues (150, 246). As in humans, transplacental transmission is also an important mode of transmission in dogs (23, 58). Domestic dogs can develop both acute and chronic disease similar to that in humans. Acute illness, particularly mortality, has been reported more frequently in very young dogs (<1 year old) and generally involves myocarditis and cardiac arrhythmias (150). Dogs that survive infection at a very young age or acquire infection as adults generally experience a chronic course of disease that may progress to significant cardiac dysfunction, typically involving cardiac dilatation, electrocardiogram (ECG) abnormalities, and clinical signs related to right-sided or bilateral cardiac failure (21, 22). In a recent seroprevalence study in Tennessee, older dogs (ages 6 to 10 years) were more likely to be infected (246), which is similar to results of studies in Latin America that reported increasing seropositivity with increasing age (97, 122). Dogs with clinically apparent infections are managed with appropriate supportive therapy. Chemotherapeutic agents developed for treatment of human Chagas' disease (benznidazole and

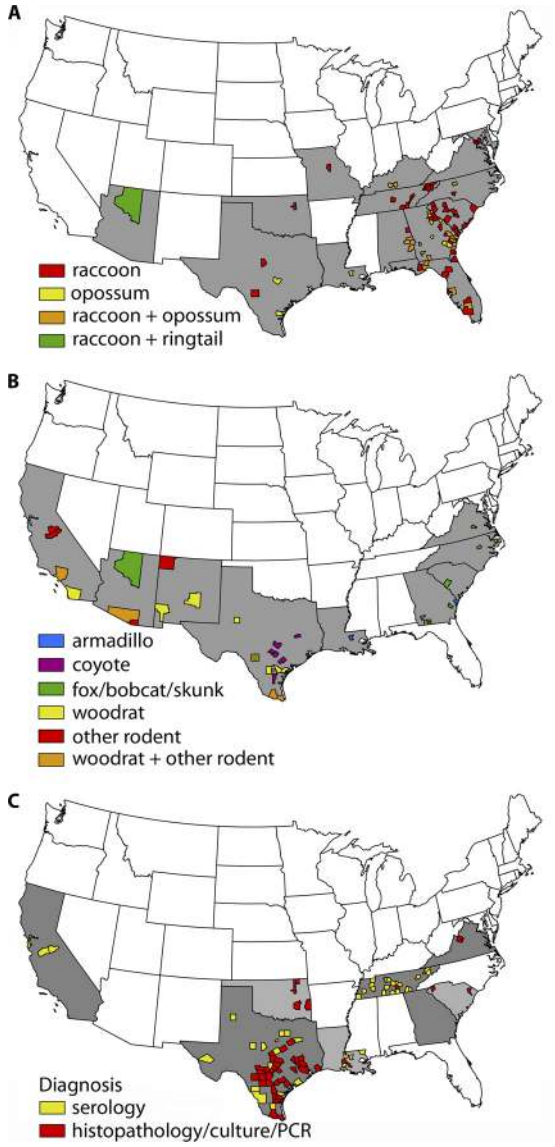

FIG. 4. Reports of natural *Trypanosoma cruzi* infection in U.S. mammals. (A) Raccoons, Virginia opossums, and ringtails; infection of opossums has been reported in Virginia, but no locality was specified. (B) Rodents and mesomammals. An additional report of infected coyotes was published from Virginia, but no locality was specified. (C) Domestic canines. In some states (California, Georgia, Tennessee, and Virginia, shown in dark gray), additional canine clinical cases were reported, but no locality was specified. References are provided in Table 4 for panels A and B and in the text for panel C.

nifurtimox) have shown some efficacy in dogs (121, 125), but they are not currently approved for veterinary use in the United States.

Primates and other exotic animals. Any mammals kept in areas where bugs may enter are at risk of acquiring *T. cruzi* infection. Because U.S. animal use guidelines require that nonhuman primates be housed in facilities with access to the outdoors, they may be at particular risk of acquiring *T. cruzi* infection. Exotic animals that acquire *T. cruzi* infection may be asymptomatic or may develop symptomatic, even lethal, clinical disease. Severe disease may be due to a large parasite inoculum from exposure to or ingestion of a large number of infected bugs but may also reflect variation in susceptibility of animal species to clinical Chagas' disease. Mortality due to locally acquired *T. cruzi* infection has occurred in groups of captive animals in the United States, including baboons (*Papio hamadryas*), rhesus macaques, crab-eating macaques (*M. fascicularis*), Celebes black macaques (*M. nigra*), sugar gliders (*Petaurus breviceps*), and a hedgehog (*Atelerix albiventris*) (8, 115, 145, 213, 313). Asymptomatic *T. cruzi* infection has been reported in lion-tailed macaques (*M. silenus*), pigtailed macaques (*M. nemestrina*), rhesus macaques, baboons, ring-tailed lemurs (*Lemur catta*), and black and white ruffed lemurs (*Varecia variegata*) in the United States (11, 128, 145, 232, 264).

MOLECULAR EPIDEMIOLOGY OF *T. CRUZI*

General Molecular Epidemiology

T. cruzi is a genetically heterogeneous species that also has wide variability in biological and biochemical characteristics (51, 174, 191, 192). The most common historical classification divided *T. cruzi* into two major groups, TcI and TcII; TcII was further divided into five subgroups (also called discrete typing units) designated TcIIa to TcIIe (51, 193, 309). Recently, a consensus was reached that the six major recognized lineages will be renamed TcI to TcVI; compared to the earlier system, TcI remained TcI, TcIIb became TcII, TcIIc became TcIII, TcIIa became TcIV, TcIId became TcV, and TcIIe became TcVI (353). For the purposes of this review, data from earlier studies that genotyped isolates as TcII (without a to d subtyping) will be referred to as "historic TcII" to differentiate these types from the current TcII, which is equivalent to the historic TcIIb lineage. The TcI and TcII lineages are considered ancestral, whereas the TcV and TcVI lineages are the products of at least two hybridization events (309, 353). The origins of TcIII and TcIV are as yet unresolved (353). Whereas some investigators consider TcIII to represent a third ancestral strain (80), others consider it to be the result of hybridization between TcI and TcII (309, 310). TcI and TcII to TcVI are estimated to have diverged between 88 and 37 million years ago (43, 175). Currently, *T. cruzi* genotypes are classified based on size polymorphism or sequence analysis of several gene loci, including the miniexon gene, the intergenic region of the miniexon gene, the 18S rRNA gene, the 24Sα rRNA gene, internal transcribed spacer regions, and numerous housekeeping genes (171, 310).

The TcI lineage is found throughout the Americas in both domestic and sylvatic cycles and is believed to have evolved with arboreal Didelphimorpha (opossums) and vectors in the triatomine tribe Rhodniini (112). In all parts of the Americas, *Didelphis* spp. are common reservoirs for this lineage, although natural infection with TcI has been reported in a wide range of mammals. TcI is the only lineage reported from humans in North and Central America and the predominant lineage reported in human Chagas' disease in areas of South America north of the Amazon Basin (40, 139, 239, 258).

Although TcI has long been recognized as genetically diverse, subtyping has not been widely conducted until very recently, and no generally accepted typing system or nomenclature currently exists. Additionally, many isolates have been

TABLE 5. Genotypes of U.S. *T. cruzi* isolates

Species	No.	State(s)	Genotype(s) (no.)	Reference(s)
Human	5	CA, TX, LA	TcI (5)	239
Opossum	15	GA, FL, LA, AL	TcI (15)	68, 239
Raccoon	79	GA, FL, TN, MD, LA, KY	TcI (2), TcIV (74), mixed (2)	45, 68, 239
Ring-tailed lemur	3	GA	TcIV (3)	239
Rhesus macaque	2	GA	TcI (1), mixed (1)	239
Nine-banded armadillo	3	LA, GA	TcI (2), TcIV (1)	239
Striped skunk	1	GA	TcIV (1)	239
Domestic dog	7	TN, OK, SC, CA, unknown	TcIV (6), mixed (1)	44, 45, 239
Triatoma spp.	8	GA, FL, TX	TcI (6), TcIV (1) mixed (1)	17, 68, 175, 239

examined only by sequencing of a single locus. Haplotypes were first recognized following sequence analysis of the intergenic regions of the miniexon genes of 12 isolates from Columbia (132). Based on single-nucleotide polymorphisms, insertions, and deletions, four haplotypes, TcIa to TcId, were proposed. Haplotypes TcIa and TcIc were associated with humans and domiciliated vectors. Haplotypes TcIb and TcId were found in specimens from one human, opossums, and sylvatic vectors; TcId was found exclusively in sylvatic samples (132). Interestingly, phylogenetic analysis of the same gene region of 20 TcI strains from the United States, Mexico, Bolivia, Brazil, Columbia, and Argentina showed that *Didelphis* sp. isolates grouped separately from other isolates (210). A fifth haplotype (TcIe) was recently detected in a human and a sylvatic vector (*Mepraia spinolai*) from Chile and in one domestic vector (*T. infestans*) from Argentina (76). Multilocus microsatellite profiling of 135 TcI isolates provided better discrimination and increased levels of variability among TcI sylvatic strains (173). However, in contrast to previous studies in which opossums were found to be infected with a particular haplotype (210), no host association was noted. The authors suggest that the ecological niche might be more important for parasite evolution and diversification than reservoir host species (173). Wider use of multilocus typing methods may provide further insight into TcI genetic diversity in the future.

Lineage TcIII (historical TcIIc) is believed to have evolved with terrestrial burrowing edentates, specifically armadillos, and bugs in the triatomine tribe Triatomini (112, 349). Edentates and marsupials were the first mammal inhabitants of South America (~65 million years ago), whereas rodents, primates, and bats arrived in South America ~25 million years ago (112). Upon arrival, these mammals became hosts to the various lineages of *T. cruzi*. TcIII is found throughout South America and is rare in domestic cycles but common in sylvatic cycles (172, 349). The primary hosts for TcIII are several different species of armadillos, primarily *D. novemcinctus*. Additionally, TcIII has been reported from limited numbers of a terrestrial marsupial (*Monodelphis domestica*), rodents, and skunks (349).

TcII, TcV, and TcVI (historic IIb, IId, and IIe, respectively) are the lineages most commonly reported in human Chagas' disease in southern South America (193). All three lineages are closely associated with the domestic transmission cycle and the domestic vector *Triatoma infestans*. TcV and TcVI have been reported in cardiomyopathy and intestinal megasyndromes in the Southern Cone (Argentina, Chile, Bolivia, and Brazil) (57, 193). In contrast, intestinal Chagas' disease is rare in northern South America, Central America, and Mexico, where TcI is the predominant lineage (191). TcV is the lineage reported most frequently in infants with congenital infection, although this may simply reflect its predominance in Bolivia and Argentina, where these studies have been conducted (72, 303). The two hybrid lineages, TcV and TcVI, are hypothesized to have evolved in armadillos (181, 349). A single isolation of TcII (historic TcIIb) was reported from *Euphractus sexcinctus* (six-banded armadillo) in Paraguay, but its original mammalian host has not been established (193, 349).

Currently, the TcIV (historic IIa) lineage is poorly understood. Studies of several gene targets indicate that TcIV strains from North and South America are genetically distinct and group separately in phylogenetic analyses (181; D. M. Roellig and M. J. Yabsley, unpublished data). In South America, TcIV is found in a wide range of mammals, including primates, rodents, armadillos, and terrestrial marsupials (349). In North America, the raccoon is the principal host for TcIV; infections have been reported in domestic dogs, striped skunks, armadillos, and primates (239).

Interestingly, two terrestrial marsupial genera (*Philander* and *Monodelphis*) can harbor both TcI and several other genotypes, whereas only TcI has been reported from the arboreal genus *Didelphis* (163, 225, 240). The genus *Philander* also displays a more severe inflammatory response to *T. cruzi* (162, 163). Experimental inoculation of *Monodelphis domestica* with TcI, TcII, and TcVI strains resulted in infections, but a North American TcIV isolate failed to establish an infection (242). Collectively, these data suggest that the marsupial genera diverged before the establishment of host relationships with *T. cruzi* and that utilization of different ecological niches resulted in distinct *T. cruzi* lineage transmission patterns (163).

T. cruzi Genotypes in the United States

In the United States, only two genotypes (TcI and TcIV) have been reported from mammals and vectors (Table 5). Consistent with the findings in South American studies of *Didelphis*, TcI is the only genotype reported from *D. virginiana*, the Virginia opossum (17, 68, 239). In raccoons, TcIV predominates, but TcI has been detected in a small number of specimens. Both TcI and TcIV have been reported from nine-banded armadillos, domestic dogs, and rhesus macaques (68, 239). Lineage TcIV has been reported from a limited number of ring-tailed lemurs and a striped skunk (239). Although the majority of isolates from placental mammals in the United States have been TcIV, all five typed isolates from human

autochthonous infection were TcI (239). Both TcI and TcIV have been reported from *Triatoma* spp. from Georgia, Florida, and Texas.

CLINICAL ASPECTS OF CHAGAS' DISEASE

Acute *T. cruzi* Infection

The incubation period following vector-borne *T. cruzi* exposure is 1 to 2 weeks, after which the acute phase begins (234). The acute phase lasts 8 to 12 weeks and is characterized by circulating trypomastigotes detectable by microscopy of fresh blood or buffy coat smears. Most patients are asymptomatic or have mild, nonspecific symptoms such as fever and therefore do not come to clinical attention during the acute phase. In some patients, acute infection is associated with inflammation and swelling at the site of inoculation, known as a chagoma. Chagomas typically occur on the face or extremities; parasites may be demonstrated in the lesion. Inoculation via the conjunctiva leads to the characteristic unilateral swelling of the upper and lower eyelids known as the Romaña sign (234). Severe acute disease occurs in fewer than 1% of patients; manifestations include acute myocarditis, pericardial effusion, and/or meningoencephalitis (3, 177). Children younger than 2 years appear to be at higher risk of severe manifestations than older individuals. Severe acute Chagas' disease carries a substantial risk of mortality.

Orally transmitted *T. cruzi* infection appears to be associated with more severe acute morbidity and higher mortality than vector-borne infection (28, 271). For example, 75% of 103 infected individuals in the Caracas outbreak were symptomatic, 59% had ECG abnormalities, 20% were hospitalized, and there was one death from acute myocarditis (82). Recent laboratory data suggest that parasite contact with host gastric acid may render trypomastigotes more invasive through changes in parasite surface glycoproteins and that this interaction may underlie the increased clinical severity seen in orally acquired Chagas' disease (75, 350).

Congenital *T. cruzi* Infection

Most infected newborns are asymptomatic or have subtle findings, but a minority present with severe life-threatening disease (32, 289). The manifestations of symptomatic congenital Chagas' disease can include low birth weight, prematurity, low Apgar scores, hepatosplenomegaly, anemia, and thrombocytopenia (35, 36, 177, 289). Severely affected neonates may have meningoencephalitis, gastrointestinal megasyndromes, anasarca, pneumonitis, and/or respiratory distress (35–37, 289). Mortality among infected infants is significantly higher than in uninfected infants, ranging from <5% to 20% in published studies (34, 289). However, even severe congenital Chagas' disease may not be recognized because signs are often nonspecific or because the diagnosis is not considered (289).

Chronic *T. cruzi* Infection

Eight to 12 weeks after infection, parasitemia levels become undetectable by microscopy, and in the absence of effective etiological treatment, the individual passes into the chronic phase of *T. cruzi* infection. Despite the absence of microscopically detectable parasites in the peripheral blood, persons with chronic *T. cruzi* infection maintain the potential to transmit the parasite to the vector and directly to other humans through blood components, through organ donation, and congenitally (177, 311).

Indeterminate form of chronic *T. cruzi* infection. Persons with chronic *T. cruzi* infection but without signs or symptoms of Chagas' disease are considered to have the indeterminate form. The strict definition of the indeterminate form requires positive anti-*T. cruzi* serology, with no symptoms or physical examination abnormalities, normal 12-lead ECG, and normal radiological examination of the chest, esophagus, and colon (194). Current baseline evaluation guidelines in the United States recommend only a history, physical examination, and ECG (30). Further cardiac evaluation is recommended only if cardiac signs or symptoms are present, and barium studies are recommended only in patients with gastrointestinal symptoms (30). An estimated 20 to 30% of people who initially have the indeterminate form of Chagas' disease progress over a period of years to decades to clinically evident cardiac and/or gastrointestinal disease (234).

Cardiac Chagas' disease. Chagas' cardiomyopathy is characterized by a chronic inflammatory process that involves all chambers, damage to the conduction system, and often an apical aneurysm. The pathogenesis is hypothesized to involve parasite persistence in cardiac tissue and immune-mediated myocardial injury (182). The earliest manifestations are usually conduction system abnormalities, most frequently right-bundle branch block or left anterior fascicular block, and segmental left ventricular wall motion abnormalities (178). Later manifestations include complex ventricular extrasystoles and nonsustained and sustained ventricular tachycardia, sinus node dysfunction that may lead to severe bradycardia, high-degree heart block, apical aneurysm usually in the left ventricle, thromboembolic phenomena due to thrombus formation in the dilated left ventricle or aneurysm, and progressive dilated cardiomyopathy with congestive heart failure (233). These abnormalities lead to palpitations, presyncope, syncope, and a high risk of sudden death (235, 236).

Digestive Chagas' disease. Gastrointestinal involvement is less common than Chagas' heart disease. This form is seen predominantly in patients infected in the countries of the Southern Cone (Argentina, Bolivia, Chile, Paraguay, Southern Peru, Uruguay, and parts of Brazil) and is rare in northern South America, Central America, and Mexico. This geographical pattern is thought to be linked to differences in the predominant *T. cruzi* genotypes (51, 192). Gastrointestinal Chagas' disease usually affects the esophagus and/or colon, resulting from damage to intramural neurons (83, 84, 199). The effects on the esophagus span a spectrum from asymptomatic motility disorders through mild achalasia to severe megaesophagus (83). Symptoms include dysphagia, odynophagia, esophageal reflux, weight loss, aspiration, cough, and regurgitation. As in idiopathic achalasia, the risk of esophageal carcinoma is elevated (13, 47). Megacolon is characterized by prolonged constipation and may give rise to fecaloma, volvulus, and bowel ischemia.

T. cruzi Infection in the Immunocompromised Host

Acute *T. cruzi* infection in organ transplantation recipients. Acute *T. cruzi* infection in organ recipients has several features that differ from those of acute *T. cruzi* infection in immunocompetent hosts. The incubation period can be prolonged: among the 15 patients for whom data were available in published reports, the mean time from transplantation to onset of symptoms of acute *T. cruzi* infection was 112 days (range, 23 to 420 days) (61, 66, 79, 99, 101, 157, 238, 279). A relatively severe clinical spectrum has been reported, with manifestations that included fever, malaise, anorexia, hepatosplenomegaly, acute myocarditis, and decreased cardiac function; two of the 18 reported patients presented with fulminant myocarditis and congestive heart failure (61, 279).

Reactivation of chronic *T. cruzi* infection in organ recipients. Patients with chronic *T. cruzi* infection can be candidates for organ transplants. In a large cohort of heart transplant patients, survival of those who received the transplant because of chronic Chagas' cardiomyopathy was longer than survival among those with idiopathic or ischemic cardiomyopathy, and *T. cruzi* reactivation was a rare cause of death (33, 38, 39). Reactivation should be considered in the differential diagnosis of febrile episodes and apparent rejection crises. In addition to fever and acute Chagas' myocarditis in the transplanted heart, common manifestations of reactivation disease include inflammatory panniculitis and skin nodules (52, 102, 238). Central nervous system (CNS) involvement has been reported but is a much less frequent manifestation of reactivation among transplant recipients than in AIDS patients (5, 102, 180).

Reactivation Chagas' disease in HIV/AIDS patients. Reactivation of *T. cruzi* infection in HIV/AIDS patients can cause severe clinical disease with a high risk of mortality. However, as in organ transplant recipients, reactivation is not universal, even in those with low $CD4^+$ lymphocyte counts. The only published prospective cohort study followed 53 HIV-*T. cruzi*-coinfected patients in Brazil for 1 to 190 months; 11 (21%) had *T. cruzi* reactivation diagnosed based on symptoms and/or microscopically detectable parasitemia (260). Even among patients without clinical reactivation, the level of parasitemia is higher among HIV-coinfected than among HIV-negative patients (261). Symptomatic *T. cruzi* reactivation in AIDS patients is most commonly reported to cause meningoencephalitis and/or *T. cruzi* brain abscesses; the presentation may be confused with CNS toxoplasmosis and should be considered in the differential diagnosis of mass lesions on imaging or CNS syndromes in AIDS patients (70, 71, 88, 260). The second most commonly reported sign of reactivation is acute myocarditis, sometimes superimposed on preexisting chronic Chagas' cardiomyopathy (260, 297). Patients may present with new arrhythmias, pericardial effusions, acute cardiac decompensation, or accelerated progression of existing chronic heart disease (100, 260). Acute meningoencephalitis and myocarditis can occur simultaneously. In the Brazilian cohort, cardiac reactivation was as frequent as CNS disease; cardiac manifestations of reactivated Chagas' disease may pass undetected or mimic progression of chronic Chagas' cardiomyopathy (260). Less common manifestations of reactivation in HIV/AIDS patients include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach, or intestine (100, 261).

DIAGNOSIS

Appropriate diagnostic testing for *T. cruzi* infection varies depending on the phase of the disease and the status of the patient. In the United States, CDC provides consultation to health care providers concerning Chagas' disease diagnostic testing (contact information is listed in "Antitrypanosomal Drugs" below).

Diagnosis of Acute *T. cruzi* Infection

In the acute phase, motile trypomastigotes can be detected by microscopy of fresh preparations of anticoagulated blood or buffy coat (311). Parasites may also be visualized by microscopy of blood smears stained with Giemsa stain or other stains. Hemoculture in one of several types of standard parasitic medium (e.g., Novy-MacNeal-Nicolle) is relatively sensitive during the acute phase but requires 2 to 4 weeks to show replication. The level of parasitemia decreases within 90 days of infection, even without treatment, and becomes undetectable by microscopy in the chronic phase (306, 311). PCR is a sensitive diagnostic tool in the acute phase of Chagas' disease and may also be used to monitor for acute *T. cruzi* infection in the recipient of an infected organ or after accidental exposure (133, 134, 157).

Diagnosis of Congenital *T. cruzi* Infection

Early in life, congenital Chagas' disease is an acute *T. cruzi* infection and similar diagnostic methods are employed. Concentration methods yield better sensitivity than direct examination of fresh blood. The microhematocrit method is the most widely used technique in Latin American health facilities. Fresh cord or neonatal blood is collected, sealed in four to six heparinized microhematocrit tubes, and centrifuged, and the buffy coat layer is examined by light microscopy (108). Parasitemia levels rise after birth and peak at or after 30 days of life (32). Repeated sampling on several occasions during the first months of life increases the sensitivity but may not be acceptable to parents (14, 32, 197). Hemoculture can increase sensitivity, but the technique is not widely available, and results are not available for 2 to 4 weeks.

Molecular techniques have higher sensitivity and detect congenital infections earlier in life than the microhematocrit method (32, 92, 247). Transient detection of parasite DNA has occasionally been reported in specimens from infants who subsequently are found to be uninfected (32, 211). For this reason, a positive PCR on samples collected on two separate occasions may be used as a criterion for confirmation of congenital infection (32). PCR is increasingly used for the early diagnosis of congenital Chagas' disease in Latin America and is the method of choice in industrialized countries (55, 140, 202, 247, 266).

For infants not diagnosed at birth, conventional IgG serology (as outlined below for chronic *T. cruzi* infection) is recommended after 9 months of age, when transferred maternal antibody has disappeared and the congenital infection has passed into the chronic phase (32, 55, 56).

Diagnosis of Chronic *T. cruzi* infection

Diagnosis of chronic infection relies on serological methods to detect IgG antibodies to *T. cruzi*, most commonly the enzyme-linked immunosorbent assay (ELISA) and immunofluorescent-antibody assay (IFA). No single assay has sufficient sensitivity and specificity to be relied on alone; two serological tests based on different antigens (e.g., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA, IFA, and immunoblotting) are used in parallel to increase the accuracy of the diagnosis (311).

Inevitably, a proportion of individuals tested by two assays will have discordant serological results and need further testing to resolve their infection status. Specimens with positive results but low antibody titers are more likely to show discordance because results obtained by less sensitive tests may be negative. Published data suggest that the sensitivity of serological assays varies by geographical location, possibly due to *T. cruzi* strain differences and the resulting antibody responses (275, 293, 299). The status of some individuals remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection (283). Assays such as the radioimmunoprecipitation assay (RIPA) and trypomastigote excreted-secreted antigen immunoblot (TESA-blot) are promoted as reference tests, but even these do not have perfect sensitivity and specificity and may not be capable of resolving the diagnosis (168, 272).

Options for diagnostic *T. cruzi* serological testing are relatively limited in the United States. Several ELISA kits based on parasite lysate or recombinant antigens are Food and Drug Administration (FDA) cleared for diagnostic application. Use of an assay with validation data (e.g., a commercial kit shown to have acceptable sensitivity and specificity in a thorough study) is preferable to reliance on in-house tests for which no performance data are available (31).

Utility of PCR for Diagnosis or Monitoring

PCR techniques provide the most sensitive tool to diagnose acute-phase and early congenital Chagas' disease and to monitor for acute *T. cruzi* infection in the recipient of an infected organ or after accidental exposure (32, 65, 133). PCR assays usually show positive results days to weeks before circulating trypomastigotes are detectable on peripheral blood smears (267). Quantitative PCR assays (e.g., real-time PCR) are useful to monitor for reactivation in the immunosuppressed *T. cruzi*-infected host. In these patients, a positive result on conventional PCR does not prove reactivation, but quantitative PCR assays that indicate rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation (89, 92).

In chronic *T. cruzi* infection, PCR is used as a research tool but is not generally a useful diagnostic test. Although PCR results will be positive for a proportion of patients, the sensitivity is highly variable depending on the characteristics of the population tested, as well as the PCR primers and methods (25, 142, 314). For these reasons, negative results by PCR do not constitute evidence for lack of infection.

TREATMENT

Antitrypanosomal Drugs

Nifurtimox and benznidazole are the only drugs with proven efficacy against Chagas' disease (73, 177). Neither drug is approved by the U.S. FDA, but both can be obtained from the CDC and used under investigational protocols. Consultations and drug requests should be addressed to the Parasitic Diseases Public Inquiries line [(404) 718-4745; e-mail, parasites@cdc.gov], the CDC Drug Service [(404) 639-3670], and, for emergencies after business hours and on weekends and federal holidays, the CDC Emergency Operations Center [(770) 488-7100].

Nifurtimox (Lampit, Bayer 2502), a nitrofuran, interferes with *T. cruzi* carbohydrate metabolism by inhibiting pyruvic acid synthesis. Gastrointestinal side effects are common, occurring in 30 to 70% of patients. These include anorexia leading to weight loss, nausea, vomiting, and abdominal discomfort. Neurological toxicity is also fairly common, including irritability, insomnia, disorientation, and, less often, tremors. Rare but more serious side effects include paresthesias, polyneuropathy, and peripheral neuritis. The peripheral neuropathy is dose dependent, appears late in the course of therapy, and should prompt interruption of treatment. Higher doses are often used in infants than in older children, and tolerance is better in children than in adults.

Benznidazole (Rochagon, Roche 7-1051) is a nitroimidazole derivative, considered more trypanocidal than nifurtimox. Dermatological side effects are frequent, and consist of rashes due to photosensitization, rarely progressing to exfoliative dermatitis. Severe or exfoliative dermatitis or dermatitis associated with fever and lymphadenopathy should prompt immediate cessation of the drug. The peripheral neuropathy is dose dependent, usually occurs late in the course of therapy, and is an indication for immediate cessation of treatment; it is nearly always reversible but may take months to resolve. Bone marrow suppression is rare and should prompt immediate interruption of drug treatment. Patients should be monitored for dermatological side effects beginning 9 to 10 days after initiation of treatment. Benznidazole was well tolerated in two placebo-controlled trials with children (12% had a rash and <5% had gastrointestinal symptoms in one study; <10% had moderate reversible side effects in the other study) (7, 277). Side effects are more common in adults than in children.

Treatment of Acute and Congenital *T. cruzi* infection

In acute and early congenital Chagas' disease, both drugs reduce the severity of symptoms, shorten the clinical course, and reduce the duration of detectable parasitemia (53, 306). The earliest trials of antitrypanosomal drugs were conducted with patients with acute Chagas' disease in the 1960s and 1970s using nifurtimox (53, 306). Serological cure was documented at the 12-month follow-up in 81% of those treated in the acute phase (306).

Treatment of Chronic *T. cruzi* Infection

Until recently, only the acute phase, including early congenital infection, was thought to be responsive to antiparasitic

TABLE 6. Autochthonous human cases of Chagas' disease in the United States

Yr	State	Patient characteristics	Evidence of autochthonous transmission	Reference(s)
1955	TX	10-mo-old girl, acute Chagas' disease, trypomastigotes on blood smear	Peridomestic infestation	342
1955	TX	2- to 3-wk-old boy, no details provided	No details provided	10
1982	CA	56-yr-old woman with acute Chagas' disease, trypomastigotes on blood smear	Adult uninfected *T. protracta* found in house	203, 265
1983	TX	7-mo-old boy, fatal acute Chagas' disease with myocarditis and pericardial effusion, postmortem diagnosis based on nests of *T. cruzi* in cardiac tissue	No vectors found, but household search was made in winter; house said to be in poor condition	209
1998	TN	18-mo-old boy, febrile illness several wk after bug was found, positive *T. cruzi* PCR in multiple blood specimens	*T. cruzi*-infected *T sanguisuga* found in child's crib	134
2006	LA	74-yr-old woman with history of triatomine bites but no symptoms of Chagas' disease; positive IgG serology and *T. cruzi* hemoculture	Peridomestic and house *T. sanguisuga* infestation; 10/18 positive by *T. cruzi* PCR	90
2006	TX	12-mo-old boy with fever, large pericardial effusion and respiratory distress; trypomastigotes by microscopy in pericardial fluid	Mother uninfected; *T. cruzi*-infected *T. gerstaeckeri* collected near house	151; CDC, unpublished data

therapy. However, in the 1990s, 2 placebo-controlled trials of benznidazole treatment in children with chronic *T. cruzi* infection demonstrated approximately 60% cure as measured by conversion to negative serology 3 to 4 years after the end of treatment (7, 278). Several follow-up studies suggest that the earlier in life that children are treated, the higher the rate of reversion to negative serology (6, 281). Together with growing clinical experience across Latin America, these studies revolutionized management of children with Chagas' disease, making early diagnosis and antitrypanosomal drug therapy the standard of care throughout the region (177, 311).

There is currently a growing movement to offer treatment to older patients and those with early cardiomyopathy (30, 302, 311). In Latin America, most Chagas' disease experts now believe that the majority of patients with chronic *T. cruzi* infection should be offered treatment, employing individual exclusion criteria such as an upper age limit of 50 or 55 years and the presence of advanced irreversible cardiomyopathy (276). This change in standards of practice is based in part on nonrandomized, nonblinded longitudinal studies that demonstrate decreased progression of Chagas' cardiomyopathy and decreased mortality in adult patients treated with benznidazole (301, 302). A multicenter, randomized, placebo-controlled, double-blinded trial of benznidazole for patients with mild to moderate Chagas' cardiomyopathy is under way and will help to clarify treatment efficacy for this group (http://clinicaltrials.gov/show/NCT00123916).

Management of the Immunocompromised Host

Antitrypanosomal treatment for reactivation in organ transplant recipients follows standard dosage regimens and promotes resolution of clinical symptoms and parasitemia. There are no data to indicate that prior treatment or posttransplant prophylaxis decreases the risk of reactivation; posttransplant prophylaxis is not routinely administered in heart transplant centers in Latin America (52). Antitrypanosomal therapy is thought to achieve a sterile cure in few, if any, adults with longstanding chronic infection, and treated patients should be considered to be at risk for reactivation. Reactivation in an HIV-coinfected patient should be treated with standard courses of antitrypanosomal treatment; antiretroviral therapy should be optimized (143).

EPIDEMIOLOGY OF CHAGAS' DISEASE

Since 1991, the estimated global prevalence of *T. cruzi* infection has fallen from 18 million to 8 million, due to intensive vector control and blood bank screening (87, 214). The Pan American Health Organization estimates that approximately 60,000 new *T. cruzi* infections occur each year (214). As other transmission routes have diminished, the proportion attributable to congenital infection has grown: an estimated 26% of incident infections now occur through mother-to-child transmission (214).

In settings with endemic vector-borne transmission, *T. cruzi* infection is usually acquired in childhood. Because the infection is lifelong, the seroprevalence in an area with sustained vector-borne transmission rises with age, reflecting the cumulative incidence (98). Before widespread vector control was instituted in the early 1990s, it was common to find that >60% of adults in an community where the disease was endemic were infected with *T. cruzi* (200, 230). In cross-sectional community surveys, most infected individuals are asymptomatic; an estimated 70 to 80% will remain asymptomatic throughout their lives (176, 234). Because cardiac and gastrointestinal manifestations usually begin in early adulthood and progress over a period of years to decades, the prevalence of clinical disease increases with increasing age (178).

HUMAN CHAGAS' DISEASE IN THE UNITED STATES

Autochthonous Transmission to Humans

Seven autochthonous vector-borne infections (four in Texas and one each in California, Tennessee, and Louisiana) have been reported since 1955 (Table 6) (10, 90, 134, 151, 209, 265, 342). Most reported cases have been in infants or small children; six of the seven infections were in the acute phase at the time of identification, and the diagnosis was sought because of symptoms and/or the presence of triatomine vectors. A survey conducted in the community of residence of the 1982 Califor-

TABLE 7. Transfusion-related cases of Chagas' disease in the United States

Yr	State	Recipient characteristics	Implicated blood component and donor origin	Reference
1988	NY	11-yr-old girl with Hodgkin's lymphoma, developed fever and pericarditis, trypomastigotes seen on blood smear; treated with nifurtimox and recovered	Platelets, Bolivia	114
1988	CA	17-yr-old male post-bone marrow transplant with fulminant acute Chagas' disease	Not specified, Mexico	113
1989	TX	59-yr-old female with metastatic colon cancer on chemotherapy, granulocytopenic, disseminated intravascular coagulation; developed fever, pulmonary infiltrates, bradycardia and atrioventricular block; parasites seen on bone marrow aspirate; died within 36 h of diagnosis	Unknown; had received >500 units, including red blood cells and platelets	67
1997	FL	60-yr-old female with multiple myeloma; *T. cruzi*-infected donor unit detected during research study; recipient asymptomatic, treated with nifurtimox; died of underlying disease several yr later.	Platelets, Bolivia	166
2002	RI	3-yr-old female with stage 4 neuroblastoma on chemotherapy, neutropenic, fever, trypomastigotes seen on blood smear; treated with nifurtimox but died of her underlying disease	Platelets, Bolivia	351

nia case demonstrated positive complement fixation results in 6/241 (2.5%) residents tested (203). The rarity of autochthonous vector-borne transmission in the United States is assumed to result from better housing conditions that minimize vector-human contact. In addition, North American vectors may have lower transmission efficiency, due at least in part to delayed defecation (153, 203, 228). However, given that the vast majority of acute *T. cruzi* infections in immunocompetent individuals pass undiagnosed in Latin America, where the index of suspicion is much higher, undetected cases of autochthonous vector-borne transmission are presumed to occur.

Chagas' Disease Burden among Latin American Immigrants

The only direct assessments in Latin American populations living in the United States come from very limited local surveys and blood bank screening (see below) (42, 59, 148, 165, 167). No large representative surveys have ever been conducted, and blood bank data cannot be extrapolated with validity because donors are not representative of the larger population. The only recent data come from a survey of Latin American immigrants attending churches in Los Angeles County; a total of 10 (1%) of 985 adults tested had positive results by serological testing (290). Based on the reported number of immigrants from countries in Latin America where Chagas' disease is endemic and the estimated national *T. cruzi* seroprevalences in their countries of origin, there are an estimated 300,000 persons with *T. cruzi* infection currently living in the United States (29). Patients with clinical manifestations of Chagas' disease, especially cardiomyopathy, are assumed to be present but largely unrecognized in hospitals and health care facilities in the United States, but systematic data are sparse (126). Recent targeted studies in a Los Angeles hospital demonstrated positive results by *T. cruzi* serological tests among 15 (16%) of 93 Latin American patients with a diagnosis of idiopathic cardiomyopathy and 11 (4.6%) of 239 patients with conduction system abnormalities on ECG and at least 1 year of residence in Latin America (190, 291).

Blood-Borne Transmission and Blood Donor Screening

A total of 5 transfusion-associated *T. cruzi* infections have been documented in the United States since the late 1980s (Table 7) (59, 67, 114, 166, 351). All infected recipients had underlying malignancies and were immunosuppressed. Platelet units from Bolivian donors were implicated in 3 of 5 cases. Several patients had severe manifestations of Chagas' disease, including acute myocarditis, acute atrioventricular block, severe congestive heart failure, pericarditis with *T. cruzi* in the pericardial fluid, and possible meningoencephalitis (67, 114, 351). The recipient of a platelet unit detected as infected during a research study had *T. cruzi* infection detected by PCR and serology during prospective monitoring but never developed symptoms (166).

In December 2006, the FDA approved an ELISA to screen for antibodies to *T. cruzi* in donated blood (59). The radioimmunoprecipitation assay (RIPA) has been used as the confirmatory test (1, 31, 257). The American Red Cross and Blood Systems Inc. voluntarily began screening all blood donations in January 2007, and in subsequent months, many other blood centers starting screening as well. As of 2 September 2011, 1,459 confirmed seropositive donations have been detected in 43 states, with the largest numbers found in California, Florida, and Texas (1). A second *T. cruzi* antibody screening test was approved in April 2010. In December 2010, FDA issued specific guidance for appropriate use of the screening tests (103). Current FDA recommendations are to screen all blood donors initially, and if a donor's sample tests negative using one of the two FDA-approved screening tests, no testing of future donations by that donor is necessary. No supplemental test has been approved, and donors are deferred indefinitely on the basis of positive screening test results alone. This strategy will be reviewed by FDA at upcoming meetings of the Blood Products Advisory Committee; the risk of newly acquired blood donor infections, including results from longitudinal studies of repeat blood donors, will be considered. Screening of blood donations remains voluntary, although most blood centers are currently following FDA recommendations.

In data from the first 16 months of screening, comprising

TABLE 8. Published reports of organ transplant-derived cases of Chagas' disease in the United States[a]

Yr	State of organ harvest	Donor origin	Implicated organ	Recipient characteristics and outcome	Reference
2001	GA	El Salvador	Kidney-pancreas	37-yr-old female with fever 6 wk posttransplant and *T. cruzi* on blood smear, died of Chagas' myocarditis 7 mo posttransplant despite prolonged course of nifurtimox	61
2001	GA	El Salvador	Kidney	69-yr-old female, asymptomatic, *T. cruzi* hemoculture positive; diagnosis sought because of recipient 1 above; treated with nifurtimox, survived	61
2001	GA	El Salvador	Liver	32-yr-old female, asymptomatic, *T. cruzi* hemoculture positive; diagnosis sought because of recipient 1 above; treated with nifurtimox but died of unrelated causes	61
2005	CA	US-born (mother from Mexico)	Heart	64-yr-old male with anorexia, fever, diarrhea; diagnosed with organ rejection, treated with steroids; 8 wk posttransplant *T. cruzi* found on blood smear; PCRs became negative on nifurtimox; died of rejection 20 wk posttransplant	157
2006	CA	El Salvador	Heart	73-yr-old male with fever, fatigue, rash, *T. cruzi* on blood smear 7 wk posttransplant; parasitemia cleared with nifurtimox; switched to benznidazole because of tremors; died of heart failure 25 wk posttransplant	157

[a] Three additional unpublished cases are known to have occurred (2 heart transplants and 1 liver transplant).

>14 million blood donations, the overall seroprevalence was 1:27,500 based on donations screened, with the highest rates in Florida (1:3,800), followed by California (1:8,300) (31). Because large blood donor studies prior to FDA approval of the screening ELISA were conducted in southern California with permanent deferral of all repeatedly reactive donors, a substantial number of infected individuals were already removed from the local donor pool, and the reported prevalence in California is thought to represent an underestimate (42, 59, 165, 167). From preliminary data, 29 (28%) of 104 *T. cruzi*-infected donors were born in Mexico, 27 (26%) in the United States, 17 (16%) in El Salvador, and 11 (11%) in Bolivia; the remaining 20 donors were born in 9 other countries of Central and South America (31). Among confirmed infected donors born in the United States, 10 individuals reported no specific risk factors for *T. cruzi* infection. All of these donors reported outdoor activities (e.g., hunting, camping, or extensive gardening) in the southern United States, which may indicate potential autochthonous exposure to the vector or animal reservoirs.

Organ Donor-Derived Transmission and Organ Donor Screening

A total of five instances of organ-derived transmission from three donors are documented in the published literature in the United States (Table 8) (60, 61, 157). Four of the five recipients died. One patient died from acute Chagas' myocarditis; *T. cruzi* infection was not the primary cause of but may have contributed to the other deaths (61, 157). In all of these instances of transmission, donor infections were not suspected until at least one recipient presented with symptomatic acute Chagas' disease (60, 61, 157).

More recently, some organ procurement organizations have begun selective or universal screening of donated organs (65). Three transmission events (in two heart recipients in 2006 and 2010 and one liver recipient in 2006) were detected through systematic laboratory monitoring when their respective donors were identified as infected shortly after the transplants occurred. All three of these recipients were treated and survived their *T. cruzi* infection (65; S. Huprikar and B. Kubak, unpublished data).

When an infected organ donor is detected, recipient monitoring relies primarily on detection of the parasite by microscopy, culture, and/or PCR, because seroconversion may be delayed or never occur in immunocompromised individuals (65, 238). Molecular techniques usually show positive results days to weeks before circulating trypomastigotes are visible by microscopy of peripheral blood. Transplant-transmitted *T. cruzi* infection may have a longer incubation period than vector-borne infection; parasitemia is usually detected within 2 to 3 months, but the delay can be as long as 6 months. A frequently recommended monitoring schedule consists of weekly specimens for 2 months, specimens every 2 weeks up to 4 months, and then monthly specimens afterwards (65, 238). In the absence of other indications and assuming no evidence of infection has been detected, the monitoring interval can be lengthened after 6 months posttransplantation.

Unanswered Questions and Priorities for Research and Programs

The United States faces important public health challenges for the prevention, control, and management of *T. cruzi* infection and Chagas' disease (86). Patients with undiagnosed Chagas' cardiomyopathy go unrecognized, impeding their optimal management. The large number of undetected *T. cruzi* infections sustains the risk of transmission through blood and organ donation and from mother to child. Currently, obstetricians have limited knowledge of congenital *T. cruzi* transmission risk, and almost no screening of at-risk women is carried out (48). Many health care providers in all specialties fail to consider the diagnosis of Chagas' disease in patients at risk and are unaware that antitrypanosomal treatment is available (280, 300); the possibility that treatment could decrease the risk of progression of disease in infected individuals is therefore not realized.

Worldwide, programs to control Chagas' disease are ham-

pered by the lack of adequate tools, and these challenges are equally salient in the United States (283). Point-of-care diagnostic tests would allow physicians to make a rapid diagnosis in patients in whom Chagas' disease is suspected and provide a practical means to identify women at risk of transmitting the infection to their infants. However, the sensitivity of current *T. cruzi* rapid tests shows wide geographic variation (275, 299); there is a need for screening tests with high sensitivity, especially for *T. cruzi* infections originating in geographic areas such as Mexico and the United States, where current tests appear to have low sensitivity (275; CDC, unpublished data). Two other diagnostic needs are critical: a practical, timely test of cure and indicators to distinguish patients who are likely to develop clinical disease from those likely to remain asymptomatic. Unfortunately, neither of these tools is currently on the horizon. Pediatric formulations of existing drugs are of immediate concern and expected to be available soon (91). However, new treatment drugs with high efficacy and better safety profiles, especially in adults, are needed (295).

To inform effective policy for Chagas' disease control in the United States, significant gaps in our knowledge must also be addressed. Systematic, rigorous population-based data to determine infection prevalence and morbidity are needed to inform prevention strategies. Pilot studies in hospitals with a high proportion of women born in Latin America would help to define practical methods to target screening for congenital transmission. More thorough identification of the *T. cruzi* strains circulating in the United States will add to our assessment of transfusion risk and understanding of the molecular epidemiology of the disease (164). More comprehensive assessment of the magnitude of local transmission risk and the factors influencing vector and reservoir host distribution and human contact are important to inform control efforts. Improved knowledge of the local epidemiology and ecology will allow more efficient, effective targeting of limited resources and raise awareness of Chagas' disease in the United States. As improved control of vector- and blood-borne *T. cruzi* transmission decreases the burden in countries where the disease is historically endemic and imported Chagas' disease is increasingly recognized outside Latin America, the United States—which confronts the challenges faced both by countries where the disease is endemic and by those where it is not—can play an important role in addressing the altered epidemiology of Chagas' disease in the 21st century.

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Caryn Bern is a medical epidemiologist in the Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, CDC. She holds an M.D. from Stanford University School of Medicine and an M.P.H. from the Johns Hopkins University School of Public Health and is board certified in internal medicine. She joined CDC as an Epidemic Intelligence Service Officer in 1990 and has worked in the Division of Parasitic Diseases since 1996. She holds adjunct appointments in the Emory Rollins School of Public Health and Johns Hopkins University School of Public Health and teaches tropical medicine courses at Johns Hopkins, the University of Minnesota, and the London School of Hygiene and Tropical Medicine. Dr. Bern's current research is focused on the treatment, immunology, epidemiology, and control of Chagas' disease and leishmaniasis.

Sonia Kjos is currently a Project Scientist in the Epidemiology Center at the Marshfield Clinic Research Foundation in Marshfield, WI. She holds an M.S. in epidemiology from The University of Texas School of Public Health, Houston, and a Ph.D. in medical and veterinary entomology from Texas A&M University, College Station, where she also completed a certification program in geographic information systems. Dr. Kjos spent 2 years in the Division of Parasitic Diseases, CDC, Atlanta, GA, as an American Society for Microbiology postdoctoral fellow. Her research focus has been on the ecoepidemiology of peridomestic Chagas' disease transmission in the United States, particularly the characteristics of the insect vectors and role of domestic animals as disease reservoirs.

Michael J. Yabsley is currently an Associate Professor of Wildlife Disease Ecology at the University of Georgia. He has an M.S. in zoology (parasitology) from Clemson University and a Ph.D. in infectious diseases from the College of Veterinary Medicine at the University of Georgia. Dr. Yabsley teaches several courses in veterinary parasitology and principles of wildlife diseases at the undergraduate, graduate, and veterinary student levels and mentors undergraduate, M.S., and Ph.D. students interested in various aspects of wildlife disease ecology. He has an active research program that principally investigates the role of wildlife as reservoirs or hosts for zoonotic and/or vector-borne pathogens. Since 1997, Dr. Yabsley has been studying the natural history of *T. cruzi* in the United States. He is an active member of the American Society of Parasitologists, the Southeastern Society of Parasitologists, and the Wildlife Disease Association. He is the author or coauthor of 112 peer-reviewed publications.

Susan P. Montgomery is currently the Team Lead for the Epidemiology Team in the Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, CDC. She has a D.V.M. from New York State College of Veterinary Medicine, Cornell University, and an M.P.H. from the Harvard School of Public Health. After 15 years in private veterinary medical practice, she joined CDC as an Epidemic Intelligence Service Officer in 2002 with the Division of Vector-Borne Infectious Diseases and was a staff epidemiologist with the Foodborne and Diarrheal Diseases Branch before joining the Division of Parasitic Diseases in 2005. Her current research activities focus on Chagas' disease epidemiology in the United States, schistosomiasis epidemiology and control, neglected infections associated with poverty in the United States, and parasitic disease blood and organ transplantation safety.