The Cost-Effectiveness
of
Blood Donor Screening Programs
to
Identify Transfusion Transmitted Chagas’ disease
in Bolivia,
Including the Use of
a Natural History Model of Chagas’ disease

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This paper is an overview of projected areas of research in the coming year. Individual papers on the natural history model of Chagas’ disease, cost-effectiveness alternatives, etc., will be developed from this paper.

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<td>BTS</td>
<td>blood transfusion service</td>
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<td>cost-effectiveness analysis</td>
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<td>CFT</td>
<td>complement fixation test</td>
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<td>disability adjusted life years</td>
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<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>GV</td>
<td>gentian violet</td>
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<td>HIV</td>
<td>human immune deficiency virus</td>
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<td>IFAT</td>
<td>indirect immunofluorescent antibody test</td>
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<td>IHA</td>
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<td>LLDCs</td>
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<td>ACD</td>
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<td>GD</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PEYLL</td>
<td>period expected years of life lost</td>
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<td>SCGH</td>
<td>Santa Cruz General Hospital</td>
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<td>TTCD</td>
<td>transfusion-transmitted Chagas’ disease</td>
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<td>WB</td>
<td>World Bank</td>
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All currency is listed in U.S. dollars.
Abstract

The cost-effectiveness of a screening system for blood donors in Bolivia was analyzed. The system’s programs were intended to improve the coverage and sensitivity of screening tests for Chagas’ disease and the usage of a trypanosomicidal agent (Gentian Violet). In Bolivia the prevalence of Chagas’ disease among blood donors is extremely high, so screening for blood donors is relatively cost-effective. However, if a program is implemented elsewhere and high coverage and/or high sensitivity obtained, the amount of discarded blood units for seropositiveness of Chagas’ disease will be very large. The use of Gentian Violet along with screening has proved to be very cost-effective because it reduces the number of discarded blood units and consequently the total costs of programs.

In this study a mathematical cohort model was developed to calculate the health outcomes of interventions. The data which were obtained from longitudinal studies for model parameters were so scarce and unreliable that to each of them was added a probability distribution function. In cost-effectiveness analysis of such a subject, with its considerable uncertainties, it is necessary to use a stochastic simulation model with probability distribution functions in order to do a multivariate sensitivity analysis.

key words: cost-effectiveness analysis, Chagas’ disease, Bolivia, transfusion-transmitted infections, donor blood screening, mathematical model, probability distribution
I. Introduction

Chagas’ disease remains one of the most important public health problems in Bolivia even after some neighboring countries such as Argentina, Brazil, and Uruguay have implemented national control programs for controlling Chagas’ disease and reported a remarkable reduction of its prevalence \(^1\)-\(^4\). Historically, efforts to control Chagas’ disease in Bolivia have been relatively isolated and limited in scope \(^5\). Although a national program for controlling the disease was planned \(^6\), only pilot studies of the control program have been implemented \(^7\). Recently the Bolivian government conducted a nationwide epidemiological investigation of Chagas’ disease \(^8\). Based on its results, a newly developed national program is expected to be initiated.

On the other hand, the large scale of rural-urban migration in these decades has changed Chagas’ disease from a disease of rural areas and of low socioeconomic class to an urban disease that affects all classes \(^8\). Transmission through blood transfusion is now becoming more frequent, in spite of the implementation of vector control programs in urban areas \(^9\). Because both demographic and epidemiological transition are rapidly taking place in Bolivia, strategies for the control of Chagas’ disease must also be changed.

We have conducted studies of the serosurvey to determine the seroprevalence of transfusion-transmitted infections among blood donors in Santa Cruz, where the Japanese governmental medical cooperation project has been assigned since 1989. We have reported the need to control transfusion-transmitted Chagas’ disease (TTCD), from a clinical point of view \(^10\),\(^11\).

Fortunately, the Bolivian government conducted a national survey of blood transfusion systems and transfusion-transmitted infections in 1992 \(^12\). This should result in action against the disease in the near future, although Bolivia is one of the poorest countries in South America and health resources are seriously limited. Allocating these scarce resources should be based on economic evaluations such as a cost-effectiveness analysis to design the most efficient control program.

Although several studies of economic analysis have been performed for the vector control programs of Chagas’ disease \(^7\),\(^13\),\(^14\), there are no cost-effectiveness analyses referred to TTCD. In this paper, first the actual situation of Chagas’ disease is reviewed and its problems are specified, then the importance of Chagas’ disease control, especially focused on TTCD in urban areas, is assessed. Finally, using cost-effectiveness analysis, several strategies for TTCD including a national plan for it are compared. A mathematical model of a natural history of Chagas’ disease (NHCM) is developed to calculate the health outcomes for this study. This should be useful for government or donor agencies as they develop policies for Chagas’ disease control.

The main objectives of this paper are summarized as follows. In summary, this paper will;
- demonstrate the impact of TTCD in Bolivia.
- discuss the cost-effectiveness of a screening system for blood donors in Bolivia.
- present a Chagas’ disease model for economic evaluation.

II. Problem specification

A. Chagas’ disease \(^15\)-\(^18\)

- Parasites, vectors, and reservoirs. Chagas’ disease (American trypanosomiasis) is a parasitic disease caused by a flagellated protozoan, *Trypanosoma cruzi* (*T.cruzi*), that occurs in Central and South America (Figure 1). *T.cruzi* has many strains and antigenic differences and they may cause geographic differences of the pathology.
The disease is normally transmitted by triatomine bugs (large blood sucking bugs, commonly called kissing bugs) through contact with contaminated feces. Over a hundred species are found in the Americas, and several genera and species serve as vectors of Chagas’ disease. In Bolivia *Triatoma infectans*, which causes 80% of the total cases of Chagas’ disease in the world, is also the main vector. Its distribution is limited in range to warm environments and low altitudes.

Originally Chagas’ disease is a zoonosis in the forest. Over 150 species of mammals are transmitted. Armadillos, raccoons, opossums, and wild rodents are major reservoirs within a sylvatic environment, whereas dogs, cats, guinea pigs, and goats are important reservoirs within a domestic one.

- **Transmission dynamics.** There are several modes of transmission; vectorial, blood transfusion transmitted, congenital, and others. The vectorial transmission is the most important; about 80% of Chagas’ disease patients are infected through this mode. In vectorial transmission, three ecological cycles are recognized; sylvatic, peridomestic, and domestic. In the sylvatic cycle, wild vectors and wild reservoirs have been balanced ecologically. If humans invade the sylvatic cycle or wild vectors or reservoirs enter the human environment, transmission will occur to human or domestic animals. In the domestic cycle, which is the main human transmission cause, vectors are adapted to the human environment.

The transmission of Chagas’ disease is closely related to the socioeconomic environment. Most of cases occur in rural areas where there are poor housing conditions, with unplastered walls of simple mud or adobe, and roofs of reeds or straw. The vectors like to live in such conditions in intimate contact with men and domestic animal reservoirs facilitating the domestic cycle. Prolonged contact with a large number of infected bugs causes high human infection rates.

*T. cruzi* can be also transmitted congenitally or through the transfusion of contaminated blood. Transfusion-transmitted Chagas’ disease (TTCD) will be reviewed in another section of this paper (II. B.). The generally accepted risk of congenital transmission of *T. cruzi* is about 1% among infected pregnant women. However other data suggest a risk of 0 to 14.8%.

Since seroprevalence of pregnant women is very high in Bolivia, so the women could constitute a large reservoir for Chagas’ disease. Congenital Chagas’ disease infection can also cause abortions or premature births. Some cases of infection through other routes of transmission such as oral (breast feeding), accidental, and by organ transplantation were reported but they were very rare compared with the other two routes.

- **Clinical stages and forms.** The natural history of Chagas’ disease is very complicated because it is modified by conditions such as age and nutrition, parasite strains, modes of transmission, etc.. It is not easy to show the natural course of the disease; however there are generally three stages; acute, indeterminate, and chronic (Figure 2).

**Acute stage.** Usually symptoms can be very mild and atypical, so the acute stage is not recognized in most cases (inapparent type). In the apparent type (classical cases), the incubation time is of 8-10 days and major general symptoms are general fatigue, fever, hepatosplenomegaly, generalized edema, and lymphadenopathy. Local inflammation signs at the portal of entry called “chagoma” are also found. An acute stage is diagnosed in only 1-2% of infected cases. In an endemic area, cases that are recognized as acute Chagas' disease are usually detected in persons less than 15 years old, and most often in children under 10.
Major morbi-mortality usually develops between birth and 2 years of age. Mortality in acute Chagas’ disease, varies from 1.2% to 45% \( \text{21,22)} \) and basically depends on the presence of acute myocardiopathy and/or meningo-encephalitis. It is generally considered that clinically apparent acute Chagas’ disease is lethal in 5% to 10% of patients \( \text{23}\). Non treated acute disease has a duration of about 4-12 weeks. It will usually, but not always, enter the indeterminate stage \(^1\). Spontaneous cure is still controversial.

**Indeterminate stage.** This stage is defined by the presence of the infection (revealed by either serological or parasitological tests) and characterized by the absent of clinical symptoms. It may last several years and may persist for the reminder of life in 40% or more of infected individuals.

**Chronic stage.** The evolution from indeterminate stage to a clinical form of Chagas’ disease occurs 10-20 years after the acute stage. It is estimated that about 60% of persons in the indeterminate stage will developed chronic forms of the disease. These may be:

**Cardiac.** This is the most important chronic form. Pathologically cardiomyopathy due to chronic myocarditis is observed and often causes thrombosis, which may be the source of embolism. Conduction defects include various arrhythmia such as A-V block and complete right bundle branch block. Patients die with congestive heart failure or with sudden death, which is caused by embolism and ventricular fibrillation, both very common in middle age patients. Cardiac failure and/or severe arrhythmia are rapidly followed by a high mortality rate in some cases. These are called “malignant evolution”, and chiefly observed among male patients in the 30-50 age group.

**Digestive.** This form of chronic Chagas’ disease is also called megaviscera syndrome, characterized by “mega” formation of digestive organs which is thought to result from the destruction of autonomic nerves. Megaesophagus and megacolon are the most common manifestations.

**Neurological.** The central, peripheral, or autonomic nervous system can be involved, but in ways that are not well known yet.

**Mixed.** Cardiac forms and digestive forms are frequently associated.

In the chronic stage, the mortality of Chagas’ disease is mainly due to the severity of heart disease. Progressive cardiomyopathy developed in 20% to 30% of chronically infected persons \( \text{23}\). Mota reported the mortality related to infection with T. Cruzi was 8.9 per 1000 person year \( \text{24}\). Geographical differences manifest themselves in term of incidence, severity, target organs affected etc.. For example, digestive forms are very rare north of the Equator, while in Brazil about 20-30% of the patients develop a cardiac form and 5-8% a chronic esophagopathy, and about 4-6% will later developed a chronic colonopathy. The reason for such geographical variances not clear, but may be explained by differences in parasite strains, vectors, and the genetic pattern and socioeconomic status (nutrition, sanitation etc.) of the population.

- **Diagnosis.** Methods for the diagnosis of Chagas’ disease are classified into two categories; parasitological and serological (Table 1). Parasitological direct methods are used mainly in the acute stage, since their sensitivity is very low in the chronic stage. While indirect

\(^1\) **Sub-acute form** is a very special and severe form of cardiopathy, in which the direct evolution from acute phase to a clinical chronic form is observed. The intense and extensive sub-acute myocarditis rapidly evolves to heart failure and death.
methods can be used in the chronic stage, they are highly specific but the sensitivity is only 50% with a single test.

The antibodies against *T. cruzi* are detected by several serological methods used for screening tests of blood donors: CFT (complement fixation test), IHA (indirect haemagglutination test), IFAT (indirect immunofluorescent antibody test), DA (direct agglutination test), ELISA (enzyme-linked immunosorbent assay), and Latex agglutination test. The results of serological methods are complicated by potential cross-reactions. WHO recommended that two tests be used, to minimize the possibility of false-negative results. Table 1 shows the sensitivity of each serological test and their combination reported from a university in Brazil [25]. In Bolivia the sensitivity of the screening tests in blood banks is believed to be much lower than these data.

In order to obtain high sensitivity and specificity for the blood screening, it is necessary to use well-defined antigens with high reliability, reproducibility, and comparability. Currently, recombinant antigens of *T. cruzi* are available for the ELISA and other techniques. The polymerase chain reaction (PCR) technique for the diagnosis of Chagas’ disease is now being tested. Preliminary reports indicate its high sensitivity and specificity. PCR could be used as a rapid, low cost, high sensitive screening assay for chronic Chagas’ disease in blood banks in the near future.

- **Treatment, prevention, and control program.** Nifurtimox and Benznidazole have some effect if they are used in the acute stage in order to prevent a development to the chronic stage. Neither drug would be expected to cure established chronic disease [26]. Symptomatic treatment is only way to improve morbidity. An effective vaccine has not yet been developed.

Two types of control programs for Chagas’ disease exist: vector control and medical surveillance and treatment. As a vector control program, chemical insecticide has been successfully applied. New tools such as slow release paints and a fumigant canister to spray all houses in infested regions with highly effective residual insecticides have been introduced. The vector control program includes housing improvements, such as plastering the mud brick walls. Health education has an important role in increasing public awareness of the problem. From the Brazilian experience a horizontal program which is based on decentralization and community participation is essential to overcome the problems [5]. Interventions and participation are necessary to secure public acceptance of control.

In July 1991, the Ministries of Health of the six countries of the “Southern cone” (Argentina, Brazil, Bolivia, Chile, Paraguay and Uruguay) signed a formal resolution calling for the establishment of an intergovernmental commission with responsibility for an eradication plan directed at Chagas’ disease [26-28]. Preliminary cost estimates for this plan suggest a total requirement of around $ 200 million for 10 years, but the estimated economic benefits are well in excess of this. It is indispensable to secure intergovernmental cooperation and international aid for the implementation of this plan.

- **Geographical distribution and economic impact.** Most of the seroprevalence data for Chagas’ disease were obtained from the surveys of limited regions or special groups. WHO estimated the population at risk and infected (Table 2) [9]. In the endemic countries of 360 million inhabitants, at least 90 million person (25%) are considered at risk of infection, 16-18 million people are infected [15]. The incidence of infection is probably close to 1.5 million per year [27] and
some 2-3 million may already have developed chronic complications. In Argentina, Bolivia, Brazil, Chile, Paraguay, Peru and Uruguay, around 300,000 new infections were occurred per year. Mortality due to Chagas’ disease is more than 45,000 deaths annually.\(^\text{17}\) WHO also estimated that the number of deaths by Chagas’ disease was 23,000 and disability adjusted life years (DALYs) lost were 2,740,000 in 1992 (Table 3)\(^\text{29}\). Among infectious and parasitic diseases (including diarrhea and respiratory infection) Chagas’ disease was the fourth most important problem measured by DALYs lost in Latin America and the Caribbean region.

As a consequence, the economic impact of Chagas’ disease is very high in Latin America, especially because chronic Chagas’ disease affects adults in the economically productive years most seriously. Pereira reported that Chagas’ disease was responsible for 10% of death in adults over 25 years of age in Brazil\(^\text{30}\), where the seroprevalence of Chagas’ disease is about 4%. Bryan and Tonn cited that the annual cost of medical care due to Chagas’ disease alone is $ 250 million, considering that at least 10% of infected people develop severe cardiac or digestive chronic involvement. Brazil loses an additional $ 5,000 million a year due to absenteeism caused by Chagas’ disease\(^\text{31}\).

Bolivia is located in the center of South America. The territory is 1,098,591 km\(^2\) wide and has nine departments (Figure 3)\(^\text{32}\). The population numbers 6.42 million and the density of population is 5.8 /km\(^2\) which is the lowest in South America\(^\text{33}\). The annual population growth rate was 2.5% in 1992\(^\text{33}\). As in the other countries in South America, urbanization in Bolivia is proceeding very rapidly. Now approximately 58% of the population live in urban area. Most people migrated from the east high land and valleys area to the low land such as the Santa Cruz department. The net migration rate of the Santa Cruz department is 18.15 in 1992, and it is highest among the nine departments\(^\text{33}\). Economically Bolivia is one of the poorest countries in Latin America, with a per capita income of $ 680 (1993)\(^\text{34}\). This statistic places Bolivia in the group of lower middle income countries, however the health indicators seem to be those of the least developed countries (LLDCs) (Table 4)\(^\text{32,34}\). For example, the infant mortality rate and the under-5 mortality are 78 and 114 respectively, which are still remarkably higher than the other South American countries\(^\text{35}\). The leading causes of morbidity are diarrhea, acute respiratory infection, malaria, and tuberculosis, all typical in LLDCs. Tropical diseases like malaria and Chagas’ disease are still major public health problems\(^\text{34}\).

In Bolivia, Chagas’ disease occurs mainly in the valleys and plains lying between 300 to 3500 meters above sea level. Infected vectors have been found in 7 of 9 departments. The endemic area covers 80% of the country’s territory. WHO estimated 1.8 million people, 30% of total population, are at risk of infection\(^\text{9}\). In 1985 it is estimated that 1,133,000 people are infected in the Cochabamba, Sucre, Tarija, and Santa Cruz departments. The Triatomime house infection rate was 41.2%, and the \(T. \text{ cruzi}\) infestation index\(^*\) in vectors was 30.1%\(^\text{15}\). Table 5 shows actual situation of Chagas’ disease in Bolivia\(^7\). Seroprevalence is so high that morbidity and mortality of Chagas’ disease are supposed to be highest in Latin American countries. Seroprevalence of pregnant woman ranged from 25 to 50 percent, and the rates of infection in infants born to seropositive mothers from 8 to 36 percent. A nationwide epidemiological study of Chagas’ disease was conducted at 109 villages in five departments (La Paz, Cochabamba, Chuquisaca, Potosi, and Santa Cruz)\(^8\). According to its results, seropositive rate was 40.4% of

\(^*\)\(2\) Net migration rate = (Number of immigration - Number of emigration) / Total population

\(^*\)\(3\) Infestation index = Number of houses infected by triatomine / Number of houses examined
total population, and Chagas' disease compatible ECG changes were recognized in 13.1% of seropositive people. The house investigation revealed 28.3% of Triatomine infestation rate.

The economic impact of the disease in Bolivia is as tremendous as that in other South American countries. The SOH / CCH *4 Chagas’ Control Program estimated total direct and indirect costs, which consisted of medical treatment and loss of productivity, as approximately $100 million annually (1992) 7). This amounts to nearly twice the national health budget of the same year. In spite of this situation a national program for Chagas’ disease control has not been initiated in Bolivia.

B. Blood transfusion and Chagas’ disease

- Blood transfusion service (BTS). WHO classified the organization of national BTS and its level of development 37). According to these guidelines organization systems are classified into four categories: centralized, regionalized, hospital-based, and mixed. Bolivia has a hospital-based organization and its level of evolution is now still in the basic stage (Table 6). There are neither blood transfusion centers nor a sophisticated Red Cross organization in Bolivia. Blood banks are affiliated to the hospitals and are usually understaffed, sometimes without doctors. Their activities depend on the level of their facilities and/or personnel. On the district level, their functions are very limited only ABO grouping and no screening tests are performed. Even referral hospitals can sometimes provide only plasma and platelets except for the whole blood.

The procedures taken for a blood transfusion in Bolivia are shown in Figure 4. There is no blood donation system, so the patient or his family must recruit blood donors. Furthermore, materials for blood transfusion, such as bags for containing blood and an infusion set, must be purchased. The total patient charge, including screening tests fee and administration fee, was between $43 to $62 in 1994. In public hospitals, patients are classified into categories by economic status, and some of these fees are paid by the government. For example, patients in the lowest category are not required to pay the fee of screening tests. However governmental subsidy is not sufficient to cover all costs. This is one of the reasons why some materials are often lacking in hospitals. Blood banks usually have small refrigerators, but these are not used for blood storage for emergency cases. Even in registered emergency hospitals, the storage system is not established. Consequently most emergency blood transfusions are performed without screening tests even now.

Screening tests for the transfusion-transmitted infections are compulsory according to a law enacted in 1986. This law requires that a test for Chagas’ disease be performed for all candidates for donating blood. However the current situation is far from ideal. In 1992 the National Institute of Health Laboratory (el Instituto Nacional de Laboratorios de Salud) conducted a nationwide investigation of BTS for 60 provincial blood banks, or “hemotherapy centers” to identify the problems 38). These centers serve about 3 million people or almost 80% of the total population in the urban area. According to this investigation, the total number of blood donors per year was approximately 40,000, but in actuality 29,000 blood transfusions were performed in every year. About 27% of blood units were discarded or not used (Table 7a). As for the type of blood donors, only 6.5% were philanthropic. 53.3% of the “hemotherapy centers” used commercial (paid) blood 34). Although it was reported that commercial blood

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*4 Secretariat of Health / Community and Child Health
donors gave 10% of the total blood, this statistic is misleading, since other categories of donors (familiar, unknown) were presumably sometimes commercial (Table 7b).

Surprisingly only 30% of 60 “hemotherapy centers” accomplished complete screening tests mostly because of financial problems (38). Our studies at Santa Cruz General Hospital (SCGH) observed two periods in 1994 when screening tests for Chagas’ disease and/or for Human Immunodeficiency Virus (HIV) infection were not performed due to shortage of materials. In these periods some blood units were transfused without these screening tests. With the deterioration of the economic situation of public hospitals, the problem is worsening.

The quality of screening tests in blood banks is another problem in developing countries. To improve and keep the reliability of the each blood bank, quality controls such as standardization of diagnoses are required. For this purpose, WHO recommended the establishment of a national laboratory network. This seems to be very difficult to establish in Bolivia because of both financial and technical problems.

- seroprevalence of transfusion-transmitted infections. There are many diseases which are transmitted by blood transfusion. Syphilis, Hepatitis (B and C), and HIV infection are recognized as the most common transfusion-transmitted infections globally. In tropical regions, some parasitic diseases such as Malaria and Chagas’ disease should be included. WHO reported that the seroprevalence of Chagas’ disease among blood donors in Santa Cruz was 63% (16). It made Santa Cruz world-famous for the highest seroprevalence of Chagas’ disease and it was quoted in several articles. However the seroprevalence of Chagas’ disease depends on the group examined. Table 8 and 9 show the seroprevalence of Chagas’ disease at several cities in South America and Bolivia (18, 39-43). Although these data were assessed only by screening test(s) and confirmatory methods were not taken, there are large geographic differences even in the same countries. Nonetheless it is obvious that Bolivia has the highest seroprevalence among them. The surveillance of the transfusion-transmitted infections was also conducted in the above-mentioned national investigation (Table 10). The seroprevalence of Chagas' diseases, Hepatitis B (HBsAg), Syphilis, and HIV infection are 17%, 0.21%, 1.61% and 0.01% respectively. It is obvious that Chagas’ disease is most serious problem in Bolivia.

Santa Cruz is the second largest city in Bolivia, located in the east sub-tropical area. The population of the department of Santa Cruz is 1.36 million, of whom 72% live in the urban area (36). Due to economic development, Santa Cruz has undergone rapid growth in these decades (36), as many people immigrated from rural areas of the department and from other departments. The author of this paper conducted a serosurvey to determine seroprevalence of the transfusion-transmitted infections among blood donors at SCGH where the Japanese governmental medical cooperation project has been underway since 1989. At SCGH four examinations (Chagas' diseases, Hepatitis B (HBsAg), Syphilis, and HIV) are being performed as blood donor screening tests. The seroprevalence of Chagas' diseases, Hepatitis B (HBsAg), Syphilis, and HIV are 23%, 0.3%, 0.3% and 0% respectively in our results (Table 11) (10). The confirmation tests for Hepatitis B, Hepatitis C, and HIV were performed for 395 blood donors of SCGH in Japan in 1992 (10). The seroprevalence of Hepatitis C (anti-HCV) was 0.5 to 1% but it was not confirmed by PCR (10). Other three different types of general hospitals in Santa Cruz were also surveyed in 1995 (Table 12). The results were almost similar to those of SCGH. It is interesting that even in private hospital for high socioeconomic level patients the prevalence of Chagas’ disease among blood donors is still very high.
- Transfusion-transmitted Chagas’ disease (TTCD) and its prevention. No more than 300 cases of TTCD can be found in the medical literature \(^{18}\). This number is an underreporting because the number of asymptomatic recipients is significant and neither blood banking professionals nor physicians have the interest and/or knowledge that would lead them to investigate a presumed case \(^{18}\).

Clinical features of TTCD are usually manifested by the original disease or postoperative course. The incubation period is 20-40 days (8-120 days), somewhat longer than that observed in triatomine infection. Symptoms are similar to cases of vectorial transmission. Fever is the most common symptom, with lymphadenopathy and splenomegaly found frequently in the acute stage. Deaths may occur in the most severe cases, usually in immunosuppressed patients or children. Because blood transfusions are performed for the severely ill cases, the mortality of TTCD is difficult to determine. Mortality also depends on the age of infection. Spontaneous recovery usually takes 6-8 weeks following the disease’s natural course to the indeterminate stage and the chronic stage. The clinical course is unclear in detail because there are few longitudinal studies about TTCD.

If seropositive blood is transfused to seronegative recipients, some but not all, will develop TTCD. The probability of infection depends on the parasitic strain, the presence of parasitemia at the time of donation, immune status of recipients, and the amount of blood transfused \(^{18}\). It is also related to the number of transfused blood units and the sensitivity of screening tests. Theoretical risk of TTCD (P) is calculated by Formula 1:

\[
P = 1 - (1 - f)^n \]

\[
P = 1 - (1 - f)^n \times k \quad \text{(unscreening components)}
\]

\[
P = 1 - (1 - f)^n \times k \times (1 - S) \quad \text{(screening components)}
\]

\[
f: \text{prevalence of infected donors in the population}
\]

\[
n: \text{number of transfused units}
\]

\[
k: \text{infectivity}
\]

\[
S: \text{sensitivity of screening methods}
\]

Infectivity (k) is the probability of a patient becoming infected when receiving one unit of infected blood. Various studies indicated it was on average 12-18% and could be as high as 50% \(^{44}\). Zuna et al reported that 10 of 21 (47.6%) seronegative recipients who were transfused seropositive blood were seroconverted and 6 of the 10 had acute clinical symptoms \(^{45}\).

There are no therapeutic methods for treatment of Chagas’ disease, especially for the chronic stage. Its prevention is essential. The most effective preventive methods for TTCD are donor history and interview, serological screening, and chemoprophylaxis. Donor history and interview is used but its usefulness is very limited because most people in rural areas do not recognize the disease even where it is endemic. Paid donors should be excluded from the history and interview because they have a higher prevalence of Chagas’ disease. A good quality serological screening procedure (mainly with high sensitivity), employing at least two different techniques, is ideal. Quality control programs should accompany the screening. As a chemoprophylaxis some dyes such as Gentian Violet (GV) have been used in some hyperendemic areas \(^{46-49}\). Although retrospective studies on the use of GV showed good tolerance, an absence of severe side effects, and an efficient trypanosomicidal action \(^{50}\), the usage of GV is very limited.
even now. There is a resistance to its use because it discolors the blood and gives a temporary bluish stain to the recipient’s skin and mucosae. In Santa Cruz City GV was used in only 3.2% of the Chagas’ seropositive blood in 1993 \(^{50}\). Another problem posed by GV is that it must be maintained for 24 hours at 4\(^\circ\)C to be effective, even with the ideal concentration \(^{48}\). Therefore it is not possible to use for emergency cases. In spite of this, chemoprophylaxis in endemic areas must be encouraged, especially under circumstances in which screening tests are not available or reliable.

In endemic countries the state has the responsibility for managing TTCD. A national blood transfusion system should be established that obligates the legislative power to make specific recommendation on GV, and limited use for the paid donors, etc. Argentina, Brazil, Honduras, Uruguay, and Venezuela have established systems to screen infected blood \(^{18}\). It is also necessary to educate health personnel and the population about TTCD.
III. A Natural History Model of Chagas’ disease (NHCM)

- **Objectives.** It is necessary to understand the natural course of a disease in order to analyze its impact, especially for cost-effectiveness analysis, in which effectiveness is measured by some health outcomes such as number of deaths averted, DALYs gained etc. There still remain many uncertainties on the natural history of Chagas’ disease and especially the natural course of TTCD. The complexity of the disease with its various modes of transmission, ecological cycles, socioeconomic effects, and demographic changes such as migration of the affected population makes the study of Chagas’ disease very difficult. There are too many factors influencing the natural course of the disease. In addition to disease complexity, the clinical and epidemiological data are not complete and well-designed longitudinal studies are too few.

Under such circumstances this paper presents a model representing a natural history of Chagas’ disease. The main object of this model is to estimate health outcomes for economic analyses of TTCD. It can also be used for the evaluation of other Chagas’ disease control programs.

- **Concept.** The natural history model of Chagas’ disease (**NHCM**) is a clinical transition model, not representing transmission cycles. It is a hypothetical cohort of 1000 *T. cruzi*-infected persons followed for 50 years. The model is expressed as a flow diagram consisting of boxes which represent transitional clinical stages or forms and absorbing stages of deaths. A flow diagram of the clinical course with some modifications was constructed according to published data. Each stage shows the number of cases at each time after infection. They are connected with arrows, each representing its own parameter, which is expressed as a transitional rate or a death rate. Epidemiological data obtained from longitudinal studies were used for calculating transitional rates as instantaneous ones. However, the data were so scarce and uncertain that parameters were added to the probability distribution functions. These functions are entered into a spreadsheet model of a microcomputer and simulation is performed. Selecting sets of values for the probability distribution functions containing cells and formulas, it calculated over and over again (iterations). The outputs have all possible outcomes with probability distributions. In this model, numbers of cases at each stage and numbers of deaths by Chagas’ disease and by general causes are shown every 20 days in order to calculate the DALYs. Using these numbers, it is possible to calculate period expected years of life lost (PEYLL) and also DALYs per infection.

Three kinds of **NHCM** can be developed theoretically according to the disease’s mode of transmission. **VNHCM**, **TNHCM**, and **CNHCM** are models for vectorial, blood transfusion transmitted, and congenital transmission respectively. This paper focuses on TNHCM.

- **Methods.** Basically **NHCM** was constructed from published longitudinal studies of Chagas’ disease. The opinions of experts were added to adjust the model to reality. The number of longitudinal studies available was small, particularly those in which transitions of clinical stages were discussed precisely. An exception was studies on chagasic cardiopathy. In those, the main cause of morbidity and mortality is due to cardiopathy, so a model can represent the natural course of the disease to a great extent.

As Chagas’ disease has remarkable geographical differences, data from the local studies of the regional control programs should be used. However, no longitudinal studies were available from Bolivia, therefore the data used were from other South American countries.
As reviewed previously, here are three major clinical stages; acute, indeterminate, and chronic. The chronic stage is classified into cardiac, digestive, and mixed forms \(^5\). Moreover, the cardiac form and the digestive form (megaesophagus) can be subclassified according to the symptoms and/or results of some examinations \(^5\). If these substages are applied completely to the model, the flow diagram is very complicated (Figure 5 above). On the other hand there are no available data for each transition. In developing countries like Bolivia, people in rural areas generally do not go to health facilities without symptoms. They might not go until a serious emergency situation arises, therefore data were captured only for symptomatic cases. It could be said that a detailed classification of the clinical stage is not useful for the model.

By unified some of sub-stages (Figure 5 below), a simplified flow diagram of transition was obtained (Figure 6). There are six transitional stages (A, I, CA, CB, MVP, MX) and two absorbing stages of deaths (CD, GD) which are defined as Table 13. Some of the definitions are different from those described above. For example, usually the indeterminate stage represents asymptomatic cases without any alterations even by examinations, but in NHCM, Indeterminate stage (I) includes some cases which have abnormal ECG or abnormal gastrointestinal studies.

Each stage progresses to the next stage according to its own parameter which is expressed as transitional or death rate. The transitional rates were determined from the number of cases in each stage (form) in the longitudinal studies. Each transitional rate was calculated by Formula 2 in the form of an instantaneous rate of every 20 days.

\[\begin{align*}
\text{Formula 2 Instantaneous rates} \\
P(t) & \quad \text{the number of disease cases left at time } t \\
S(t) & \quad \text{the number of cases of stage } S \text{ at the time } t \\
D(t) & \quad \text{the number of cohort dead at the time } t \\
P(t) &= P(0)e^{(r+m)t} \\
S(t) &= \frac{r}{r+m}P(0)(1-e^{(r+m)t}) \\
D(t) &= \frac{m}{r+m}P(0)(1-e^{(r+m)t}) \\
\end{align*}\]

\[\begin{align*}
r & \quad \text{Instantaneous transitional rate} \\
m & \quad \text{Instantaneous death rate} \\
r &= \frac{S(t)}{S(t)+D(t)}\ln\{1-((S(t)+D(t))/P(0))\}/t \\
m &= \frac{D(t)}{S(t)+D(t)}\ln\{1-((S(t)+D(t))/P(0))\}/t \\
\end{align*}\]

Deaths might occur directly at any stages. There are two kinds of death rate, one the general death rate(\(\mu\)) and the other the Chagas’ disease death rate(\(m\)). The former was age-

\(^5\) The neurological form was excluded because its data were not available.
specific, drawn from the life-table of Bolivia\textsuperscript{53}. The latter was calculated from the data of longitudinal studies in the same way as other transitional rates were done. Both were also expressed in the form of an instantaneous rate of every 20 days.

The number of stages (forms) was obtained by the solving following equations mathematically:

\[
\begin{align*}
\frac{dP(t)}{dt} &= -(m+r)P(t) \\
\frac{dS(t)}{dt} &= rP(t) \\
\frac{dD(t)}{dt} &= mP(t)
\end{align*}
\]

\[P(0) = 1, S(0) = 0, D(0) = 0\]

Using small $\Delta t$, numerical solutions such as the followings may be obtained and set up to a spreadsheet model:

\[
\begin{align*}
P(t+1) &= -(r+m)P(t)+P(t) \\
S(t+1) &= rP(t)+S(t) \\
D(t+1) &= mP(t)+D(t)
\end{align*}
\]

Each parameter had several values derived from longitudinal studies. It was difficult to decide uniform value because of the number and the size of the studies. No longitudinal study was large enough to obtain a generally recognized value. Furthermore, the results of studies were sometimes significantly different. In this study, each parameter was given its probability distribution \textsuperscript{6}.

The probability distributions were defined by their functions based on the number and type of the data. Probability distribution functions included normal distribution, triangular distribution, and uniform distribution. If only 2 data were available, the uniform distribution function; “UNIFORM” was chosen. If three or more data were available, the triangular distribution function; ”TRIANG” was used giving three values: the most likely, the minimum, and the maximum. The mean value of data was used as the most likely value. Some data were not used because of their reliability. A normal distribution function; “NORMAL” was not used in this model because the number of data was too small. Each probability distribution function is defined as Table 14 \textsuperscript{54}. To simplify the transition flow diagram and data limitation, it was necessary to use several assumptions. The assumptions used in NHCM are as follows:

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Model assumptions & \\
\hline
1) general aspects: & \\
\hline
\textbf{a}) The clinical course does not depend on the mode of transmission.} Although NHCM was based on the data of longitudinal studies of vectorial transmitted cases, it was used for TTCD. & \\
\hline
\textbf{b}) Differences caused by sex and race composition of cases are not considered.} Some studies showed differences of the clinical course by sex and race \textsuperscript{55,56}. However they were not proven and not significant for an economic study. & \\
\hline
\textbf{c}) Model (30) is used for the transfusion-transmitted model (TNHCM).} It is very difficult to get an age distribution of patients infected by the transfusion. The age distribution of blood recipients is not available in Bolivia, or elsewhere in South America. The only data & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{6} The probability distributions of each parameter were calculated by the @RISK\textsuperscript{®} (Palisade Corporation) which is a risk analysis software for spreadsheet such as Lotus 1-2-3\textsuperscript{®}.

16
obtainable from developing countries are from Africa. According to these data, the main reasons for blood transfusion are childhood anemia caused by malaria and, for women, complication related to pregnancy and delivery. In Bolivia malaria is also widespread and the socio-economic conditions are relatively similar to Africa. Therefore the age distribution of blood recipients could be similar to these data. Finally, two age groups are considered for blood recipients. One is a child group of which the average age of infection is 10 and the other is an adult group of which the average age of infection is 30. Model (10) (Child type) is a cohort of 1000 10-year-old persons and Model (30) (Adult type) is that of 1000 30-year-old persons.

Ideally an age distribution of recipients and models of each age group of infection are necessary for TNHCM. In this study Model (30) is used for TNHCM to simplify the model. (Model (10) is used for the VNHCM). The combination model of Model (10) and Model (30) with changeable combination ratio can be used to indicate effects of the age of infection.

d) Reinfections are not considered. Reinfection is considered to have some effect on the natural history. The data used in this study are from the studies on vectorial Chagas’ disease, so the effects of reinfection should be included. However in cases of TTCD, reinfection seems to be rare because most persons live in the urban area.

e) The disease is progressive. Although some cases remain in the indeterminate stage (I) even after 50 years of infection, there is neither cure nor resolution of the disease.

2) parameters;
a) Mortality in the acute stage (m0), which is defined as death within 60 days after infection, depends on the age of infection. This assumption is particularly true in vectorial transmission but TTCD mortality can also depend on age. The recipients of blood transfusion often have such severe conditions, that mortality is higher than that expected in vectorial transmission cases comparing the same age groups. Mortality in the acute stage was calculated as 0.0112 (Table 15). The data mainly represented the mortality of children, so they are used for Model (10). From expert opinions the mortality of adults (for Model (30)) is used and calculated at 0.0022, which is one-fifths that for children.

b) Mortality and transitional rates in chronic stage (m1-5) are not age specific. The number of cases in longitudinal studies were used for the calculation of rates (Table 15). Only data which showed a set of the number of cases of each stage at definite periods of observations were used. These data were not age specific.

c) \( v_4 = a_1, v_2 = v_1, v_3 = v_1, m_4 = m_1, m_5 = m_2 \); Some of the transition rates could not be calculated because of lack of data. With experts opinions other parameters were substituted for these. Table 16 shows transitional and death rates used in Model (10) and Model (30). Figure 7 shows probability distributions of each parameter.

d) General death rates (\( \mu \)) are age specific. General death rates were decided from the published age specific mortality of Bolivia (Table 17).

- Results. Six clinical stages (A, I, CA, CB, MV, MX), general death (GD), Chagas’ disease death (CD), and each parameters (a, v, m) were set up in a spreadsheet. The simulations were performed 2000 times (iterations) and the numbers of cases in each stage every 20 days until 18000 days (50 years) were calculated.

the number of cases and deaths (acute and chronic). The numbers of cases in each stages (I, CA, CB, MV, MX) for 1000 infections at each time were obtained. In NHCM, the
number of cases in the acute stage (A) was not indicated. Because its symptoms were not apparent in most cases, only 1-2% of them were diagnosed. All cases except deaths were assumed to enter the indeterminate stage. Only the number of deaths in the acute stage (ACD) was shown. Total (cumulative) number of deaths by Chagas’ disease (TCD) and those from general causes (GD) at each time were also obtained. Table 18 and Figure 8 are the results for Model (10) and Model (30). In these tables the numbers of outputs were represented every 5 years. The number of ACD per infection of Model (10) and Model (30) were 22.2 and 4.4 respectively. TCD in 50 years were 502.7 (270.6) and 494.4 (259.6) for Model (10) and Model (30) respectively. (Discounted number, discount rate was 0.03).

**PEYLL (Period expected years of life lost).** Years of life lost measures health outcome in units of time. In PEYLL, death at each age can be weighted by the expected years of life at each age. Using Formula 3 it is possible to calculate PEYLL. A set showing age-specific life expectancy in Bolivia was drawn from the published data (Table 17).

<table>
<thead>
<tr>
<th>Formula 3</th>
<th>PEYLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(x=L)</td>
<td>(\text{PEYLL} = \sum_{x=0}^{\infty} d_x e_x)</td>
</tr>
<tr>
<td></td>
<td>(d_x): number of deaths</td>
</tr>
<tr>
<td></td>
<td>(e_x): expected years of life at age (x)</td>
</tr>
<tr>
<td></td>
<td>(L): potential limit to life</td>
</tr>
<tr>
<td></td>
<td>(x); age at death</td>
</tr>
</tbody>
</table>

Discounted forms (Continuous, equal age weights)
\(1/r-(1/r) * e^{-rn}\)
\(r\): discount rate
\(n\): expected years of life at age \(x\) (\(e_x\))

PEYLL per infection of Model (10) and Model (30) were 5.67 and 3.70 respectively (Table 19). The discount rate used here was 0.03.

**DALYs (Disability-adjusted life years).** The number of DALYs is an indicator of a) the time lost due to premature death and b) the time lived with disability. Unhealthy life-years are given lower weights than healthy ones, depending on degree of disability. Time lived at different ages has been valued using an exponential function. Also the stream of lost life has been discounted with a continuous form. This indicator can be used to make comparisons across a wide range of different diseases. The general formula and its solution, using a discount rate on the streams of benefits and unequal age weights, are as follows:

<table>
<thead>
<tr>
<th>Formula 4</th>
<th>DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(x=a+L)</td>
<td>(\text{DALYs} = \int_{x=a}^{x=L} DCxe^{-\beta x}e^{-r(x-a)}dx)</td>
</tr>
<tr>
<td></td>
<td>(\text{approximation} = {DCe^{\beta a}/(b+r)^2} e^{(\beta+r)(L)} (1+(\beta+r)(L+a))-(1+(\beta+r)a))</td>
</tr>
<tr>
<td></td>
<td>(D): disability weight</td>
</tr>
<tr>
<td></td>
<td>(C): age-weighting correction constant</td>
</tr>
</tbody>
</table>
L: duration of disability or lost duration of life  
r: discounted rate  
ββ: parameter from the age-weighting function  
a: age of onset  

D is the disability weight, which represents 1 for premature mortality and 0 for a healthy state. In this study the disability weights used are 0, 0.092, 0.2499, 0.0066, and 0.10 for I, CA, CB, MV, and MX respectively using the same calculation method as Murray et al.73 with expert opinions. C is the age-weighting correction constant, and 0.16243 was used for it as in World Bank report. The discounted rate (r) and the parameter from the age-weighting function (β) were 0.03 and 0.04 respectively.73

a) The time lost due to premature death. The number of deaths in each age group were obtained by NHCM. The standard expected years of life lost (Formula 4, D=1) at each age group were calculated and multiplied by the number of deaths in this age group. The sum of them is DALYs lost for premature death for 1000 Chagas’ disease cases.

b) The time lived with disability. The duration at each stage was calculated by NHCM. The sum of cases with each stage multiplied by the duration (20 days) and divided by 360 days is indicated as case-year per 1000 cases of Chagas’ disease. The DALYs lost for unhealthy life-years was calculated with Formula 4. Their sum at each stage was DALYs lost for unhealthy life-years of Chagas’ disease.

DALYs lost per infection for premature death and unhealthy life-years were 7.15 (Model (10)) and 4.79 (Model (30)) as shown in Table 20a, b.
IV. Cost-effectiveness analysis of a screening system for blood donors

- Programs. Cost-effectiveness analysis (CEA) compares the costs of a health intervention with some measures of health outcome or effectiveness such as mortality rates or number of life-years saved. CEA is used to evaluate alternative ways of achieving objectives to establish the least costly means of saving a defined project, or to derive the maximum benefits that can be achieved from a fixed budget.

The first step in CEA is to define a program and its alternatives by specifying the problems. As discussed above, an extremely high prevalence of Chagas’ disease is observed in many regions in Bolivia. The problems are so serious that a national vector control plan for Chagas’ disease will be implemented from the results of a pilot study. This plan is thought to be justifiable morally and politically and feasible technically, but problems remain for controlling TTCD in urban areas. Countermeasures for TTCD must be integrated into the national program as a complementary activity. Causes for the high incidence of TTCD are most probably:

1) the high prevalence of Chagas’ disease among blood donors in urban areas,
2) the low coverage of screening tests for Chagas’ disease,
3) poor quality of screening tests,
4) others causes, such as limited usage of GV and unnecessary blood transfusion.

The objective of an effective screening program is defined as decreasing the incidence of TTCD. Its strategies are to improve the coverage of screening tests by providing screening tests material, since the shortage of material at blood banks is the most dominant reason for underuse of screening tests. In addition, three alternative strategies have been identified: to promote GV usage, to improve the quality of screening tests by the combination of screening tests, and a combination of the two above. A national plan for transfusion-transmitted infections was also compared to the program and alternatives.

The following are proposed screening programs for TTCD control in Bolivia:

Program 1 (P1): P1 has a very simple strategy in which screening tests material for Chagas’ disease, Hepatitis B, Syphilis, HIV infection and some related basic equipment are provided to blood banks of public hospitals, with the objective of strengthening functions of blood banks in existing facilities. Under this program the coverage of screening tests is increased, but it cannot cover emergency cases in the current situation. Our study showed that emergency cases made up about 4% of the total number of blood transfusions\(^{10}\). Therefore maximum coverage with P1 is potentially 96%. The quality of the screening tests, however, will not be increased.

Program 2 (P2): Among P-2 alternatives, GV as a trypanosomicidal agent is used in Program 2-1 (P2-1). If P-1 is implemented and the coverage and sensitivity of screening tests increased as a result, the incidence of seropositive blood would become very high. GV would be provided for all seropositive blood. Because of the strong resistance to using it, the coverage of the GV usage would probably be limited. In Bolivia a single method (usually IHA) is now used for the routine screening test for Chagas’ disease. In Program 2-2 (P2-2) a combination of examination methods (IHA and IFAT) is applied to increase the sensitivity of the screening tests. If IFAT is added to IHA, the sensitivity of the screening tests is increased up to 98%. Program 2-3 (P2-3) is combined P2-1 and P2-2.

Program 3 (P3): The national blood transfusion system plan (Plan Nacional de Sangre para el Control de la Transmisión Sanguínea de Enfermedades)\(^{12}\) was chosen to compare with P1 and P2. This program (P3) is intended to establish a referral transfusion system in each
region. It consists of the promulgation of blood screening law, the organization and development of a network of blood banks and transfusion centers, training of personnel, promotion of blood donation, and quality control of screening tests (Table 21). P3 also uses the blood banks and laboratories of existing public health facilities. The main strategy of P3 is to organize a regionalized BTS. Most emergency cases will also be covered because a storage and referral system of blood transfusion services will be functioning. The coverage of screening tests is assumed to be 99% in urban areas. Under P3 the quality of screening tests will be improved because of the supply of good quality material and the quality control activities.

For the calculation of costs and effectiveness, the following assumptions were used. Parameters with best and worst case estimation were decided according to the official data and the local experts opinions. A baseline estimation, the best and worst value, were used for triangular probability distribution function for number of recipients (N), average number of blood units transfused (n), prevalence (f), infectivity (k), sensitivity (S1, S2, S3), coverage of screening tests (c1, c2, c3), and GV usage rate (g) (Table 22).

Program assumptions

a) The number of recipients (N) is 20,000 (the range 15,000-30,000) per year, and is estimated from the results of the national investigation (Table 9a). For comparability, the number of recipients of each program is fixed.

b) The average number of blood units transfused per recipient (n) is 2 (1.5-3), with a total number of blood transfusions estimated at 40,000 (baseline) per year \(^{38}\).

c) The prevalence of infected donors (f) is 0.30 (0.20-0.45) in Bolivia \(^{42,43}\). The results of SCGH were used for the baseline estimation.

d) Infectivity (k) is used 0.30 (0.12-0.50) \(^{44,45}\).

e) The sensitivity of the screening tests is 0.95 (0.8 - 0.99) for P1 and P2 (S1), 0.98 (0.90-0.99) for P2-2 and P2-3 (S2), and 0.99 (0.95-0.995) for P3 (S3) \(^{25}\).

f) The coverage of the screening tests is 0.5 (0.3-0.7) currently (c1). It will be elevated 0.95 (0.9-0.96) for P1, P2 (c2), 0.98 (0.95-0.99) for P3 (c3) respectively. It should be noticed the coverage is limited to the urban area.

g) The GV usage rate for seropositive blood units (g) is 0.8 (0.6-0.9) for P2-1 and P2-3, taking into account the persistent resistance to using GV among the population.

- Costs. Cost analysis was based on the study at Santa Cruz in January 1995 and the official data. The data were collected mainly at SCGH, San Juan de Dios Hospital (SJDDH), and Centro Nacional de Enfermedades Tropicales (CENETROP). There are some problems in projecting costs estimated in Santa Cruz to apply throughout all over the country. However, since the programs are limited to urban areas, this estimation can be applied to other regions. Each program cost was calculated an average cost per screening test, per blood transfusion and total cost.

All costs included three other screening tests (Hepatitis B, Syphilis, and HIV infection), because these tests are usually performed as a set in screening blood donors. They need almost the same equipment and can be done simultaneously. So costs in this paper refer not only to the

\(^{a7}\) Only 30% of the “hemotherapy center” performed complete screening tests, so it is estimated approximately 50% of blood units were not screened.
screening test for Chagas’ disease but also for the other transfusion-transmitted infections. Costs were calculated using following assumptions;

<table>
<thead>
<tr>
<th>Costs assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Personnel: Calculated as one medical doctor and three technicians in a blood bank, with salaries calculated using the salary scale (Escala salarial) of SCGH.</td>
</tr>
<tr>
<td>b) Supplies: Costs for kits and reagents of four screening tests, for Chagas’ disease, Hepatitis B, Syphilis, and HIV infection were calculated using the expenditure records of SCGH and SJDH. Costs of bags and infusion sets for blood transfusion were included.</td>
</tr>
<tr>
<td>c) Equipment and infrastructure: Blood banks had their proper space in the hospital and their own equipment such as small refrigerators for storage, a centrifuge, a microscope, etc. Basic equipment for the laboratory methods associated with blood transfusion, cleaning glassware, utilities, waste disposal, decontamination by autoclaving and by means of disinfectants etc. were shared with laboratory of the hospital. Using the official data, the cost of equipment and infrastructure was calculated as $2.75 for their depreciation$^{12}$.</td>
</tr>
</tbody>
</table>

Costs of P1 (C1). The average cost of a screening tests was estimated at $16.12 (Table 23a). In the current situation (P0) the costs of a) and c) were the same as P1, while costs of material b) were paid by patients. So the cost of P0 (C0) was defined as the sum of a) and c). A unit cost per screening test of the current situation was calculated as $6.07. In the current situation, with all units of seropositive blood discarded or not used, the necessary number of blood units was calculated to be 56,835 $^{8}$. The total cost of P0 was $172,439. Table 24 summarizes the unit costs and total costs of the programs.

In P1, materials of screening tests were provided for public hospitals where 52 % of a total amount of blood is transfused. A unit cost per screening test of P1 was $11.29 $^{9}$. Total costs were calculated as unit cost per screening test multiplied by number of screening tests. In P1, with all units of seropositive blood were discarded or not used, the necessary number of blood units was 69,652. The total costs of P1 increased to $736,838.

Costs of P2 (C2). In P2-1; GV is normally used in 125 mg/500 ml of whole blood, and does not require special equipment or procedures but only injection into bags of blood. Its cost was calculated $1.295 for a unit of blood $^{10}$, including only cost of the material not its preparation and distribution. Although GV should be added to all seropositive blood units, in this study costs were calculated as 80% usage of GV. The necessary number of blood units of P2-1 was 50,809 and total costs were $558,129 $^{11}$. In P2-2, Costs of IFAT were calculated at $1.933 per examination and added to C1. All screening tests (coverage 95%) were performed in combination of IHA and IFAT. In this program the seropositive blood was not used as in P1, so the necessary number of blood units was 66,735 and total costs were $768,835. In P2-3 for

$^{8}$ Suppose the necessary number of blood units is x, prevalence of Chagas’ disease is 0.3167, sensitivity of screening test is 0.88, specificity of screening test is 0.9; 0.5x+0.5*0.3167*(1-0.9367)x+0.5*(1-0.3167)*0.9x=46994, x=56835

$^{9}$ 16.12*0.52 + 6.07*0.48 = 11.30

$^{10}$ GV 125mg= 0.125US$, 1 small bottle (0.5 US$) contained 62.5mg.of GV2 bottle and 1 syringe (0.17US$) are necessary. 0.125 + 0.5*2 + 0.17 = 1.295US$

$^{11}$ 11.29*50809+0.9367+1.18*22707*0.7667= 558129
seropositive blood GV was used and its coverage was also 80%, the necessary number of blood units 50,434 and total costs $ 599,009.

**Costs of P3 (C3).** For the cost estimation of P3, financial costs of the national plan were used. P3 is a four year program and total costs are estimated at $ 1,891,090 (Half of these funds require external aid) \(^{12}\). Since the activities of P3 are not only for blood screening tests directly, it is difficult to calculate the unit cost for the screening tests for blood donors. However, all activities are aimed to reduce transfusion-transmitted infections, so in this paper all costs are assumed to be used for this purpose.

Costs were calculated as follows; a) Personnel (in each region): responsible persons in laboratories and blood banks, a health promoter team (medical doctor and co-medical), and educational promoters of Red Cross and community. b) Equipment and materials (in each blood bank): existing equipment and material for the laboratory and blood bank, reagents for Malaria, Chagas’ disease, Hepatitis B, syphilis, and HIV, and educational printed material and audiovisual material c) Depreciation for the infrastructure and equipment: 4% and 8% respectively \(^{12}\). In the first year 40,000 and in the second year 50,000 serologic tests for Chagas’ disease, Hepatitis B, syphilis, and HIV will be performed in P3. The average cost of P3 for a unit of blood is estimated $ 17.37 (Table 23b). In P3 the necessary number of blood units was calculated to be 68,162, however total costs were fixed at $ 694,700 in the budget plan (Table 24).

**- Effectiveness.** In the process of estimating effectiveness it is important to select appropriate indicators. The seroprevalence of *T. cruzi* infection among children is a sensitive indicator for assessing the effectiveness of programs for control of Chagas’ disease \(^{74, 75}\). However it is not suitable for this study because the control of TTCD is a part of the control program of Chagas’ disease and the impact to the prevalence is smaller than the vector control itself. It cannot capture the differences among the alternative interventions. Therefore the following measurements were used for the indicators of health outcomes gained by the programs in this paper; 1) the number of infections averted, 2) the number of deaths averted (ACD and TCD), 3) PEYLL gained, and 4) DALYs gained.

Costs of all programs included those of three screening tests other than Chagas’ disease, so the benefits of them could be calculated. However in this paper these were excluded. In other words the costs were overestimated for the TTCD control program.

**the number of infections averted.** The number of infections with Chagas’ disease caused by blood transfusions is calculated with the formula 3. Using the parameters with probability distribution shown in Table 22, it is estimated that the risk of TTCD is 0.172 \(^{*12}\) and 3732 infections would occur per year unless screening tests were performed \(^{*13}\) (Table 25).

The coverage of the screening tests in P0 is assumed to be 0.5 in the urban area and the sensitivity of the tests is 0.8833. The risk of infection and annual number of infections of P0 are 0.09619 and 2084 respectively. In P1 the coverage and the sensitivity of screening tests will be 0.9367 and 0.8833 in the urban area. The risk of infection and annual number of infections of P1 are 0.02974 and 644 respectively (Table 25).

The coverage of the screening test in P2 will not be changed with P1 (0.9367). The sensitivity of the screening test in P2-2 and P2-3 will be increased to 0.9567. The risk of

\(^{*12}\) In the case of baseline value, the risk of the transfusion-transmitted Chagas’ disease= 1-(1-0.3)^2 x 0.3= 0.153

\(^{*13}\) In the case of baseline value, the number of infection= 20000 x 0.153= 3060
infections (annual number of infections) of P2-1, P2-2, P2-3 are 0.0153 (331.6), 0.0179 (387.9), and 0.0125 (271.8) respectively (Table 25).

The coverage of the screening tests in P3 can be almost 0.9733 in urban areas and the sensitivity of the screening tests is 0.9883; the risk of infection and annual number of infections are 0.00655 and 141.9 respectively. The number of infections averted with each program was calculated by reducing the calculated number of infections after screening from the number of current infections (P0) (Table 25).

**the number of ACD and TCD averted.** Using the TNHCM (Model (30)), it is possible to calculate the number of deaths averted for each program. For each infection, 0.0044 of ACD will occur 60 days after infection and 0.2596 of TCD in 50 years after infection (III. 4). The total number of ACD (TCD) averted by P1, P2, and P3 were summarized in Table 26.

**PEYLL gained.** PEYLL per one TTCD infection was 3.703, obtained from Model (30). PEYLL gained by P1, P2, and P3 were summarized in Table 26. A discount rate of 0.03 was used for calculation.

**DALYs gained.** DALYs per one TTCD infection were 4.790 also obtained from Model (30). DALYs gained by P1, P2 and P3 were summarized in Table 26.

**- Cost-effectiveness analysis.** Using NHCM, it is possible to obtain the numbers of ACD, TCD, PEYLL, and DALYs per infections. It is also possible to estimate the numbers of infections averted through the effectiveness of each program. Both numbers have their probability distribution according to the probability distribution functions of parameters. Costs of the programs also have been calculated. By combining these data, the cost-effectiveness of each intervention can be calculated.

In this paper the incremental cost-effectiveness analysis was used to indicate the cost-effectiveness of the interventions. Incremental cost-effectiveness of replacing Program 1 with Program 2 is defined as (Cost 2 - Cost 1) / (Benefits 2 - Benefits 1). In this paper benefits were the following health outcomes: The number of cases averted (acute and chronic), The number of deaths averted (ACD and TCD), PEYLL gained, and DALYs gained. Results are summarized in Table 27.

Compared current the current situation (P0), incremental costs and also incremental effectiveness were calculated (Table 27a). Figure 9 shows the relation between total DALYs gained and Cost/ DALYs gained ratio of each program. P2-1 has the least cost-effectiveness ratio, so it is thought to be the first option. Although P2-3 and P3 have larger cost-effectiveness ratios, they can get more total DALYs gained. Figure 10a shows the marginal cost-effectiveness of P2-3 and P3 compared to P2-1. P2-3 has a less marginal costs/ DALYs ratio than P3, so P2-3 is the second option. In the same way their marginal cost of P3 to P2-3 can be calculated. If a willingness to pay of decision maker exceed a value of these costs, they could be chosen to get more benefits (Figure 10b). The marginal costs P2-3 and P3 are relatively high comparing a Costs/DALYs ratio of P1 to get the additional health outcome of DALYs.

**- Sensitivity analysis.** In this study many assumptions were used and some of the parameters had a large range of value. These uncertainties and variations were due to the complexity of the disease and the scarcity of epidemiological data. They should be recomputed whether the results were insensitive to these assumptions or not. Parameters used in this study
had four kinds of value estimates: baseline (most likely), best, worst, and value with probability distribution function. Parameters used for the sensitivity analysis were as follows;

**Parameters related to the blood transfusion;**
1) number of recipients (N)
2) average number of blood units transfused per recipient (n)
3) prevalence of infected donors (f)
4) infectivity (k)
5) sensitivity of screening tests (S)
6) coverage of screening tests (c)
7) GV usage rate (g)

**Parameters related to Chagas’ disease;**
1) mortality (m)
2) transitional rates (a, v)

There are two methods of assessing uncertainty \(^{76,77}\):

1) **A deterministic sensitivity analysis; best case and worst case scenarios**

In deterministic (conventional) sensitivity analysis points estimates are analyzed such as “best case” and “worst case” scenarios. Usually one input variable is changed and the others are held constant. **Figure 11** shows results of classical sensitivity analysis. Infectivity (k) is the most sensitive to the costs/DALYs gained ratio in the range of this study. High infectivity of 0.476 was reported from Bolivia. However in this study 0.3 was used for the baseline estimation. Prevalence (f) is also sensitive especially in a low situation. For example if it is 0.01, the number of cost/ DALYs gained will be increased to 2530 US$. Sensitivity of screening tests (S) and coverage of screening tests (c) were not so sensitive within the rage used in this study. Rate of GV usage is directly related to total cost programs and also the number of discarded blood units (**Figure 12**).

2) **A stochastic simulation**

In stochastic simulation input variables are characterized as probability distributions which are assigned according to familiar distributions. In this study triangular and uniform distributions are used based on the number of data with expert opinions. Computer software is available for this calculation. **Figure 13a** shows the probability distribution of the incremental cost-effectiveness ratio (costs/ DALYs gained) of each program. Using this figure, it is possible to say that **P2-1** and **P2-3** have a high probability of low incremental cost-effectiveness ratios. **Figure 13b** shows the probability distribution of a marginal cost-effectiveness ratio compared to **P2-1**. **P3** has a high probability of positive DALYs gained; however the probability of a cost-effectiveness ratio is lower than **P2-3**. **Figure 14** shows the probability distribution of the incremental costs/DALYs gained ratio compared with **P2-1**. **P2-3** has a ratio of smaller than 1 with high probability while the other programs have that of larger than 1. From these results, it is possible to say that **P2-1** is preferable to **P1, P2-2, and P3**, but **P2-3** is preferable to **P2-1**. Using a graph of probability distribution, it is possible to compare the interventions visually.
V. Discussion

Health policy is crucial in establishing national programs. In Bolivia, major health policy shifts were announced in 1982. More emphasis was placed on preventive health, however, the allocation of public funds still favored curative care. It is quite obvious that Chagas’ disease is still a very serious public health problem in Bolivia. The control of Chagas’ disease should receive high priority among several health interventions. A national plan for Chagas’ disease control has been announced officially in 1989, but it has not yet been put into actions yet. Only a pilot project was started in 1989. Presumably the delay is not due to technical problems which have been largely overcome, but to operational and financial ones.

On the other hand, the importance of the control of TTCD is increasing. As a result of the recent huge scale of rural-urban migration, the problem of Chagas’ disease is expanding to urban areas rapidly, with blood transfusion the most important mode of transmission in these areas. The prevalence of HIV infection is increasing throughout Latin America. Several cases of Chagas’ disease associated with AIDS patients were reported as a new type of Chagas’ disease which involved multifocal or diffuse meningoencephalitis with pseudotumoral formation. AIDS is thought to be a factor that may favor the reactivation of T. cruzi infections. The importance of screening tests for blood donors is recognized more than ever before. This is an opportune time to establish an overall screening system for Chagas’ disease as well as others transmitted through transfusion. In short, transfusion medicine is indispensable for the development of modern medicine. Bolivia is now at the stage of creating transfusion medicine. A firmly structured BTS is necessary to develop transfusion medicine in near future. The screening system for the transfusion-transmitted infections is the first step toward this goal.

This paper emphasizes the importance of countermeasures for TTCD. Needless to say, the vector control program remains essential and the first most obvious option to reduce the incidence of Chagas’ disease. If the incidence of Chagas’ disease among the total population were reduced, its prevalence among blood donors would also be reduced. However vector control will take long time and will be very costly. For example, CCH project in Bolivia reported housing improvement cost $ 144.63 per house and insecticide spraying cost $ 10.95 per house (1993). Schofield also reported unit cost of house spraying $ 30.04 in Brazil (1991). These results which were not indicated benefits of the programs, cannot be compared to this paper. Generally speaking total costs of the vector control program is significantly high, especially in attack phase. By contrast, countermeasures for TTCD can be implemented with for less capital cost by using existing facilities. Furthermore they have the advantage of preventing that transfusion-transmitted infections other than Chagas’ disease with small shared costs. In conclusion, both a vector control program and a program for TTCD should be integrated as complementary approaches to controlling Chagas’ disease.

Programs and its alternatives.

In P1, materials for screening tests were provided for blood banks of public hospitals. A unit cost for an examination and for a blood transfusion are $ 11.3 and $ 31.6 respectively. Incremental cost-effectiveness ratios expressed as costs per DALYs gained compared to the current situation were $ 82 per DALYs gained. These results were also acceptable compared to an economic evaluation of other medical interventions. For example, costs per DALYs gained for core group of HIV infection are $ 7.42 ($ 2 per tests) and $ 37.08 ($ 10 per test), if proportion of donors infected with HIV infection is 0.1%. The high prevalence of Chagas’
disease in Bolivia is one of the reasons for the relatively good cost-effectiveness as presented in sensitivity analysis.

As the coverage of screening tests is improved, more seropositive blood will be discarded. The amount of discarded blood is shown in Table 25. Even in P1, at least 40% of the total blood will be discarded or not used. Blood is a precious limited resource and these opportunity costs will be enormous. WHO recommended to using some trypanosomicidal agents like GV for seropositive bloods, because its efficiency and safety were proved \(^{15}\). In P2-1 the usage of GV was added to P1. Unit costs for an examination and for a blood transfusion were $11.3 and $32.4 respectively. Incremental cost-effectiveness ratios of costs per DALYs gained compared to the current situation were $46 per DALYs gained. This was the best incremental cost-effectiveness ratio in all the programs. GV will be prepared and distributed for all serological positive bloods. Its cost is relatively low and no additional equipment necessary. Incremental cost-effectiveness is the highest in all options.

Another option which improves the sensitivity of screening tests is their combination (P2-2). This is also recommended WHO \(^{15}\). To get high sensitivity in screening tests is very difficult, especially in developing countries. Ideally, a laboratory network system with a quality control program is required. The combination of two methods of screening tests is a relatively easy way to get high sensitivity. In P2-2, unit costs for an examination and for a blood transfusion are $12.3 and $33.0 respectively. Incremental costs of combining two methods are not high. However, the better the sensitivity of screening tests, the more seropositive blood is discarded. Therefore to increase more cost-effectiveness it is recommended to use GV together also (P2-3).

The national control program for TTCD (P3) has several strategies besides screening tests for blood donors. These include donor recruitment, establishment of BTS networks, including storage and transportation system for blood units, and education for personnel in blood banks. In P3, the unit cost of the screening tests for transfusion-transmitted infections was $17.4 for a unit of blood. The incremental cost-effectiveness ratios ($75 per DALYs gained) was relatively high among the programs in this study, however, the largest health outcomes were obtained (Table 27).

Ideally, a national BTS network would be established immediately. However financial and operational problems are great obstacles to the implementation of the network. Actually the national program presented in this study cannot be implemented without foreign aid, because the budget of the original plan consists of both national and external funds.

For developing countries, a step-by-step approach that utilizes functioning existing facilities is feasible financially and operationally. Starting with hospital based blood transfusion systems and then integrating other activities to establish a regional blood transfusion service system is a realistic solution. GV is strongly recommended for its high cost-effectiveness.

**Other interventions.**

Donor recruitment is a generally recognized problem in developing countries \(^{83}\). In Bolivia the rate of blood donation is very low (Table 9b). The promotion of blood donation can be achieved by a national policy for example by enactment of a law \(^{18}\). However, since donation is also related to socio-cultural aspects, a national campaign and mass education are necessary. Education about blood transfusion for practitioners is also very important, to reduce unnecessary blood transfusions \(^{84}, 85\). This is one of the most reliable ways to reduce transfusion-transmitted infections. For example, a 10% reduction of both indications of patients and volume of blood
units reduces 16.2% of Chagas’ disease infections in baseline scenario of current situation (Figure 13). Strict criteria are necessary for blood transfusions, to promote the rational and efficient use of the blood supply. Indication for the children should be especially restrict. Model (10) will produce more health outcomes than Model (30) (Figure 14).

This paper has discussed the program for preventive TTCD in urban areas. There still remain problems in rural areas, where 42% of the total Bolivian population exist. From the viewpoint of equity, a comprehensive program should include countermeasures for rural areas. It is necessary to establish not only a blood storage and delivery system but also infrastructures such as transportation and communication, and a referral health system to improve accessibility, although the costs for them will be very large and they are not easy to implement.

Methodological issues.

To calculate health outcomes of the programs, a model was used in this study. It is necessary to evaluate the reality of the model. In Model (10) (which can represent natural history of vectorial transmission) after 20 years of chagasic infection, there are 69.1% of indeterminate stage, 21.7% of cardiopathy (CA+CB), 8.5% of digestive form (MV+MX). 26.5% of the digestive form (MV+MX) has cardiopathy (MX). Severe heart disease with heart failure (CB) is recognized as 0.7%. It is comparable with other studies in terms of the ratio of clinical forms to the cumulative number of deaths. Prata reported that after 20 - 30 years of infection, 40% of patients were still in the indeterminate stage 55). In Brazil, 20 - 30% of infected persons developed a cardiac form of the disease 5 - 8% a chronic esophagopathy and 4 - 6% a chronic colonopathy 18). Manzullo reported that among 5710 seropositive patients 1598 (28%) were symptomatic and that patients with signs of cardiac insufficiency numbered 104 (1.8%) 86). Many of digestive form were associated with cardiopathy. Rezende reported chagasic cardiopathy was found in 49.6% of cases with megaesophagus 87). In conclusion, NHCM can be comparable to these reports. Therefore it is possible to say that Model (30) can reasonably represent the natural history of TTCD under above-mentioned assumptions.

A Chagas’ disease model was reported by Ravinovich 88, 89). This was a transmission model and the clinical stages are not included. NHCM is the first model for the clinical course of Chagas’ disease. With limited data and also for the simplification, the model was compelled to be a assumptive. However the requirements of a model; realism, generality and precision are maintained in some balance 74). It can be developed easily adding more detailed data.

The data of a little-known disease like Chagas’ disease, which are from published literature and expert opinions, are not reliable. Moreover, data which are available in developing countries are very limited. In cost-effectiveness analysis, multiple uncertain values influence costs and effectiveness simultaneously. In such circumstances, a deterministic sensitivity analysis has limitations, especially variation of uncertain parameters one at a time carries a risk that interactions between parameters may not be captured 77). In case of multivariant sensitivity analysis, a stochastic simulation using model is more useful. It is very important to show how the uncertainties are, because usually the decision should be made under such kind of situations. To initiate the program, its strategies should be specific and rational. Moreover they should be pointed out clearly to decision makers. Deterministic sensitivity analysis can not demonstrate these interactions clearly.

Research on TTCD.
These are several critical research themes related to TTCD. An especially well designed prospective longitudinal study is one of the most desirable research subjects. Because longitudinal studies have been very few, many uncertainties of the clinical course of TTCD remain. An international standard protocol is necessary for the analysis and comparison of results. As more valuable specific data for some regions become available, the NHCM will be more complete. New chemical additives other than GV should also be developed especially to reduce the incubation time for emergency cases. New screening tests appropriate for developing countries are also urgently needed.

Economic study on Chagas’ disease control program is another important research theme. There are very few studies of economic evaluation and none for TTCD. The economical study concerning to the newly developed instruments should be performed to set the priority in national health policy making. It also will be contributed to the policy of donor nations or organizations. Economic analyses concerning the newly developed instruments should be performed to prioritize in national health policy and contribute to the policy of donor nations or organization.

VI. Summary and Conclusions

Chagas’ disease in Bolivia is very serious and has a great impact on society. Underuse of screening tests and the poor quality of screening tests are the most important problems. A control program for Chagas’ disease is urgently necessary and a control program for TTCD should also be included in it. As a strategy for transfusion-transmitted Chagas’ disease (TTCD), providing screening material including Gentian Violet is feasible and most cost-effective.

A Natural History Model of Chagas’ disease has been developed based on longitudinal epidemiological studies. Using this model, it is possible to calculate the number of infections and deaths averted, as well as PEYLL and DALYs gained as health outcomes by Chagas’ disease control programs. The data were not complete, so variables were added and probability distribution functions were used along with several simplifying assumptions.

Methodologically, this paper shown incremental cost-effectiveness analysis using a stochastic simulation. Stochastic simulation is very useful, especially in multivariant sensitivity analysis. A model for economic analysis with probability distribution functions has advantages to evaluate interventions using scarce data in developing countries. Incorporating more detailed data into this model will make it more complete and more useful.
Reference


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Tables and Figures