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Congenital transmission of *Trypanosoma cruzi*: an operational outline for detecting and treating infected infants in northwestern Argentina

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Summary We designed a set of procedures for first-line local health services to detect and treat the congenital transmission of *Trypanosoma cruzi* at a province-wide scale, and field-tested the programme in the province of Tucumán, northwestern Argentina, from 1992 to 1994. The programme consists of routine screening of pregnant women for seroreactivity to *T. cruzi*, serological and parasitological follow-up of the newborn at least twice during the first year of age, treatment of the infected infants, and evaluation of the outcome. 927 (5.5%) of 16 842 pregnant women were seroreactive to *T. cruzi* by indirect haemagglutination assay and ELISA. Twenty-one (6.7%) of 315 newborns to seroreactive mothers were diagnosed as infected with *T. cruzi* parasites microhaematocrit concentration before 30 days of age. Five newborns who initially tested negative had a *T. cruzi* infection detected by microhaematocrit and/or serological techniques at 3 or 6 months of age. Thus, congenital infection was diagnosed in 26 (7.1%) infants born to seroreactive women and residing in houses free of triatomine bugs. Four of 6 infants born to seroreactive mothers died during the first year of age and had some evidence of *T. cruzi* infection; one of the deaths was attributed to *T. cruzi* based on clinical evidence. After specific treatment with nifurtimox or benznidazole, 30 of 32 infants remained parasitologically and serologically negative. This study shows the feasibility of controlling the incidence of congenitally acquired *T. cruzi* infections at a province-wide scale by means of a specific screening programme at first-line health services level.

keywords congenital, Chagas disease, transmission, trypanosomiasis, control, benznidazole, nifurtimox, serodiagnosis

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Introduction

Chagas disease, caused by the flagellate *Trypanosoma cruzi*, is mainly transmitted by triatomine bugs. Due to increasing control of transmission routes mediated by vector, blood transfusion and organ transplant, vertical transmission has become more relevant in terms of public health, as it is a continuous source of newly infected infants born to *T. cruzi*-infected mothers. The prevalence of *T. cruzi* infection in pregnant women in different countries of South America ranged from 2% to 51% in some urban centres and from 23% to 81% in some rural areas (Bittencourt 1988; WHO 1991; Freilij *et al*. 1994). The likelihood of vertical transmission from women seroreactive to *T. cruzi* has been

extremely variable among countries and geographical areas, ranging from 0.7% to 4% in Argentina (Schmuñis & Szarfman 1977; Zaidenberg & Segovia 1993; Streiger *et al*. 1995), 10.5% in Paraguay (Russomando *et al*. 1998), and 2%-21% depending on birthweight in Bolivia (Azogue *et al*. 1985).

Congenital transmission cannot be prevented, and the effects of anti-*T. cruzi* treatment of women, of reproductive age, aimed at preventing or reducing the likelihood of vertical transmission remain unknown. However, early detection of the congenitally infected infant ensures over 90% of therapeutic success using nifurtimox (Lampit®, Bayer)(Moya *et al*. 1985). Unfortunately, in most countries endemic for Chagas disease neither pregnant women nor newborns are routinely tested for *T. cruzi* infection at present. Congenital cases are frequently asymptomatic (Schmuñis & Szarfman 1977; Freilij *et al*. 1994), thereby passing unnoticed unless specific tests are made. The clinical manifestations range from oligosymptomatic (e.g. hepatosplenomegaly) to severe, which may include meningoencephalitis, myocarditis and, less frequently, pneumonitis and megaviscera (Bittencourt 1988). Neonatal deaths in premature newborns infected with *T. cruzi* are fairly common (Saleme *et al*. 1971; Szarfman *et al*. 1975). It remains controversial if maternal infection with *T. cruzi* determines an increased frequency of prematurity, abortion and stillbirths (Votta *et al*. 1974; Schmuñis & Szarfman 1977; Hernández-Matheson *et al*. 1983; Bittencourt 1988).

Early diagnosis of congenital *T. cruzi* infection is essential for treatment. Direct detection of *T. cruzi* in newborns is more effective by the microhaematocrit (or micro-Strout) concentration technique than by fresh blood examination (Freilij *et al*. 1983). Histopathological examination of the placenta, xenodiagnosis and haemoculture are more costly and time-consuming than other direct methods, and the results only become available long after the infant and mother left the health facility. These methods may not be feasible in low-complexity or overburdened maternity hospitals serving the most affected areas. Standard serological diagnosis of *T. cruzi* infection in infants born to seroreactive women has a low positive predictive value because the presence of anti-*T. cruzi* IgG antibodies in the newborn may be due to passive transfer of IgG maternal antibodies, which in the noninfected infant would normally disappear between 5 and 7 months of age (Moya *et al*. 1989). Conversely, detection of infant IgM antibodies against *T. cruzi* has been taken as conclusive evidence of *T. cruzi* infection, unless such antibodies were present in the mother and a placental leakage occurred (Schmuñis & Szarfman 1977). Unfortunately, this situation is often found when *T. cruzi* epimastigotes are used as antigen, but not with recombinant antigens (Reyes *et al*. 1990; Lorca *et al*. 1995).

The purpose of this study was to design and test a set of procedures or programme as part of first-line health care to identify and treat congenital cases of *T. cruzi* in newborns at a province-wide scale. We tested such a programme in the province of Tucumán for 28 months before extending it to other provinces. The control programme included passive detection of pregnant women seroreactive to *T. cruzi* at the main provincial public maternity hospital and 37 peripheral health centres, serodiagnosis of the infants at least twice during the first year of age, treatment of infected infants, and evaluation of the outcome. The system operated under a quality assurance programme of serological diagnosis of *T. cruzi* infection.

Materials and methods

The province of Tucumán, north-western Argentina, was selected for the pilot project because it has a long history of control of *Triatoma infestans*, the only domestic vector of *T. cruzi*, through insecticidal spraying and vector surveillance. The last notified acute case of Chagas disease in Tucumán occurred in 1985, and the prevalence rate of seropositivity to *T. cruzi* in children < 5 years of age in 1994 was < 1% (Segura *et al*. unpublished data). The infant mortality rate was 26 per thousand live newborns in 1991.

The project was initiated at the Maternidad de Nuestra Señora de la Merced in September 1992 and then expanded throughout Tucumán's primary health care system, to end in December 1994. The Maternidad is a public hospital with 150 beds and a daily average of 32 deliveries which exceed the capacity of its facilities. It specializes in acute cases, offering gynaecological and obstetrical as well as neonatal care, and serves as referral centre throughout the Province. The hospital manages 10 500 deliveries per year, which constitute approximately 57% of the deliveries in the province of Tucumán. Physicians, biochemists, nurses and technicians were trained in the use of technical manuals prepared for the project (Ministerio de Salud y Acción Social de la Nación 1995).

Follow-up of pregnant women and the newborns also took place at the First Line of Health Care Centres (FLHCC) and Community Attention Centres (CAC). There are 30 provincial FLHCC and 7 municipal CAC whose staff include physicians (only in FLHCC), sanitary agents, nurses and administration employees. Peripheral centres are mainly responsible for the primary health care of pregnant women and newborns, free distribution of milk from the last trimester of pregnancy to the age of two years, vaccination, and health counselling.

Diagnosis of pregnant women

Pregnant women coming voluntarily to a medical check up in

the maternity hospital, FLHCC and CAC were examined clinically, and an individual record containing details of family, current residence as well as medical, obstetrical and perinatal history was kept for each patient. A blood sample was taken for routine laboratory diagnosis and serology for *T. cruzi*. Blood samples collected at FLHCC and CAC were sent to the maternity hospital or the Chagas National Service laboratory for serodiagnosis. Pregnant women lacking a prenatal screening test were examined serologically for *T. cruzi* on admission at the Maternidad or immediately after delivery.

The serological diagnosis of *T. cruzi* infection was carried out by indirect haemagglutination (IHA) and enzyme-linked immunosorbent assay (ELISA) using soluble extracts of cultured epimastigotes of *T. cruzi* as antigen in commercially available kits (Polychaco, Buenos Aires, Argentina, and Wiener, Buenos Aires, Argentina). For ELISA, rabbit anti-human IgG conjugated with peroxidase as secondary antibody was used (Instituto Nacional de Chagas 1994). Blood samples positive by two serological techniques were considered seroreactive to *T. cruzi*. A 10% random sample of all serological tests was re-tested at the National Referral Centre of the Instituto Nacional de Parasitología 'Dr Mario Fatala Chabén' following procedures described by Cura and Segura (1998).

Mothers seroreactive for *T. cruzi* were given a card with the serological results and the dates when the infants should be brought for examination. The card also alerted on the likelihood of transmission of *T. cruzi* to the child, and emphasized the importance of the control visits to diagnose the infection and start treatment as early as possible.

Diagnosis and treatment of infants

Infants born to *T. cruzi*-infected women were examined for infection at birth before leaving the maternity ward. Approximately 2 ml of blood were taken from the heel for parasitological and serological studies. The blood samples were examined for *T. cruzi* by the microhaematocrit concentration technique using six 75 µl-capillary tubes per infant (Freilij *et al*. 1983). Infants with a positive parasitological test were frequently not examined serologically to save labour, and they were immediately treated as described below. Infants with a negative microhaematocrit at birth but with suspect signs and symptoms were re-examined by microhaematocrit before 30 days of age. All children were serologically examined at least by IHA (Polychaco), and ELISA with antihuman IgG and IgM, using the same standardized procedures as before. In case of discordant IgG-serology results, the sera were examined by indirect immunofluorescence antibody test (IFAT). Cut-off titres were 32 for IHA and IFAT, and an optical absorbance of 0.2 for ELISA. Infants with two or more reactive serological tests detecting IgG antibodies were considered seroreactive to *T. cruzi*. Results for IgM-ELISA were considered separately because IgM-ELISA did not have a satisfactory performance in this study.

Regardless of the serological result, infants who were parasitologically negative at birth were scheduled for a new examination for *T. cruzi* infection at 6 months of age, unless the infant showed any health problems. Two procedures were used for follow-up: The mother took the infant to the maternity laboratory, as recommended in the health card, and mother and infant went to the peripheral health centres in response to the summons of the sanitary agents, but the serological tests were performed at the maternity laboratory. The same procedures used at birth were followed to diagnose *T. cruzi* infection. Infants with a negative microhaematocrit test and a decrease in specific antibodies below the cut-off titres were considered seronegative and were not followed-up further. When the decrease in antibody titres did not fall below the cut-off titres, the infant was scheduled for another examination before 12 months of age.

All infants with *T. cruzi* detected by the microhaematocrit test, or persistence of IgG antibodies to *T. cruzi* above the cut-off titres by two serological techniques after 6 months of age (Schmuñis & Szarfman 1977) were considered infected. Thirty-two infants were then referred to the Hospital Pediátrico del Niño Jesús for specific treatment with nifurtimox at a dose of 10 mg/kg per day for 60 days taken orally and divided into 2 or 3 fractions after meals, according to official guidelines (Ministerio de Salud y Medio Ambiente de la Nación 1983). Three infants showing an adverse reaction to nifurtimox were treated with benznidazole (Radanil®, Roche, Argentina) at a dose of 5 mg/kg for 30 days taken orally and divided into 2 or 3 fractions after meals. The outcome was evaluated immediately after treatment, and at least once a year for 2 years after treatment by means of clinical, electrocardiographic, serological and parasitological examinations using the same procedures as before.

To exclude the possibility that any of the infected infants had acquired the infection through triatomine bugs, each case's house was searched for triatomine bugs by expert staff of the National Chagas Service using timed manual capture assisted with an irritant spray of 0.2% tetramethrin to flush out the bugs from its hiding places.

Data analysis

Thirty infants who lacked enough data for a reliable identification and 3 infants infected with *T. cruzi*-whose usual residence was in rural areas from Santiago del Estero, where vector-mediated transmission of *T. cruzi* might have occurred, were excluded from the data base of putative congenital cases.

Table 1 Age specific prevalence of seroreactivity to *T. cruzi* in pregnant women, Tucumán (1992–94)

Age group (years)	No. of pregnant women examined	No. seroreactive	Percentage seroreactive
< 20	2734	147	5.4
21–29	5946	367	6.2
30–39	2836	240	8.5
40–49	365	46	12.6
50–59	7	3	42.9
Total	11888	803	6.8

Results

A total of 16 842 pregnant women were examined serologically during the 1992–94 period. Considering that an annual average of 10 500 pregnancies occurred in public health services at that time, the estimated coverage of the screening programme was 69% (16 842 of 24 500). Of these, 927 (5.5%) women were seroreactive to *T. cruzi*. The prevalence rate of seroreactivity to *T. cruzi* was 5.1% in 1992 ($n = 3928$), 7.0% in 1993 ($n = 6191$), and 4.5% in 1994 ($n = 6723$), the differences being statistically significant among years ($\chi^2 = 40.6$, two degrees of freedom (d.f.), $P < 0.001$) but with a weak trend (χ^2 for trend = 5.12, 2 d.f., $P = 0.024$). The mean age of 803 seroreactive women (29.9 years; 95% confidence interval (CI), 29.3–30.5), who documented their age properly, was significantly greater than the mean age of 11 085 seronegative women (25.6 years; CI, 25.5–25.7). Most (86.4%) of the examined pregnant women resided in Tucumán, followed by those from the provinces of Santiago del Estero (5.7%), Salta (2.8%), Buenos Aires (2.7%), Jujuy (0.8%), and Catamarca (0.8%).

The prevalence of seroreactivity to *T. cruzi* showed a significantly increasing trend (χ^2 for trend = 41.99, 4 d.f., $P < 0.0001$) with age from 5.4% in women < 20 years of age to 12.6% in those aged 40–49, and jumped to 42.9% in women aged > 50 years (Table 1). This table only includes women who documented their ages properly.

Maternal seroreactivity to *T. cruzi* in 1994 was not significantly associated with history of previous spontaneous abortion, history of frequency of stillbirths, and history of newborns with a birthweight < 2500 g (Table 2). Numbers vary for each 2 × 2 table because the respondents sometimes refused to answer, or did not recall, or the information was not recorded.

A total of 364 (39% of 927) newborns to seroreactive mothers were examined for *T. cruzi* infection by microhaematocrit and/or serology at birth or before 30 days of age (Table 3). Congenital infection, as determined by detecting *T. cruzi*, was diagnosed in 21 (6.7%) of 315 (294 + 21) infants examined by the microhaematocrit concentration technique before 30 days of age. Among the 21 parasitologically confirmed cases, 6 of 8 (75%) were positive for anti-*T. cruzi* IgM, and 17 of 19 (87%) were positive for IgG. Of 40 (34 + 6) IgM-positive newborns, only 6 were concurrently microhaematocrit-positive, 8 (20%) were IgG-negative by two tests, and 12 (30%) reactive to only one IgG test. Of 186 (2 + 175 + 9) IgM-negative newborns, 2 were microhaematocrit-positive, and 51 were seroreactive. The National Reference Laboratory confirmed 100% of all the positive and 96% of all the negative serological results of the local laboratories during the follow-up.

The last column of Table 3 shows the distribution of 6 infant deaths according to their parasitological and serological diagnosis. Two newborns with parasitaemia died at 3 months of age; one of them had received no specific treat-

Table 2 History of previous spontaneous abortion, stillbirths, birth weight less than 2500 g, and type of delivery according to maternal seroreactivity to *T. cruzi*, Tucumán (1994)

Outcome of pregnancy	Maternal seroreactivity to *T. cruzi*				Total	χ^2	*P*-value
	Seroreactive	(%)*	Seronegative	(%)			
History of previous abortion							
Yes	144	(25.1)	1003	(28.6)	1147	3.15	0.076
No	432		2506		2938		
Stillbirths							
Yes	27	(5.1)	161	(5.2)	188	0.01	0.92
No	502		2932		3434		
Low birth weight (in g)							
< 2500	68	(12.5)	419	(13.0)	487	0.10	0.75
≥ 2500	474		2795		3269		

* Percentage of the worse outcome among seroreactive (exposed) and seronegative (not exposed) pregnant women.

Table 3 Parasitological and/or serological examination at birth or before 30 days of age of 364 infants born to mothers seroreactive for *T. cruzi*, Tucumán (1992–94)

Seroreactivity * Microhaematocrit	ELISA-IgM	Positive	Negative	ND	Total	No. dead
Positive	Positive	5	1	0	6	0
	Negative	2	0	0	2	0
	ND	10†	1	2	13	2
	Subtotal	17	2	2	21	2
Negative	Positive	15 ‡	19 §	0	34	2
	Negative	47	128	0	175	0
	ND	26	53 ¶	6	85	1
	Subtotal	88	200	6	294	1
ND	Positive	0	0	0	0	0
	Negative	2	7 **	0	9	1
	ND	17	23	0	40	0
	Subtotal	19	30	0	49	1
Total		124	232	8	364	6

* Positive by at least two of the following tests: HAI, ELISA-IgG, IFAT. †Two infants died: one, untreated, on the third month of age; the other, treated, had anaemia and an abnormal ECG. ‡ One ELISA IgM-positive, seroreactive infant died from Chagas disease on clinical evidence. § One ELISA IgM-positive, IHA-positive infant died. ¶ One ELISA IgG-positive, IHA-negative infant died. **One IFAT-positive infant died at 6 months of age from meningoencephalitis.

ment against *T. cruzi*, while the other had been treated with nifurtimox but also had anaemia and an abnormal electrocardiograph attributable to *T. cruzi* infection. Another 2 microhaematocrit-negative, IgM-positive infants who had IgG antibodies detected by one or two techniques and were not treated for *T. cruzi* died at three months of age; one was considered a death from Chagas disease based on clinical evidence. Only two deaths occurred among seronegative infants who were either IFAT or ELISA IgG-positive; the former died from meningoencephalitis at six months, the latter at two months of age.

A total of 161 (47%) of 343 infants who had been microhaematocrit-negative or had no microhaematocrit data at birth were examined at least once by serological methods, and sometimes also by microhaematocrit, at 3, 6 or 12 months of age (Table 4). Five (3.2%) *T. cruzi*-infected infants were detected at 3 or 6 months of age, and these were considered congenital cases in the absence of triatomine infestation in their houses. Among newborns initially seronegative for *T. cruzi*, 4 (3.7%) seroreactive cases occurred, three of which were also microhaematocrit-positive. Only one seroreactive case occurred among 48 initially seroreactive newborns, and this case was also microhaematocrit-positive. Most of the initially seroreactive newborns switched to a seronegative status. However, 4 newborns still seroreactive at 3 months of age were not examined subsequently. Overall, 56% (59 of 106 survivors) of the initially seroreactive, non microhaematocrit-positive newborns were lost to follow-up. Extrapolation of the proportion of *T. cruzi*-seroreactive infants found among those that were

Table 4 Serological follow-up of parasitologically nonpositive newborns born to mothers seroreactive for *T. cruzi* during the first year of age, Tucumán (1992–94)

Initial serological result at birth *	Serological results at 3–12 months of age			Lost to follow-up	Total
	Seronegative	Seroreactive	(%)		
Seronegative	103	4†	(3.7)	123	230
Seroreactive ‡	47	1§	(2.1)	59	107
Not examined	6	0	(0)	0	6
Total	156	5	(3.2)	182	343

*Includes microhaematocrit-negative or microhaematocrit-no data newborns. Seroreactive means reactive to at least 2 serological techniques (IFAT, IgG-ELISA, IHA). †Three cases were also microhaematocrit-positive. ‡ Excludes four cases still seroreactive at three months of age not examined thereafter. All the remainder who were seroreactive at birth had at least one seronegative diagnosis thereafter. § Also microhaematocrit-positive.

followed up after birth to those that were lost to follow-up in Table 4 suggests that approximately 5 of the initially seronegative newborns (123 times 0.037) and one of the initially seroreactive ones (59 times 0.021) might have progressed to a detectable *T. cruzi* infection left untreated. This calculation is based on the assumption that infants lost to follow-up were a random sample of all children eligible for follow-up. Therefore, the estimated total number of congenital cases would be 32 (21 parasitologically positive cases, plus 5 cases detected by serological or parasitological follow-up, plus 6 estimated cases amongst losses from follow-up), which divided by 364 newborns examined for *T. cruzi* infection at birth, yields an upper limit for the likelihood of congenital transmission of 8.8%.

As a by-product of the screening programme, three groups of infants were examined for the first time at 3, 6 or 12 months of age (23, 30, and 79 infants, respectively), which allowed the detection and treatment of 6 additional infections (not shown in tables). All these cases may or may not have been congenital cases, but as we could not establish whether they had travelled to an infested rural area and some even showed specific IgM at 12 months of age, they were considered separately.

Over a 28-month period, a total of 32 infants infected with *T. cruzi* were detected and treated. Most (84%) of the cases were born at term, and 81% were breast-fed. There were 2 pairs of infected twins, 4 premature newborns, 3 cases of foetal malnutrition, and 4 infants with antecedents of perinatal hypoxia. None of the cases exhibited a portal of entry of *T. cruzi*, and no clinical signs of Chagas disease were observed in 40%. Hepatomegaly, in 39% of cases, was the most frequently encountered sign. Splenomegaly and hepatosplenomegaly were each present in 12% of the cases; heart failure in 3%, incomplete hemiblockage in 6%, oedema in 3%, and meningoencephalitis with seizures and positive cerebrospinal fluid in 3%.

All 32 infants treated with nifurtimox or benznidazole tested negative parasitologically when examined 6 months to 2 years after treatment. Serodiagnosis for IgM and IgG against *T. cruzi* was negative in 30 infants. Two infants who failed to return still were seroreactive four months after treatment. Except for 3 infants that experienced adverse reactions with nifurtimox (gastroenteritis, weight loss, hypersensitivity) and were treated with benznidazole, all the cases tolerated the treatment well.

Discussion

This study shows the feasibility of controlling the incidence of congenitally acquired *T. cruzi* infections at a province-wide scale by means of a specific screening programme as part of first-line health services. The programme increased the prenatal maternal screening for *T. cruzi* infection from an average of 30% before 1992 (abstracted from the existing files) to 70% in 1994, and enhanced the probability of detecting congenital infection in reference to past data collected in the same location (Saleme *et al*. 1971). Also important, the likelihood of congenital transmission has been estimated in the range of 7.1%-8.8%. Congenital transmission of *T. cruzi* clearly represents a public health problem in formerly highly endemic areas, even after years of triatomine surveillance.

Argentina has made progress in the control of the vectorial transmission of *T. cruzi*, as evidenced by nationwide serological and triatomine surveys (Segura *et al*. 1985, 2000; Chuit *et al*. 1989). A large percentage of rural dwellings are under surveillance against reinfestation by *T. infestans* (Segura *et al*. 1994). No acute case of Chagas disease has been reported in Tucumán since 1985, which reached the surveillance phase in 1995. Blood donors in Argentina have been routinely screened for antibodies to *T. cruzi* since 1983 (Pérez & Segura 1989). All congenital cases had their house free of triatomine infestation and resided in the city of Tucumán. These facts therefore exclude the likelihood of both bug and transfusion-mediated transmission of *T. cruzi* to mothers and infants during the present study.

With a mean age of 26 years, the prevalence of seroreactivity to *T. cruzi* in pregnant women (5.5%) was very close to that of blood donors of similar mean age attending public blood banks in Tucumán in 1997–98 (5.6%). In our study 10.4% of pregnant women aged 18 were seroreactive to *T. cruzi*, compared to 2% of seroreactive, unselected 18-year-old men from Tucumán drafted into military service in 1993 (Segura *et al*. 2000). In the absence of gender-specific asymmetries in the prevalence of seroreactivity to *T. cruzi* in field surveys (e.g. Gürtler *et al*. 1998), the observed differences in Tucumán most probably arose because the public maternity hospital served a low-income population with an above-average prevalence of *T. cruzi*. The prevalence of infection in pregnant women increased with age, as observed in many rural communities (Chuit *et al*. 1989). The marked increase in prevalence after 40 years of age may be explained by the fact that triatomine control actions in Argentina started in the early 1960s (Segura *et al*. 1985), when that age group was in the second decade of life.

The likelihood of congenital transmission of *T. cruzi* herein reported (7.1%) clearly exceeded most estimates for Argentina reviewed by Schmuñis and Szarfman (1977) in the 1970s (median, 1.9%; range, 0.1%-3.5%), and by Freilij *et al*. (1994) in 1970–80s (median, 2.5%; range, 0.7%-10.4%). In the same maternity hospital as in the present study but more than 20 years earlier, only 2.5% of live newborns to seroreactive mothers examined in the first few days of age were infected with *T. cruzi* (Saleme *et al*. 1971). More recent studies in Argentina estimated the probability of trans-

mission as 4.0% in Jujuy (Zaidenberg & Segovia 1993), 2.6% in Santa Fe (Streiger *et al*. 1995), and 5.3% in the city of Buenos Aires (Arcavi *et al*. 1993). Estimates of congenital transmission were even greater for newborns < 2 kg or stillbirths (10.5%) in Brazil (Bittencourt *et al*. 1972), and unselected rural population in Paraguay (10.5%), as determined by the polymerase chain reaction and serodiagnosis (Russomando *et al*. 1998). A meaningful comparison among these figures is difficult because diagnostic methods and time of follow-up were heterogeneous among studies. It is noteworthy that as detection efforts and methods progress, the estimated probability of congenital transmission tends to increase.

Approximately 81% (21 of 26) of the congenital cases were diagnosed early after birth using the microhaematocrit technique either once or repeatedly in the presence of suspect *T. cruzi* infections, which may explain the relatively higher chance of detection herein found. However, 5 cases were diagnosed at a later stage, including 4 initially seronegative infants. These cases likely had a low intensity of parasitaemia at birth, probably because they had acquired the infection during the late stage of pregnancy or subsequently. The evidence emphasizes the need for extended clinical, parasitological and serological follow-up of all infants born to seroreactive mothers without detectable parasitaemia at birth. In the absence of a positive microhaematocrit test and clinical signs of Chagas disease, serological examination of the infant at 6–7 months of age would provide the final evidence on which to decide specific treatment. Other studies with a more limited follow-up, such as that by Saleme *et al*. (1971) in the same maternity, most probably missed asymptomatic cases with a late seroconversion and thus underestimated the likelihood of vertical transmission.

Use of IgM-ELISA did not contribute to an enhanced detection of congenital infections in this study. Infant IgM antibodies to *T. cruzi* are not always detectable at birth (Votta *et al*. 1974; Lorca *et al*. 1995; Russomando *et al*. 1998) because the infection may be very recent, or transmission occurred early in pregnancy, or there is an excess of maternal IgG that suppresses the foetal synthesis of specific IgM (Reimer *et al*. 1976), or the infant lacks a normal immune response. Moreover, many infants had IgM antibodies against epimastigote-derived antigens of *T. cruzi* without subsequent evidence of infection or Chagas disease.

Clinical features of congenital infection vary among geographical regions, ranging from premature infants with severe symptoms and high mortality rate to asymptomatic or oligosymptomatic infants (Bittencourt 1988). In our study, 40% of the infants showed no symptoms of Chagas disease. Hepatomegaly was the prominent feature in symptomatic infants, but 1 case of heart failure, 2 cases of incomplete heart blockage and 1 case of meningoencephalitis were also found. These data and the suspect deaths from Chagas disease justify efforts to detect *T. cruzi*-infected mothers and infants. As observed by others (Moya *et al*. 1985; Zaidenberg & Segovia 1993; Freilij *et al*. 1994), early treatment with nifurtimox or benznidazole (currently available on request to the manufacturers) obtained a high level of cure and was well tolerated in this age class.

Four of 6 live newborns who died during the first semester of age had some evidence of *T. cruzi* infection, one of them having been treated with nifurtimox. However, in the absence of anatomo-pathological evidence or because of the presence of other contributory factors (anaemia, low birthweight), *T. cruzi* cannot be implicated as the ultimate cause of death. In any case, the suspect deaths may help increase our awareness of the potential effects of lost-to-diagnosis, untreated congenital *T. cruzi* infections. Approximately 50% of premature newborns die as a consequence of *T. cruzi* infection (WHO 1991). Our study did not produce sufficient evidence to support that maternal infection with *T. cruzi* is a risk factor for the likelihood of foetal or neonatal death, but the evidence is based on the patients' recall, and stillborns or dead foetuses were not investigated. History of previous spontaneous abortion, stillbirths, or low birthweight were not significantly associated with maternal infection with *T. cruzi* in a crude analysis. These results are consistent with other studies (Votta *et al*. 1974; Schmuñis & Szarfman 1977; Bittencourt 1988), but those for spontaneous abortions contradict a study at Córdoba, Argentina (Hernández-Matheson *et al*. 1983). For a thorough analysis, age of the mother should be considered as a potentially confounding factor.

Why do a large proportion of seroreactive mothers in Tucumán and elsewhere (Russomando *et al*. 1998) fail to bring the infants for follow-up? The reasons for such large amount of noncompliance remain unclear, but there is little doubt that improvements of this aspect (e.g. more active search of the mother, education campaigns) is of crucial importance given the limited sensitivity of diagnostic tests at birth. As a result of the Argentine national programme for controlling the congenital transmission of *T. cruzi*, a total of 524 cases (annual average, 131 cases; range, 101–167 cases) have been detected, treated, and notified from 1994 to 1997 (Ministerio de Salud y Acción Social de la Nación 1997). The finding and treatment of several additional cases of *T. cruzi*-seroreactive, likely noncongenital infants who were first examined at 6 or 12 months of age was another positive by-product of the screening programme.

The results presented here show that it is feasible to transfer the control protocol to the first line of health services, and in doing so a measurable, not marginal burden of disease can be prevented in areas that had been infested. For the detection and treatment of congenital cases we suggest routine screening of pregnant women for seroreactivity to *T. cruzi* and

follow-up of their newborns in health centres attending populations in areas under triatomine surveillance, where the seroprevalence in women of reproductive age is higher than 1%. In areas where women have lower infection rates, prenatal screening using appropriate questionnaires and selective serological examination may be more cost-effective. We recommend both parasitological and serological (using two techniques) examination of the infant at birth in laboratories operating under a quality assurance programme, and close clinical, parasitological and serological follow-up during the first semester of age; and specific treatment of seroreactive infants > 6 months of age with nifurtimox or benznidazole in both effective and well tolerated treatment regimes. However, a cost-effectiveness analysis of such a screening programme in the context of other local health problems is clearly needed to define priorities on a rational basis and decide on launching such a programme.

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