The Initiatives for the control of Chagas disease in the Americas and in non-endemic countries: overview and perspectives

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ASBTRACT

Multinational Initiatives for the control of Chagas disease exist in the Southern Cone Countries, the Andean Countries, Central America and Mexico, the Amazon Region, and the Non-Endemic Countries. These international efforts allowed for huge advances in the prevention of vector-borne and transfusion-related Chagas disease transmission. However, major challenges lie ahead, including: (I) to foster or re-establish political priority for Chagas disease; (II) to enhance international co-ordination and evaluation of national programs through the Initiatives; and (III) to define and enforce quality standards for all preventive actions. Priority must be given to vector control and patient care, including specific treatment for acute cases and chronic patients up to 15 years old.

Key-words: Chagas disease. Prevention. Multinational initiatives.

RESUMO

As Iniciativas Multinacionais para o controle da doença de Chagas existem nos países do Cone Sul, nos países Andinos, na América Central e México, na Região Amazônica e nos Países Não-Endêmicos. Estes esforços internacionais permitiram enormes avanços na prevenção da transmissão vetorial e transfusional da doença de Chagas. Contudo, quedam grandes desafios pela frente, incluindo: (I) o estímulo ou re-estabelecimento da prioridade política para a doença de Chagas; (II) o reforço da coordenação internacional e da avaliação dos programas nacionais através das Iniciativas; e (III) a definição e implementação efetiva dos padrões de qualidade para todas as ações preventivas. Deve se conceder prioridade ao controle vetorial e ao cuidado dos pacientes, incluindo o tratamento específico dos casos agudos e dos pacientes crônicos de até 15 anos de idade.

Palavras-chaves: Doença de Chagas. Prevenção. Iniciativas multinacionais.

THE SOUTHERN CONE INITIATIVE

The Ministers of Health of Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay met in Brasilia in July 1991 to discuss zoonotic disease control strategies. They issued Resolution 04-3-CS, by which they created an "Inter-Governmental Commission for Chagas disease, with a PAHO Secretariat, for the design of a sub-regional program and plan for action aimed at the elimination of domestic *Triatoma infestans* and the interruption of *Trypanosoma cruzi* transmission by blood transfusion. This endeavor should take particularly into consideration each national context and extant national plans, and the inter-country technical co-operation mechanisms; it must be ready within a six-month period"[3].

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The goals of this sub-regional Southern Cone Initiative (INCOSUR) were:

1. Elimination of *T. infestans* from houses and peridomiciles in endemic areas;
2. Reduction and elimination of domestic infestation by other triatomine species that co-occur with *T. infestans* in the same areas; and
3. Reduction and elimination of transfusional transmission through the strengthening of the Blood Bank Network and the effective screening of donors.

Vector elimination interventions were scheduled over 10 years. These included quarterly campaigns of residual insecticide spraying from the first year on (attack phase) complemented by epidemiological and entomological surveillance operations and by serological monitoring of the infection status of the population. Such surveillance activities were designed to be permanent, and therefore require active community participation. Insecticide spraying was to be resumed whenever household re-infestation was detected[4].

The first meeting of the Inter-Government Commission (IC) was held in Buenos Aires, Argentina, in 1992. The excellence of the work carried out up to that date was underscored. From August 1991, the Southern Cone countries set up their national programs for the 1992-1995 period and prepared action plans for 1992. In most countries, political will for the interruption of Chagas disease transmission by the two main routes was mirrored by the provision of local funds for the effecting of prevention and control activities[4]. Spraying interventions were also scheduled in each country to attain the intermediary aim of interrupting vector-borne *T. cruzi* transmission. The following numbers of Domiciliary Units (DUs) were to be sprayed: in Argentina, 746000; in Bolivia, 875000; in Brazil, 4532600; in Chile, 328500; in Paraguay, 350000; and in Uruguay, 24500. This constituted the baseline for the ascertainment of future treatment needs for households and their peridomestic areas[5].

The second IC meeting took place in Santa Cruz de la Sierra, Bolivia, in 1993; official national representatives were joined by a delegate of the Peruvian Ministry of Health, by PAHO-WHO officials, and by staff of several International Cooperation Agencies. The aim of this meeting was to assess activities and progress in relation to the proposed aims and objectives[6].

The third IC meeting was held in Montevideo, Uruguay, in March 1994; activities carried out during 1993 were reviewed vis a vis the goals defined by the countries for the elimination of *T. infestans* and the interruption of transfusional transmission of *T. cruzi*[6].

The fourth meeting took place in Asunción, Paraguay, in 1995. In addition to assessing activities carried out in 1994, sub-regional and country action plans for 1995 were discussed. Two intermediary goals were also defined for the Initiative: the interruption of (I) vector-borne and (II) transfusional transmission of *T. cruzi*[7].

Progress made during 1995 in each country and at the sub-regional level was appraised in the fifth IC meeting in Porto Alegre, Brazil, 1996. For the first time in the Initiative, and in accordance with previous agreements, the results of international evaluations that had taken place in Chile and Brazil were discussed. The renewed presence of Peruvian representatives in the IC meetings was also of note[8].

Santiago de Chile was chosen as the venue of the 1996 IC meeting; Chilean public health officials underscored that Chagas disease, the last major tropical disease still prevalent in the country, had been considered as a national priority for years. In addition to reviewing vector control interventions, the efforts Chile had made towards a more effective and efficient blood bank safety system were highlighted. As for previous meetings, the following activities were undertaken: (I) critical review of country activities with regard to the goals of eliminating *T. infestans* and interrupting transfusional transmission of *T. cruzi*; (II) analysis of the degree to which the conclusions and recommendations from the 1995 meeting had been achieved; (III) specify working targets aimed at the consolidation of previous achievements; (IV) appraise international evaluations carried out in Argentina, Brazil, Bolivia, Chile, and Paraguay; and (V) establish a new information system that would be operational between 1997 and 2000.

Later IC meetings confirmed the success of the Initiative. By 1997 all Southern Cone countries had passed legislation making the serological screening of blood bank donors for anti-*T. cruzi* antibodies compulsory. Uruguay achieved interruption of *T. cruzi* transmission by *T. infestans* in 1997. *T. infestans* was not completely eliminated, but residual foci are so small that the likelihood of *T. cruzi* transmission to humans is extremely low. Similar realizations were achieved in Chile in 1999 and in Brazil by 2006. Transmission of *T. cruzi* by *T. infestans* was also interrupted in five Argentinean provinces and in the Oriental Region of Paraguay.

THE NEW INITIATIVES

Chagas disease control in the Initiative of the Andean Countries

The Initiative of the Andean Countries (IPA) was officially launched in 1997; Venezuela, Colombia, Ecuador, and Peru participate. The high ecological diversity of the Andean sub-region is reflected in the diversity of triatomine vector species; this poses particularly difficult challenges for the control of vector-borne Chagas disease. **Table 1** presents a summary of the distribution, biology, and vector status of each species.

Rhodnius prolixus is the principal domestic vector in Venezuela; it maintains sylvatic populations in palm trees of the Llanos and some Andean states, and re-infestation of treated households is therefore a continuing challenge for disease control. *T. maculata* is a secondary domestic vector in some areas of the country. In Colombia, the main goal of the control program is the interruption of transmission by *R. prolixus* in priority areas that were defined after confirmed records of domestic disease transmission. In some regions, *T. dimidiata* and, to a lesser extent, *R. pallescens* are candidate vectors. In Ecuador, vector control is aimed at eliminating *T. dimidiata*, which was artificially introduced into the coastal region; additionally, domestic *R. ecuadoriensis* populations are of concern across the Western coast and the Southern inter-Andean valleys. This species is also present in households in Northern Peru, but these populations are genetically distinct and can be targeted independently from those in Ecuador – except in the immediately adjacent areas along the border. *P. herreri* is another locally important vector, particularly in the Marañón River Valley. In Southern Peru, the elimination of *T. infestans* populations is the main priority.

In spite of recent progress in vector control across the sub-region, the capacity to assess the actual efficacy of interventions is limited by the lack of systematic, standardized information from national vector control programs. An effort must be made to improve the quality of the data and foster the dissemination of information; otherwise, progress is hard to measure and the impact of vector control interventions cannot be quantified. Only one Peruvian department, Tacna, has documented progress in the elimination of *T. infestans* that may justify an evaluation of the interruption of *T. cruzi* transmission by that species.

On the other hand, entomological research on Chagas disease vectors has considerably advanced over the last decades (**Table 1**). The main contribution of these investigations to disease control efforts has been the definition of priority intervention areas. It must be stressed that concentrating operational resources in such areas could greatly enhance the efficacy and efficiency of control programs.

Serological screening of blood donations to detect *T. cruzi* infection is now mandatory in all IPA countries.

Chagas disease control in the Initiative of the Amazon Countries

Chagas disease has traditionally been considered as an enzootic condition involving wild mammals and vectors; this fact dates back to the first description, by Carlos Chagas himself, of *T. cruzi* infections in squirrel monkeys (*Saimiri sciureus*). H. Floch described the first human cases in French Guyana, and J.J. Shaw and coworkers later reported the first acute cases in Amazonian Brazil[1]. Since then, hundreds of acute cases have been described in all Brazilian states within Amazonia. Many of them were related to family outbreaks likely due to oral transmission, but a similar number of isolated cases, without any apparent relationship with food-borne outbreaks, has been reported. This suggests that the invasion of households or food-processing sites by adventitious adult triatomines is the most widespread and important mechanism of *T. cruzi* transmission in Amazonia. This idea receives support from further cases recorded throughout the region, including Guyana, Surinam, Venezuela, Colombia, Peru, Ecuador, and Bolivia. In addition, discrete foci of domestic vector populations have been documented in Venezuela, Brazil, Peru, and Bolivia.

Chagas disease in Amazonia can therefore be conceptualized as fitting one of the following patterns:

1. A zoonotic disease that is accidentally transmitted to humans when they become exposed to forest environments where infected sylvatic vectors naturally occur;
2. A professional hazard of forest extractivist workers, mainly those engaged in *Leopoldinia piassaba* palm fiber collection; these workers, often accompanied by their families, spend months in precarious huts within natural *piassaba* palm stands, where they are routinely attacked by triatomines of the species *Rhodnius brethesi*;

TABLE 1 - Chagas disease vectors in the Andean countries

Vector status	Species	Notes
Main vectors	*Rhodnius prolixus*	• Native in the Colombian-Venezuelan Llanos • Introduced in Northwestern Colombia and the Magdalena Valley (elimination possible)
	Triatoma dimidiata	• Native in Northern Colombia and Venezuela • Introduced in the Ecuadorian coast (elimination possible)
	Rhodnius ecuadoriensis	• Highly variable species • A domestic vector in the Ecuadorian coast and inter-Andean valleys and in the Northern Peruvian Andes • Ecuadorian and Peruvian forms are genetically distinct (i.e., they can be targeted independently by control actions)
Locally important vectors	*Triatoma carrioni*	• Domestic in the valleys and highlands of Southern Ecuador and Northern Peru • Seems to be a highly efficient vector
	Triatoma venosa	• Domestic in parts of Colombia
	Triatoma maculata	• Domestic in parts of Venezuela (and in Roraima, Brazil)
	Panstrongylus herreri	• Domestic in the Marañón River Valley, Peru
	Panstrongylus chinai	• Domestic in valleys of Southern Ecuador and Northern Peru
	Panstrongylus howardi	• Domestic in the central coast of Ecuador
Occasional and non-domiciliated vectors	*Panstrongylus geniculatus*	• Very wide distribution • Frequently invades households • May occasionally colonize in or around houses
	Panstrongylus rufotuberculatus	• Very wide distribution • May occasionally colonize in houses
	Rhodnius pallescens	• Colombia and Central America • Invades houses (evidence of disease transmission in Panama) • May very rarely colonize in or around houses
	Rhodnius colombiensis	• Magdalena Valley, Colombia • May very rarely colonize in or around houses
	Triatoma nigromaculata	• Occasionally domestic or peridomestic in the Colombian-Venezuelan Llanos
	Rhodnius pictipes	• Amazonia • Invades houses very frequently (sporadic transmission likely)
	Rhodnius robustus	• Amazonia • Invades houses very frequently (sporadic transmission likely) • Several cryptic species; no data on the epidemiological importance of each taxon
	Rhodnius brethesi	• Amazonia • Transmission to *piaçava* palm fiber collectors
	Rhodnius stali	• Southwestern Amazonia (Bolivia and Brazil) • Domestic or peridomestic foci in Bolivia

3. An endemic disease that is transmitted constantly, albeit with a relatively low intensity when compared to areas with domestic vector colonies. Oral transmission by contaminated fruit juices or other foodstuffs seems to be the most frequent mechanism; its prevention strongly depends on standard food safety measures complemented by educational interventions targeting producers, handlers, traders, and consumers of potentially dangerous products. The importance of direct transmission mediated by contact between humans and infected adult vectors that invade houses is being increasingly recognized. *T. cruzi* detection in malaria blood smears is emerging as a useful means for understanding the importance of this mechanism of transmission in the epidemiology of Chagas disease in the Amazon. Thus, recent data from Amazonian Brazil are compatible with an estimate of 2000 new cases of the disease in 2009 (that is, an incidence of about 10 cases per 100,000 inhabitants), most of them attributable to this transmission route. Detailed studies revealed that in the Ecuadorian Amazon, where there are no confirmed cases of neither oral transmission nor domiciliated vectors, *T. cruzi* infection prevalence reaches 2.4%[1]; the age-class distribution of infection is strongly suggestive of continuous transmission and endemic disease.

Chagas disease in Amazonia was the subject of a first international expert meeting in Palmari, on the Brazilian-Peruvian border, in 2002[2], and subsequently in Manaus, Brazil, in 2004[9]. The Initiative for Surveillance and Prevention of Chagas disease in Amazonia (AMCHA) was officially launched in this latter meeting; Brazil, Colombia, Ecuador, Guyana, French Guiana, Peru, Suriname, and Venezuela participate in AMCHA. The main aim of the Initiative was defined as the prevention of the establishment of endemic, vector-borne transmission of the disease in the region. Three kinds of measures were proposed to reach this goal: (I) a basic surveillance scheme, (II) priority research lines, and (III) an international collaboration organizational framework. Even though there was no concrete definition of disease control strategies, substantial advances in epidemiological and entomological knowledge, as well as in the design and implementation of innovative surveillance schemes, particularly in Brazil and Ecuador, have followed since AMCHA launching[1].

Promoting Chagas disease control in Amazonia entails the strengthening of epidemiological and entomological surveillance; the following recommendations were made after AMCHA meetings:

1. Specific training of primary school teachers so that they can act as multipliers of knowledge about Chagas disease and its surveillance;
2. Active participation of schoolchildren (enrolled in activities developed after item 1) in entomological surveillance;
3. Training of malaria technicians in the identification of *T. cruzi* in microscope blood slides used in routine diagnosis within Malaria Control Programs, increasing the sensitivity and coverage of acute case detection. These technicians would also be able to check for natural infection in triatomines collected within households;
4. Serological surveys with sub-regional sampling, both in the general population and in extractivist forest workers such collector of as palm fiber and other plant products; thus, prevalence rates by sub-region and professional group could be established, aiding in risk mapping and resource allocation. Blood samples on filter paper could be gathered through malaria posts; once labeled, samples could be sent to local/regional reference labs by using the already functional quality control system for malaria slide reading;
5. Training of regional health staff in the diagnosis and treatment of acute Chagas disease, as well as in the management and/or referral of chronic and severe acute cases for diagnosis confirmation and specialized care whenever necessary.

Control of Chagas disease in the Central American Initiative

The epidemiological significance of Chagas disease in Central America was formally acknowledged in Resolution 13 of the Meeting of the Health Sector in Central America, held in Belize in September 1997. This Resolution states that control of Chagas disease is to be regarded as a priority in the region.

As a consequence of this Resolution, an international Meeting on Vectors of Chagas Disease was held in Tegucigalpa, Honduras, in October 1997; the main recommendation arising from this meeting was that a Multinational Initiative for the Interruption of Chagas Disease Transmission in Central Amarica be established. The main aims would be as follows:

1. Interrupting Chagas disease transmission by *Rhodnius prolixus*, which should be eliminated from the region;
2. Reducing household infestation rates by *Triatoma dimidiata*;
3. Interrupting transfusional transmission of *T. cruzi*.

In Guatemala, Government-led spraying interventions in 100% of domiciliary units in *R. prolixus* occurrence areas, carried out with support from the Japanese International Cooperation Agency (JICA), resulted in the interruption of transmission by this vector species by 2008. In El Salvador, housing improvements (mainly in walls and roofs of rural areas), together with malaria control interventions, seem to have resulted in the elimination of *R. prolixus* (and therefore of transmission mediated by this species), which has not been recorded in any of the recent entomological surveys across the country.

About 90% of the territory of Honduras is considered suitable for triatomine occurrence. However, house infestation seems to be only a major problem for neglected indigenous groups that live under extreme poverty. The main vectors are *R. prolixus* (domestic) and *T. dimidiata* (sylvatic). While the standard strategy for Chagas disease vector control entails three phases (basal entomological survey, household spraying, and surveillance), the Honduran Control Program devised a somewhat unorthodox approach to fit their specific needs and resource availability; it nonetheless resulted in large-scale operations allowing for the progressive coverage of most of the known range of *R. prolixus*. First, higher-risk areas are identified and stratified using historical data on vectors, household traits, or human infection. A rapid serological test (Stat-Pak) was then used to search for evidence of infection in a random sample of 30 schoolchildren of all communities within higher-risk areas. At the same time, educational activities took place that allowed for the detection of infestation foci with the aid of the schoolchildren, their families, and teachers. Whenever the rapid test results indicated a high proportion of reactive samples (>20%), suggesting a focus of active transmission, full serological surveys with ELISA on filter paper blood samples were conducted, together with systematic entomological surveys. If the initial rapid test was reactive in <20% of schoolchildren, only those with a reactive test were further tested by ELISA. Overall, this methodology allowed for the definition of priority areas, which were progressively expanded as new data became available, for the implementation of control measures in those areas, and for the detection of infected children (from 6 months to 13 years) who, after confirmatory diagnosis, were to be treated. Even if vector surveillance with community participation still needs strengthening, and comprehensive serological surveys in children under 6 years of age need to be conducted to establish whether there is transmission in high-risk areas, the advances achieved to date suggest that an evaluation of the possible interruption of transmission by *R. prolixus* could be conducted in 2010.

Such an evaluation is currently ongoing in Nicaragua, whereas *R. prolixus* is not known to occur in Costa Rica, Belize or Panama; its presence in southern Mexico is currently dubious. In all the countries of the region *T. dimidiata* is the main native vector; its proven ability to reinvade and reinfest treated households makes it necessary to implement continuous entomological surveillance systems. In Panama, invasion of houses by *R. pallescens* infesting peridomestic palm trees is common, and maintains disease transmission in the absence of vector domiciliation; this situation is similar to that identified in Amazonia, and may require similar approaches to surveillance and disease prevention.

Control of Chagas disease in European countries

The American population of European origin first arrived with the conquistadores, and a second major wave came about during the XIX century; it is estimated that over 10 million Spanish, Italian, and Portuguese immigrants arrived to Latin America between 1880 and

the 1950s. But from the 1960s on, political repression and economic factors forced millions to leave their Latin American homeland; looking for better opportunities, they migrated to the US, Europe and, to a lesser extent, Australia and Canada. Economic stagnation in the 1990s also resulted in a strong wave of emigration, this time preferentially towards Europe; this process, initially slow, was later stimulated by the strength of European economies during the early 2000s. Currently, over 3 million Latin American legal and illegal immigrants originating from countries where Chagas disease is endemic live in Europe. With them, Chagas disease turned into a problem that is also European.

Spain receives most of these Latin American immigrants; by 2008, they were 1.8 million people, most of them (about 1.7 million) coming from Chagas-endemic countries. It is estimated that about 5% of these may be infected by *T. cruzi*. Other European countries, such as Italy, Portugal or Germany have also received thousands of immigrants from Latin America, and it is estimated that about 3% of them may be infected. It came therefore as no surprise that positive blood donors were identified among those immigrants, or that several cases of transfusion- and organ transplant-related acute Chagas disease were diagnosed in Spain; congenital Chagas disease was also identified in Spain and Switzerland. As a result, and mainly in Spain, a network for the clinical care of Chagasic patients has been established, and serological screening for *T. cruzi* is now mandatory in Spain and France for individuals at risk (those who either lived in Chagas-endemic areas, were born to women that did, or received blood transfusion in Chagas-endemic countries) before they can donate blood.

THE FUTURE

Eighteen years after the Southern Cone Initiative was launched, the original mandates of this and the later Initiatives keep expanding. From the original "chemical control" and "environmental management of the domestic and peridomestic areas", new components on "information, education and communication", "medical care", and "community participation" were progressively incorporated. To make these actions effective, PAHO recently required, in addition to its regular funds, extra support of US$ 500,000 from the Spanish International Cooperation Agency (AECI) in 2009. A similar amount is being negotiated for 2010. Further major donors were the Canadian International Development Agency (CIDA), the WHO, or JICA.

In addition to the need for adequate funding, the following challenges have been identified:

1. Weak National Control Programs, which have to operate in a context where priority is not given to the prevention of Chagas disease and where municipal-level surveillance systems need much strengthening;
2. Quality control activities have not been incorporated into routine practice; these aim at ensuring that interventions for vector control/surveillance, as well as for the prevention of transfusion-related transmission, disease diagnosis, and patient care, are all carried out under the established norms and procedures;
3. There are sylvatic foci of the main vectors, *T. infestans* (in Bolivia and Argentina, and probably in other areas of the Chaco) and *R. prolixus* (in the Colombian-Venezuelan Llanos);
4. Secondary vectors of local importance frequently reinvade and reinfest treated households;
5. Possible emergence of insecticide-resistant vector populations in discrete foci.

In analyzing these problems, most of which are not country specific, it becomes clear that a multi-national forum is required for the discussion of priorities and co-ordination of activities for the prevention and control of Chagas disease. The main goals of such a forum would be:

1. To develop a work plan for the next 5 years; it must include the actions need to promote the political will needed to foster, or re-establish, priority for Chagas disease across the region. The Inter-Government Initiatives must be strengthened as the framework for inter-country co-ordination and the monitoring and evaluation of National Control Programs;
2. To define mechanisms aimed at guaranteeing the quality standards of all actions developed under the Inter-Government Initiatives for
   - Insecticide spraying and entomological surveillance;
   - Prevention of transfusion-related transmission;
   - Effecting of integral medical care for the Chagasic
   - patient;
   - Secondary prevention (diagnosis and treatment) of congenital Chagas disease, both in Latin America and in non-endemic countries of Europe and North America.
3. To stress the concept that priority actions of the Initiatives must be directed towards vector control and patient care, specifically (I) acute cases of any age class and (II) children and adolescents (up to 15 years old) with chronic infection. There is currently not enough evidence that specific treatment brings clear benefits for adult chronically infected patients; the mass delivery of such treatments cannot therefore be recommended, neither in areas where vector control achieved interruption of transmission or elsewhere.

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