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LONG-TERM EFFECTS OF A NATIONWIDE CONTROL PROGRAM ON THE SEROPOSITIVITY FOR *TRYPANOSOMA CRUZI* INFECTION IN YOUNG MEN FROM ARGENTINA

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Abstract. Unselected nationwide cohorts of Argentine men 18 years of age summoned for military service were tested for antibodies to *Trypanosoma cruzi* each year from 1981 to 1993. After an initial screening using indirect hemagglutination test, the positive sera were retested by titrated indirect hemagglutination and immunofluorescence antibody tests at 39 laboratories or at the national reference center in Buenos Aires. Nearly 1.8 million men were examined for *T. cruzi* antibodies using the same standardized procedures under a quality assurance program. The prevalence of seropositivity for *T. cruzi* decreased significantly from 5.8% in 1981 to 1.9% in 1993, but the decrease was not homogeneous among provinces within each region or constant over time. Prior to the nationwide control campaign initiated in 1961–1962, 15 provinces had high (> 20%) percentages of houses with domiciliary infestation by *Triatoma infestans* bugs, which decreased to nine provinces in 1982, and four provinces in 1992. The observed decrease in the prevalence of seropositivity for *T. cruzi* may be mostly attributed to the spraying with insecticides to eliminate the domiciliary populations of *Triatoma infestans.* The lack of a sustainable triatomine surveillance program set a limit to the decrease of seropositivity rates and prompted a revised strategy based on community participation.

INTRODUCTION

Trypanosoma cruzi, the causative agent of Chagas' disease, is mainly transmitted by triatomine bugs, but also from mother to child, by blood transfusion, and organ transplantation. Approximately 16–18 million people in the Americas,[1] including 2.3 million people from Argentina,[2] were estimated to be infected with *T. cruzi*. In Argentina, *Triatoma infestans* is the main or only domiciliary vector of *T. cruzi*; historically, it had a wide distribution range from the northern border with Bolivia and Paraguay to 45° 35′ S in the province of Chubut, thus excluding Santa Cruz and Tierra del Fuego.[3] Since 1992, *Triatoma infestans* has been the subject of a regional elimination program ('Iniciativa del Cono Sur') based mostly on house sprayings with residual insecticides.[4]

Serologic surveillance of rural residents after insecticidal campaigns have documented a rapid decrease in the rates of seropositivity for *T. cruzi*.[5,6] However, these studies have been few and pose problems of external validity (i.e., the degree to which local studies on non-randomly selected communities can be extrapolated to the general population).[7] The annual rate of acute cases of Chagas' disease notified by each province might be used as an index of present human transmission of *T. cruzi*, but most primary cases are not apparent, patients may not seek medical attention because of distance to health facilities and lack of transportation or economic means, and under-reporting within the health system may be frequent. The prevalence of seropositivity for *T. cruzi* among voluntary blood donors, who are not a random sample of the population, pose insurmountable problems of selection bias. In contrast, school children[8] and military recruits[9] constitute accessible population groups that may be used to identify risk factors or assess the impact of control programs at various spatial scales.

According to Argentine law, all native or naturalized men born within a calendar year were summoned for military service at the age of 21 (until 1976) or 18 years (since 1977) until 1994, when the mandatory draft was discontinued. Each year, a general health survey of all recruits was carried out by the National Ministry of Public Health and Social Action. These annual surveys gave the unique opportunity to define the geographic distribution of human *T. cruzi* infection and assess the long-term effects of the combined triatomine and blood bank control program initiated between 1961 and 1963. This is the first study using nationwide, unselected cohorts of all men born throughout a country to assess the impact of a Chagas' disease control program over a period of approximately 30 years.

The combined control program reduced the seroprevalence of *T. cruzi* from 10.1% in some 210,000 Argentine men 21 years of age born from 1944–1947 to 5.8% in those born in 1963 and examined for antibodies in 1981.[9] At this time, however, some provinces still showed high prevalence rates of seropositivity for *T. cruzi* for undetermined reasons. In addition, the triatomine control program experienced several changes over time among and within provinces whose long-term impact on the transmission of *T. cruzi* has not been assessed. Therefore, a sustained effort to monitor the expected decline in prevalence rates of seropositivity for *T. cruzi* was considered necessary and feasible.

In this study we report the nationwide serologic results of nearly 1.8 million military recruits drafted from 1981 to 1993, i.e., 20–31 years after the onset of the control program in Argentina. Province-specific prevalence rates of domiciliary infestation by *Triatoma infestans* assessed in 1982, 1987, and 1992 were correlated with the rates of seropositivity for *T. cruzi* in young men. Data published in initial or interim reports[9–12] are here refined, clarified, and corrected when necessary.

MATERIALS AND METHODS

The Argentine Chagas' Control Program. Attempts to control *Triatoma infestans* were initiated in the Provinces of Chaco, La Rioja, Santiago del Estero, and Catamarca in the late 1940s.[13,14] The serologic and electrocardiographic surveys carried out by Rosembaum and Cerisola[15,16] documented high seroprevalence rates of *T. cruzi* infection and associated heart disease in rural communities. These findings stimulated the organization of a national triatomine control program in 1961 and the creation of two institutions: the National Chagas Service, to carry out triatomine control actions, and the National Institute for Research and Diagnosis of Chagas' Disease ''Dr. Mario Fatala Chabén'' (INDIECH, formerly Sanitary Laboratory), to perform serologic diagnosis of *T. cruzi* infection, and control blood donors. Eleven provinces (Chaco, La Rioja, Salta, Jujuy, Santiago del Estero, Catamarca, Tucumán, San Juan, Córdoba, Santa Fe, and San Luis) started the program in 1961–1962,[17] and nine other provinces joined the program in the early 1970s (Formosa, La Pampa, Neuquén, Mendoza, Río Negro, Misiones, Corrientes, Entre Ríos, and Buenos Aires). The program planned to employ 1,100 spraymen to treat nearly 2.2 million houses in 3–5 years at a cost of (1964) US $51 million. By 1968, nearly 450,000 houses had been sprayed, but the program objectives were not achieved due to budget constraints.[18] *Triatoma infestans* bugs infected with *T. cruzi* were detected in every province within its distribution range.[3] Triatomine control actions were carried out in all of the affected provinces by 1979.

The triatomine control program was based on the application of insecticides to domestic and peridomestic premises by qualified personnel organized under a vertical, centralized structure.[17] After an initial preparatory phase, in the attack phase all houses in a given community were sprayed with insecticides and re-treated after approximately two or three months. In the subsequent vigilance phase, the program included regular assessments of house infestations through timed manual capture and selective treatments of the reinfested houses. A massive spray of all house units was recommended when the rate of house reinfestation surpassed 30%. These guidelines were followed also in the 1980s.[19] In practice, many areas never reached the vigilance phase, and some sparsely populated departments were treated for the first time in the late 1980s (e.g., Department Moreno in Santiago del Estero).[20] The chlorinated insecticide gamma-benzene hexachloride, at an intended dose of 0.5 g/m^2 of sprayed surface, was decreasingly used until 1983; organophosphorous insecticides (fenitrothion and mercaptothion, 2–2.5 g/m^2) were used from 1976 to 1989. Pyrethroids, mainly deltamethrin in a suspension at a concentration of 25 mg/m^2, have been increasingly applied since the early 1980s. Since 1979, the triatomine control program was decentralized and the operational responsibility was transferred to the provinces. In some provinces, control actions were inserted successfully within the primary health care system (e.g., Jujuy) while in others the experience was unsuccessful (e.g., Santiago del Estero). The main characteristic of this period was the heterogeneity, both spatial and temporal, in the execution of control actions. The annual number of houses sprayed with insecticides at each province was obtained from the available records kept at the National Chagas Service in Córdoba. The total number of units potentially at risk of infestation with *Triatoma infestans* was estimated as 800,000 houses in 1992.[10]

The serologic control of blood donors for antibodies to *T. cruzi* was initiated in Buenos Aires and Córdoba in 1963–1964.[21] This was later extended to all provinces in the 1970s to achieve complete coverage of blood banks when a national law enacted in 1980 enforced such practice.

Selection of study subjects. Prospective military recruits from all over the country were randomly selected from each 18-year–old birth cohort according to their identity card number. The prospective recruits were summoned at 34 reconnaissance centers according to their permanent residence place when they were 16 years old, as stated in the identity cards. The total number of young men finally drafted depended on annual budget allocations, which followed a decreasing trend until the mandatory draft was discontinued in 1994. Thus, the number of young men that were examined for antibodies to *T. cruzi* decreased from 212,615 in 1981 to 80,068 in 1993 (Appendix 1), but this did not produce any selection bias because each study cohort was randomly selected. The Argentine National Ministry of Public Health and Social Action reviewed and approved the study procedures.

Serology. Blood samples were obtained by venipuncture and allowed to clot; after centrifugation and separation, the sera were mixed 1:1 in buffered glycerin for preservation at room temperature[22] and then shipped to the 39 members of the national laboratory network. There the sera were screened for antibodies to *T. cruzi* by indirect hemagglutination (IHA) using a 1:8 serum dilution as the cut-off value to ensure a sensitivity of 100%; the specificity was 95%.[9] In a second step, the samples reactive in the screening were re–tested by IHA and indirect immunofluorescence assay (IFA) for confirmation using double serum dilutions from 1:8 to 1:1,024 (for IHA) or 1:32 to 1:128 (for IFA). Only in 1981 were all the positive sera shipped to the national reference center (INDIECH) for confirmation. The antigens used were a mixture of 20 human and animal strains of *T. cruzi* that originated from Argentina and neighboring countries. The standardized serologic procedures used by all laboratories from 1981 to 1993 were previously described.[9] Seroreactivity for *T. cruzi* was demonstrated by IHA and IFA titers $\geq$ 32. These tests have a sensitivity of 99% and a specificity of 98%, giving cross-reactions with *Trypanasoma rangeli* (not yet detected in Argentina) and *Leishmania* sp.[23] Samples reactive by both tests were considered seropositive. However, in case of discordant results between techniques a new blood sample was taken and the tests were repeated. In cases of new discordant results, these individuals were considered seronegative for *T. cruzi*. All seropositive individuals were excluded from military service.

Quality control procedures were indispensable for such a long-term program that included numerous and widespread laboratories. The aim of this program was to improve the performance of the participating laboratories and assess the reliability of the serologic results. Quality control procedures were based on the agreement of serum panel results submitted for confirmation to INDIECH by all participating laboratories from 1981 to 1986.[24] The quality control program included: 1) internal quality control tests, in which positive and negative control sera were monitored on a daily basis, and 2) external quality control, consisting of proficiency tests with unknown positive and negative control sera provided by the national reference center, and confirmation of serum results submitted to the national reference center by the participating laboratories. These proficiency and confirmation tests were carried out annually before the mass serologic screening; probable sources of error were identified and implementation of corrective measures were introduced when necessary.[24] In cooperation with the neighboring countries, the national reference center has been coordinating an international reference serum panel for the control of Chagas' disease serology since 1993.

Entomology. Triatomine surveys were carried out in every province as part of their ongoing programs. Skilled teams from the Chagas′ Control Services visited each house and searched for domiciliary *Triatoma infestans* before and after spraying the roof and walls with 0.2% tetramethrin, totaling 30 min per house (one person–hour per house). At some provinces (Salta and Jujuy), most of these searches were carried out by primary health care agents and did not use a flushing-out agent.

Statistical analysis. The relationship between seropositivity for *T. cruzi* (SEROPOS, the dependent variable) and survey year was studied by maximum likelihood logistic multiple regression analysis using the logistic-binomial model for indistinguishable data from EGRET software.[25] Logistic regression analysis was preferred to standard linear regression because the data for *T. cruzi* infection are binary for an individual person, and for a sample of persons yield fractions between 0 and 1 that tend to have a binomial distribution. Seropositivity was indexed as 1 and seronegativity as 0. Survey years were enumerated from 1 to 13.

RESULTS

Nearly 1.8 million men 18 years of age were examined for antibodies to *T. cruzi* from 1981 to 1993 (Appendix 1). The sampling fraction among provinces varied little over years except for 1990–1991, when a significantly greater proportion of all recruits came from the Province and City of Buenos Aires. After a seropositivity rate of 10.1% was determined for recruits examined in 1965–1969 (as determined by IHA and complement fixation tests), a highly significant decrease occurred in the overall prevalence of seropositivity for *T. cruzi* from 5.8% in 1981 to 1.9% in 1993 (Figure 1), as determined either by a logistic regression (SEROPOS = −2.717–0.0848 × YEARS, standard error (SE) of intercept = 0.007, SE of coefficient = 0.0012, χ^2 = 5533.8, degrees of freedom (df) = 1, $P < 0.0001$) or a linear regression analysis (SEROPOS = 0.0595–0.00369 × YEARS, SE of intercept = 0.00315, SE of coefficient = 0.00040, F = 72.2, df = 1 and 11, $P < 0.0001$). These prevalence rates of seropositivity for *T. cruzi* were mistakenly taken as incidence rates of *T. cruzi* infection elsewhere.[11,12]

The time series of cross-sectional surveys shows apparent

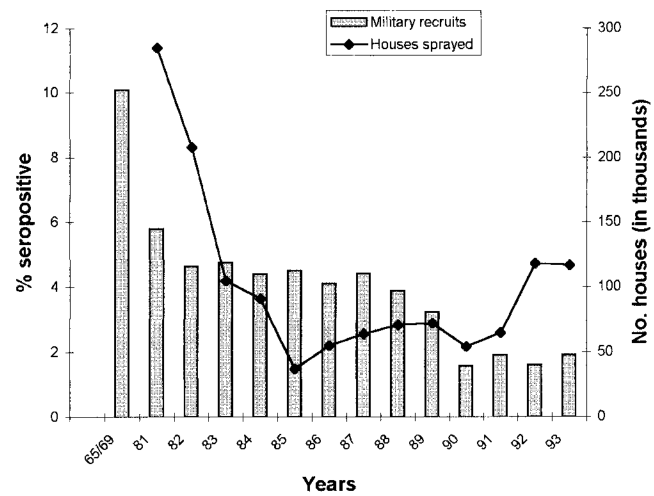

FIGURE 1. Prevalence rate of seropositivity for *Trypanosoma cruzi* in young men summoned for military service and annual rate of insecticidal sprays between 1965 and 1993 in Argentina.

deviations from a linearly decreasing trend (Figure 1). After a marked decrease from 1981 to 1982, overall seropositivity rates were nearly constant around 4.5% until 1987 and then showed a steady decrease until 1990, in which they stabilized at nearly 1.8%. The annual rate of insecticidal treatments decreased from 216,000–300,000 sprays in 1978–1981 to nearly 37,000 sprays in 1985, and then increased to nearly 120,000 sprays in 1993, although with a decrease in 1990–1991 as a consequence of the 1989 economic crisis. The annual rate of spraying surpasses the actual number of different houses sprayed because according to the control program guidelines, houses would have to be sprayed twice in the same year when BHC was used.

The overall temporal decrease of seroprevalence for *T. cruzi* by geographic region and province between 1981 and 1993 was heterogeneous (Figure 2), as determined by logistic regression analysis (Table 1). For comparison, Figure 2 also shows the prevalence of seropositivity in 1965–1969 as isolated points on the left of each graph. In Patagonia, with very low or null domiciliary infestations, seropositivity rates decreased from the 2.2–6.0% range in 1981 to less than 1.6% in 1993 (Figure 2A). This reduction was due mostly to highly significant decreases in Río Negro, Neuquén, and Chubut ($P < 0.001$), while Santa Cruz ($P = 0.52$) and Tierra del Fuego ($P = 0.08$) showed no statistically significant differences over this period of time. The seropositivity rates of recruits from the City and the Province of Buenos Aires, where established domiciliary infestations had not been detected, decreased in a highly significant way from 2.3–2.5% in 1981 to 0.7% in 1993 (Figure 2B). Seropositivity rates from the neighboring provinces of Córdoba and Santa Fé showed a highly significant decreasing trend throughout, although with a clearly anomalous estimate for Santa Fé in 1986. In the northeastern provinces (Misiones, Corrientes, and Entre Ríos), which usually had lower domiciliary infestation rates than other northern provinces, the period seropositivity rates showed a statistically highly significant decreasing trend, though with irregular fluctuations in Entre Ríos and Corrientes (Figure 2C). All northwestern provinces

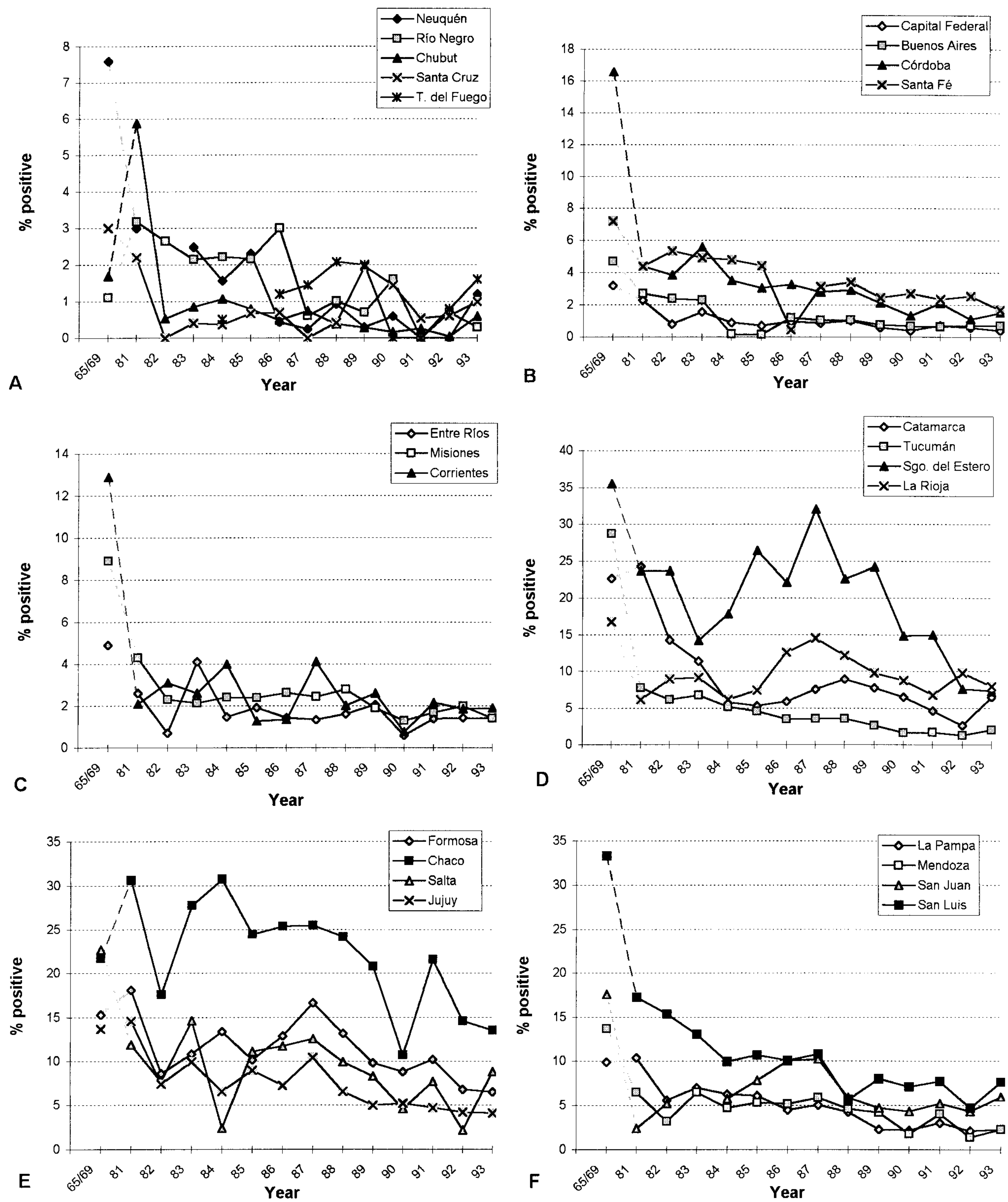

FIGURE 2. Province-specific prevalence rate of seropositivity for *Trypanosoma cruzi* in young men summoned for military service according to geographic area between 1981 and 1993 in Argentina.

TABLE 1

Logistic regression analysis of seropositivity rates for *Trypanosoma cruzi* in military recruits according to source province, Argentina, 1981–1993

Province	Intercept	SE of intercept	Coefficient	SE of coefficient	χ^2	*P*
Triatomine control program started in 1961–1962						
Santa Fé	−2.7900	0.0240	−0.0873	0.0044	417.5	<0.001
Chaco	−0.9005	0.0184	−0.0439	0.0034	166.6	<0.001
Córdoba	−2.8690	0.0260	−0.0989	0.0049	441.3	<0.001
Catamarca	−1.4664	0.0436	−0.1512	0.0085	371.4	<0.001
Salta	−2.1133	0.0303	−0.0309	0.0053	35.2	<0.001
Jujuy	−1.9492	0.0371	−0.0953	0.0070	202.6	<0.001
Tucumán	−2.3365	0.0325	−0.1393	0.0071	424.1	<0.001
Santiago del Estero	−1.2156	0.0209	−0.0155	0.0037	18.0	<0.001
La Rioja	−2.4649	0.0549	0.0238	0.0078	9.3	0.002
San Juan	−3.2582	0.0478	0.0630	0.0071	76.4	<0.001
San Luis	−1.5744	0.0440	−0.1001	0.0075	193.1	<0.001
Triatomine control program started in the 1970s						
Buenos Aires	−3.6760	0.0190	−0.1473	0.0037	1796.7	<0.001
Entre Ríos	−3.7212	0.0536	−0.0445	0.0081	31.3	<0.001
Misiones	−3.3870	0.0519	−0.0558	0.0092	38.3	<0.001
Corrientes	−3.5476	0.0510	−0.0232	0.0082	8.1	0.005
Formosa	−1.8950	0.0394	−0.0269	0.0066	16.8	<0.001
La Pampa	−2.2077	0.0606	−0.1293	0.0111	156.6	<0.001
Mendoza	−2.6947	0.0294	−0.0589	0.0049	151.8	<0.001
Neuquén	−3.3208	0.1088	−0.1923	0.0190	120.6	<0.001
Río Negro	−3.1453	0.0819	−0.1785	0.0150	166.6	<0.001
Without triatomine control program						
Chubut	−3.1805	0.1077	−0.2959	0.0262	195.5	<0.001
Santa Cruz	−5.0571	0.2974	−0.0231	0.0364	0.4	0.520
Tierra del Fuego	−5.6907	0.6893	0.1170	0.0698	3.0	0.085
Ciudad de Buenos Aires	−3.9695	0.0468	−0.1221	0.0090	206.5	<0.001

showed statistically significant decreases in seropositivity rates except La Rioja, where a significant increasing trend ($P = 0.002$) occurred (Figure 2D). In the neighboring provinces of Santiago del Estero and Catamarca, the seropositivity rates started from nearly 24% in 1981 to reach 6% in 1993 but with quite contrasting trajectories (Figure 2D). Other northern provinces (Salta, Jujuy, Formosa, and Chaco) experienced a highly significant decreasing trend in seropositivity rates (Figure 2E). In western and central provinces, seropositivity rates for military recruits from San Luis, La Pampa, and Mendoza exhibited highly significant decreasing trends while those from San Juan showed a highly significant increase with a peak in 1987 (Figure 2F).

The logistic regression coefficients for each province give an indication of the impact of the control program on the seropositivity rates of each province's recruits (Table 1). Two of the 11 provinces that started the program in 1961–1962 showed a significant increase in seropositivity rates, whereas the nine provinces that started actions in the early 1970s experienced significant decreases. In spite of the difference of 10 years between the onset of actions in both groups, regression coefficients were not significantly different between groups (*t* test for independent samples = 1.12, df = 18, $P = 0.28$).

Table 2 shows the province-specific distribution of prevalence rates of seropositivity for *T. cruzi* in military recruits examined in 1965–1969 (born in 1944–1948 prior to the existence of any control action), 1981, and 1993. Comparison between 1981 and 1993 seropositivity rates yielded either highly significant ($P < 0.001$) or significant ($P < 0.01$) reductions in all provinces except Corrientes, La Rioja, and

TABLE 2

Prevalence rates of seropositivity for *Trypanosoma cruzi* infection in 18-year-old men from Argentina drafted into military service in 1965–1969, 1981, and 1993

Provinces	Percentage of seropositive men			*P*†
	1965–1969*	1981*	1993	
Buenos Aires	3.2	2.5	0.4	<0.001
City of Buenos Aires	4.7	2.3	0.7	<0.001
Catamarca	22.7	24.3	6.5	<0.001
Córdoba	16.6	4.4	1.5	0.001
Corrientes	12.9	2.1	1.9	NS
Chaco	21.7	30.6	13.5	<0.001
Chubut	1.8	6.0	0.6	<0.001
Entre Ríos	4.9	2.6	1.4	<0.001
Formosa	15.3	18.1	6.5	<0.001
Jujuy	13.7	14.6	4.1	<0.001
La Pampa	9.9	10.4	2.3	<0.001
La Rioja	16.8	6.2	8.0	NS
Mendoza	13.7	6.5	2.3	<0.001
Misiones	8.9	4.3	1.4	<0.001
Neuquén	7.6	3.0	1.2	<0.001
Río Negro	1.1	3.3	0.3	<0.001
Salta	22.7	11.9	8.8	0.01
San Juan	17.6	2.4	5.9	<0.001
San Luis	33.3	17.3	7.6	<0.001
Santa Cruz	3.0	2.2	1.0	NS
Santa Fé	7.2	4.4	1.7	<0.001
Santiago del Estero	35.5	23.7	7.3	<0.001
Tucumán	28.7	7.8	2.0	<0.001
Tierra del Fuego	ND	ND	1.6	ND
Total	10.1	5.8	1.9	<0.001

† χ^2 test with one degree of freedom comparing 1981 and 1993. NS = not significant; ND = not done.
* Data taken from published sources.[3,9,18,21]

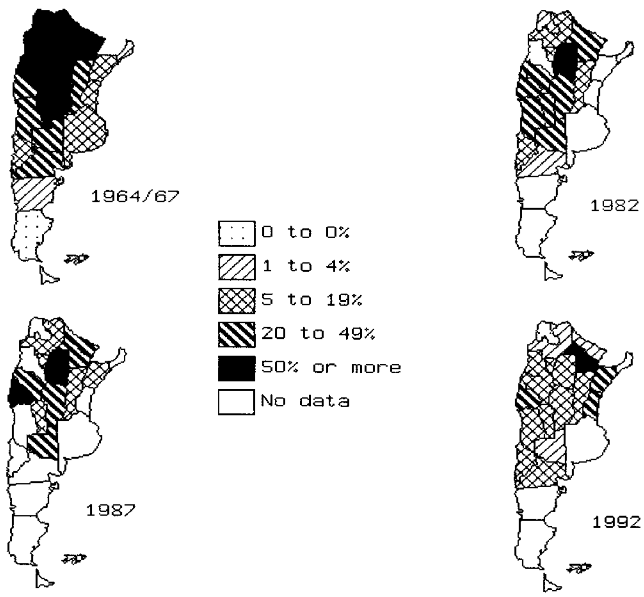

FIGURE 3. Province-specific domiciliary infestations by *Triatoma infestans* between 1964 and 1992 in Argentina. Data sources: 1964–1967,[3] and Servicio Nacional de Chagas, Córdoba, Argentina (Segura EL, unpublished data).

Santa Cruz ($P > 0.05$), and a statistically highly significant increase in San Juan from 2.4% to 5.9% ($P < 0.001$). In recruits examined in 1981 who had been born in 1963, high seropositivity rates surpassing 10% were observed in eight provinces. Of recruits examined for antibodies in 1993 who had been born in 1975, only those from Chaco still showed seropositivity rates greater than 10%, while recruits from seven provinces had seropositivity rates that ranged from 5% to 10%.

Three years after the start of the control campaign, in 1964–1967, 15 (68%) of 22 provinces within the distribution range of *Triatoma infestans* had high (> 20%) prevalence rates of domiciliary infestation (Figure 3). The number of provinces with a high rate of domiciliary infestation decreased to 9 (41%) provinces in 1982, 7 (32%) provinces in 1987, and 4 (18%) provinces in 1992. The total number of houses inspected for evidence of domiciliary infestation was 2,716 between 1964 and 1967[3] (Carcavallo RU, unpublished data), 185,233 houses in 1982, 52,347 houses in 1987, and 391,389 houses in 1992. The province-specific prevalence of infestation by *Triatoma infestans* in 1982 correlated positively and significantly with seropositivity rates in every survey year (range of correlation coefficients, $r = 0.50–0.77$, $n = 16$, $P < 0.05$), except in 1981 and 1983, which were marginally significant ($0.05 < P < 0.1$). Infestation in 1987 was significantly and positively correlated with seropositivity rates only in 3 of the 13 cross-sectional surveys, whereas infestation in 1992 showed no significant correlation with any survey.

DISCUSSION

This study unequivocally demonstrates a marked decrease in the overall prevalence rates of seropositivity for *T. cruzi* in young men from Argentina, and shows that the decrease has been heterogeneous among and within regions over time. Most of the decrease in the seropositivity rates of 18-year old men may be attributed to insecticidal sprays against *Triatoma infestans* because: 1) There was a statistically significant positive correlation between the province-specific prevalence rates of domiciliary infestation by *Triatoma infestans* in 1982 and seropositivity for *T. cruzi* in military recruits, which gives support to a causal relationship between both variables. 2) Screening of potential blood donors for antibodies to *T. cruzi* was initiated in 1963–1964 (when the 1981 cohort was born) and achieved almost complete coverage of blood banks in the early 1980s. Furthermore, individuals < 18 years of age usually constitute a very small fraction of the patients receiving blood transfusions. These facts suggest that all the study individuals were exposed to a reduced and decreasing likelihood of acquiring *T. cruzi* infection via infected blood. 3) Control of congenital transmission of *T. cruzi* at some large hospitals and maternities was started in 1992; therefore, this program could not have affected the risk of vertical infection of the cohorts born prior to this specific program. 4) Transmission of *T. cruzi* infection through organ transplants is of marginal occurrence.

Demographic changes over decades may confound or modify the long-term effects of a nationwide control program. Although housing, working, and living conditions in some of the affected rural areas experienced visible improvements over the three decades (1960–1990) relevant to this study, such changes have been relatively slow and heterogeneous among and within provinces. For example, the nationwide number of houses with roofs or walls that may favor triatomine infestation (adobe, mud-stick, wood, thatch) increased 1.7 times from 1960 to 1991 (from 440,000 to 813,000 houses), while the human population increased proportionally by a factor of 1.85 (from 20 to 34 million) in the same period.[26,27] Among the most affected northern and western provinces, with high fertility rates and high rates of pre-adult or adult migration to other provinces, the size of the human populations was fairly stable in 1960–1970, and increased thereafter.[28] The observed tendency of rural inhabitants to migrate to urban centers over time[28,29] probably exerted a greater impact on the age structure of the rural populations left behind than on their size because most of the migrants were 15 years of age or older. Rural communities in northern Argentina were, and still are, composed of many school age children and few working age adults, many of whom migrate seasonally or transiently to other areas for temporal jobs. It is fairly common that rural families in need receive some regular economic support from their first-degree relatives employed elsewhere. Therefore, the long-term decrease in seropositivity rates for *T. cruzi* cannot be attributed to significant and mass improvements in housing conditions or to rapidly decreasing populations in the affected rural areas.

Demographic factors may also help explain some of the patterns observed. Internal migrations from the impoverished northern provinces to Buenos Aires (City and Province) and Patagonia in search of permanent jobs and more resourceful environments undoubtedly explain the persistent detection of seropositive men in areas without domiciliary infestation. These migratory flows were important since

1947 to the 1970s (particularly those headed for Patagonia in the 1960s and 1970s), but only comprised 8% (in 1965–1970) or 6% (in 1975–1980) of the total Argentine population at those times, and only one-third of the migrants originated from rural areas.[28] Most of the inter-provincial migrants were men between 15 and 44 years of age, an age class that shows high rates of seropositivity for *T. cruzi* at the source provinces. The available evidence is still insufficient to assess whether people infected with *T. cruzi* have an increased odds of emigrating to other provinces. The overall temporal decrease in seropositivity rates in Buenos Aires and the southernmost Patagonian provinces may therefore reflect the decreasing likelihood of *T. cruzi* infection at the source provinces that fed the migratory flow.

The study subjects comprised unselected cohorts regarding place of residence, exposure to triatomines, and health or socioeconomic status, and thus constituted a representative fraction of each provincial population. Individuals judged to be in an unhealthy state at the general survey were excluded after examination, not before blood samples were taken. Military recruits were summoned according to their permanent residence place at the age in which they obtained their identity cards (16 years old), regardless of their address at the time of the draft. At a province-wide spatial scale and with such large sample sizes, small discrepancies between places of birth or permanent residence and reconnaissance center may be negligible for detecting time trends. The reduction in the total number of recruits since 1985 did not produce any selection bias because those finally summoned were randomly selected from each cohort according to their identity card number. The province-specific sampling fraction of each cohort was almost constant over the study years, with the exception of 1990 and 1991, in which a proportionally greater number of recruits from the City and Province of Buenos Aires was examined as a consequence of the 1989 economic crisis and subsequent budget constraints. Since many community-wide studies failed to obtain significant evidence of a gender-specific greater risk of infection with *T. cruzi* in bivariate[30,31] or multivariate analyses,[32] we believe that the present results for young men may be generalized to each complete birth cohort.

Our study gave detailed attention to the design of a quality assurance program to warrant the reliability of the serodiagnoses carried out at 39 laboratories over more than a decade. In spite of such controls and the observed good performance of the laboratory network, the time series of seropositivity rates presented some outlying, suspect values (Salta in 1984, Santa Fé in 1986) that remain unexplained. Regarding the entomologic information, domiciliary infestation estimates of *Triatoma infestans* did not arise from a random sample of localities or houses, but as part of regular program operations focusing on affected rural areas within operational feasibility by each provincial program. In addition, some provinces (Salta and Jujuy) did not use the standard method of timed manual capture, which makes the assessments not directly comparable among provinces over the years. Therefore, the entomologic indices should be taken as gross, possibly biased indices of domiciliary infestation.

Age-prevalence curves obtained at 13 rural areas from seven Argentine provinces[6] or Brazil[30] suggest that most cases of *T. cruzi* infection are produced before the age of 20 years, possibly at a constant or slightly decelerating rate. For example, seropositivity rates for *T. cruzi* in 18 year old men reached nearly 70% in the most affected rural departments of the Chaco province in 1981.[33] Longitudinal studies have documented a shift to the right of the age-specific seroprevalence curves both for humans[5] and dogs[34] infected with *T. cruzi* after effective control measures against triatomines were undertaken. In theory, therefore, the effects of such actions on cohort-seropositivity rates should become apparent without the need of a latent or waiting time.

Results of each annual serologic evaluation of military recruits was immediately available to chief officers of the provincial control programs and health authorities, and might have been helpful to monitor the expected effects of past actions and target more precisely current control actions. However, in the context of a disorganized decentralization of the national control program, the dominant scenario since the late 1970s was lack of political decision and sufficient funding to sustain insecticiding operations and set up the planned vigilance phase. In the absence of further control actions after the attack phase with the modern pyrethroids, domiciliary reinfestation by *Triatoma infestans* most probably increased exponentially and renewed human transmission of *T. cruzi* occurred 3–4 years after intervention.[20] Reinfestation surely proceeded even more rapidly with organo-chlorine insecticides in the past. Therefore, the results of the present study mostly reflect the impact of a control campaign in which little or no sustained surveillance against domiciliary reinfestation was carried out. The more distant the community, the less likely that the control teams would repeat insecticidal sprays in due time, likely leaving behind less protected areas in which human transmission of *T. cruzi* resurged in a few years. Notwithstanding these shortcomings, control actions exerted a highly significant impact on seropositivity rates, probably because vector-mediated transmission of *T. cruzi* to humans is relatively inefficient and requires high density infestations.[35] The irregularity of control actions likely resulted in the irregular fluctuations in seropositivity rates at some provinces. Such lack of sustainability, especially in large provinces with dispersed rural populations, set a limit to the decrease of seropositivity rates and prompted a revised control strategy in which the attack and vigilance actions were carried out with community participation.[36,37]

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APPENDIX 1

Annual number of military recruits examined for antibodies to *Trypanosoma cruzi* in Argentina, 1981–1993*

Provinces	Survey year												
	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993
Ciudad de Buenos Aires	16,239	15,406	15,792	15,594	17,775	8,238	8,521	7,985	12,323	4,326	6,132	3,978	5,530
Provincia de Buenos Aires	79,425	79,931	75,182	78,714	82,447	41,512	43,640	42,173	58,631	22,952	28,734	26,265	32,266
Entre Ríos	8,196	4,700	4,535	8,341	8,481	3,984	3,920	4,039	5,569	692	3,155	3,682	5,514
Misiones	5,726	6,384	6,149	6,704	6,618	3,363	3,290	3,248	4,110	224	1,704	1,685	1,779
Corrientes	6,648	4,913	6,968	7,028	7,237	3,382	3,790	3,697	4,263	533	2,031	2,469	2,219
Santa Fé	18,698	18,914	18,986	19,012	19,145	8,282	8,362	8,650	13,032	2,977	4,992	4,900	4,726
Formosa	1,538	3,250	3,242	3,648	3,768	1,514	1,553	1,809	2,480	285	510	575	790
Chaco	7,141	7,541	7,114	8,086	8,213	3,013	3,044	3,149	4,394	457	421	874	1,330
Córdoba	16,906	19,092	18,188	18,680	19,930	8,792	9,066	9,357	12,086	2,331	4,454	4,416	4,874
Catamarca	2,158	2,049	2,098	2,067	2,222	906	1,084	1,156	1,493	325	563	691	1,084
Salta	4,104	6,317	6,508	6,494	7,128	3,214	2,783	2,876	4,555	887	1,044	1,118	1,075
Jujuy	3,778	3,710	3,819	3,934	4,038	1,656	1,652	1,849	2,772	518	835	930	1,082
Tucumán	8,796	8,759	8,678	8,417	9,412	4,013	4,547	4,623	5,686	616	632	1,040	636
Santiago del Estero	5,963	6,305	6,382	6,173	6,616	3,138	3,034	3,192	4,158	431	709	723	1,298
La Rioja	1,625	1,716	1,706	1,656	1,690	794	850	867	1,274	429	278	633	1,094
La Pampa	1,745	1,782	1,827	1,740	1,803	966	946	826	1,242	181	510	1,026	1,292
Mendoza	9,921	9,617	9,205	8,419	9,607	4,376	5,179	5,507	7,151	1,456	3,597	3,701	4,023
San Juan	4,635	4,285	4,115	4,036	3,948	1,930	2,145	2,375	2,827	725	689	980	1,054
San Luis	1,873	1,904	1,888	1,808	2,066	855	1,008	1,099	1,558	778	731	696	935
Neuquén	2,005	510	2,049	2,370	2,375	1,142	1,249	1,296	2,184	333	2,051	2,630	2,161
Río Negro	3,074	1,060	3,230	2,348	3,224	1,405	2,021	1,972	2,435	638	1,779	2,213	2,415
Chubut	2,065	2,475	2,459	2,240	2,139	1,245	858	1,324	1,719	639	1,552	2,308	1,948
Santa Cruz	356	372	448	834	897	1,676	352	473	668	69	556	815	699
Tierra del Fuego	ND	118	167	195	188	83	207	144	196	19	141	261	244
Total	212,615	211,112	210,735	218,518	231,167	109,488	113,104	113,686	156,806	42,821	67,800	68,609	80,068

* ND = not done.