Modelling spatial variation in the cost-effectiveness of infectious disease prevention: a case study of controlling Chagas disease in the Andean region

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Abstract: this project assesses the relevance of spatial patterns of Chagas disease transmission *(Trypanosoma cruzi)* to the geographical allocation of resources for surveillance and control. We use a net benefit approach to cost-effectiveness analysis to compare alternative strategies and levels of implementation.

We developed an economic model to estimate the costs and effects of different Chagas control strategies in Colombia and Venezuela. These strategies which consider entomological survey and fumigation of houses were defined to reflect current and past approaches in the Andean region, and the opinions of experts and local policy makers. The model uses epidemiologic and demographic data at the village level from a Geographical Information System. Cost data on the current sampling, spraying activities and cost treatment are being collected in the two countries. Outcomes will be estimated in terms of expected infections and DALYs averted. The model will generate rankings of villages according to the expected net benefit of the strategies analysed.

This paper discussed the methodological aspects of specifying a model for economic evaluation of infectious diseases. We focus our analysis on four aspects of the model structure: optimization versus 'what if' approach, period of evaluation, number of iterations to be evaluated and extrapolation of infections adverted into DALYs averted.

We will model the impact of 'second-order' uncertainty over the input parameters by the use of probabilistic sensitivity analysis. Bayesian value of information techniques will be used to identify the model parameters and assumptions that should be targeted for future research.

1. Introduction

1.1 Purpose of the study

Decisions on the use of interventions are often applied uniformly across a 'State' or 'municipality' area. This does not necessarily represent the best use of limited resources when there are significant variations in incidence and/or in other socio-economic factors across the area. However, predicting spatial patterns of disease, and the consequent variations in the costs and effects of healthcare interventions, is not easy, particularly in developing countries where epidemiological data may be sparse. This problem is compounded for infectious diseases because of the need to predict the dynamic spread of infection over time. The information provided by a Geographical Information System (GIS) has the potential to help decision makers to target control strategies in such situations.

A GIS to develop predictive maps of the risk of Chagas disease is being developed by a collaborative group of researchers from the UK, Colombia and Venezuela. Chagas is a disease caused by a parasitic organism transmitted to humans by blood-sucking bugs that live in houses in many areas of Central and South America. A proportion of those infected go on to develop heart disease, sometimes many years later, with associated morbidity, mortality and healthcare costs. Through the GIS, all villages in Colombia and Venezuela are being given a priority index to reflect the risk of infection. This priority index is calculated as a weighted sum of variables such as altitude, temperature and vegetation, and also population and epidemiological data. The prime motivation behind the development of the GIS is to provide information to target preventive interventions. However, the existing system does not include information on the costs or effects of alternative control strategies.

The purpose of this present study is to develop the GIS to model the cost-effectiveness of selective control strategies for Chagas disease in endemic areas of Colombia and Venezuela. We consider strategies based on entomological testing and insecticide spraying to reduce levels of house infestation with the bugs that transmit the disease, For each strategy we estimate the costs and effects (in DALYs) at the village level. The study is based in four endemic 'departments' in Colombia (Casanare, Boyacá, Santander and Norte de Santander) and the State of Barinas in Venezuela. Approximately 10,000 villages in these highly endemic areas will be included in the analysis. Initially all strategies will be compared with a 'do nothing' option. We will then perform incremental analysis among the strategies. The development of a GIS linking cost data and epidemiological outcome data offers a unique opportunity for exploring variation in cost-effectiveness across space.

The purpose of this paper is to describe and discuss the structure of the model developed to perform economic evaluation of Chagas control disease. The following section of the paper describes the background on Chagas disease. Section three discusses the current strategies for vector elimination in place in Colombia and Venezuela. Section four discusses the methods, emphasising the model structure, the sources of data and the analysis. Finally we present a

discussion based on the main issues of the model structure which impact on the economic evaluation.

2. Background on Chagas disease

Chagas disease was first described by Dr Carlos Chagas in Brazil in 1909 (Chagas 1909). This condition also known as *American Trypanosomiasis* is caused by the protozoan parasite *Trypanosoma cruzi* which is transmitted to humans by blood sucking triatomine bugs. The triatomines ecological environment are poor constructed houses mainly in rural areas. These bugs are most likely to be found in houses with unplastered mud wall (in their cracks), mud floor and thatch or palm roofs.

The disease aetiology progresses in three stages, starting with the acute phase just after the bug bite, which for many patients passes unnoticed while other develop symptoms similar to flu. The acute phase can last from 6 to 8 weeks. The second phase of Chagas disease is an indeterminate period where patients with T. cruzi positive serology can remain for 15 or more years without presenting further symptoms. Finally the chronic phase of the condition developes in around 15-30% of the population when patients can experience different degree of heart disease, with some dying from heart attack. Other clinical complications found and reported in the southern cone include severe damage to the nervous and digestive systems of the patients (Schofield and Dias 1991; Basombrio, Schofield et al. 1998; Schenone 1998; Moncayo A 1999; WHO 2002)

Chagas disease is exclusive to the American continent. WHO has estimated that around 90 million people live in high risk areas whereas near 18 million are infected (WHO 1991(WHO 1991). Risky areas are rural areas where the vector is known to be endemic. Recent studies using a Geographical Information System (GIS) in Colombia and Venezuela have explored the correlation of altitude, temperature and vegetation with the presence of vectors.

There is no cure for Chagas infection, apart from the palliative care alongside the chronic symptoms, for the 15-30% that develops the chronic pathology. But recently a treatment for patient carriers of the infection in the acute and indeterminate stages has been recommended for schoolchildren, even though it has proved to be effective in only 60% of the cases (WHO 2002). This treatment comprises benznidazole medication, which can have side effects, and is not routinely provided in Andean or Central American countries.

Historically the control of Chagas disease has been targeted through insecticide spraying of houses at risk. In 1990 the 'Southern Cone Programme' eradicated Chagas in Uruguay (1997), Chile (1999) and in 8 of the 12 endemic states of Brazil in 2000 (Moncayo 2003). In the 1997 a new initiative supported by a Resolution of the World Health Assembly, defined the aim of interrupting Chagas transmission in Andean and Central American countries by 2005.

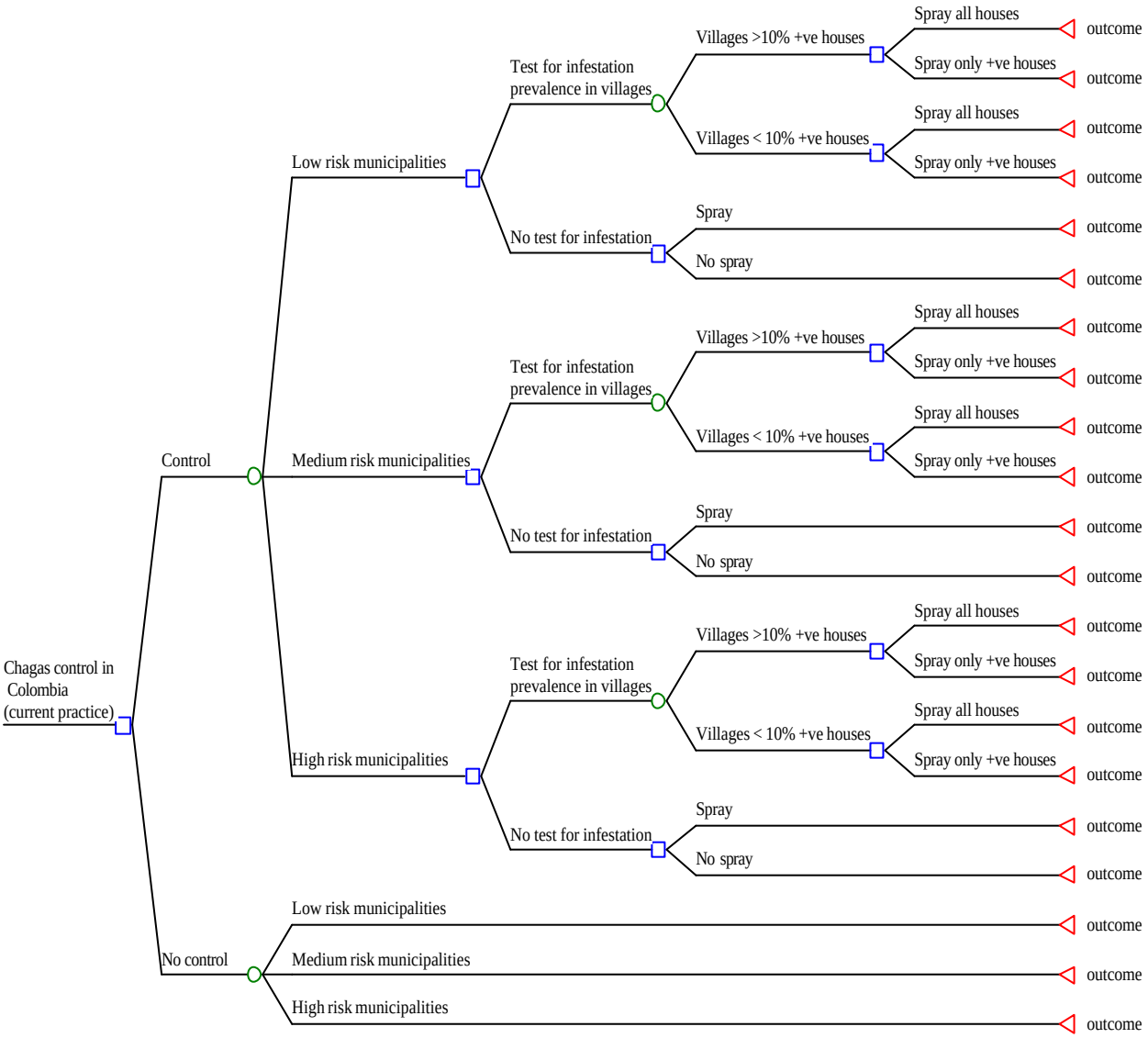
Colombia and Venezuela are two of the countries seeking to interrupt transmission by 2005. These countries have quite different experiences in

terms of controlling Chagas disease. In Venezuela the onset of the control programme was in 1945 when spraying programmes targeting malaria were shown to be effective against the triatomines; whereas in Colombia a pilot vector control programme was first implemented in the Departments of Cundinamarca and Santander only in 1996 (Guhl 1999) . In Venezuela the programme has managed to reduce prevalence of infection from 45% in 1960 to only 8.1% in 1990s in rural areas (Feliciangeli, Campbell-Lendrum et al. 2003). In Colombia the MoH and other local research institutions (CIMTROP, CIMPAT, UIS, ICMT) have estimated a prevalence of infection of 7% for the whole population, while 23% of the population are estimated to live in highly endemic areas (Guhl and Nicholls 2001)

3. Current interventions for Chagas control

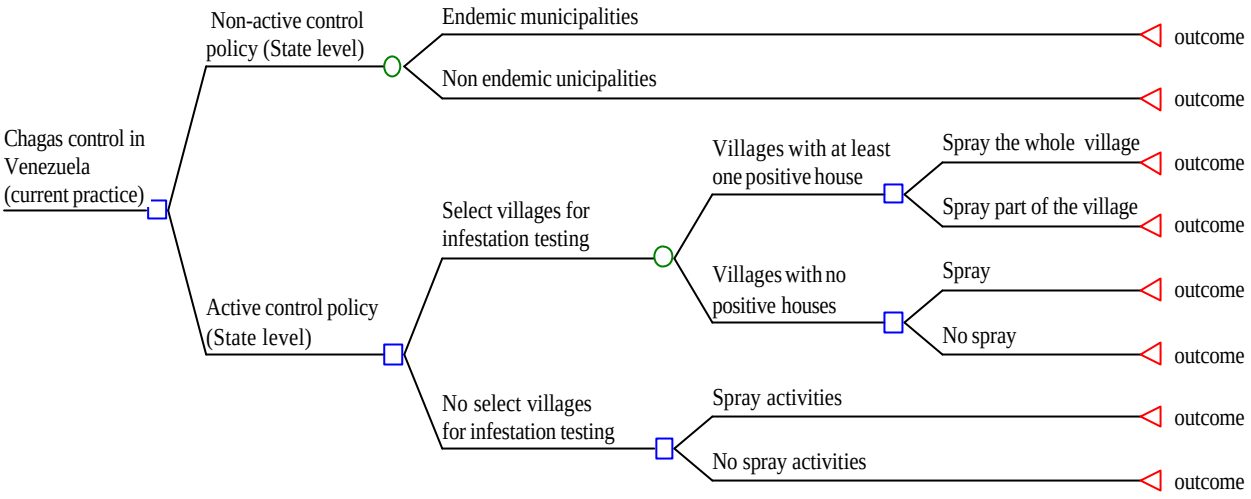
Interventions for Chagas control normally comprise three phases; preparation, attack and surveillance. In the preparation phase an entomological survey is conducted in the pre-selected villages. This is carried out by 2 trained health staffs who search for triatomine bugs for 30 minutes covering inside the houses and the peridomestic areas. The attack phase consists of applying insecticide inside the houses and peridomestic areas (according to the specific policy). The surveillance phase consists of evaluating reinfestation in the intervention areas, normally six months after the attack phase.
Colombia and Venezuela have slightly different policies for Chagas control. We have used decision trees to map out some existing testing and control policies used in these countries (see figure 1 for Colombia and 2 for Venezuela).

Figure 1: Colombia current Chagas control programme



As shown in figure 1 municipalities in Colombia have been categorised in low, medium and high risk for Chagas infestation. This was based on a large randomised cross-sectional survey on the distribution of *T. cruzi* infection in children and triatomine infestation of houses, conducted in 2001. At present control activities are carried out in high risk municipalities according to budget availability. Some Departments (such as Casanare and Boyacá) test all villages for infestation, while other Departments carry out control only in areas that were surveyed in the cross-sectional survey. A threshold of 10% house infestation in a village is used to decide whether to spray the entire village (when infestation is >10%) or to spray only the houses found positives (when infestation is <10%)

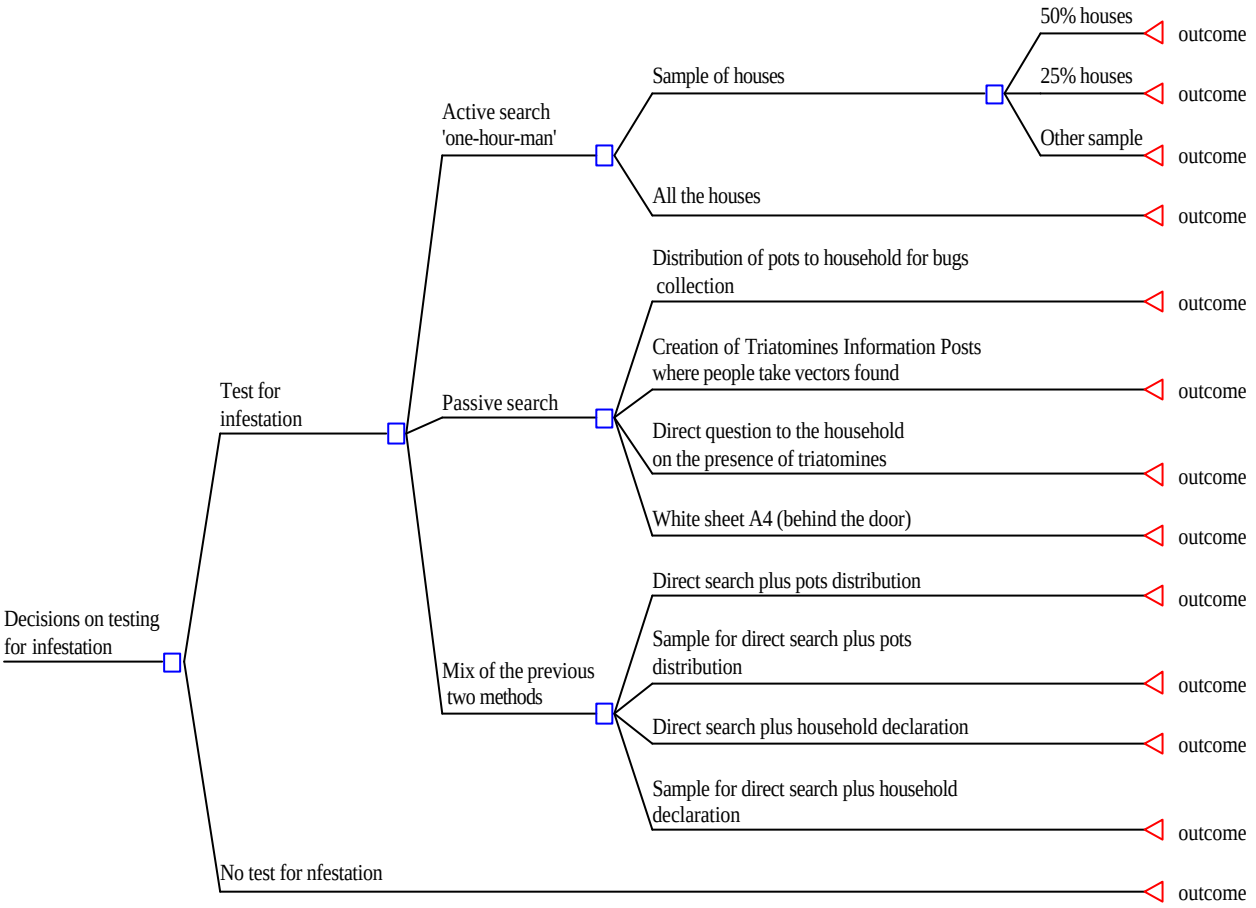
Figure 2: Venezuela current Chagas control Programme



In Venezuela there are some States that do not have an active policy against Chagas disease. In States that do have an active policy villages are chosen for sampling principally on the basis of the experience/knowledge of local policy makers regarding the possible infested areas. The sampling strategy in Venezuela consists of finding at least one positive house. The spray criterion states that if at least one house in the village is found positive, the entire village should be sprayed.

Entomological surveys conducted by health staff (also known as 'active search') constitute the typical approach for sampling for infestation. However, other 'passive' methods have also shown to be effective at detecting triatomine infestation. For example 'Sensor boxes' developed in Argentina showed to be more sensitive than direct searching (Chuit, Paulone et al. 1992). Recently, approaches based on community participation have improved detection and reporting of vectors. Householders are trained in the identification of triatomines and plastic 'pots' are distribute to capture the vector. This strategy has proven particularly effective for vectors that enter houses at night, and are therefore not easily found by direct searching ('one-hour-man' method), during the day. We have used a decision analysis approach to map out some of the potential options that policy markers have to carry out the entomological survey pre-spray. Figure 3 shows options for active search, passive search and a range of possible combinations of both.

Figure 3: Possibilities to carry out entomological survey for triatomines infestation



Predictive maps of infestation at the village level provide the possibility of trying a different approach. This is to eliminate testing for infestation but make a decision of spraying based on the predicted infestation priority index. The latter will be drawn from the GIS work and will be available for decision making from December 2004.

Regarding spraying approaches, the decision about how many houses to spray seems to be simpler. Historically most of the countries have use a 10% house infestation for a village as the 'threshold' to decide whether to spray only positive houses (plus the house in a radius of 200 metres), if the village infestation is less than 10%, or spraying the entire village if infestation is greater than 10%. As reported for Venezuela, finding only one house positive was considered sufficient evidence to spray the whole village.

From figures 2 and 3, which state current practices for Chagas control in Colombia and Venezuela, it can be seen that not all priority areas are covered. Furthermore, even in areas with active control, the programme is not always carried out strictly according to the definition. The lack/diminution of resources for Chagas control activities, some time due to the outbreak of other infectious diseases in the area such as dengue or malaria could force policy makers to divert resources, consequently the rules for testing and spraying for Chagas have to be relaxed.

Although other 'no-spray' methods to reduce house infestation have been tried, such as house improvement (Rojas de Arias, Ferro et al. 1999), insecticide treated bed nets (Kroeger, Villegas et al. 2003), insecticide treated curtains (Herber and Kroeger 2003) the evidence so far suggests that spraying houses has been the most effective and cost-effective method to reduce (and in some cases eliminate) house infestation (Oliveira-Filho 1989; Schmunis GA, Zicker F et al. 1996; Basombrio, Schofield et al. 1998; Moncayo A 1999; Rojas de Arias, Ferro et al. 1999; Nakagawa, Cordon-Rosales et al. 2003).This study has therefore focussed only on strategies based on spraying houses with insecticides.

4. Methods

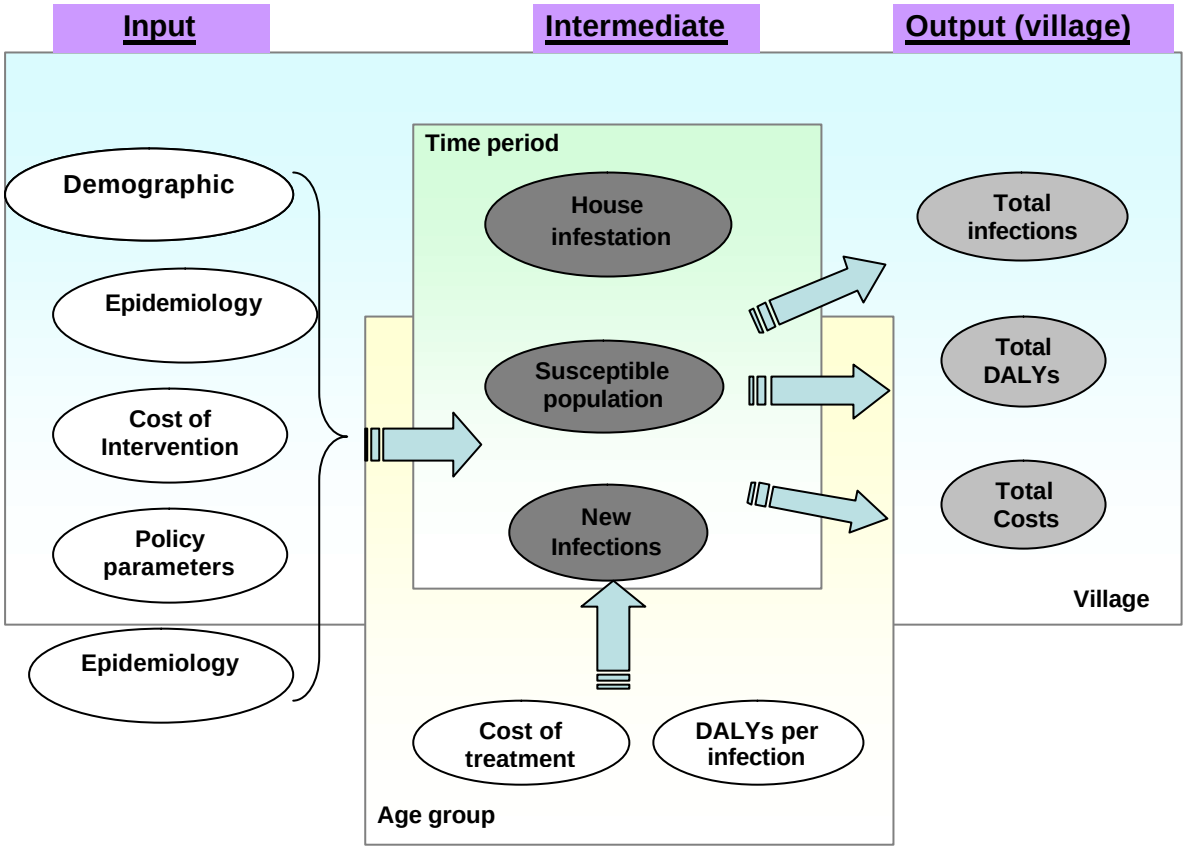
4.1 Model structure

We have attempted to develop a relatively simple model that integrates epidemiology, population, and policy parameters to predict cost-effectiveness at the village level. We use a deterministic Markov model to represent the dynamics of house infestation, which given a starting prevalence of infection in the population allows the determination of the population of susceptible people and hence the number of new infections per year. The dynamics of house infestation at the village level depends of the current level of infestation, the effectiveness of any control activities and the reinfestation rate. The dynamics of person infection depend on the estimated number of susceptible (ie non infected) people living in infested and non-infested houses and the annual risk of infection for each of these groups. The model thus allows us to predict the number of infections by age of infection for a given control strategy. The DALY loss and healthcare cost of Chagas-related heart disease is then estimated for the given strategy, along with the costs of entomological testing and spraying associated with the control strategy. Estimates of the short-term control intervention costs, the long-term health care costs and DALYs are thus obtained for a range of scenarios at the village level.

A simplified representation of the model is shown in Figure 4. The parameters and variables of the model are defined for up to three different indices, as shown by the three rectangular 'plates': the village', the age groups, and the time period. Parameters outside the boxes are general for all villages. The parameters are categorised as input parameters (un-shaded), intermediate parameters (strongly shaded) and output parameters (lightly shaded). Input parameters include demographic information (i.e. number of houses, number of people per house…), epidemiological information (i.e. initial levels of house infestation, reinfestation rates, prevalence of infection…), policy parameters that define the control strategy being evaluated (i.e number of houses tested, number of houses sprayed…) and cost parameters (cost per house sampled, cost per house sprayed…). Intermediate parameters are those calculated within the model as a function of the input parameters (i.e expected number of houses infested in village i at time t, number of people infected in village i at time t, new infections per year per village). The output variables defined at the village

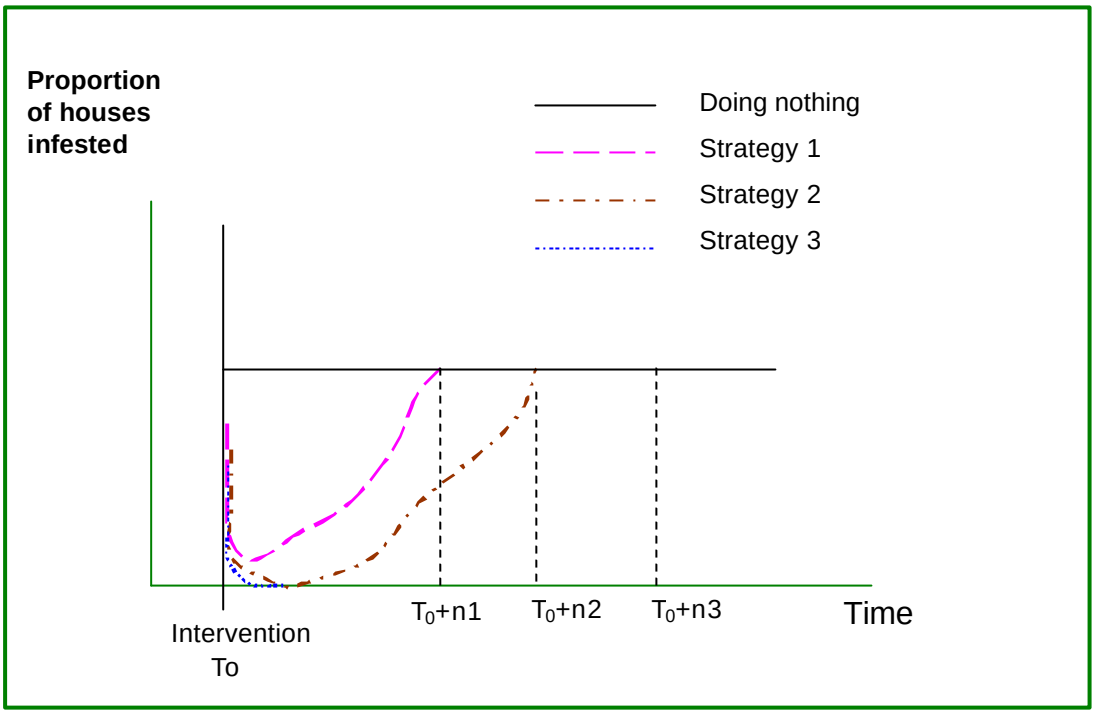
level are the number of infections, estimated DALYs and treatment costs associated with these infections, and the cost of the control strategy.

Figure 4: Basic features of the model structure



The time horizon for evaluating each strategy should correspond to the whole period during which the strategy is effective. The effectiveness of each strategy is measured by its capacity to reduce the number of infested houses in a village, which in turn has a direct impact on the number of new infections. For simplicity, we assume a one-off implementation of the testing/spraying strategies, as illustrated in Figure 5. For example, consider strategy 1. Following an initial reduction in house infestation at time T_0, there is a gradual increase over time until the number of infested houses is indistinguishable from what it would have been in the absence of intervention (after n_1 years). The number of *infections avoided* will be related to the area between the 'do nothing' and the appropriate strategy line on this diagram. The question of how to select an appropriate time horizon is addressed further in the discussion section below.

Figure 5: Prevalence of infection and temporary dip due to intervention



We have initially modelled the population from zero to ten years of age in ten different cohort groups, with an additional group for people over ten years of age. We focus our model on children under 10 years, as they are relatively more affected by Chagas infection: if a person is infected at an early age they can potentially develop the chronic condition before their thirties, constituting a great burden of disability and premature mortality. In addition, blood screening for Chagas infection has been carried out systematically in children to evaluate the effectiveness of the control policies over time. Therefore, there is a reliable source of data on prior prevalence for these age groups. Although we are focusing on the young population (0-10 years old), by keeping track of the cohort which comprises all the population above 10 years old, we will monitor the aggregated impact that new infections in this group can have over the whole population.

4.2 Sources of data

Most of the data used to populate the model are being collected from primary sources in Venezuela and Colombia. The Disease Control and Vector Biology Unit (DCVBU) of the Department of Infectious Tropical Diseases at LSHTM have been working in Colombia and Venezuela since 2001 producing predictive maps for infestation of the villages. Updated data on population structure at the municipality level has been provided by the National Institute of Statistics in Venezuela and by the health administration Departments in Colombia. The number of houses per village is being drawn from census data. Estimates of the parameters determining the dynamics of house infestation and person

infections will be obtained from local studies where possible, or from the literature or 'expert opinion' if necessary.

The cost of the current control programme (cost of spraying per house, and cost of testing a house) is being collected in Colombia and Venezuela. Two studies from other countries report costs for vector control activities (Oliveira-Filho 1989; Basombrio, Schofield et al. 1998). Estimates of the cost of spraying per house ranged from US$20 (1984/85 currency) in Brazil to US$65 (1998) in Argentina.

Data on treatment costs and health services utilization is generally scarce for this condition and particularly for the countries of study. Many chronic patients living in rural areas do not seek healthcare and some of the patients die without a diagnoses for Chagas. We identified two studies reporting on the cost of hospitalization for Chagas treatment (Schenone 1998; Vallejo, Montenegro et al. 2002), although the latter does not report resource quantities and unit costs separately. In Colombia we found a locally published study reporting patterns of morbidity for chronic Chagas patients based on a retrospective review of 120 patients records hospitalised in a cardiologic clinic in Bogotá (Rosas, Velasco et al. 2002). Another observational study, also based on chronic Chagas patients, was carried out in primary care centres in the Boyacá Department. In the latter study 405 individuals (comprising 205 seropositive and 200 seronegative patients) were characterised from a clinical and electrocardiography point of view. Further, retrospective studies of Chagas patients will be conducted in selected hospitals to estimate the costs of treating chronic Chagas patients. Data on utilization of health services will be drawn from an expert panel meeting to be carried out next August in Bogotá Colombia.

There are studies of the effectiveness, cost-effectiveness and cost-benefit of using insecticides for vector control, (Schofield and Dias 1991; Basombrio, Schofield et al. 1998; Nakagawa, Cordon-Rosales et al. 2003). However, we have not found any good evidence of the effectiveness of using different sample size to evaluate infestation, although one study was identified (Acevedo F, E et al. 2000), there were problems with the study design and therefore we can not draw valid conclusions. We will estimate the impact of sample size for example by sampling from a binomial distribution in the probabilistic sensitivity analysis.

4.3 Methods of analysis

The costs and DALYs associated with each strategy will be estimated at the village level. This increases the size and complexity of the model since there are more than 10,000 villages in the areas of research. However, it allows great flexibility for posterior analysis at the national, municipality or department/state levels. For example we can determine the aggregated incremental cost-effectiveness ratio for one strategy compared with another at a national level and at a municipality level. However, we can also examine variations in cost-effectiveness between different villages within a municipality.

Given an estimate of the cost-effectiveness threshold, which can be crudely approximated by the GDP per capita for Colombia and Venezuela, we can also calculate a monetary net benefit from cost-effectiveness information.

We will model the impact of 'second-order' uncertainty over the input parameters by the use of probabilistic sensitivity analysis (Monte Carlo simulation). By using value of information analysis we will attempt to inform which the key parameters are, where future research on Chagas should be focused. This is potentially important since Chagas has been considered one of the neglected diseases for research (Morel 1998)

5. Discussion

There are various methodological issues that have arisen during the development of our model. We focus here on four key issues: optimisation versus a 'what if' approach; the choice of time horizon for evaluation; the number of iterations to be evaluated; and extrapolation of DALYs for economic evaluation of infectious diseases.

5.1 Optimisation vs 'what if approach'

The problem of having to allocate a unique budget between two complementary activities such as searching for infestation and spraying infested houses suggests the idea of optimisation. The dilemma for decision makers lies in the need to know where the triatomines are before deciding which villages to target and which houses to spray within each village. This problem suggests that there is an optimal sample size and strategy. The sample size impacts on costs but also on the ability to effectively target spraying activities. However, the more money that is spent of sampling, the less that is left over for spraying.

In practice we found that many policy makers are reluctant to consider sampling sizes other than those they are familiar with. Since historically the control activities have been linked to prevention, education and population census, a survey pre spraying has normally been done in all houses of a village. Most of the searching is done by health services staff and no more than three criteria are used: searching for one positive house, searching 10% of houses and survey according to the village size (in the State of Cojedes in Venezuela villages with less than 50 houses are searched completely, 50% are sampled if village size is between 50 and 100 houses, and 25% are sampled if there are more than 100 houses). A potentially different sample size per village could be difficult to implement when some municipalities have around 100 different villages. It is possible that the costs of organising this implementation could offset any gain.

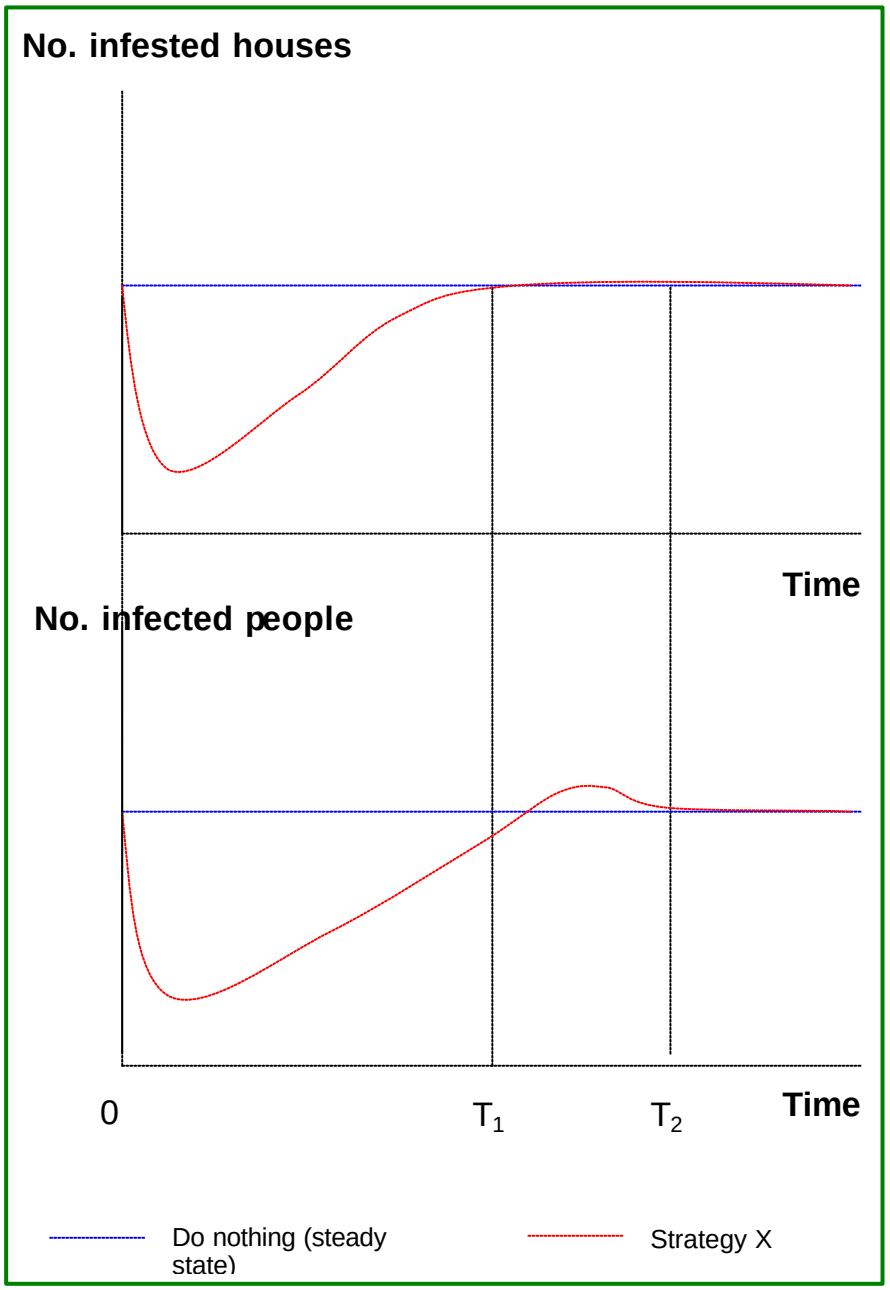
These practical constraints discouraged us from considering an optimisation approach. Instead, we opted for a 'what if' approach, estimating the costs and effects of a discrete number of sampling/spraying strategies that according to local policy makers could be implemented in Venezuela and Colombia.

5.2 Time horizon for evaluation

Defining the right evaluation period for cost-effectiveness analysis can be difficult. This seems to be even more confusing when dealing with infectious diseases where most of the interventions do not provide immunity but only protection during the intervention period. The evaluation period should clearly be long enough to capture the whole time in which the strategies are effective. As shown in figure 5, different strategies could be associated with different reinfestation rates and therefore different periods of evaluation might be necessary. However, as illustrated in Figure 6 the time for the number of infested houses to return to steady state (T1) is not the same as the time for number of infected people to return to steady state (T2). At T1 the annual probability of a susceptible person becoming infected following intervention is the same as if we had done nothing. However, there are more susceptible people following intervention, so the number of newly infected people must be higher and the total number of infected people must still be rising. The values of the parameters in the model determine the shape of the infestation and infection graphs.

In this situation it is necessary to follow the model for time T2 (in figure 6) to capture the whole effect of the intervention and therefore not overestimate the number of infections averted. The fact that T2 differs between strategies is not a problem, since we can track each strategy until the number of people infected (hence DALYs and treatment costs) becomes indistinguishable from the do nothing option.

Figure 6: The relationship between house infestation and population infection

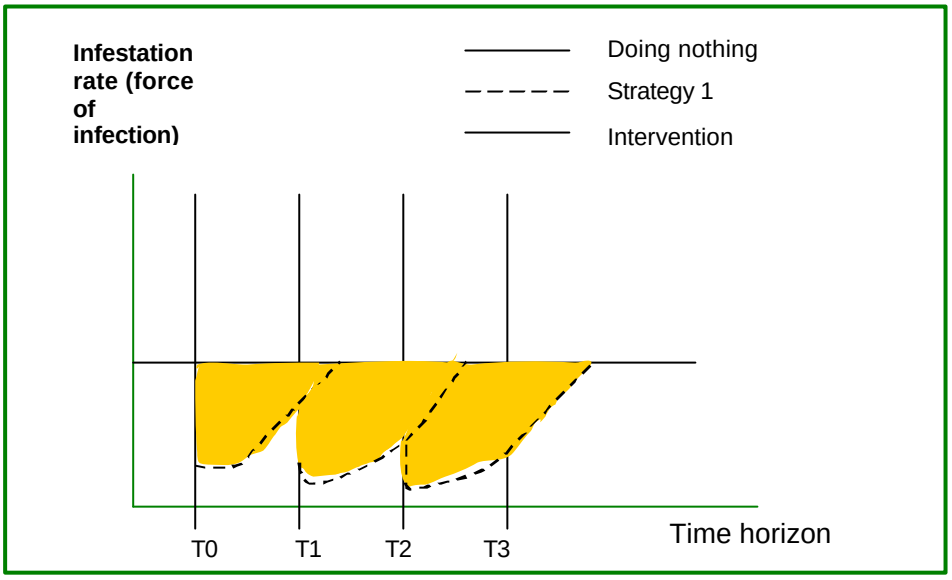


5.3 Number of iterations to be evaluated

In real life control interventions are likely to be applied in an ongoing fashion. It would be possible to model this. However given the size and complexity of the model, together with the time constraints for project completion, we aim to evaluate each strategy for only one iteration. If strategies are to be repeated at time intervals T, where T is less than the total time in which the strategy is effective ('n') we expect that subsequent interventions will be even more

effective in reducing the overall infestation rate (see figure 7). Therefore, we think that our baseline results based on the one-off intervention will be conservative. This approach will also reduce the necessary time horizon for analysis, and consequently reduce the degree of uncertainty over the results. This model aims to provide a decision support platform for local decision-makers. If necessary, the model could be fed with updated parameters and re-run yearly if necessary.

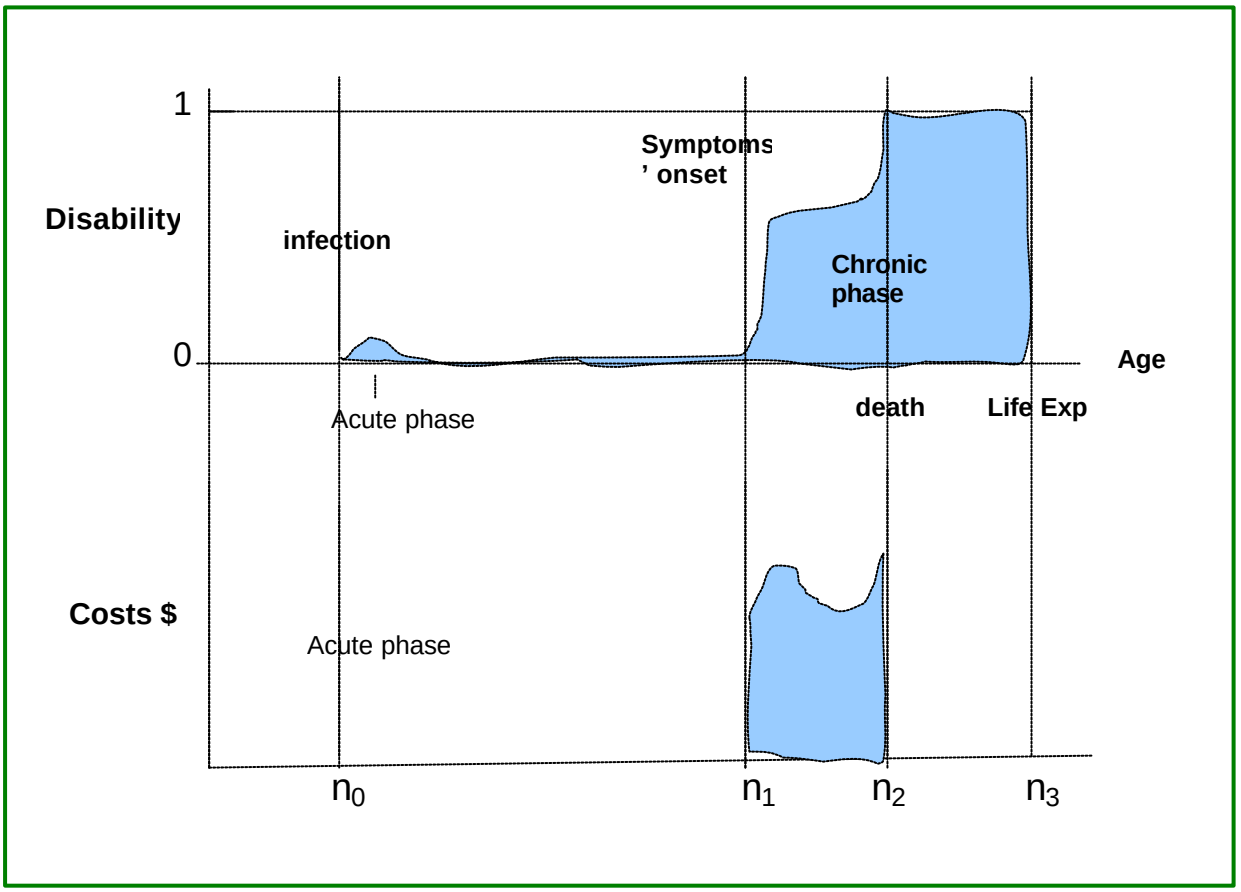
Figure 7: Modelling more than one iteration for intervention.



5.4 DALY estimation

For the baseline case we will estimate the number of 'net' infections (and hence DALYS and treatment costs) incurred for each year at the village level. The expected profile of DALYs over time for an infected individual is illustrated in Figure 8. The upper graph relates to the morbidity and mortality of the condition, which comprises the acute phase of the disease (just after infection) and the chronic phase for patients who develop Coronary Heart Disease (CHD). As shown in figure 8, the expected number of DALYs lost per infected person will be estimated over peoples' expected lifetimes, by calculating the discounted sum of DALYs due to premature mortality (n_3-n_2) and by disability (shaded area between n_1 –n_2). Similarly, the graph below in figure 8 illustrates the expected treatment costs over time for an infected individual. These costs are expected to occur between the onset on the condition and the death of the patient (from n_1 to n_2). We assume that there is no treatment for the acute or the indeterminate phase of the condition. The expected lifetime cost of treatment is estimated by taking the discounted sum of annual costs. Both DALYs and lifetime treatment costs will be negatively related to the age of infection.

Figure 8: Estimation of DALYS due to Chagas disease



Extrapolation of the number of infections averted into DALYs averted is not a straightforward exercise. This is especially true when dealing with an infectious disease. The strategies that we are modelling here have the advantage of protecting susceptible people from getting infected. However that protection is reduced or disappears in the absence of a continuing control strategy. Therefore, assuming that infections averted, in a period when susceptibles are temporarily protected, guarantees DALYs averted, might be thought to constitute an overestimation of outcomes. Only when the intervention protects people through the entire life time we will be certain that the infections averted constitute DALYs averted. Hence a comprehensive model for the case of Chagas (also applicable to other infectious disease such as malaria, dengue, HIV/AIDS) needs to account for the risk of infection after the intervention period. As discussed earlier there are two approaches that could be used in this case , one is to carefully select the horizon of evaluation (T_2 rather than T_1 in figure 6). Secondly, we could model repeated interventions so as to maintain the protection level (as in figure 7).

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