

Transfusion-associated Chagas disease (American trypanosomiasis) in Mexico: implications for transfusion medicine in the United States

Louis V. Kirchhoff, Patricia Paredes, Abel Lomelí-Guerrero, Mario Paredes-Espinoza, Carlos S. Ron-Guerrero, Manuel Delgado-Mejía, and José G. Peña-Muñoz

BACKGROUND: *Trypanosoma cruzi*, the protozoan cause of Chagas disease, causes life-long infection and is easily transmitted by blood transfusion. Our goals were to determine the prevalence of Chagas disease among donors in five Mexican blood banks, to look for evidence of transmission of *T. cruzi* by transfusion, and to evaluate two serologic assays for Chagas disease.

STUDY DESIGN AND METHODS: Blood samples from donors were tested initially with the Abbott Chagas EIA or the Meridian Chagas' IgG ELISA. Samples giving readings that were at least 50% of the cutoffs were run in a confirmatory radioimmune precipitation assay (RIPA), as were samples from recipients of blood products from RIPA-positive donors.

RESULTS: The overall prevalence of Chagas disease was 1/133 (55/7,296; 0.75%). In addition, 4 of 9 surviving recipients of blood products from *T. cruzi*-infected donors were in turn infected. Using the manufacturers' recommended cutoffs, the sensitivity and specificity of the Abbott test were 92.0% (23/25) and 99.8% (2,865/2,872) respectively, and the corresponding values for the Meridian assay were 70.0% (21/30) and 100.0% (4,369/4,369).

CONCLUSIONS: These findings indicate clearly that transfusion-associated transmission of *T. cruzi* is occurring in the study areas. Serologic testing of blood donors for Chagas disease should be performed there and in the rest of Mexico. The two screening assays evaluated may lack the accuracy necessary for blood donor testing when used as suggested by the manufacturers.

Chagas disease, or American trypanosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi*.^{1,2} This disease is only found in the Americas, where an estimated 16 to 18 million persons harbor the parasite chronically and approximately 45,000 die each year of the illness.³ Most new cases of Chagas disease are acquired through contact with feces of insect vectors containing infective forms of *T. cruzi*, but transmission also occurs by transfusion of blood products donated by persons who carry the infection. *T. cruzi* infection is lifelong and most persons who harbor the parasite chronically are asymptomatic and unaware of their being infected. This sets the stage for transfusion-associated transmission of *T. cruzi*, which historically has been a major public health problem in endemic countries and continues to be a problem in endemic areas where donated blood is not screened for antibodies to *T. cruzi*.^{4,5}

ABBREVIATION: RIPA = radioimmune precipitation assay.

From the Departments of Internal Medicine and Epidemiology, University of Iowa, and the Department of Veterans Affairs Medical Center, Iowa City, Iowa; the Hospital Civil Fray Antonio Alcalde (Fray Antonio Alcade Public Hospital), Guadalajara, Jalisco, Mexico; the Hospital General de Occidente (Western General Hospital, Jalisco Secretariat of Health), Secretaría de Salud Jalisco, Zoquipan, Jalisco, Mexico; the Instituto de Seguridad Social para los Trabajadores del Estado and the Secretaría de Salud de Nayarit (State Workers Healthcare System and the Nayarit Secretariat of Health), Tepic, Nayarit, Mexico.

Address reprint requests to: Louis V. Kirchhoff, MD, MPH, 4-403 BSB, University of Iowa, Iowa City, IA 52242; e-mail: louis-kirchhoff@uiowa.edu.

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Mexico is one of the countries in which Chagas disease is endemic.⁶ The epidemiology of Chagas disease has been studied much less intensively in Mexico than in the other endemic countries and broad perspectives are lacking. Descriptions of patients from most states in Mexico with acute or chronic *T. cruzi* infections have appeared over the years, as have a small number of population-based studies. By and large the studies in the latter group were limited in scope, employed nonstandardized diagnostic methods, and produced varied results. As an example, a national Chagas disease prevalence of 0.2 percent was found in a serologic study based on a sample of blood specimens obtained in the late 1980s for other purposes.⁷ In contrast, in a serosurvey performed in the mid-1990s among blood donors in 18 of the 31 states and the Federal District, state-specific prevalence rates ranged from 0.2 to 2.8 percent, with a 1.5 percent overall rate.⁸ In studies published this year, the rate of seropositivity among blood donors in several regions of the state of Puebla ranged from 0 to 2.6 percent,⁹ and the rate among 43,048 persons who donated blood in the Federal District during 1999 to 2003 was 0.37 percent.¹⁰ The question of possible transmission of *T. cruzi* by transfusion in Mexico has not been studied directly. No case reports of its occurrence have appeared in the indexed literature and no descriptions of retrospective, or lookback, studies have been published.

The goals of our study were to determine the prevalence of Chagas disease among donors in five blood banks in the cities of Guadalajara and Tepic, located in the states of Jalisco and Nayarit, respectively; to look for *T. cruzi* infection in recipients of blood products from donors shown to harbor the parasite; and to evaluate the sensitivities and specificities of two commercially available serologic assays for Chagas disease.

MATERIALS AND METHODS

Study design

The study was carried out in the Hospital Civil Fray Antonio Alcalde (Fray Antonio Alcade Public Hospital) (Guadalajara), the Centro Estatal de Transfusión Sanguínea del Estado de Jalisco (Jalisco State Transfusion Center) (Zoquepán), the Instituto de Seguridad Social para los Trabajadores del Estado de Nayarit (Nayarit State Workers Healthcare System), the Hospital del Instituto Mexicano de Seguro Social Nayarit (Mexican Healthcare System Hospital in Nayarit), and the Centro Estatal de la Transfusión Sanguínea de la Secretaría de Salud Nayarit (State Blood Transfusion Center, Nayarit Secretariat of Health) (Tepic).

Plasma specimens were collected from November 1, 1998, through August 31, 2001. In all five blood banks questionnaires conforming to the Official Mexican Health Regulations¹¹ were used to screen prospective donors, and this process included questions relating to exposure to

insects that transmit *T. cruzi*, symptoms suggestive of chronic Chagas disease, and a previous diagnosis of Chagas disease. In the Hospital Civil in Guadalajara, some persons who were deferred from donation because of affirmative answers to any of the questions relating to Chagas disease provided samples for Chagas serology. In all study sites, prospective donors who gave negative answers to the questions relating to Chagas disease and were otherwise acceptable were then screened for markers of infection with hepatitis B virus, hepatitis C virus, human immunodeficiency virus, *Brucella*, and syphilis. We obtained specimens from all acceptable donors on days when staff were available for processing samples for our study. Specimens were stored at -20°C until tested.

Demographic information routinely collected from prospective donors, including age, sex, birthplace, and residence during the past 5 years, was tabulated for the donors in Guadalajara.

Diagnosis of *T. cruzi* infection

Specimens were screened with the Abbott Chagas' EIA kit (Abbott Laboratories, Abbott Park, IL)¹² or the Meridian Chagas' IgG ELISA kit (Meridian Biosciences, Cincinnati, OH),¹³ following the instructions provided by the manufacturers. All results reported here are from procedures in which the criteria for validity established by the manufacturers were fulfilled. Confirmatory testing was performed on all specimens positive in the screening assays with a highly sensitive and specific radioimmune precipitation assay (RIPA) described in earlier reports.^{13,14} In addition, in an effort to detect false-negative results, specimens initially negative but at least 50 percent of the cutoffs in the screening assays were also run in the RIPA. In this assay, radiolabeled *T. cruzi* antigens precipitated by specific IgG in test samples are separated electrophoretically. Precipitation of the 72- and 90-kDa glycoproteins of *T. cruzi*, detected by autoradiography, constitutes the criterion for positivity in this assay. The laborious nature of the RIPA precluded our use of it to test the specimens that gave results less than 50 percent of the cutoffs in the screening assays.

Statistical analysis

The sensitivities and specificities of the two screening tests were calculated by use of the results obtained in the RIPA as the basis for comparison. Sensitivity was determined by dividing the number of RIPA-positive samples detected as positive in the screening assay by the number of RIPA-positive samples. Specificity was calculated as the sum of the number of specimens below 50 percent of the cutoffs plus the number of negative samples in the screening assay that were RIPA-negative, divided by the sum of the number of specimens below 50 percent of the cutoff

plus the number of RIPA-negative samples. The probability of finding four or more *T. cruzi*-infected persons among the nine recipients of *T. cruzi*-tainted blood products studied in Guadalajara was calculated with chi-square analysis with the Yates correction. For this calculation the background prevalence of *T. cruzi* infection among recipients was assumed to be the same as that of the donors.

RESULTS

Fifty-one specimens from 7296 donors were positive in the initial assays and 44 of these were positive in the RIPA (Fig. 1). In addition, 11 of the 120 specimens in the 50 to 100 percent range of the cutoffs in the initial assays were RIPA-positive (Fig. 2A). Thus the overall prevalence of Chagas disease among donors was 1 in 133 (55/7296; 0.75%). It was 1 in 126 (41/5183; 0.79%) in Guadalajara and 1 in 151 (14/2113; 0.66%) in Tepic, a difference that is not significant (Fig. 2B).

At the two study sites in Guadalajara, the records of 17 recipients of blood products from RIPA-positive donors were examined, and blood samples were obtained from the 9 who were alive at the time of our follow-up investi-

gation, in all cases more than 1 year after transfusion. Two of the latter had received whole blood and 2 had received platelet transfusions. Four of the 9 were in turn RIPA-positive ($p < 10^{-6}$), including both of the patients who had received whole blood.

The age distribution of the donors in the two blood banks in Guadalajara was as follows: 15 to 25 years (41.1%), 26 to 35 years (42.1%), 36 to 45 years (13.3%), 46 to 55 years (3.0%), and 56 to 65 years (0.5%). A total of 76.4 percent of the donors were male. As shown in Table 1, only 1 of the 41 *T. cruzi*-infected donors on whom we obtained demographic data was born in Guadalajara, whereas more than one-third of the uninfected donor group had been born in that city. Moreover, all but 2 (95%) of the *T. cruzi*-infected donors had been born in the state of Jalisco, but outside of Guadalajara, whereas only 60.5 percent of the uninfected group were born in the rural areas of the state.

Fifteen specimens from prospective donors who had been deferred from donation because of affirmative responses to questions relating to Chagas disease were tested by RIPA and all were negative. The sensitivity and

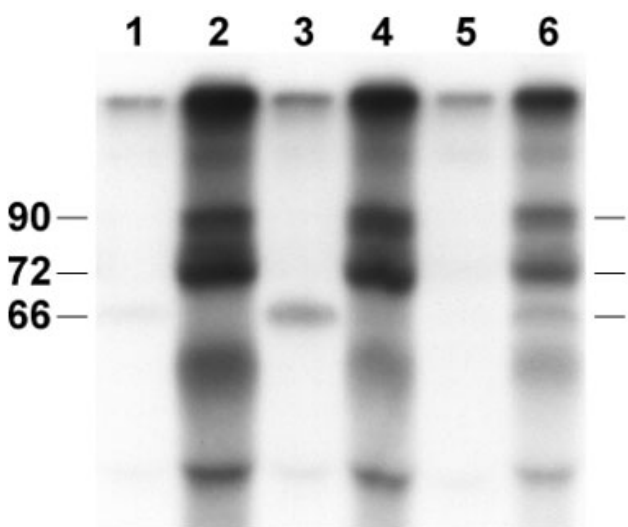


Fig. 1. Representative electrophoretogram obtained with a RIPA for antibodies that bind to ¹²⁵I-labeled *T. cruzi* surface antigens in plasma samples from blood donors in Jalisco and Nayarit, Mexico. Lane 1, negative US control; Lane 2, positive Brazilian control; Lane 3, negative Bolivian control; Lane 4, positive Mexican donor; Lane 5, negative Mexican recipient of blood from a *T. cruzi*-infected donor; Lane 6, positive Mexican recipient of blood from a *T. cruzi*-infected donor. The numbers on the left indicate relative molecular weights. The 72- and 90-kDa bands in Lanes 2, 4, and 6 are indicative of *T. cruzi* infection. The 66-kDa bands in Lanes 1, 3, and 6 are nonspecific.

A. Screening assay		B. Gdl Tepic	
		+	-
SA±RIPA*	+	44	11
	-	7	7234
		51	7245
		55	7241
		5183	7296
		(Prevalence 1/133, 0.75%)	
		41	14
		5142	2099
		5183	2113
		55	7241
		5183	7296
		(Gdl 1/126, Tepic 1/151)	
C. Abbott Chagas EIA		D. Meridian Chagas ELISA	
		+	-
SA±RIPA*	+	23	2
	-	7	2865
		30	2867
		25	2872
		21	4369
		21	4378
		Sensitivity 92.0%	
		Specificity 99.8%	
		Sensitivity 70.0%	
		Specificity 100.0%	
E. Abbott Chagas EIA (0.7x cutoff)		F. Meridian Chagas ELISA (0.5x cutoff)	
		+	-
SA±RIPA*	+	25	0
	-	18	2854
		43	2854
		25	2872
		28	4359
		38	4361
		Sensitivity 100.0%	
		Specificity 99.4%	
		Sensitivity 93.3%	
		Specificity 99.8%	

Fig. 2. Results of serologic assays for *T. cruzi* infection in blood donors in five Mexican blood banks. *Screening assay results for specimens of less than 50 percent of cutoffs; RIPA results for all others (see text).

TABLE 1. Birthplace and residence during the past 5 years of *T. cruzi*-infected and uninfected blood donors in Guadalajara (%)

Location	Infection status:	Birthplace		Residence	
		Positive (n = 41)	Negative (n = 4692)	Positive	Negative
Guadalajara		2.4	36.1	24.4	45.1
Jalisco state		95.2	60.5	68.3	48.5
Other states		2.4	3.3	2.4	5.7
Industrialized countries		0	0.04	4.9	0.7

specificity of the Abbott Chagas EIA were 92.0 percent (23/25) and 99.8 percent (2865/2872), respectively (Fig. 2C), and the corresponding values for the Meridian Chagas IgG ELISA were 70.0 percent (21/30) and 100.0 percent (4369/4369) (Fig. 2D).

DISCUSSION

Two cases of acute Chagas disease were first reported in the state of Jalisco, where Guadalajara is located, in 1967,¹⁵ and descriptions of several dozen acute and chronic cases have appeared subsequently.^{16,17} Additional perspectives were provided by three population-based studies. A prevalence of 0.1 percent was found in a serosurvey performed on 3360 specimens collected in Jalisco in 1987,⁷ and two surveys performed in 1992 and 1996 involving a total of 7500 blood donors showed prevalence rates of 0.7 and 1.28 percent.^{8,18} The only information available relating to the prevalence of Chagas disease in Nayarit, the state in which Tepic is located, was a prevalence of 0.1 percent reported in the 1987 survey.⁷

Against this backdrop of limited and highly variable data relating to the prevalence of Chagas disease in the study area, we employed a two-step algorithm with standardized tests for antibodies to *T. cruzi* and found that 55 of the 7296 (1/133; 0.75%) donors we examined were infected. The rates were similar in Guadalajara and Tepic and in both places higher than the rates of the five infectious agents for which serologic screening currently is being carried out. The prevalence of *T. cruzi* infection we found clearly carries with it a substantial risk of transfusion-associated Chagas disease, because historical studies performed in other endemic countries have indicated that the rate of transmission of the parasite is 13 to 26 percent per unit of contaminated blood transfused.⁴ The probability of transmission of the parasite per contaminated donation may be increased by separation of the blood into components. Our lookback study confirmed that transmission of the parasite by transfusion is in fact occurring, because four of the nine recipients of blood products from RIPA-positive donors were in turn infected with *T. cruzi*. The probability that all four of these patients could have had Chagas disease before receiving the contaminated blood is exceedingly small. Acute Chagas disease had not

been diagnosed in any of the four infected transfusion recipients we identified, all of whom were adults. This is not surprising because the acute phase of the illness is usually mild, especially in adults, and also because physicians in the hospitals in which we performed our study are largely unaware of the risk of transfusion-associated Chagas disease.

These results constitute compelling evidence that transfusion-associated transmission of *T. cruzi* is occurring in the hospitals in which we performed our study and that serologic testing protocols to identify *T. cruzi*-infected donors should be instituted. By use of data on the number of blood donations per year,⁸ the prevalence rate we found, and an assumed transmission rate of 18 percent, we estimate that in Jalisco alone more than 100 instances of *T. cruzi* transmission by transfusion of contaminated blood are occurring each year. Moreover, the obvious question that follows from this analysis is whether blood donors in the rest of Mexico should be screened for *T. cruzi* infection. The 1996 serosurvey of blood donors in 18 states and the Federal District mentioned above⁸ sheds light on this question. In that investigation the overall weighted prevalence of *T. cruzi* infection was 1.0 percent, and the range of state-specific prevalence rates was 0.2 to 2.8 percent. Importantly, prevalence rates were higher in 12 of the 18 states studied as well as in the Federal District, where about 25 percent of all transfusions in Mexico take place, than they were in Jalisco. A calculation based on state-specific prevalence rates and donation data indicate that roughly 1800 new cases of Chagas disease occur each year due to transfusion of contaminated blood. Given these background data and estimates, as well as the fact that large internal migrations have occurred historically in Mexico and continue today, it is clear that screening of blood donors for *T. cruzi* infection should be undertaken throughout the nation.

Information regarding the risk of transfusion-associated transmission of *T. cruzi* in Mexico that has accumulated over the years has not gone completely unnoticed. A set of regulations relating to blood products written by the Interinstitutional Committee on Transfusion Medicine and approved by the national legislature in 1992 included a suggestion that prospective donors who had resided in areas in which Chagas disease is endemic should be tested serologically, but endemic areas were not defined.¹¹ Unfortunately, although some progress has been made in establishing a national organizational structure for serologic testing of donors for *T. cruzi* infection, the Pan American Health Organization estimated recently that only 13 percent of blood donated in Mexico is being tested.¹⁹ Thus transfusion-associated transmission of the parasite continues largely unabated. A new set of regulations relat-

ing to blood products that mandates nationwide testing of all donated blood has been written and is awaiting legislative action. Preliminary results of the current study were presented to the committee that drafted the new legislation and played a role in the decision to recommend nationwide testing.

The age and sex distributions of the donors in our study group are interesting in that they are significantly different than those of US donors. Mexican donors are much younger, as 83.2 percent of them are 35 years old or less, whereas only 34.0 percent of US donors fall into this age group. Also, blood donors in Mexico tend to be mostly male, as 76.4 percent were men, whereas only 53.9 percent of US donors are male (E. Notari, American Red Cross, personal communication 2004). These demographic patterns could be advantageous if a national donor screening program for *T. cruzi* infection is implemented in Mexico, because blood bank authorities would have two relatively untapped groups of potential donors, specifically somewhat older persons and women, to approach for replacing those deferred because of *T. cruzi* infection.

We analyzed the birthplace and residence data summarized in Table 1 with the goal of finding factors that might be used in a questionnaire for identifying donors at high risk for *T. cruzi* infection. Although there was a tendency toward a higher prevalence of *T. cruzi* infection among donors who were born or resided outside Guadalajara, this information could not be exploited for screening because the majority of donors were from outside the city. It is of interest that two of the infected donors were long-term residents of the United States and had donated in Guadalajara while visiting relatives.

Our findings relating to the questions being used to identify prospective donors at high risk for Chagas disease are noteworthy. On the one hand, none of the 15 prospective donors deferred because of their responses to the Chagas disease questions were infected with *T. cruzi*. On the other hand, obviously none of the 55 *T. cruzi*-infected persons allowed to donate gave answers that prompted deferral. Thus it appears that in the study sites the questions do not serve the purpose for which they are intended.

Determining by serologic methods who is and who is not infected with *T. cruzi* has been a difficult task since testing began many decades ago. Our results exemplify some of the problems inherent in this process and thus the two-stage serologic testing protocol used in our study merits comment. The RIPA^{13,14} was developed almost two decades ago as a sensitive and specific confirmatory assay. It has been used in essentially all studies of Chagas disease among blood donors in the United States.^{20,21} The Abbott Chagas EIA and the Meridian Chagas IgG ELISA both have received 510(k) clearance from by the Food and Drug Administration (FDA), which means that they can be marketed for clinical testing in the United States. Neither assay

has been cleared for screening donated blood here. The Abbott test is available in Latin America but not in the United States. Production of the Meridian assay was discontinued in 2002.

The sensitivities we calculated for the Abbott and Meridian assays were considerably less than the values given in the package inserts that accompanied the test kits. One possible explanation for these differences may be that the values listed in the package inserts were determined by testing panels of positive specimens selected with other, usually multiple, assays. This approach to evaluating an assay can introduce a strong bias toward a sensitivity higher than that which the test actually would reach in a serologically unselected population such as that we studied. In view of this it is reasonable to conclude that the sensitivities of the two assays studied may not be as high as those listed in their respective package inserts. In considering this issue, however, it is important to keep in mind that the number of discordant results in each case was small and that larger studies could lead to different conclusions. Both the Abbott and the Meridian assays are based on South American strains of *T. cruzi*. The sensitivities we determined in the current study were not significantly different from those we found when testing blood samples from Argentina (L.V.K., unpublished data). This suggests that the donor-strain geographic mismatch is unlikely to account for the low sensitivities we found in Mexico. Moreover, the results of several other studies support the view that the origins of the *T. cruzi* strains used in diagnostic assays do not substantially influence the accuracy of the tests.²²⁻²⁴

An obvious question prompted by the patterns of low sensitivity and high specificity we found for the Abbott and Meridian assays is whether altering the cutoff formulas recommended by the manufacturers of the kits would substantially increase the sensitivities without intolerably decreasing the specificities. To address this question, we reanalyzed our data after altering to various degrees the formulas used to calculate the cutoffs. The results thus obtained for the Abbott assay are shown in Fig. 2E, where it can be seen that lowering the cutoff to 70 percent of that recommended raised the sensitivity to 100 percent while only dropping the specificity a bit to 99.4 percent. Similarly, reducing the Meridian cutoff to 50 percent of that recommended raised the sensitivity substantially to 93.3 percent, while only dropping the specificity from 100 to 99.8 percent (Fig. 2F). These analyses suggest that it may be useful to reevaluate the formulas used for calculating the cutoffs for these assays.

Finally, the implications of our results in terms of the risk of transfusion-associated transmission of *T. cruzi* in the United States merit mention. It is estimated that more than 12 million Latin American immigrants from Chagas-endemic countries currently live in the United States, approximately 8 million of whom are Mexicans.^{25,26} The

rate of immigration is illustrated by the fact that during the entire decade of the 1990s, net emigration from Mexico to the United States was approximately 1000 persons per day, 5 to 10 of whom likely harbored *T. cruzi*. In addition, it is noteworthy that almost all of the 4 million non-Mexican Latin American immigrants from Chagas-endemic nations now living here have come from countries where the prevalence of Chagas disease is higher than it is in Mexico. The presence in the United States of this large population at risk for Chagas disease carries with it the risk of transmission of *T. cruzi* via transfusion. Not surprisingly, 6 such cases have been reported to date, all of which occurred in severely immunocompromised patients in whom the diagnosis of acute *T. cruzi* infection was made because of the fulminant nature of the courses of their illnesses.²⁷⁻²⁹ Because most transfusions are given to immunocompetent patients in whom acute *T. cruzi* infection would not likely be noticed, it is reasonable to conclude that many additional instances of transfusion-associated transmission of *T. cruzi* have occurred in the United States but have not been diagnosed.

Several *T. cruzi* seroprevalence studies have been performed in US blood banks with testing algorithms essentially identical to that used in our study. Notably, in Los Angeles and Miami, 1 in 8800 donors was found to be infected with the parasite,^{20,30} and 1 in 605 donors with Hispanic surnames in five southwestern US blood banks was found to harbor *T. cruzi*.¹² By use of data from these studies and demographic information obtained in surveys carried out by the American Red Cross (D.A. Leiby, personal communication 2004), and assuming a transmission rate of 18 percent per transfused unit from an infected donor, it can be estimated that as many as 100 instances of transmission of *T. cruzi* by transfusion may occur in the United States each year. This calculation does not include instances of transmission resulting from blood donated by persons having autochthonous congenital²¹ and vector-borne³¹ infections.

The question of how best to deal with the risk of transfusion-associated transmission of *T. cruzi* in the United States has been a topic of considerable debate for more than a decade. Common sense would dictate that if screening for *T. cruzi* infection is indicated in the endemic countries from which the 12 million Latin American immigrants living here have come, then we should screen them when they present for donation here. For the past 4 years, at the suggestion of the FDA, all prospective donors are asked to report a history of Chagas disease. The efficacy of doing this is not known, but as pointed out above, our results suggest that asking questions relating to Chagas disease does not work well, and this also was the case with other studies performed in the United States³² and in Brazil.³³ It is possible, however, that the sensitivity of this approach in detecting at-risk donors could be increased by refinement of the questions asked. It is note-

worthy that one of the instances of transfusion-associated transmission of the parasite occurred here after the questions relating to Chagas disease were incorporated into the interview (P. Losikoff, personal communication 2004).

Many US blood bank authorities favor instituting serologic screening to identify *T. cruzi*-infected persons who present for donation. This effort could take several forms. In one approach, serologic testing would be limited to donors judged by questionnaire to have geographic risk for *T. cruzi* infection (i.e., birth, extended stay, or transfusion in an endemic country or having been born to a mother with any of these risk factors). In another scenario, all donors would be tested once, and then on subsequent donations, donors found to be negative previously would not be tested again unless they had visited an endemic country. In a third approach, all donors would be tested. Each of these approaches for reducing the risk of transfusion-associated transmission of *T. cruzi* has its own set of advantages and drawbacks. Simply stated, selective testing approaches would be less expensive, could be complicated logistically and administratively, and might lack sensitivity. Testing all donors would be relatively expensive but would have the advantages of being organizationally straightforward and highly sensitive. In any event, options involving serologic testing cannot be implemented at the present time because no assay for screening donated blood for *T. cruzi* has been cleared by the FDA.

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