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ALTERNATIVES. What alternatives to the chemical control of Chagas disease vectors?

Frédéric Lardeux

To cite this version:

Frédéric Lardeux. ALTERNATIVES. What alternatives to the chemical control of Chagas disease vectors?. 2011. ird-03370290

HAL Id: ird-03370290

https://ird.hal.science/ird-03370290v1

Preprint submitted on 7 Oct 2021

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Acronyme / Acronym	**ALTERNATIVES**		
Titre du projet / Proposal title	Quelles alternatives au contrôle chimique des vecteurs de la maladie de Chagas ?		
Titre du projet / Proposal title	What alternatives to the chemical control of Chagas disease vectors?		
Axe(s) thématique(s) / Thematic axis	☐ 1 ☒ 2 ☐ 3 ☐ 4		
Type de recherche / Type of research	☒ Recherche Fondamentale / Fondamental ☐ Recherche Industrielle / Industrial		
Aide totale demandée / Requested budget	260 936 €	**Durée du projet / Duration**	36 mois / months

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1. CONTEXT AND POSITIONNING OF THE PROPOSAL

1.1. BACKGROUND, STATE OF THE ART, ISSUES AND HYPOTHESIS.

The present project proposes to study the population dynamics of *Triatoma infestans*, the main vector of Chagas disease in southern South America, in order to explore **new alternatives to the chemical control of the vector**, the present universal control strategy.

Chagas disease is a parasitic anthropozoonosis of the Americas. The WHO reports more than 15-20 million infected people, more than 100 million people at risk (25% of the south American population), more than 50.000 annual deaths, and is responsible of a burden of 670 000 disability adjusted life years (DALY) (WHO 2004), making this human parasitic disease the most important of the American continent. Some 50,000 people are diagnosed every year, but it has until now remained mainly a disease of very poor and isolated populations, "making it a commercially unviable candidate for drug development," according to SciDevNet in Reuters AlertNet which adds: "Chagas is the disease with the highest impact in Latin America. It is probably causing over two-and-a-half times more lost years of healthy life than malaria, leprosy, bilharzia and leishmaniasis combined." These numbers, yet alarming, are unfortunately likely to be underestimated (Reithinger et al. 2009).

The disease is caused by *Trypanosoma cruzi*, a protozoan parasite transmitted by Triatomines which are hematophagous bugs (*Hemiptera, Reduviidae*). Vector transmission is responsible of >80% of human cases (other transmission routes are mainly through blood transfusion and congenital) (Schofield 1994) and in the countries of the Southern Cone (Argentina, Brazil, Bolivia, Chile, Paraguay and Uruguay) *Triatoma infestans* is the major vector. It is a species strongly associated to Man: its life cycle takes place essentially inside or close to human dwellings. As no vaccine or prophylaxis is available today and because of the epidemiology of the disease, **the best control technique is currently based on the control of the vectors** (WHO 1991). At present, it consists in insecticide sprayings (pyrethrinoids) inside and outside houses. They are carried out by specialized governmental services, with nevertheless the risk of negative impact on the environment. **This strategy is universally used in all endemic countries of Central and South America.** The necessity to reduce the use of pesticides in public health has been clearly announced during the "Grenelle de l'Environnement "in France and by the Biocide directive of the European Union (directive 98/8/CE). In the developing countries and particularly in South America, Health Ministries are aware of pesticide problems and ask more and more for environmental safe approaches when health is concerned.

Due to the actions of these national control programmes, including the general use of pesticides, vector borne transmission has been reduced and even halted in some of the southern cone countries such as Chili and Uruguay (Dias et al. 2002). However, elsewhere, transmission is still very

active as in Bolivia, Argentina, Paraguay, Peru etc. Moreover, Chagas disease appears to be spreading from isolated rural areas to urban areas as people move to cities. Vector transmission is now proven in suburbs of large growing cities in Bolivia (Albaracin et al. 1999, Medrano-Mercado et al. 2008) and Peru (Fraser 2006, Levy et al. 2006, Bowman et al. 2008) and are clear alarming signals of the spreading of the disease in epidemiologically sensible areas.

The legitimate questions are therefore if "insecticide alone" strategies are well suited to fight Chagas disease and why a better control cannot be achieved in the entire distribution range of the vector?

Chagas vector control has been carried out without any scientific background. Indeed, population dynamics and possible responses of vector populations to control actions have never been taken into account to plan effective interventions. Because *T. infestans* has a rather long developmental cycle for a vector (6-12 months), it reacts on a longer time scale as compared for example to mosquitoes. Therefore, one did not notice real vector fluctuations on the long term. Erroneously thinking that insecticide sprayings (going back to the 1960's) were really effective, no scientific study has been carried out to identify parameters to optimize this control strategy. This strategy is also hampered by several operational and knowledge gaps, of which **insecticide resistance** are the most important (Tarleton et al 2007). Insecticide resistance in Chagas disease vectors is a recent emerging problem that challenges vector control and can jeopardize the long term success of this control strategy. Focuses of high insecticide resistance in *T. infestans* populations have been identified in Argentina (Picollo et al. 2005) and most of Bolivian populations are resistant to pyrethroid insecticides that are used by the National Program for Control of Chagas Disease, leading to operational failures (Lardeux et al. Submitted).

Recent studies have demonstrated that *T. infestans* population dynamics is an important issue to understand why parasite transmission is still active, after decades of insecticide control. The **vectorial capacity of the insect** (Garret-Jones, 1964) is dependant on several bio-ecological factors such as vector longevity, the proportion of blood meal taken on a host, the density of vectors relative to the number of hosts and the duration of the extrinsic cycle of the parasite in the vector and also behavioural ones (domesticity of the species, speed of defecation etc.) (Dujardin et al. 2000). Some of them are moreover interdependent, leading for example to **density dependant processes** (Schofield 1980, 1994, Gürtler et al. 2009). In some instances, it is hypothesized that these processes are responsible of difficulties in controlling the parasite transmission because diminishing vector densities may favours transmission! The (false) idea that the current vector control strategies (insecticides) are sufficient (because some success in control have been achieved in some places) and **gaps in understanding vector dynamics to detect the real impact of vector control** on transmission are likely responsible of the insufficient results observed. Therefore, because a global understanding of the vector dynamics has never been achieved, reduction of transmission is not achieved in most of the distribution area of *T. infestans* (Bolivia, Argentine, Paraguay, Peru etc.).

Apart from these focuses on population dynamics, control strategies should also take into account some **spatial parameters**. In fact, from an economical point of view, control efforts can be better distributed if vector focuses (and therefore disease focuses) are well identified. Chagas disease vectors are "aggregated", not only at the scale of a house (these insects live in colonies), but also in terms of house infection: in a same village, some houses are heavily infested when other are not. In a same way, there exist villages with few infested houses and other where a majority of them are.

The question is therefore if a global treatment of a geographic area (all the houses of all the villages) as carried out nowadays is justified, spending billions of US$, or focus treatments in specific areas (villages or houses), taking into account insect migration capabilities (and therefore its

reinfestation potential) and its panmictic geographical area. If reducing interventions is a viable strategy, economical gains will be obtained, as well as a better use of pesticides if they are part of the strategy, limiting bad environmental impacts and preserving human health.

Therefore, **alternative control strategies are urgently needed** to face (1) the insecticide resistance problem, (2) the lack of immediate alternative control strategy, (3) the recrudescence of the disease prevalence in some countries and (4) the spreading of the disease in new areas. Some keys are already suggested, such as house improvement (Cecere et al. 2002), which impedes the installation of Triatomine colonies, but the impact of such measures has never been quantitatively analyzed. One can also think of zooprophylaxy, pulling insects to hosts where the parasite cannot develop (i.e., birds, such as chicken for example), or manual elimination of bugs by the inhabitants themselves, or the pushing and fixing of triatomine colonies in areas where contact with humans is reduced (i.e. outside houses). In a same way, the perfecting of the actual insecticide strategy is recommended until the designing of new strategies. However, the impact of insecticide resistance on disease transmission is not well quantified and new insecticide strategies (focus treatments, intervention frequencies etc.) would also be compared to the actual one. All these techniques are not 100% effective and therefore their (combined) impact is difficult to analyze. A **mathematical model** will therefore help in understanding interactions between the bug dynamics and new potential vector control strategies.

To sum up, the objectives of the ALTERNATIVES program are: (1) to study the population dynamics of *T. infestans* to better understand its **vectorial capacity** from a qualitative point of view (i.e. what are the influential parameters) and quantify its parameters, (2) study the **spatial aggregation** of Triatomes at different geographical scales (houses, villages etc.) and (3) to combine the above results in a **mathematical model** to better explore new (integrated) vector control strategies aimed at minimizing pesticide approaches.
The "Chagas" model might serve other vector transmitted diseases, such as dengue which shares various eco-bio aspects.

The ALTERNATIVES project will therefore benefit to National Vector Control Programs, in Bolivia but also in other endemic countries of the southern cone where *T. infestans* is the main vector (Argentina, Paraguay, Peru in particular…).

1.2. CONTEXT OF THE PROPOSAL

The ALTERNATIVES project will attempt to resolve several important issues that have important social, economic and environmental stakes. Indeed, for this re-emerging parasitic disease, optimizing the present chemical control strategy is in keeping with the general worldwide guidelines of a better use of pesticides in health policies and the protection of the environment. The search for an optimal control strategy by integrating several approaches is also in keeping with the diminishing of the number of diseased people, the control of the spread of the disease, the fight against poverty and the help to developing countries to improve public health.

The project is innovative because the research aspects under study are new for Triatomines, in particular the building of a mathematical model aimed at exploring the actual insecticide strategy and new ones to improve the control of transmission and limit the use of pesticides in the human environment.

The project can also serve as a baseline study to construct similar approaches on vectored diseases: Chagas disease is a general model and other diseases transmitted by insects can be considered as sub-models because their life cycle is less complex.

In the frame of this ANR-CES call, the ALTERNATIVES project is perfectly suitable. It enters the problematic of axis 2 (*Ecosystem Dynamics and Contaminant Impacts*) for which the theme "*Interactions between pathogens and ecosystem components*" has been displayed. In this theme, there is a call for modelling parameters of disease transmission, resistance and control strategies compatible with a healthy environment.

At an international level, several groups working on Chagas disease are focusing their research on vector control, looking for new insecticide strategies or integrated strategies. Some research groups work on bio-ecological characteristics of *Triatoma infestans* and have pointed out some parameters that can interfere with vector control actions and transmission success, such as density dependence processes. However, none intends to study the vector in ALL its dynamics components to understand its dynamics, its spatial distribution and the parasite transmission. In that sense, the ALTERNATIVES project will be the first project of this kind on Chagas disease, integrating field data and vector transmission modelling to explore new vector control strategies aimed at minimizing the use of insecticides.

Chagas disease can be used as a **general model** to study vector transmitted diseases, as its eco-bio-social aspects include almost all aspects of other vectored diseases. In particular, the dynamics of the vector in the human environment is comparable to that of *Aedes aegypti*, the mosquito vector of dengue or *Aedes albopictus*, vector of Chikungunia virus which also can be characterized as "domestic" vectors. Therefore, the approaches developed in the ALTERNATIVES project for Chagas might be **usefully employed later on other vectored diseases**. The integrated approach in the ALTERNATIVES project is similar to the one used in the late 1970's for malaria in the GARKI project (Molineaux and Gramiccia, 1980) which definitely improved our knowledge on this disease.

The ALTERNATIVES is based on the collaboration of two disciplines: medical entomology and mathematical modelling. Within this framework, research teams of the Southern Cone countries, in particular in Bolivia will be involved, in particular in tasks which necessitate field samplings. Academic formation of **researchers of the South**, either in their country (Bolivia), or during exchanges with the laboratories of North is a significant part of this project whose finality remains **public health improvement**.

2. SCIENTIFIC AND TECHNICAL DESCRIPTION

2.1. BACKGROUND, STATE OF THE ART

Insecticidal control of Triatomines has been effective for many years (Schofield, 1994) and therefore, insecticides were practically the only tool used and applied on large geographical scales. Since the advent of pyrethrinoid insecticides like deltamethrin, lambda-cyhalothrin and alpha-cypermethrin, only these insecticides are used for Triatomine control. Indeed, they are effective and harmless to Man. Despite first signs of resistance detected since 1969 in Venezuela with dieldrin (Gonzalez-Valdivieso et al. 1971, Cockburn 1972), risks of insecticide resistance appearance within the *Triatominae* family were under-evaluated. However, in 2000, Brazilian populations of *T. infestans* were detected **resistant to pyrethrinoids** (Vassena et al. 2000), and in 2002, high levels of resistance led to operational failures in Argentina (Salta) and in 3 distinct and distant areas of Bolivia (Picollo et al. 2005). These resistances seem to be the direct consequence of insecticidal vector control strategies (against Triatomines, but also against sympatric *Anopheles*). Preliminary results of our team in Bolivia

tend to show a geographical generalization of pyrethrinoid resistance, with variable but high levels of resistance from one population to the other (Lardeux et al. submitted). In Bolivia, *T. infestans* seem always sensitive to organophosphorous and carbamate insecticides although some tolerance has been detected (Lardeux et al. submitted). To face this emerging problem, the insecticide control strategy should be re-thought and within this frame, a model to simulate new approaches would be needed.

Indeed, various mathematical models on Chagas disease transmission have pointed out the essential role of the decrease of vector densities to control the disease (Inaba & Sekine, 2004; Chiyaka et al. 2008; Massad 2008 among others). In the field, reducing vector densities with insecticides has also proven to be an effective measure to control the disease (Rassi et al. 2003) **although it was not always the case** indicating that interrelations between population dynamics parameters play an important role: Indeed, Chagas disease has not been reduced to an epidemiologically unimportant disease: it is still an important health problem, with recent new spreads in cities. Models and field results indicate that **a more efficient vector control is needed to really slow transmission** (Cardinal et al. 2007). However, these models are basically qualitative because few quantitative data are available to build a real quantitative model of vector transmission. Available data are partial and/or poorly collected and therefore a generalization is uncertain. There is a lack of a global study aimed at analyzing *T. infestans* population dynamics in order to quantify parameters of interest and understand what real impacts have vector control actions. Indeed, some characteristics of *T. infestans* dynamics are qualitatively determined such as its aggregative behaviour at various geographical scales (house, villages, regions…) (Schofield 1994) but there is no quantitative measure of such aggregation phenomenon. In a same way, age structure and longevity of the bug is not well quantify, as well as its relation to temperature (and climate) which control densities and the number of generations per year (Gorla and Schofield 1994). Density dependence phenomenon has long been recognized in *T. infestans* (Schofield 1980, 1982, 1985, 1994; Schofield et al. 1986), and some of the impacts on life traits (survival, fecundity), bug population dynamics and parasite transmission hypothesized. For example, density dependence can modify the bug trophic preference (and therefore the risk of transmission if the bug prefers to go up to humans) (Gürtler et al. 2009). Unfortunately**, all these aspects of population dynamics have never been modelled together**, and such a tool is urgently needed to better understand in what direction efforts should be put to improve the control of the disease.

As for control, alternative methods reducing the use of insecticides have been proposed. Indeed, the transmission of *T. cruzi* by *T. infestans* to humans occurs mainly at night while people are sleeping in their houses. Limiting man-vector contact will limit the parasite transmission. This can be achieved not only by reducing vector populations inside human dwellings (which seems to be the key factor to reduce (and even eliminate) transmission (Inaba and Sekine 2004), but also by keeping away the vectors from the sites where transmission occurs (*i.e.* inside houses in case of human transmission by *T. infestans*). Therefore, if one can evict Triatomines from their resting places inside houses (cracks in the walls, thatch roofs etc.), transmission will diminish and even disappear. Pushing away vectors and redirecting them to sites where their elimination is easier has been called "push-pull" strategy**.** Control interventions such as the distribution of insecticide impregnated material (bednets or curtains with repulsive effect) can be used to limit insect populations and to keep them away from transmission sites (essentially bedrooms)(Kroeger et al. 1999, Heber and Kroeger 2003), even in areas where insecticide resistance is present. They have proved to be effective on vector densities and even on the limitation of the invasion by *T. infestans*. Indeed, repulsive effects of insecticides such as pyrethrinoids or other molecules with slow-release vapours may keep Triatomines away from their resting sites (Borda 1978, Cichero 1978). In the same way, parasite transmission among domestic animals can be controlled by treating them and/or controlling animal-vector contact using insecticide "pour-on's" or repellents on animals. Other methods can be proposed to limit the parasite transmission by Triatomine vectors, in particular housing improvement that limits the sites where

Triatomine populations can develop (OPS 1998). Some improvement methods such as wall plastering can have an impact on the colonisation of houses by Triatomines (Dias and Dias 1982, Schofield and Marsden 1982, Schofield and Matthews 1985). They are cheap and easy to implement by communities or individuals, especially where houses are made of adobe walls and where plaster can be advantageously replaced by local coating material (Rozendaal 1997). Active capture of Triatomines and their progressive elimination from the domestic and peridomestic environment by simple hygienic and cleaning methods may help to maintain house infestation levels below an epidemiologic threshold (Dujardin et al. 2000). This implies that inhabitants might capture and eliminate from time to time the Triatomes from their houses. Cleaning houses may help in reducing vector populations. Domestic animal that live inside houses such as hens, guinea pigs or even dogs can maintain high level of Triatomine infestation. Therefore, keeping such animals away, in appropriate shelters and outhouses can considerably limit the presence of Triatomines inside houses (Schofield and White 1984). Even if the "eradication" of *T. infestans* is not achievable when only one of these "stand alone" control methods is used, the permanent interruption of transmission can probably be achieved through an integrated control program combining various techniques and including a social development and sustained surveillance component. Indeed, combining several control methods may have a good impact on the decrease of house infestation (Guillen et al. 1999) and efforts must be continued to improve such integrated approaches (Cardinal et al. 2007). Once again, **without a mathematical model mimicking *T. infestans* population dynamics, impact of these new control methods on transmission cannot be estimated**.

Early attempts to model *T. infestans* population dynamics have focussed on computer simulation using variation of biological parameters (Rabinovich 1971, Rabinovich and Himschoot 1990, Rabinovich and Rossel 1993). Other deal with a general analysis of Chagas disease transmission, including vectors and other transmission routes (blood transfusion, congenital transfusion etc.) with a more or less theoretical approach (Velasco-Hernandez 1994, Hinaba and Sekine, 2004 among others) or theoretical epidemiological view point (Slimi et al. 2008). Chagas disease has also been used to explore theoretical aspects of mathematical modelling (Das and Mukherjee 2005, 2009, Inaba 2003) and are of less interest to vector control. Vector control has rarely be the subject of model building for Chagas disease. Only an Argentinean team has summarized its experience in models in which some vector control ideas could be tested (Castanera et al. 2003, Cohen and Gürtler 2001). However, these interesting approaches are likely to reflect local characteristics of the vector and a generalization of their results to other geographic areas would be necessary. On the other hand, these models deal with local transmission, i.e., transmission at the scale of a house and therefore, no attempt has been made to measure the impact of control measures at a large geographical scale, taking into account the aggregative characteristic of *T. infestans* populations in a village and among villages. Therefore, new insights in modelling of Chagas disease vectors are needed and are partly the aim of this ALTERNATIVES project. From a pragmatic view point, such a new model will only be a tool to better understand vector control impacts and should respond to questions such as (non exhaustive list): (1) what is the impact of resistance on control? (2) Where should control actions take place (i.e., what is the geographic strategy? (all or some places?) (3) What would be the impact of partial control coverage? (4) What would be the impact of an alternative control strategy (alone or in combination)? (5) How long should control actions be maintained to get a sustainable control? (6) What would be the minimum effort needed to control transmission?

Such questions are real scientific stakes that summarise the present international research carried out on Chagas disease transmission. The actual ALTERNATIVES project will therefore focus on the necessary steps to **significantly move forward**, beginning with **field experiments** to clearly

understand vector's population dynamics and to explore alternative vector control strategies through modelling.

2.2. AIMS OF THE PROPOSAL, RELEVANCE TO THE CALL FOR PROPOSALS HIGHLIGHTING THE ORIGINALITY AND THE NOVELTY

The ALTERNATIVES project is clearly directed towards the Public Health and proposes **pragmatic objectives** for the improvement of the control strategies of *Triatoma infestans*, the principal vector of Chagas disease in the Southern Cone countries of America. ALTERNATIVES however proposes new ideas and new original insights to Triatomine control because of its integrated approach.

Taking into account the scientific and technical recent advances and the emergence of specific problems in the control of Triatomines, **the main objective of the ALTERNATIVES project is:**

The in-depth analysis of *Triatoma infestans* population dynamics to explore new vector control strategies aimed at minimizing (or at least optimizing) the present "insecticide » strategy in the framework of sustainable and environmentally safe approaches.

In the project, modelling is only a tool developed to explore qualitatively and quantitatively new control strategies, and not an end in itself.

The significant scientific advance of the ALTERNATIVES project is <u>the complete</u> and in-depth study of *T. infestans* dynamics. For that, 3 secondary objectives have to be achieved. They also define the 3 tasks of the project. Two objectives are directed toward the acquisition of quantitative field data (objective 1 and 2) in order to correctly model the dynamics of the vector and simulate new control strategies (3rd objective).

<u>Objective 1</u>: *Spatial distribution of Triatoma infestans*
The aggregative distribution of *Triatoma infestans* (densities inside human dwellings, infection rate of houses inside a village, global infection rate of villages etc.) should be assessed. The spatial distribution of the vector is a key factor for vector control actions and the diminishing of house infection rates. Indeed, this spatial distribution is equivalent to the infection rate observed in humans for macroparasite diseases such as filariasis. In this kind of disease, aggregative distribution of worms is observed among humans and therefore, depending of the ecology of the parasites, various modes of control have been suggested such as: the global control of the human population, the control of heavily infested hosts only, the control of these hosts and relatives etc. In the case of Chagas disease, not only the description of (house and village) infection rates should be assessed, but also the possible vector exchanges between houses and/or neighbouring villages should be quantified to correctly model the dynamics of infestation. This objective can be achieve by counting bugs in human dwellings, mark-recapture techniques at small scale (migrations among houses in the same village) and genetics (to quantify population flows between houses or neighbouring villages for example), exploring that way the modes of dispersion of the vector and the speed of colonisation or re-colonization after a control action.

Scientific or technical difficulties for that objective: There is no difficulty in obtaining such field data. Samplings methods for Triatomines are well known and used in routine. Mark-recapture

techniques are of common practice in ecological studies and even some refinement can be done using for example radio tracking technology. As for genetics, quantification of gene flows between populations can be assessed using microsatellites which are described for *Triatoma infestans*. The only difficulty would reside in marking-release-recapture protocols as it is unethical, once captured, to leave alive possible disease vectors in human dwellings. For such experiments, a protocol using special enclosures with animals and without humans is planned (see the description of tasks)

Objective 2: *Population dynamics of Triatoma infestans*
Crucial parameters of population dynamics of *T. infestans* should be assessed, in particular those defining the vectorial capacity of the species: host blood preferences, population age structure, densities of insects relative to possible blood-hosts (including humans), infection rate by *T. cruzii*, etc. These parameters should be studied under seasonal changes (*T. infestans* abundance is known to fluctuate with temperatures) at least during a 2 year survey, and interrelationships among them described: for example, density dependent processes influencing the blood source choice, survival, abundance etc.. These parameters should also be quantified, or at least defined allowing to their range values. Without quantitative information the built model (Objective 3) would be only qualitative, which is not sufficient to explore impacts of vector control actions.

Scientific or technical difficulties for that objective: there is no particular difficulty in planning these field experiments. Field survey of *T. infestans* in villages is a routine practice within the participating laboratories of this project. Techniques fore identifying blood meal sources of blood sucking insects are well known and of current use as well as those for studying vector infection rate, population age structure, densities etc…The only difficulty would reside in the rather long life cycle of *T. infestans* (6-12 months), forcing some field surveys to last at least 2 years. The observation of density dependence processes would also, in some cases, need large samples (for example, sampling several dozen of houses to carry out analysis such as regressions of one parameters on others) which is time (and money) consuming.

Objective 3: *Mathematical modelling and vector control*
Once the population processes identified and quantified in objective 1 and 2 , a mathematical model describing the population dynamics and population structure of *T. infestans* will be built. This model will be based on a compartmental analysis of the Chagas situation, using differential equations to describe the various processes of population growth and structure. As much as possible, the model will be based on biologically meaningful parameters in order to better analyze results of a sensibility analysis. If the model correctly describes present results, it will be used to simulate various scenarios of vector control strategies which modify the vectorial capacity of the insect.

Developed end- products, expected results, innovating character of research

The innovating character of the research is the **integrated approach** of a vector transmitted disease. The goal is the **exploration of new control strategies** which are not based on the use of pesticides alone. Modelling will help in quantifying the probable impacts on transmission. Indeed, to date, only qualitative studies have given orientations on vector control actions (i.e., acting on "this" will have an impact on "this"), without any quantitative result. In the same way, Chagas vector control has always neglected the necessary integrated vision of the spatial distribution AND population dynamics (of

which density dependence phenomenon where largely underestimated!). The ALTERNATIVES project will thus serve as a baseline to further studies on other vector transmitted disease.

List of the principal expected results:

1. A better knowledge of *T. infestans* population dynamics and ecology.
2. A better knowledge of *T. infestans* spatial distribution and house colonization dynamics
3. A model to explore new control strategies of Chagas disease and to give keys to take decisions concerning the use of insecticides (while waiting for the development of alternative control methods), and keys to manage vector control.

List of expected repercussions:

1. A pragmatic tool for National Control Programs (Argentina, Bolivia, Paraguay etc.) to control *T. infestans*.
2. A base for reflexion on the use of "insecticide" alone strategies to efficiently control vectors.
3. A base of reflexion on the use of alternative strategies to control *T. infestans*
3. The intervention of other specialists in vector control, in particular those with knowledge of alternative methods (not based on the use of pesticides) aimed at acting on one or other parameter of the vectorial capacity of *T. infestans*.
4. A better control of house infestation by *T. infestans* and therefore of Chagas transmission, resulting in a lower burden of the disease in the human population.
5. A brake on growth of the geographic spread of the disease and its re-emergence in endemic countries.

The stakes of the ALTERNATIVES project are thus multiple:

Scientific: The project attempt to model the dynamics of *T. infestans,* not only at a biological scale (*i.e.* the modelling of the vectorial capacity, its seasonal variations and the relationships amongst parameters leading for example to density dependence processes), but also taking into account the aggregative characteristic of the species at small and large scales (from house to village and more extended geographic areas).

Social: If control of *T. infestans* is not enhanced, Chagas disease is likely to return at epidemiologically high levels of transmission, in geographically extended rural areas and concerning more human populations than currently (cities are nowadays under transmission risk).

Environmental: The project will also give keys to decide if insecticide control is still a viable alternative, and if so, in which geographical areas, on which local populations and under which conditions of use. Indeed, an unreasoned use of insecticides with unsuited (high) dosages or unsuited class of insecticide is likely to seriously pollute the environment. Recent examples of misuse of insecticide when an unreasoned decision is taken have unfortunately pointed out the gravity of the repercussions in term of human (and animal) health (Grossman 2004).

3. SCIENTIFIC AND TECHNICAL PROGRAMME PROJECT MANAGEMENT

3.1. SCIENTIFIC PROGRAMME , SPECIFIC AIMS OF THE PROPOSAL

The ALTERNATIVES project is structured in two complementary phases: (1) field acquisition of data and (2) statistical analysis and mathematical modelling. To conclude it, 2 teams from France and one team from Bolivia will be involved:

-1- The research Unit 16 "Characterisation and Control of Vector Populations" (CCPV) from IRD (Institut de Recherche pour le Développement), of which two components will be directly involved in the project:

- The LIN-IRD (Laboratoire de Lutte Contre les Insectes Nuisibles) in Montpellier. *Participating researchers* in the project: **F. Chandre** (head) and **S. Duchon**.
- IRD-Bolivia, which is a LIN extension in Bolivia. *Participating researcher*: **F. Lardeux** (coordinator of the project)

-2- The UMR 2724 GEMI (Génétique et Evolution des Maladies Infectieuses), Montpellier, of which the group DySMI (Dynamique des Systèmes - Maladies Infectieuses). *Participating researcher* of DySMI : **M. Choisy + a post-doc student .**

-3- Laboratory of Medical Entomology at INLASA (Instituto Nacional de Laboratorios de Salud) in La Paz, Bolivia. *Participating researchers*: **T. Chavez** (head) and **S. Depickère.** This Laboratory belongs to the network of IRD-CCPV and therefore, the personnel of IRD-Bolivia is working inside its building. For the project management and ANR rules, this Bolivian laboratory will therefore be associated to the IRD-CCPV unit.

The ALTERNATIVES project first requires field data to incorporate in the mathematical model and make it operational. These data will be collected according to the two ecological dimensions of interest in vector control: the **spatial analysis** and the **bio-ecological dynamics** of the vector populations. Then, a **mathematical model** will be built to incorporate the various bio-eco processes described during these phases.

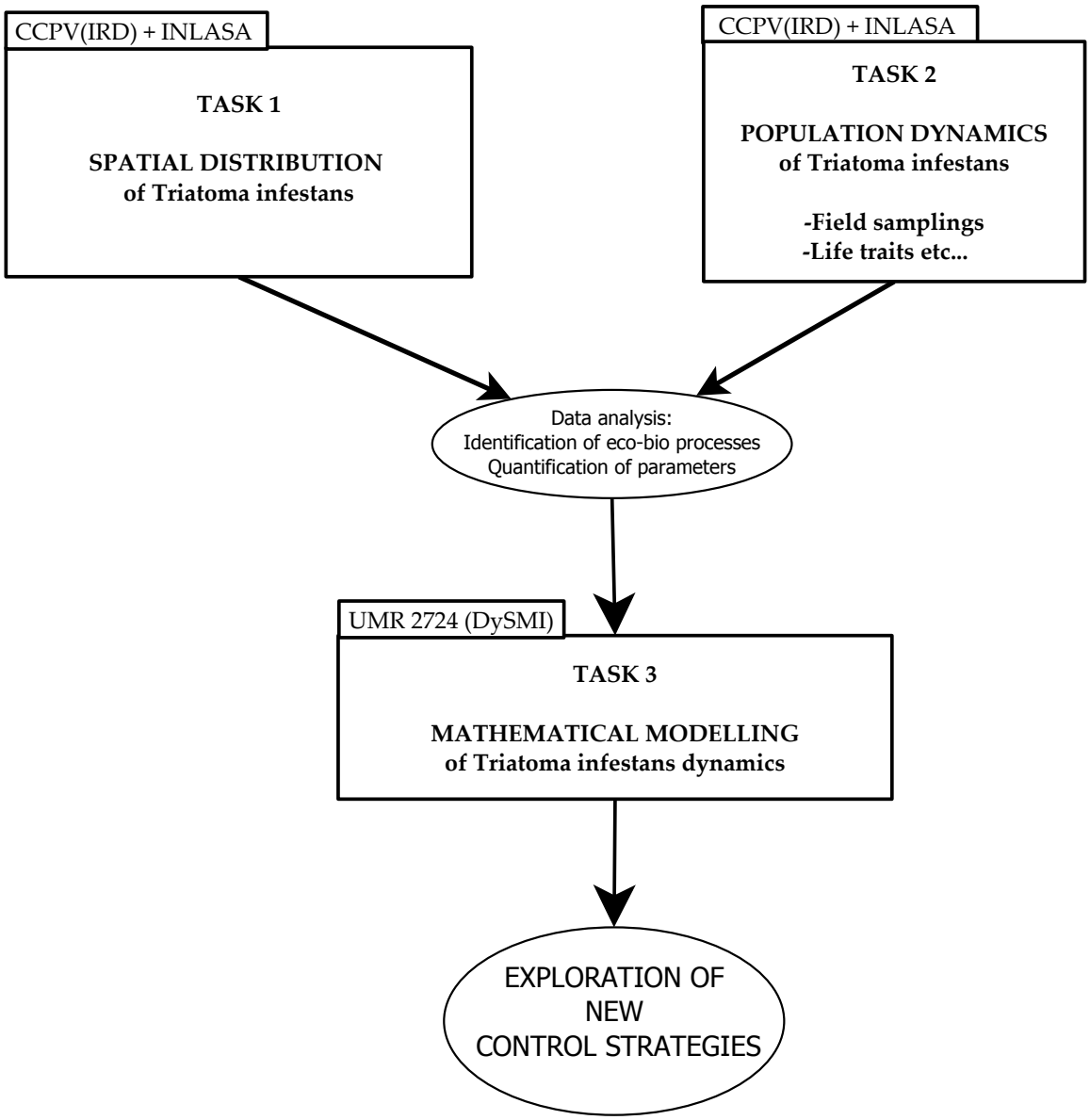
The scientific program can thus be summarized as follow:

- (1) Triatomines will be sampled in the field to study the various parameters of its **population dynamics**. This will be carried out in a Chagas endemic village. Collected insects will be analyzed in details in the laboratory for age structure, blood-meal sources, infection by parasites, genetics etc. In the field, houses will be geo-referenced to facilitate the interpretation of genetic structures and dispersion related to spatial structures. Possible animal hosts will also be identified, numbered etc. House characteristics will also be recorded. Some mark-release-recapture experiments will be carried out at small scale to better understand Triatomine movements (and therefore colonization and (re)colonization processes) inside a same village. These data will complete the genetic data. Seasonal variations will be studied in particular experiments allowing the release of captured Triatomines (ethic: not to be released in human environment) Life traits of *T. infestans* will be recorded in climatic chambers in France, according to temperature, hygrometry and bug densities (actors: IRD-Bolivia and INLASA Bolivia for field collections, with scientific complements by IRD-LIN France, in particular for genetic analysis and life traits).

- (actors: IRD-Bolivia and INLASA Bolivia, with scientific complements by IRD-LIN France, in particular for genetic analysis).
- (2) Triatomines will be sampled in the field to study the **spatial structure.** This phase will be carried out at a larger geographical scale than the first one. Therefore, only insect densities will be recorded. Several villages will be sampled for Triatomine abundance and inside these villages, several houses. This will enable to describe the aggregative behaviour of Triatomines at various geographical scales, from houses inside a village to a regional scale (among villages). The insecticide resistance status of the sampled populations will be determined and genetic structure within and among villages analyzed using the collected material. (actors: IRD-Bolivia and INLASA Bolivia)
- (3) A **statistical analysis** of all the collected data during phase 1 and 2 will enable to better understand the bugs' dynamics and to point out relationships between the dynamics parameters, in particular the density dependence processes. A **mathematical model** will be built to include all these data and their variations in order to mimics the population dynamics and spatial repartition of *T. infestans* and simulate various kinds of control interventions. (actors: DySMI France with the help of IRD-Bolivia and LIN-IRD)

Therefore, according to these objectives, the ALTERNATIVES project can be **structured in 3 distinct scientific tasks** corresponding to the 3 phases of the project described above**,** and a **task 0 for project management.**

The tasks of project ALTERNATIVES, their relationships and the actors involved are schematized hereafter



3.2. PROJECT MANAGEMENT

As explained above, two French teams and a Bolivian one will be involved in the ALTERNATIVES project:

- CCPV-IRD in Montpellier (with the LIN laboratory, Dr. F. Chandre, responsible) and its Lab. extension in Bolivia (Dr. F. Lardeux, responsible)
- DySMI laboratory (UMR 2724), with M. Choisy.
- Medical entomology laboratory at INLASA (Bolivia) (Dr. T. Chavez, responsible).

The financial and juridical management of the project will be under responsibility of IRD-France.

IRD-Bolivia (F. Lardeux) will be responsible of the field experiments, carried out in collaboration with INLASA (Bolivia) (Task 1 and 2). Most of laboratory experiments will be carried out in Bolivia (blood meal identification, population genetics etc.). Some refinement of techniques will be carried out in France at LIN-IRD (microsatellites, for example) along with results analysis and *T. infestans* life traits experiments using climatic chambers.
The model (Task 3) will be built in France (DySMI), with a strong collaboration from the field teams to make the model realistic.

The project will be managed as follow:

TASK 0: Project management, technical coordination, and valorisation of results (Project coordinator: F. Lardeux)

This task is dedicated to the administrative management of the tasks of the project in order to:

- verify that the chronogram of the tasks will be followed
- coordinate the technical and scientific actions amongst the tasks
- prepare the technical annual and final reports
- Management of financial aspects
- Management of the web site for the presentation of results
- Diffusion of the results to the National Program for Chagas Control in Bolivia
- Diffusion of the results to other interested entities (for example, other Control Programs from neighbouring countries)

TASK 1: Study of the spatial distribution of *T. infestans*.

As stated above, this task deals with samples collected on a large geographical scale (inter-villages). The scientific and technical aspects of this task will be managed in the field (Bolivia) by the responsible of this task (IRD-Bolivia).

TASK 2: Study of the population dynamics of *T. infestans*

As stated above, this task deals with samples collected within a same village. The scientific and technical aspects of this task will be managed in the field (Bolivia) by the responsible of this task (IRD-Bolivia). Because the task 1 and 2 share many technical aspects and will be carried out by the same technical personnel in the field (i.e. researchers and technicians from IRD-Bolivia and INLASA), task 2 will be managed by the same responsible as for task 1 (i.e. F. Lardeux, IRD-Bolivia). Climatic chamber experiments for the study of life traitsd will be carried out at LIN-IRD in France with insects from the insectary.

TASK 3: Statistical analysis of data and mathematical modelling for simulation of vector control strategies

As stated above, this task will first analyze the field collected data and then built a mathematical model incorporating theses results to calibrate the model. DyMSI (M. Choisy) will manage this task.

3.3. DETAILED DESCRIPTION OF THE WORK ORGANISED BY TASKS

The Task 0 is dedicated to the administrative management of the project (see above)

3.3.1 TASK 1 SPATIAL DISTRIBUTION OF *TRIATOMA INFESTANS*

Objective: To describe and estimate parameters of the aggregation pattern of *T. infestans* within and amongst villages.

Person in Charge: F. Lardeux (IRD-Bolivia)
Involved partners: INLASA (T. Chavez, S. Depickère)
Contributions: F. Lardeux will organize the sampling scheme and participate in field surveys. T. Chavez and S. Depickère will help in organizing the field work, along with the technicians and students of the INLASA laboratory.

Program work and methods. A series of 30 villages will be randomly selected in the endemic Chagas region of Bolivia (inter Andean dry valleys and Chaco regions). In each village, depending of its size, a series of houses (>= 30) will be randomly sampled for Triatomine abundance. Basic characteristics of each house will be recorded (i.e. its construction material, size etc.) and geo-referenced. Insects will be collected following the "man-hour" active capture (golden standard for Triatomine sampling), consisting in an active search for insects in all the places where they can breed such as cracks in the walls, inside furniture and clothes etc… and carried out by trained personnel. This method enables the computation of relative abundance index. All captured insects will be identified, counted and classified following its developmental stage (Nymph 1 to 5, adult (male or female)). Statistical analysis will be carried out using standard analysis of distribution functions (frequency histograms), comparing sampling places and geographic scales. Collected insects will be labelled to indicate the exact place of capture and kept in the laboratory at -20°C. Then, population genetics will be carried out with microsatellites (Garcia *et al*. 2004 ; Marcet *et al.* 2006). At least 10 microsatellites will be used to infer results on population structures at 3 geographic scales: within a same house (i.e., "family" structure of Triatomines), within houses of a same village and within villages. Each population will be composed of 30-40 individuals to enter the genetic study At a village scale, data on aggregative structures will be completed by mark-recapture methods (Schtickzelle et al. 2003 for example) using individual marking (paints) and radio tracking (Lovei et al. 1997, O'Neal et al. 2004 among others) to better quantify the force of rapid exchange between close places.
Success indicator: The computation of aggregation indices such as k of the negative binomial distribution for example, with an acceptable variance. The size of the sampling universe could therefore be modified with increasing results, up to an acceptable confidence interval for parameter estimation.

Risks: There is no particular risk in obtaining such data which are commonly acquired in medical entomology: field and laboratory techniques are well known. Field data will be obtained with the collaboration of technicians of the Ministry of health of Bolivia who work with INLASA, diminishing the risk of sampling failures.

3.3.2 TASK 2 POPULATION DYNAMICS OF *TRIATOMA INFESTANS*

Objective: To quantify population dynamics parameters and their interrelationships such as density dependence processes

Person in charge: F. Lardeux (IRD-Bolivia)
Involved partners: T. Chavez and S. Depickère (INLASA) and S. Duchon (IRD-LIN)
Contributions: F. Lardeux will organize the sampling scheme and participate in field surveys. T. Chavez and S. Depickère will help in organizing the field work, along with the technicians and Master students of the INLASA laboratory. S Duchon (LIN-IRD) will be in charge of laboratory experiments in climatic Chambers.

Program work and methods: The studied population parameters will be: (1) in the field: seasonal densities, gender and age (longevity) structure, origin of blood meals, insect nutritional status (fast period), hosts (for blood meal) densities, insect infection rates and (2) in the laboratory: mortality rates, developmental stage duration and fecundity according to temperature and humidity. In the field, basic climatic information will be recorded using continuous data collection of temperature and humidity in some of the sampled houses(automatic small recorders).

Seasonal densities: Experiments will be carried out in small experimental enclosures where animals such as Guinea pigs will be reared. Experimental enclosures will be constructed in the two ecological regions where *T. infestans* breeds (Inter Andean dry valleys and Chaco regions). In each enclosure, a fixed population of guinea pig will be reared. A population of *T. infestans* comprising of adults and nymphs will be introduced in each one and each population will be captured monthly, counted and released. Because of the "release" characteristic of the experiment and the potentiality of parasite transmission in the long term, this cannot be carried out in open environments where humans live.
The experimental houses will also enable to compute population dynamics statistics such as the evolution of age-structure with time, mortality rates among developmental stages, etc. and even density dependence processes. In each of the ecological regions mentioned, about 20 Triatomine populations will be monitored during a 30 month period to give reliable results and tendencies.

The remaining population parameters will be studied in real situation, *i.e.*, a village (one village in each of the two ecological regions already mentioned will be chosen) where data will be collected. For that, houses will be randomly sampled and in each house, Triatomines will be actively collected (man-hour sampling). **Two sampling periods** will be planned, one during summer and the other during winter. These sampling will be carried out during two consecutive years. From these samples, insects will be processed as follow:

Age structure: Insects will be categorized following their developmental stage (nymph 1 to 5, male, female) and results will be combined to obtain age structure of the population. With the laboratory data collected on stage duration (see below), it will then be possible to infer natural mortality rates and longevity data according to season (summer, winter).

Blood meals: At the moment of capture, the nutritional status of insects will be recorded, comparing the size/weight of insects to a standard curve obtained in the laboratory with insects fed and followed during a fats period. The nutritional status is a good indicator of movement initiation (or even migration and active flight for adults) in Triatomines, because fast insects will search for blood sources. Blood meals will be determined using PCR techniques (Alcaide et al. 2009, among others) and in the filed, all possible blood sources will be identified and numbered (type of animals, their number

and their location in relation to te location of the Triatomine colony, enabling later a correct analysis of blood sources preferences.

Insect infection rates: will be determined by microscopic examination of faeces, obtained by forced defecation (mixed with saline solution 0.9%) from live insects. Parasites will be identified morphologically in stained smears according de Souza (1999) and Ferreira, Bezerra & Pinheiro (2006). Negative insects will be PCR processed for verification, using Pennington et al. (2009)

Developmental stage duration and fecundity. This experiment will be carried out in the laboratory where Triatomines will be reared in climatic chambers where temperature and humidity will be controlled. Different densities of Triatomines in cages will be used to better understand the effect of crowding on some life traits. The life cycle of Triatomines will be recorded, in particular mortality between developmental stages, stage duration and fecundity of females.

Risks: There is no particular risk to obtain such data. The long development time of *T. infestans* and its seasonal variation force to continue the samplings during at least 2 years.

3.3.3 TASK 3 DATA ANALYSIS, MATHEMATICAL MODELLING AND VECTOR CONTROL SIMULATIONS

Objective: To built a mathematical model of *T. infestans* dynamics to explore alternative vector control strategies and simulate their results in term of vector densities and if possible, parasite transmission.

Person in charge: M. Choisy (DySMI)
Involved partners: The IRD and INLASA Teams
Contributions: M. Choisy will be in charge of building the theoretical mathematical model. The IRD and INLASA teams will analyse quantitatively the field data to compute values for the model parameters, and will help M. Choisy in designing an ecologically tractable and real model with biologically interpretable parameters.

Program work and methods: Mathematical modelling is a tool complementary to experimental and field works in understanding the mechanisms at work in the biological systems under study. Its usefulness pertains to its formalism that helps disentangling and revealing mechanisms that may be unreachable to the human intuition. Coupled with field and/or experimental data through statistical procedures such as maximum likelihood estimations, mathematical models can be used to estimate key biological parameters and make quantitative predictions of practical importance. Lastly, these models, when properly parametrized, can be used to test and compare the efficiency of different control strategies, before developing them in natura.

The transmission of Chagas disease through Triatoma bites presents several complex characteristics for which mathematical modelling may be useful in helping understanding it. *A priori*, two broad question may be explored with such an approach.

(1) Feeding behavior. Triatoma can feed on several mammalian host species, including humans, but also dogs, cattle, etc... that live in the vicinity of human populations. Published field data suggest that host preference and feeding behavior of the Triatoma depends not only on the host species available, but also on the density of Triatoma. A key question then is to understand how this phenomena may interact to shape the relationship between the Triatoma density and the human risk of disease

transmission. A simple determinist mathematical model based on differential equations can be easily developed to explore such questions. Parameters on such a model can be estimated from both field data and behavioral experiments. This model will be used to estimate the efficiency of the use of insecticides on the diminution of Chagas disease transmission in the human compartment.

(2) Spatial dynamics. In a second stage, this one-house model will be extended to a several houses model in order to understand the spatial dynamics of the Triatoma at the scale of a whole village. Indeed, field data reveal a strong heterogeneity in the number of Triatoma between the different houses of a same village. Depending on the migration of the Triatoma, we aim at understanding how the local dynamics (at the scale of one house) may affect the global dynamics (at the scale of a whole village). For this purpose, we will develop a stochastic spatially explicit model. Such a model, parametrized with field data, will help identifying efficient Triatoma control strategies at the scale of a village.

3.4. PLANNING OF TASKS, DELIVERABLES AND MILESTONES

					Chronogramme (mois) / *Timing diagram (months)*											
TASKS	Partenaires/*Partners*				Année / *Year* 1				Année / *Year* 2				Année / *Year* 3			
	N°1 IRD -France (+ IRD Bolivie + INLASA Bolivia)	N°2 DySMI			3	6	9	12	15	18	21	24	27	30	33	36
Task 1 Spatial structure of T. infestans	X				X	X	X	X								
Task 2 Population dynamics of T. infestans	X				X	X	X	X	X	X	X	X				
Task 3 Data analysis and Mathematical modelling	X	XX						X				X	X	X	X	X
Livrables /Jalons *Deliverables/Milestones*																
Suivi des projets *Project reporting*								☺				☺				☆

☺ : Annual report
☆ : *Final report + expenses summary*

Meetings :

An annual meeting between the various team members is scheduled to evaluate the state of progress of the project (end of year 1, end of year 2 and end of year 3: the last meeting will be organized to write the final report). The first meeting will be held in Bolivia in order to show the "field" reality to the members of the modelling team.

4. DATA MANAGEMENT, DATA SHARING, INTELLECTUAL PROPERTY AND USE OF RESULTS

In a general way, the criteria of evaluation of the project are the **scientific publications** which will result from it. They will be also the principal source of valorisation, along with communications **in international congress** of ecology / modelling. Scientific literature will deal with subjects such as Triatomine ecology, population dynamics, parasite transmission, vector control actions and of course, mathematical modelling.

For the "general" public, results will also be available through the **websites** of the teams (http://www.mpl.ird.fr/ur016/ and http://gemi.mpl.ird.fr/dysmi/index.html).

Expected results will also be presented directly to the **National Program of Control of Chagas Disease** of Bolivia for immediate application and reflexion on control strategies and risks. Therefore, the ALTERNATIVES project will benefit directly to the health services of the concerned countries which are aware of the necessity of searching for alternative control strategies and the minimization of the use of pesticides in such strategies.

Depending on suggested orientations of control strategies from the model, the National Program for Control of Chagas disease of Bolivia might evolve. From an "all insecticide" strategy, one might expect an integrated approach. If so, new specialists in new vector control strategies will have to intervene to generalize the results of the model (phase III studies, for example, before generalizing a strategy to the whole country). The ALTERNATIVES project has therefore a strong implication on the future orientation of disease control at the scale of a country. Moreover, the ALTERNATIVES project might be followed by other countries in which *T. infestans* is the main vector of Chagas disease and in which National Control Programs are in course and face the same control problems (insecticide resistance, increased transmission etc.), such as. Argentina and Paraguay. Therefore, the ALTERNATIVES project will have strong relations with the Ministry of health of Bolivia (where of the field experiments will be carried out). This will be done through the participation of the Entomological Laboratory of INLASA, which is an Institute depending of the Ministry of Health and to which reports will be regularly given.

5. CONSORTIUM ORGANISATION

5.1. DESCRIPTION, ADÉQUATION ET COMPLEMENTARITE DES PARTENAIRES / RELEVANCE AND COMPLEMENTARITY OF THE PARTNERS WITHIN THE CONSORTIUM

There are 2 French teams in the project

(1) The LIN Laboratory from the UR16 "Characterization and control of the populations of vectors" of IRD -Montpellier with its extension in Bolivia at INLASA (La Paz)

(2) the laboratory DySMI from the GEMI-UMR 2427 at Montpellier.

The principal investigator (from IRD) will be based in the Bolivian laboratory at INLASA to supervise and participate in the field sampling experiments.

For clarity, the Bolivian laboratory (laboratory of medical entomology at INLASA) is presented thereafter as Partner 3, although attached to the UR16 in France.

Partner 1: *LIN- IRD-UR16 "Characterization and Control of the Populations of Vectors"*

(http://www.mpl.ird.fr/ur016/index.php?lng=fr)

The main research objective of UR16 (Research Unit 16) of the IRD (Institut de Recherche pour le Développement) is to better understand the underlying factors of the vectorial transmission of pathogens in order to improve the control of vectored diseases (malaria, dengue and arboviruses, Chagas disease, leishmaniasis). Scientists and partners of UR016 are interested more particularly in the biology, genetics, anthropic and sylvatic environments of the vectors. The UR is structured in three inter-connected research axis: (1) characterization of vectors, (2) relations between vectors and parasites, and (3) vector control. The present ANR project will primarily develop studies in relation with the third axis, which develops researches on new control strategies. The head laboratory of the UR is the LIN (Laboratoire de Lutte contre les Insectes Nuisibles), in Montpellier. It is a WHO Collaborating Centre for insecticides, and is certified ISO 9001 ver. 2000. Forty seven researchers, engineers and technicians, 15 thesis students, and about 20 partner scientists from other countries take part in the activities of the UR. Many scientific publications in international reviews account for the activities of the UR, in particular on vector ecology, parasite transmission and vector control.

The UR16 will give to the ANR project its competences **in population dynamics studies** and impacts of new control strategies on parasite transmission.

The UR is also established in Bolivia where it worked on malaria and dengue and currently develops programs on Chagas disease vectors, in collaboration with INLASA (La Paz) also part of this project (see partner 3 further). It thus has an excellent knowledge of South American fields and collaborating partners in the Southern countries.

The LIN team will take part in this ANR project in the realization of field samplings (collection of environmental data and of Triatomine populations), in close relation with the partner of the South. Two researchers of this group will be more particularly involved in the ALTERNATIVES project: **F. Lardeux and F. Chandre**. Technicians of the LIN laboratory also participate in the studies, in particular **S. Duchon** (Ingenieur-IRD). The IRD allows its researchers to work in foreign countries where research proceeds. F. Lardeux, for example, is based in Bolivia at INLASA.

Partner 2: *DySMI "Dynamique des Systèmes et Maladies Infectieuses »*

(*http://gemi.mpl.ird.fr/dysmi/index.html*)

DySMI is one of the team of the UMR 2724 « Génétique et Evolution des Maladies Infectieuses » (GEMI) at Montpellier. DySMI intends to understand (1) how infectious and parasitic diseases interact with their environment, including host-vector-reservoir diversity at various scales and organization, and (2) why and how pathogens (re-)emerge and spread in host populations. Researches focus on spatio-temporal diffusion of pathogens in heterogeneous environments and aimed at giving keys on zoonosis emerging factors, as well as on optimal control strategies. Transdisciplinary studies involve researches in France, South America and West and North Africa with empiric approaches (data collection) and theoretic ones (statistical and mathematical modelling to better understands the circulation of pathogens in host populations. DySMI has created the observatory of malaria in French Guyana.

Researches at DySMI are focused on 3 main questions in infectious and parasitic disease epidemiology: (1) What are the mechanisms that can explain the persistence of pathogens in the environment? (2) How a pathogen can spread in its host population and how infection can have repercussions on host susceptibility to other pathogens? and (3) What are the consequences of human intervention on transmission dynamics (for example, vaccination, modification of ecosystems etc.)?

In the ALTERNATIVES project, the DySMI team will model *T. infestans* population dynamics in the framework of vector control impacts, using data collected in the field by partners 1 and 3. **M. Choisy**, a researcher of this team will be particularly involved in this study.

Partner 3 : Instituto Nacional de Laboratorios de Salud (INLASA, Bolivia). Laboratorio de Entomologia Medica.

The South American team will work below the supervision of the coordinating team (IRD) and will actively participate in the realization of various tasks of the project (samplings, study of vectorial capacity and density dependence phenomenon).

The INLASA is a governmental institute whose principal function is the assistance to National Health Programs. Thus, the Laboratory of Medical Entomology at INLASA works in collaboration with the National Control Programs of malaria and Chagas disease. It is normative and gives advices to optimize the vector control strategies of the National Programs. It has also a role of expertise for these Programs. This laboratory develops in particular scientific researches useful to these Programs and initiates more fundamental research on the transmission of parasites by vectors. The principal objectives are a better knowledge of the ecology of the vectors and transmission of the parasites in order to develop more powerful approaches to the control of the vectors. The research topics are centred on insecticide resistance (Mosquitoes, Triatomines), the study of parasite transmission in various ecological situations, and the development of molecular biology techniques for studying population genetics. The Laboratory exists since 2003, but its personnel are active in the field of the vector entomology since many more years. The laboratory is head of the entomology laboratories network of Bolivia (ten basic Units) and therefore, field sampling is easily carried out with the help of these field Units. The Laboratory of entomology has an excellent knowledge of the Bolivian field and related vectors. It can undertake studies at a laboratory level (from molecular ecology) as well as in field ecology.

In the ANR Project, the laboratory will bring its experience in Triatomine samplings.

Since its creation, this laboratory lodges researchers of the LIN-IRD who work on Chagas disease, dengue and malaria vectors, closely collaborating with its Head: **Dr. T. Chavez**. This laboratory belongs to the **network of the UR16-IRD partners**.

5.2. QUALIFICATION OF THE PROJECT COORDINATOR

The coordinator of the project is **Frederic Lardeux** (CR1, HDR), of the LIN-IRD. He has competences in population dynamics of vectors, transmission of vectored diseases (lymphatic filariasis, malaria, Chagas disease, dengue) and in vector control.

Experiment in work coordination : F. Lardeux has coordinated ten multi-disciplinary projects in French Polynesia on integrated mosquito control (Bancroftian filariasis and dengue vectors, as well as *Culicoides* midges), funded by WHO-TDR and CORDET. He has managed several multi-disciplinary teams (entomology, epidemiology, molecular biology) in the course of these projects. As a medical entomologist, he also collaborated to epidemiologic multi-disciplinary projects dealing with the use of anti filariasis drugs in French Polynesia and prophylaxis of Onchocerciasis in West Africa. In French Polynesia and latter in Bolivia, he has managed, the local laboratories of medical entomology (composed of several senior and junior researchers and technicians) and has oriented the research there. In Bolivia, it has managed a PAL+ project on Bolivian malaria vectors which needed the participation of various multi-disciplinary teams and has leaded a CDD project for the installation of a laboratory of medical entomology (national reference) consisting in the construction of a building, its equipment, the training of the technicians and the coordination of several bolivian projects on malaria and Chagas disease transmission. He has also developed many international collaborations (Australia, New Zealand, various countries of South America: Argentina, Guatemala, Colombia). He recently has initiated researches on new control strategies of Triatomines in South America (PAHO project in 2008 in collaboration with Bolivia and Argentina). He participates in a WHO project on the use of insecticide impregnated material to fight Chagas disease in collaboration with CIPEIN (Argentina). He coordinates a WHO-TDR international project (2010-2012) on Eco-Bio-Social approaches for Chagas disease control (impact of participating communities to vector control). He has been appealed several times as an expert to work with WHO (worldwide control of filariasis) and with several National Vector Control Programs (dengue program in New Caledonia, dengue program in Bolivia, malaria program in Bolivia).

5.3. CONTRIBUTION AND QUALIFICATION OF EACH PROJECT PARTNER

Partenaire n	Nom	Prénom	Emploi actuel	Discipline*	Personne. mois	Rôle/Responsabilité dans le projet 4 lignes max
Coordinator CCPV :IRD - Bolivia	LARDEUX	Frédéric	CR1 IRD	Medical entomology	15	Field samplings, data analysis, Coordination with South American partner.
Other members DySMI - Montpellier	CHOISY	Marc	CR2-IRD	Mathematical modelling	5	Building of the mathematical model
CCPV :LIN – IRD (Montpellier)	CHANDRE	Fabrice	CR1 IRD	Medical entomology	5	Population genetics, analysis of vector control impacts
CCPV :LIN – IRD (Montpellier)	DUCHON	Stéphane	Assistant Ingénieur IRD	Medical entomology	20	Laboratory experiments in climatic chambers
INLASA (Bolivia)	CHAVEZ	Tamara	Chargée de Recherches	Medical entomology	20	Field samplings. coordination with the national program of Chagas Control in Bolivia
INLASA (Bolivia)	DEPICKERE	Stéphanie	Ingénieur	Medical entomology	20	Field samplings, data analysis
Post-Doc student for mathematical modelling	To be identified			Mathematical modelling	12	Building of the mathematical model
Master students (from Bolivia) to help in field experiments	To be identified			Medical entomology	10	Field samplings, data analysis

6. SCIENTIFIC JUSTIFICATION OF REQUESTED BUDGET

The project is based on the acquisition of precise data in the field, which is the task of partner 1. Therefore, most of the budget is dedicated to the tasks of this partner (IRD CCPV) which will distribute the budget amongst the groups responsible of the various research actions (i.e. LIN, IRD-Bolivia and INLASA Bolivia)
Partner 2 (for model building) only needs a small amount of money corresponding to the training of a post-doc student in mathematical modelling and a mission to Bolivia to apprehend the reality of Chagas transmission and better understand the vector's dynamics.

6.1. PARTNER 1 : IRD – « UR CARACTERISATION ET CONTROLE DES POPULATIONS DE VECTEURS »

This partner is divided in 3 groups: (1) IRD-LIN in Montpellier with F. Chandre and S. Duchon, (2) IRD-Bolivia with F. Lardeux and (3) INLASA-Bolivia (associated IRD foreign laboratory) with T. Chavez and S. Depickère

- *Équipement / Equipment*

For laboratory experiments, in particular the study of life traits of *T. infestans* according to temperature and humidity, a climatic chamber is needed to complete the one already in use in the laboratory at IRD-France : **15000 euros** (Binder model)
In the field, the study of *T. infestans* movements and dispersion using harmonic radar will need a detector : Recco system R9 + diodes. **5500 euros**
The construction of experimental enclosures in Bolivia for the study of seasonal variations of *T. infestans* densities is estimated to **4000 euros**

- *Staff*

A post doc student is budgetized for a 12 month period to work in Bolivia on field samplings. He/she will have to participate in the field samplings but above all, to analyze the collected data in the framework of the dynamics population of *Triatoma infestans*. The research profile is therefore: (1) knowledge of sampling techniques and statistical analysis of sampling scheme, (2) population dynamics of insects. The post doc student will be helped by Master Students from Bolivia which are also budgetized, but for which the help of ANR is not required. The practice of Spanish is sincerely hoped for collaborating with the Bolivian students.

- *Subcontracting*

No external service is required

- *Missions, travels*

Field missions for sampling insects:
In the field, a sampling mission requires the participation of at least 4 people (sampling technicians), to efficiently sample a Triatomine population, and for the sampling of an entire village, about 5 days are needed. The daily field fees for one local technician are of approximately 30 euros/day.

For studying the spatial distribution of *T. infestans*, about 30 villages will be sampled. Therefore, the work will require 30 villages x 5 days x 4 people x 30 euros = **18000 euros**. The access to the various field villages will be done by car, rent by IRD-Bolivia (0.2 euros/ km). Villages are dispersed on a large territory and therefore, an approximation of 20 000 km will be done including travels from La Paz to the village and intra-village travels (and therefore **4000 euros** to rent the car for the whole study). Gasoline is estimated to 4 000 litres (and the cost in Bolivia is about 0.5 euros / litre). Therefore, a total of **2000 euros** is needed for gasoline.
For studying the population dynamics of *T. infestans,* only monthly missions will be carried out in the same village during 2 years. The cost of a mission is identical as above (4 people x 5 days x 30 euros/ day = 600 euros). Therefore, for the 2 year observation period, the total cost is 24 months x 600 euros = **14400 euros**. Travel by car from La Paz to the village in southern Bolivia (1000 km return) is estimated to 500 euros including gasoline and rent expenses. Therefore, for the 2 year survey, the total cost is 12000 euros. As two villages will be surveyed, one in each of the two main ecological regions where Chagas disease is endemic, a total of **24000 euros** is needed.
Missions of the consortium: For the last meeting (drafting of the final report), the presence of the two persons in charge of the South American laboratories (IRD Bolivia and INLASA) in France (Montpellier, is wished: total cost for the 2 persons: **7000 euros** (plane 2000 euros per person + daily fees: 100 euros/day/person during 2 weeks).

- *Expenses for inward billing*

No internal service is required

- *Other expenses*

The total cost for reagents for PCR studies (blood meal identification and vector population genetics using microsatellites) is estimated to approximately **20.000 euros/yr**.
The maintenance of the insectariums (France, Bolivia) is approximately **5000 euros/yr** (maintenance of rabbits and hens for blood feeding, breeding pots, maintenance of the air-conditioning equipment etc).
For laboratory studies of life traits in climatic chambers in Montpellier, the total cost for small equipment and reagents is estimated to 5.000 euros/year , i. e. **15 000 euros** for the whole project.
A budget of **3000 euros** for the 3 years is required to contribute to the publication of articles in international reviews.

6.2. PARTNER 2 : DYSMI – DYNAMIQUE DES SYSTEMES ET MALADIES INFECTIEUSES (UMR 2427)

- *Equipment*

No special equipment is needed for modelling

- *Staff*

A post-doc student is needed during a 12 month period to help in the design of the mathematical model. The profile of the student is therefore a mathematical modeller with knowledge on epidemic models based on differential equations describing the various compartments.

- *Subcontracting*

No external service is required

- *Missions, travels*

Field missions:
A field mission to Bolivia for M. Choisy and the post doc student is needed to better apprehend the field reality (Vector eco-biology and possible vector control actions). These missions will take place during a scheduled field sampling for Task1 or Task2. This will help to correctly model the vector dynamics with biologically and ecologically tractable parameters and will enable more constructive discussion among field entomologists and modellers. A mission of 1 month is needed. Plane fare is about 2000 euros/ pax and 100 euros /day per-diem. Therefore, a total of 5000 euros / pax is needed (total: **10 000 euros**).

- *Expenses for inward billing*

No internal service is required

- *Other expenses*

Small expenses for modelling such as statistical software updates and office material : **2000 euros**
A budget of **3000 euros** is required to contribute to the publication of articles in international reviews.

7. ANNEXES

7.1. REFERENCES

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7.2. BIOGRAPHIES / CV, RESUME

7.2.1 PARTICIPANT 1 : FREDERIC LARDEUX (COORDINATOR, IRD-BOLIVIA)

Age: 51 years
Current position: Chargé de Recherches IRD
Speciality : Medical entomologist
Research topics : Ecology and dynamics of populations of vectors, transmission of parasites, vector control strategies.

Course:

Diplôme d'Ingénieur Agronome in 1980,
Doctoral Thesis (Population dynamics) in 1986,
Habilitation à Diriger des Recherches (HDR) in 2000 (medical entomology).
Recruited IRD in 1991.
Head of Medical entomology laboratory at Institute Malardé (Polynesia) from 1990 to1997
Head IRD medical entomology Lab at INLASA (Bolivia) from 2001 to 2006

Scientific and technical competences
Competences in population dynamics, modelling and data analysis, parasite transmission by vectors insecticides and vector control.
Other professional experiences: Expertises in Lymphatic filariasis and dengue transmission for the WHO and the Countries of the Southern Pacific, expertises in vector control for the National Vector Control program of Bolivia (malaria, dengue)
Has developed several control strategies of vectors in French Polynesia, studied various vector systems and their relationships to environmental variables (dengue, Bancroftian filariasis in Polynesia, malaria and Chagas disease in Bolivia). Since 2008, has initiated studies on the resistance of Triatomines to insecticides in Bolivia.
Has an excellent knowledge of the Bolivian field and vectors in this country.

In this ANR project, he will be responsible of the field samplings and vectorial capacity studies in Bolivia. He will manage the study of resisatnce profiles (bio-assays and enzymatic dosages). He will be responsible of the relations with the American partner at **INLASA (Bolivia)** (his ancient laboratory) with which he still collaborates. F. LARDEUX has good experience as a multidisciplinary team director and project coordinator (see the preceding paragraph 5.2).

Some publication on vectors and vector control

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Lardeux F, Chavez T, Rodriguez R, Torrez L. 2009. *Anopheles* of Bolivia: new records and an annotated checklist. *CR Biologies* 331. doi:10.1016/j.crvi.2008.11.001

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Lardeux F, Rivière F, Séchan Y, Loncke S. 2002. Control of the *Aedes* vectors of the dengue viruses and *Wuchereria bancrofti*: the French Polynesian experience. *Ann Trop Med Parasitol* 96: 105-116.

7.2.2 PARTICIPANT 2 : MARC CHOISY (DYSMI)

Age: 33 year-old
Current position: Chargé de recherches IRD
Specialty: population and evolutionary dynamics
Research topics: epidemiological and evolutionary dynamics of infectious diseases

Course:
MSc Evolutionary Biology and Ecology (2000)
MSc Biostatistics (2001)
PhD Integrative Biology (2004)
Post-doc Institute of Ecology, University of Georgia, USA (2005-2006)
Researcher at IRD since 2006

Scientific and technical competences:
Mathematical modelling and statistical analyses in population biology.
Differential equations, stochastic simulations, time series analysis, optimisation, parameter estimation.

Publications:

Choisy M., De Roode JC. 2010. Mixed infections and the evolution of virulence: effects of resource competition, parasite plasticity and impaired host immunity. The American Naturalist. In press.

Godreuil S., Renaud F., **Choisy M.,** Depina J., Garnotel E., Morillon M., de Perre PV, Banuls AL. 2009**.** Highly structured genetic diversity of *Mycobacterium tuberculosis* population in Djibouti. Clinical Microbiology and Infection.

Prugnolle F., **Choisy M**., De Meeûs T. 2008. Clonality v0.4: a randomization-based program to test for heterozygosity-genet size relationships in clonal organisms. Molecular Ecology Resources 8 (5): 954-956.

Nettle D., Grace JB, **Choisy M.,** Cornell HV, Guégan JF, Hochberg ME. 2007. Cultural diversity, economic development and societal instability. PLoS ONE 2 (9): e929.

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Choisy M, Brown SP, Lafferty KD, Thomas F. 2003. Evolution of trophic transmission in parasites: Why add intermediate hosts? The American Naturalist 162 (2): 172-181.

7.2.3 PARTICIPANT 3 : FABRICE CHANDRE (LIN-IRD)

Age: 45 years
Current position:

Chargé de Recherhes IRD
Head of the IRD-UR16 axis "Vector Control" (UR16= "Characterization and Control of Vector Populations")
Director of LIN at IRD Montpellier (WHO Collaborating Centre for Insecticides)
Speciality : Medical entomologist
Research topisc : Resistance of vectors to insecticides, genetics of resistance

Course
Veterinary doctor (1990), DEA in parasitic-hosts Interactions (1992), phD (resistance to insecticides) in 1998, Chargé de Recherche IRD (1995)

Scientific and technical competences

Its competences relate to insecticide resistance of vectors and the search for improvement of vector control methods. His research on resistance mechanisms aims to the identification of implied genes and their phenotypic effects (level of resistance, cross spectrum of resistance, predominance, genetic cost, impact on insect behaviour…), and to determine the factors which influence their evolution in natural populations (population genetic structure, origin of selective pressures by insecticides, spatial and temporal variations of resistant alleles…).

His research on vector control relates to the evaluation of insecticides and the development of strategies to improve the effectiveness of control or to prevent/delay the evolution of resistance in natural populations. For this reason it contributed to the majority of the recent findings on the resistance of *Anopheles gambiae*, the main malaria vector in Africa.

Its competences allowed him to study resistance problems in other insect species such as the mosquito *Culex quinquefasciatus* (vector of West Nile virus) and *Aedes aegypti* (vectors of yellow fever and dengue viruses), and even a crop pest, *Helicoverpa armigera*.

Experiment of coordination of project

He took part and/or coordinated several Research programs on malaria vector resistance financed by various agencies (OMS/TDR, OMS/WHOPES French Ministry of Research (VIHPAL, PAL+), French Ministry of Foreign Affairs , Industry). He is member of the WHO network "African Network for Vector Resistance" and carried out several consultations for the wHO/EMRO concerning the installation of a monitoring system of malaria vector resistance in Morocco.

It has been head of laboratory Genetic Resistance laboratory at P. Richet Centre (Bouaké, Ivory Coast), then Head of the "Resistance laboratory" at the Entomological Research Centre of Cotonou (Benin).

At present, Head of the research axis "Vector Control" of the UR16-IRD "Characterization and Control of Vector Populations" (Dir. D. Fontenille) and manager of the LIN-IRD Laboratory in Montpellier (WHO Collaborating Centre for insecticides).

Recent publications

Pennetier C, Costantini C, Corbel V, Licciardi S, Dabiré RK, Lapied B, **Chandre F**, Hougard JM. 2009. Synergy between repellents and organophosphates on bed nets: efficacy and behavioural response of natural free-flying *An. gambiae* mosquitoes. PLoS One. 9;4(11):e7896.

Djènontin A, Chabi J, Baldet T, Irish S, Pennetier C, Hougard JM, Corbel V, Akogbéto M, **Chandre F**. 2009. Managing insexcticide resistane in malaria vectors by combining cabamate-treated plastic wall sheeting and pyrethroid-treated bed nets. Malar J. 20;8:233.

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7.2.4 PARTICIPANT 4 : STEPHANE DUCHON (LIN-IRD)

Age: 40 years

Cursus and current position:

- Assistant Ingénieur IRD
- Since1996 : based at LIN (laboratoire de Lutte contre les Insectes Nuisibles) in IRD Montpellier. OMS Collaborating centre for evaluating insecticides in public Health.

Scientific and technical competence

He has a strong experience in insect (mosquitoes and triatomines) bioassays with pesticides and vector control strategies. At present develops vector control approaches based on vector behaviour, and develops experiments on video tracking of insects.

Publications representatives

Duchon S, Bonnet J, Marcombe S, Zaim M, Corbel V. 2009. Pyrethrum, a mixture of natural pyrethrins has potential for malaria vector control. Journal of Medical Entomology 46(3):516-22.

Bonnet J, Pennetier C, **Duchon S**, Corbel V. 2009. Detoxification enzymes are involved in the synergistic interactions occurring between repellents and insecticides in mosquitoes. Parasites & Vectors. 2(1):17.

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Hougard JM, **Duchon S**, Darriet F, Zaim M, Rogier C, Guillet P. 2003. Comparative performances, under laboratory conditions, of seven pyrethroid insecticides used for impregnation of mosquito nets. Bull World Health Organ. 81(5): 324-33.

Brengues C, Hawkes NJ, Chandre F, McCarroll L, **Duchon S**, Guillet P, Manguin S, Morgan JC, Hemingway J. 2003. Pyrethroid and DDT cross-resistance in Aedes aegypti is correlated with novel mutations in the voltage-gated sodium channel gene. Med Vet Entomol. 17(1): 87-94.

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7.2.5 PARTICIPANT 5 : TAMARA CHAVEZ (INLASA – BOLIVIA)

Age : 34 ans

Cursus and current position

MsC in Biology (1998)
MsC in Public Health (2008),
Head, Laboratory of Medical Entomology at INLASA (Instituto Nacional de Laboratorios de Salud, la Paz, Bolivia).
speciality: medical entomology,
research topic: ecology of vectorial systems and resistance to insecticides

Scientific and technical competences

She has an excellent knowledge of the Bolivian field and its Triatomine fauna. Has worked for the National "Chagas disease" Control Program (consulting scientist in entomology) and has worked on several alternative control techniques against Triatomines, in particular of insecticide paints. She has a good practice in biochemical techniques applied to insects (ELISA, isoenzymes). Excellent taxonomist, she can manage morphometry techniques and data analysis (see bibliography). Her laboratory has also competences in GIS analysis and other spatial techniques (software of species distribution etc)

Experience in project coordination and team direction

Head of the medical entomology laboratory at INLASA, she has created the Bolivian network of basic entomology Units (ten laboratories) with which this ANR project will collaborate for field samplings. She is coordinating 5 scientific programs financed by the French Ministry of Foreign Affairs on the taxonomy of *Anopheles*, on vector resistance to insecticides in Bolivia, on dengue, on molecular biology of Anopheles, and on Chagas disease vectors in Bolivia.

Publications

Chávez T, Dujardin JP. 1998. Tipificación del género *Rhodnius* mediante la morfometría. Libro de resúmenes de la I Jornada Nacional de Parasitología, La Paz-Bolivia.13-14 de Marzo

Dujardin JP, **Chávez T**, Moreno J, Machane M, Noireau F, Schofield CJ. 1999. Comparison of Isoenzime Electrophoresis and Morphometric analysis for Phylogenetic Reconstruction of the Rhodniini (Hemiptera: Reduviidae: Triatominae). *J. Med. Entomol 92 (5), 653-659.*

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Lardeux F. Depickere S., Duchon S. Chavez T. 2010. Insecticide resistance in *Triatoma infestans*, Chagas disease vector in Bolivia. Submitted. Trop. Med. Int. Hlth.

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7.2.6 PARTICIPANT 6 : STÉPHANIE DEPICKERE (INLASA – BOLIVIA)

Age : 33 ans

Cursus and current position

MSc – Behavioral Biology, University Paris XIII (1999)
PhD Thesis Biological Sciences University of Brissels (Belgium) / University Paris XIII (France) (2003)
Post doc European Project LEURRE Brussels (Belgium) (2004)
Post Doc Fyssen Fellowship at INLASA (Bolivia) (2006)
Present: researcher INLASA (Bolivia)
speciality: Behavioural entomology / medical entomology,
research topic: Ecology of Chagas disease vectors / resistance to insecticides

Scientific and technical competences

She has experience in insect behaviour and the study of aggregation amongst social insects. Since 2005, she has begun studies in Bolivia where she developed researches on Chagas disease vectors and the epidemiology of the disease (epidemiological surveys to study the role of secondary vectors such as *R. stali* or *E. mucronatus* in Chagas transmission)

She has managed field teams to sample Triatomines and survey human populations for Chagas infection and collaborate with the Ministry of Health of Bolivia to study insecticide resistance in *Triatoma infestans*.

She has an excellent knowledge of the Bolivian field and field studies of Triatomines, and manages laboratory studies such as blood sources identification, infections rates, insecticide bio-assays, statistical analysis of epidemiological data etc.

Publications

Lardeux F. **Depickere S.,** Duchon S. Chavez T. 2010. Insecticide resistance in *Triatoma infestans*, Chagas disease vector in Bolivia. Submitted. Trop. Med. Int. Hlth.

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Depickère, S., Ramírez Ávila, G.M., Fresneau, D., & Deneubourg, J.L. 2008. Polymorphism: a weak influence on worker aggregation level in ants. Ecological Entomology, 33: 225-231.

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Sempo, G**., Depickère, S.,** & Detrain, C. 2006. Spatial organization in a dimorphic ant: caste-specificity of clustering patterns and area marking. *Behavioral Ecology,*17(4): 642-650.

Sempo, G., **Depickère, S.,** Amé, J.M., Detrain, C., Halloy, J. & Deneubourg, J.L. 2006**.** Integration of an autonomous artificial agent in an insect society: experimental validation. *From Animals to Animats 9* (LNCS/LNAI), 4095: 703-712.

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Depickère S., Fresneau, D. & Deneubourg, J.-L. 2004. the influence of the red light on the aggregation of two castes of the ant *Lasius niger*. *Journal of Insect Physiology*, 50: 629-635.

7.3. INVOLVEMENT OF PROJECT PARTICIPANTS INTO OTHER GRANTS, CONTRACTS, ETC ...

Part.	Nom de la personne participant au projet	Personne . mois	Intitulé de l'appel à projets Source de financement Montant attribué	Titre du projet	Nom du coordinateur	Date début & Date fin
N°1	Lardeux Frédéric	6	OMS-TDR- IDRC Chagas EBS-LAC 300 000 $	Eco-Bio-Social approach for Chagas disease control	F. Lardeux	2010-2012
N°1	Lardeux Frédéric	3	OMS TDR – Working network – Chagas disease 300 000 $	Control of Triatominae with impregnated mosquito-nets	M.I. Picollo	2008-2010
N°1	Chavez Tamara	6	OMS TDR – Working network – Chagas disease 300 000 $	Control of Triatominae with impregnated mosquito-nets	M.I. Picollo	2008-2010
N°1	Chandre Fabrice	6	AFSSET 388 000 Euros	Evaluation de nouveaux candidats insecticides et de nouvelles strategies de lutte contre les moustiques vecteurs du paludisme à Mayotte	F. Chandre	2010-2012