NEGLECTED DISEASES

Science and Technology for National Development
Strategic Studies

NEGLECTED DISEASES

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Brazilian Academy of Sciences
Neglected Diseases

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INTRODUCTION

Among other activities, the Brazilian Academy of Sciences (ABC) has been performing studies and analysis about the actual stage of Brazilian Science in the most diverse areas. As a result of these studies, it has identified areas which deserve special attention due to their strategic importance in Brazil´s scientific development. It's the case of the so-called "Neglected Diseases". I have been invited by the academic Jacab Palis, president of ABC, to coordinate a group of researchers with the objective of performing an analysis about the neglected diseases in our country. Through informal meetings held at the headquarters of ABC and through internet discussions, we have reached a basic document which has been amply advertised. We also organized, at the headquarters of ABC, a symposium on the 3rd of May, 2010, as part of the already traditional ABC's Annual Magna Reunion which precedes the tenure solemnity of its new members. During the symposium a Preliminary Proposal was announced for the discussion of what the base of a Study Program on Neglected Diseases would be. Researchers who work in this area, and authorities of the Ministry of Health supplied important contributions during the above mentioned symposium. Following, the Preliminary Proposal was placed for public consultation for a period of 30 days, where we received innumerous suggestions from several researchers. I would like to highlight the comment made by our colleague Herman Schatzmayr, from the Oswaldo Cruz foundation.

The document hereby published by ABC is the result of the efforts of many. Here we have included only the content which reached a consensus, which is why some infectious and parasitic diseases were not mentioned. We understand that this document represents a starting point for a program which will reinforce the participation of Brazilian Science in this very important area for the development of the country. In closing, I would like to thank Dr. Gerson Pena, secretary of Health Surveillance of the Ministry of Health, for authorizing the utilization of several pictures which illustrate the current aspects of epidemiology of some of the neglected diseases.

Rio de Janeiro, August 2010.

Wanderley de Souza
Study Group Coordinator

DIAGNOSIS OF A GREAT CHALLENGE IN THE AREA OF HEALTH

This is yet another memorable document whose reading as of now will be mandatory for any study or monitoring in the governmental offices and the academic environments.

It belongs to a series elaborated with scientific precision and unique cultural ampleness as is usually the case with documents like these produced under the competence of the Brazilian Academy of Sciences. In the same way as it occurred with the "Amazonia" and "The teaching of Science and the Elementary Education", which have already been published in this collection of "Strategic Studies" organized by ABC with the support of the FCW (Conrado Wessel Foundation).

We are talking about Science and Technology for National Development: Strategic Studies.

We are therefore, thinking of Brazil as a whole and thinking in terms of decades of public planning.

The study which we preface is of indisputable value to model a governmental program in the fields of Public Health and in the academic world which is where the knowledge on prevention of diseases is offered to society. Nevertheless, this publication is also a bedside table book to all academics and conscientious citizens, who are aware of the reality in Brazil.

In the area of Health, in particular, the difficulties and the illnesses are tremendous; to know them, to identify their causes and to prevent their effects is the imperative responsibility of those who find themselves involved with them constantly and intensely.

The neglected diseases require the indistinct involvement of the entire society in order to minimize the damages and be able to gradually reduce the mortality they cause among us.

The resources available in our country are scarce and to transform them into results compatible to our social needs is a permanent challenge. It's an intricate challenge which demands competence, pertinacity and creativity to be able to diagnose it in all of its meanders and be able to elaborate a recipe to overcome it.

Well, that is the line of work presented in this book by the team of the Brazilian Academy of Sciences, coordinated by Wandeley de Souza (UFRJ/Inmetro/ABC): Afrânio Lineu Kritski(UFRJ),Carlos M. Morel (Fiocruz-Rio/ABC), Elba Regina Sampaio de Lemos (Fiocruz-Rio), Eloi Garcia (Fiocruz-Rio and Inmetro/ABC), Erney P. Camargo (ICB-USP/ABC), Jorge Guimarães (Biotechnology Center-UFRGS/ABC), José Rodrigues Coura (Fiocruz-Rio/ABC), Manoel Barral Neto (Fiocruz-Bahia/ABC), Milton Ozório Moraes (Fiocruz-Rio), Pedro Vasconcelos (Evandro Chagas Institute, MS/Belém), Sônia Rozental (UFRJ), Sérgio Fracalanza (UFRJ).

This illustrious team teaches us the most convenient *modus faciendi* so that the "neglected diseases" are focused on correctly and fully.

The word “neglected” leads us to a very fortunate preliminary consideration, even though it is only an exercise of literal interpretation: it derives from “to neglect”, which originates from the conjunction formed by “nec” (Latin) and “lego” (Greek). Here “nec” is changed to “neg” and means “no”; it is a negative prefix; yet and the Greek root “lego” means “to gather for oneself”, “to choose” and also “to read”; therefore, neg-lego means “I do not gather for myself”, “do not choose”, “do not read”; so in summary “neglected” represents “not chosen”, “not elected”.

The original meaning of “not chosen”, “not read”, absorbed changes and today carries the interpretation of “contempt”, “little attention” and “indifference”. These diseases do not arouse the interest of pharmaceutical industries due to the lack of demand, and they do not receive substantial support towards research and study. It is a “vicious” situation, the least conceptualized due to the lack of knowledge justifying the least known for lack of resources.

In other words, everyone failed in assigning to the subject the needed attention it required. Thus the need to include the theme in a State scope, as ABC and FCW have been doing, considering the issue yet another theme for the “Strategic Studies”.

If others are neglectful, ABC and FCW do not depreciate the issue.

Dear Readers, carefully absorb the merit of this document and you will see that the diseases in question are not neglected by our scientists; if they receive this title it is because those who should be responsible, belittle them.

As of now, with this new “Strategic Study”, we forward a contribution in the form of research and privileged study to all those responsible – and you Reader are also responsible, and instate a new paradigm to prevent more costly consequences and meet the social needs in the fields of Health, with safety and total coverage.

Américo Fialdini Júnior
Director-President of Conrado Wessel Foundation

SUMMARY

1. INTRODUCTION

The use of the term “neglected diseases” is relatively new and polemic. It was originally proposed in the decade of 1970, in a program of the Rockefeller Foundation as “the Great Neglected Diseases”, coordinated by Kenneth Warren. In 2001, The Non-Governmental Organization “Doctors without Borders” (MSF) in its document “Fatal Imbalance” proposed to divide the diseases into Global, Neglected and Most Neglected (MSF 2001). In this same year the Report of the Commission of Macroeconomics and Health (WHO, 2001) introduced a similar classification, dividing the diseases into Type I (equivalent to the global diseases of MSF), Type II (Neglected/MSF) and type III (Most neglected/MSF). This typology has been since then utilized to refer to a group of diseases caused by infectious and parasitic agents (viruses, bacteria, protozoa and helminthes) which are endemic in populations with low income, who live mainly in developing countries of Africa, Asia and in the Americas. The adjective “neglected” originally proposed, was created based on the fact that on one hand they do not arouse the interest of great multinational pharmaceutical companies, who do not perceive in these diseases potential buyers of new medications, and on the other hand, the study on these diseases has been poorly financed by the funding agencies. For many, the utilization of the concept of emerging and re-emerging diseases is more adequate in referring to this group of diseases.

At first, the following diseases were included in the concept of “neglected diseases”: Chagas disease, Sleeping Sickness, leishmaniasis, malaria, filariasis, schistosomiasis. Later, other diseases were included such as: leprosy, tuberculosis, dengue, yellow fever and HIV/AIDS. Most recently other diseases such as ascariasis, tricuriasis, necatoríase, ancylostomiasis, trachoma, dracunculiasis, and the buruli Ulcer have also been included. With regards to the level of international funding for research, HIV/AIDS, tuberculosis and Malaria have receive significant investments and can no longer be considered “neglected” if we consider financing alone. On the other hand, with regards to Brazil, we cannot forget to include some other diseases caused by fungi like Paracoccidioidomycosis, Lacaziosis (or Jorge Lobo´s disease), Sporotrichosis and Chromoblastomycosis, among others. With regards to the viruses we cannot forget the arboviruses found in the Amazonian region, some of which are producing diseases in mankind. We should also include the diseases caused by the inoculation of toxins which come from the

most diverse organisms such as the poison of snakes and arthropods, some poorly known such as the toxins from tocandeira or tocandira ants, responsible for frequent and extremely painful accidents in the Amazonia, and that of plants, as is the case of the Mammon. Widely used today in the production of Biodiesel.

2. HISTORICAL CONSIDERATIONS

The parasitic diseases caused by protozoa and helminthes have been at the base of Brazilian scientific development for about a century. In 1908 Pirajá da Silva, one of the leaders of the so-called Bahian Tropicalist School, performed fundamental studies in the area of biology of schistosomiasis, providing important contributions toward the better understanding of the evolution cycle of *Schistosoma mansoni*. In this same year A. Splendore in São Paulo described the protozoa known today as *Toxoplasma gondii,* one of the most important pathogenic agents with universal distribution. In 1909 C. Chagas described the *Trypanosoma Cruzi* and the Chagas disease, according to some, the most important contribution to Brazilian Science until today. In 1911 Gaspar Viana described *Leishmania braziliensis*, an important agent of one of the clinical forms of leishmaniasis. Later, innumerous Brazilian scientists further developed theses studies and supplied important contributions in the area of Parasitology and on infectious and parasitic diseases.

The Brazilian researchers who work in the area of Protozoology, especially those who are more involved in the study of *Trypanosoma cruzi*, created in the 70´s the basis for a profound transformation of the Brazilian biomedical sciences by introducing the most modern cellular, biochemical, molecular and immunological approaches for the state of the *T. cruzi*, of its interaction with the host cell and of the Chagas Disease. This fact is in the base of the quantitative and qualitative scientific production of our science. Recent data indicates that in this area, Brazil already occupies the second position in terms of contribution of scientific articles published in magazines of international circulation.

Certainly a preponderant factor for the development of the Brazilian Parasitology was the creation and the regular functioning, between 1976 and 1986, of the Integrated Program for Endemic Diseases (PIDE), which successfully invested significant resources for that time (something equivalent today to around

US$12 million) in the groups which worked in the area and which attracted, as a consequence of the differentiated financing politics, other groups to work in this area. Later, the World Health Organization created the TDR (Tropical Diseases Research) Program which also contributed towards the consolidation of various groups initially supported by PIDE and stimulated the formation of new groups.

Despite the existence of financing programs for research in the area of Neglected Diseases, above all through the DECIT-MS (Department of Science and Technology in Health – Ministry of Health) and some state foundations, funds are insufficient for us to continue to advance in an area in which Brazil should pursue worldwide leadership.

3. DISEASES OF SPECIAL INTEREST IN BRAZIL

Taking into consideration the comments above, we identify as a priority that the various financing agencies of the federal government (MCT – Ministry of Science and Technology: FINEP – Financer of Studies and Projects and CNPq – National Council of Scientific and Technological Development; MEC – Ministry of Education and Culture: CAPES – Coordination for the Improvement of Higher Education and MS – Ministry of Health: SCTIE/DECIT – Secretary of Science, Technology and Strategic Inputs/Department of Science and Technology in Health and SV – Secretary of Health Vigilance) and of the state governments (FAPs – Research Support Foundations) get together in a sense of establishing a strong long term program with the objective of supplying consistent support to research and to the formation of human resources to work on a set of diseases which are listed below which affect the Brazilian population. Such measure has a few implications. First it could consolidate the leadership of Brazilian research in areas of significant economic and social impact. Second, take on the responsibility of stimulating the Brazilian scientific, technological and industrial parks to work on themes which do not arouse the interest of more developed countries. Third, consolidate the capacity of the Brazilian scientific community to work on an integrated network system, as demonstrated in a recent study by Morel and collaborators which clearly show a strong integration in this area among research groups spread throughout the entire country (Fig.1). Fourth, constitute one of the relevant themes for the international cooperation programs with countries in the Southern hemisphere whose populations are affected by several of the same

diseases. We cite as examples the interest on (a) Chagas disease, in all of the countries of Latin America, (b) leishmaniasis, in various countries of South America and some Asian countries (India, Nepal, Pakistan, Bangladesh), (c) malaria, in countries of South America, Asia (China and India) and in Africa, among others, and (d) toxins of animal origin, especially from snakes, in all under developed regions and countries which possess savannas and forests.

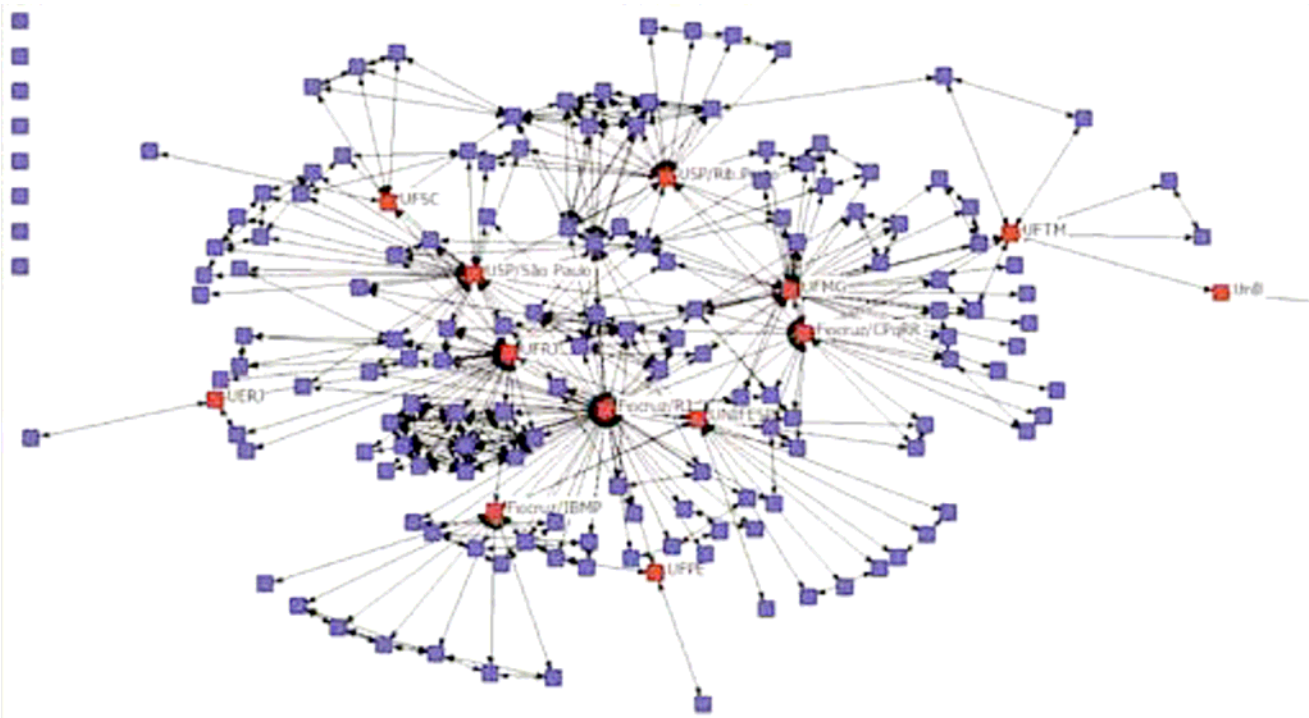


Figure 1. – Integration network between Brazilian groups which study Chagas Disease

4. PRELIMINARY ACTION PLAN

1. We suggest that the Brazilian Academy of Sciences forwards to the Ministries of Science and Technology, Health and Education, the suggestion that a big program to support basic and applied scientific research and technological innovation in the areas of neglected diseases and emerging and re-emerging diseases, be articulated. This program should aggregate the participation of the state foundations which support research and count on the support for research projects, scholarships and company support. We also suggest that the program be discussed in the scope of the National Academy of Medicine and in a few scientific societies which work in the area (Protozoology, Parasitology, Tropical Medicine, Immunology, Biochemistry and Molecular

Biology, among others). This program shall prioritize some specific details of the diseases listed which still require deeper research. Other details are already being financed by various existing initiatives.

2. We also suggest that ABC forwards a proposal to The Academy of Sciences of the Developing World (TWAS) with the objective of considering this area as one of the priorities in the process of scientific integration among countries of the Southern Hemisphere.

5. PRESENTATION OF THE CLASSIC NEGLECTED DISEASES MOST RELEVANT IN BRAZIL

5.1 Chagas Disease

Without a doubt, Chagas disease gathers the biggest number of researchers of a country working on a same problem. Figure 2 shows that Brazilian authors are the ones who produce the most articles on Chagas disease or the *Trypanosoma cruzi*.

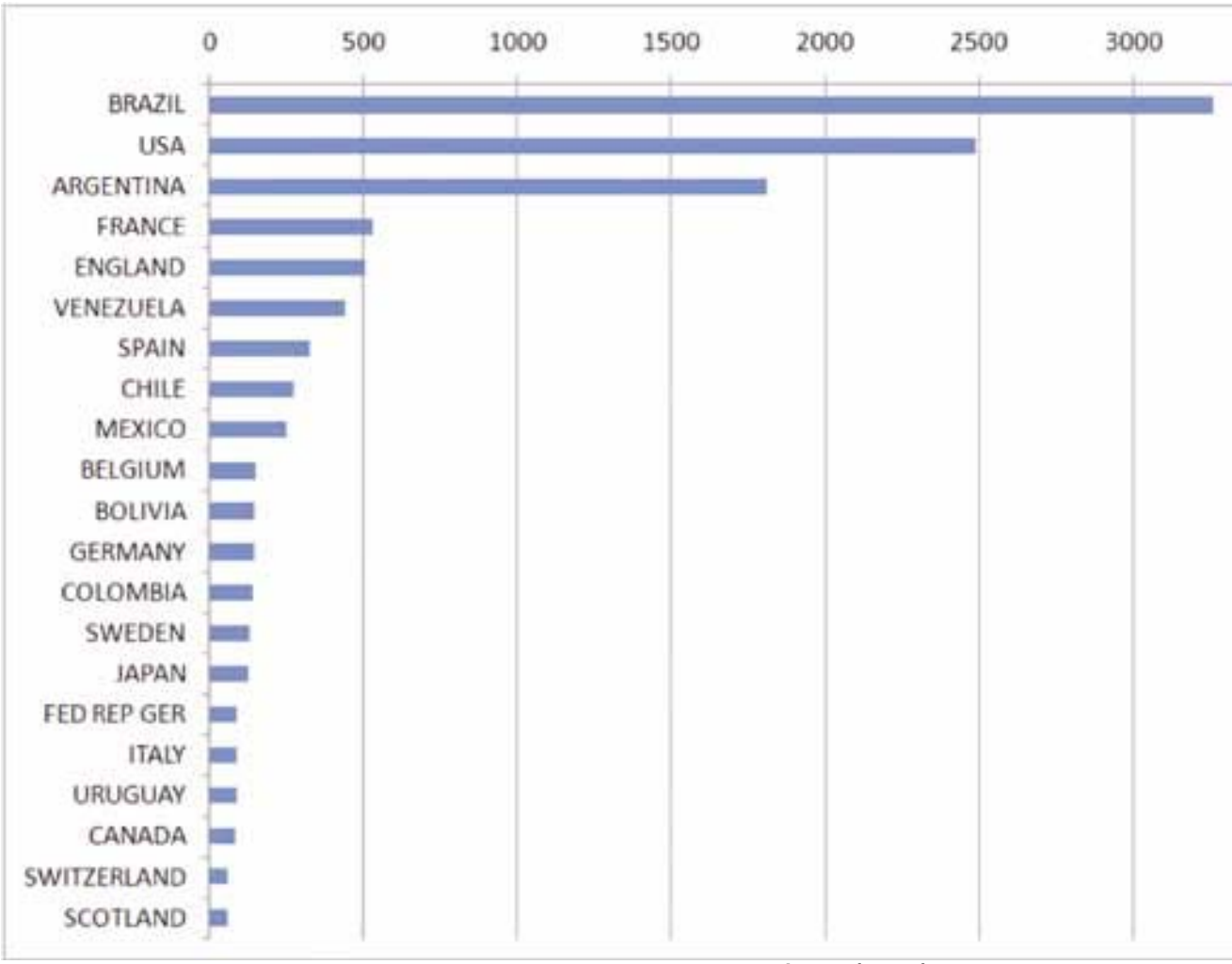


Fig.2 Production of Scientific articles on Chagas disease

Despite the significant advance in the control of the vector borne infection and through blood transfusion, still today there are around eight million people infected. Of these, around two million are in the chronic phase. It is estimated that only 0.5% of them receive treatment. It is also estimated that around 23% of the infected patients live in Brazil. The number of deaths is today around fourteen thousand per year. It still constitutes the parasitic disease responsible for the greatest number of deaths in Latin America, overcoming malaria. Despite the work of various research groups, the advances towards obtaining drugs which are more effective yet less toxic are relatively few.

Acute Chagas Disease (DCA), Brazil, 2000 to 2009

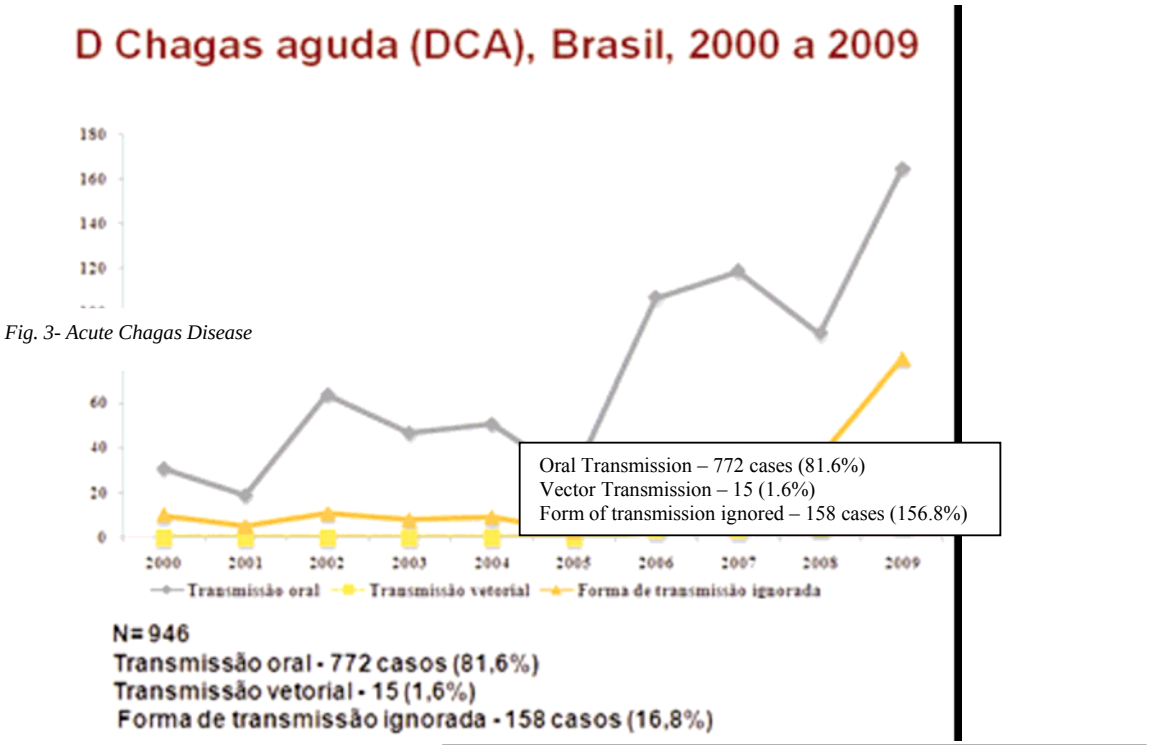
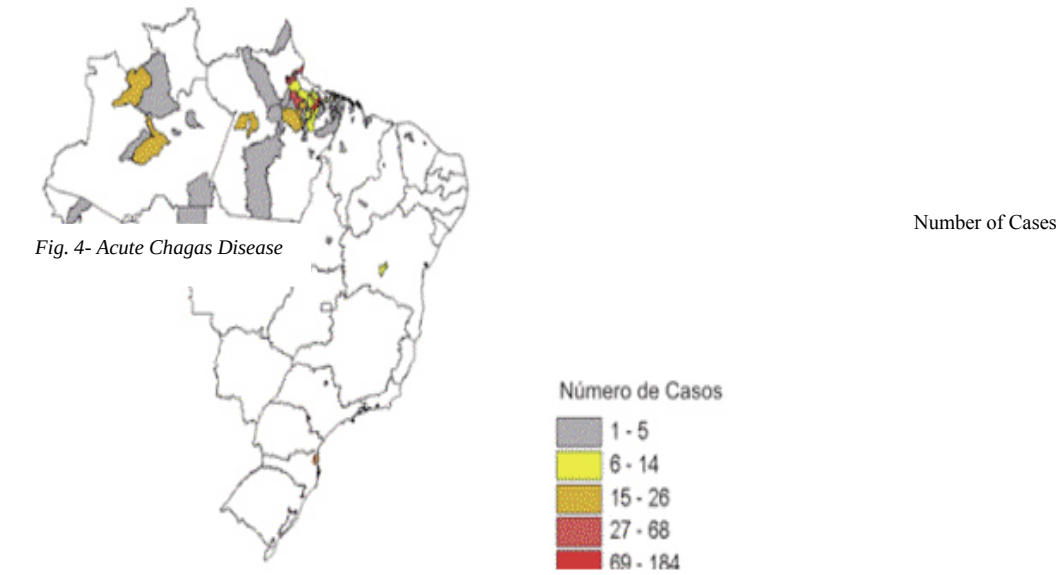


Fig. 3- Acute Chagas Disease



Municipalities with registered cases of Acute Chagas Disease. Brazil 2000 to 2009

Fig. 4- Acute Chagas Disease

Figure 3 shows the evolution of the cases of acute Chagas disease resultant from the main transmission

mecanisms, in figure 4 we find the distribution of these cases in the several states, and figure 5 shows the distribution of the main vector the *T. infestans*, throughout several years in the diferent states.

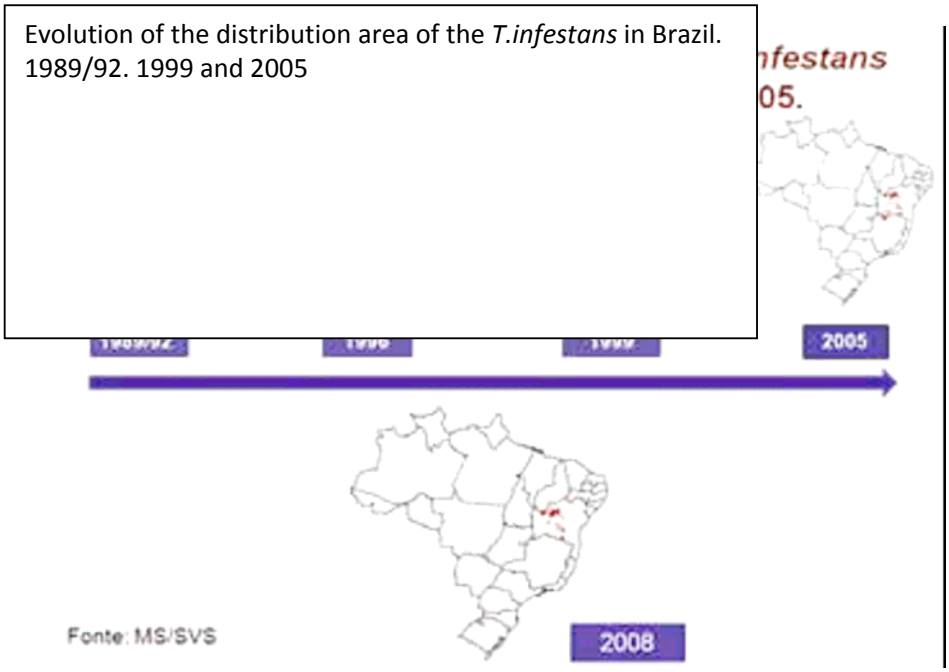


Fig. 5 – Evolution in Brazil

5.2. Leishmaniasis

The several clinical forms of leishmaniasis are caused by approximately twenty species of protozoa of the genus *Leishmania.* The visceral form is fatal when not treated. Some cutaneous forms can lead to great deformations. There are today around twelve million people infected in 88 countries, with Brazil, together with Bangladesh, India, Ethiopia, Kenya and Sudan being the most affected. Around 90% of the cases of leishmaniasis in Latin America occur in Brazil. The data of 2007 revealed 3505 cases, especially in children. The treatment is still done above all with antimonials and anphotericin B. Most recently, the Mitelfosina is being used with success in Asia.

Aside from the lack of appropriate drugs, leishmaniasis has represented a sanitary concern not only for its geographic expansion but also for its urbanization tendency. In Brazil the disease advances in the Midwest Region and can already be found in the periphery of the big cities of the Northeast and the Midwest. The study on human leishmaniasis cannot be performed in an integral way without the

understanding of canine leishmaniasis. The dog is an important host of leishmaniasis, it is very important as a pet in the endemic areas and represents an important reservoir capable of infecting the sandflies (phlebotamine). The control of the infection in dogs is what will block the transmission of Leishmaniasis to its vectors.

Brazil has various leishmaniasis research groups renown internationally. An effort to promote the adequate financing of these groups is necessary, seeing that Brazil, with a great number of cases, needs to develop appropriate knowledge with regards to control and management of the disease.

The main Brazilian groups which are dedicated to the study of leishmaniasis have turned their attention mainly to the investigation of the parasite or to the pathogenesis of the disease, leaving a gap in the studies of themes and topics pertinent to the full understanding of the transmission of leishmaniasis and of the control of the cases which develop the disease.

There are relatively few studies dedicated to the vectors of leishmaniasis, leading to gaps in knowledge about species involved in the transmission in several areas, as well as limited comprehension of the biological aspects of the vector related to the transmission of the illness. Studies on vectors are necessary both for those involved in the transmission of visceral leishmaniasis as well as for those involved in the transmission of integumentary leishmaniasis.

A great part of the studies performed in men or on experimental models, have concentrated in aspects of the pathology or of the immunorregulation of the disease. In the case of the visceral leismaniasis, several important topics, like the problems of coagulation, effects of parasitism on the activities of the bone marrow and the special placement of parasites, have received very little attention.

The diagnosis of visceral leismaniasis was recently benefitted by the creation of a test which can be performed in a practical and fast way (rK39). A limiting aspect with regards to the diagnosis of leismaniasis in man, is the lack of a test capable of identifying, with efficiency, the cases of the disease which are not severe. With regards to the dog, the situation is even more problematic due to the fact that this fast and practical test, which can be done easily and endemically, does not work adequately in this species.

Figures 6 and 7 show the evolution of the integumentary and visceral forms over the years. The figures show the highlights of the cases in the different regions of the country. Figures 10 and 11 further clarify this reading.

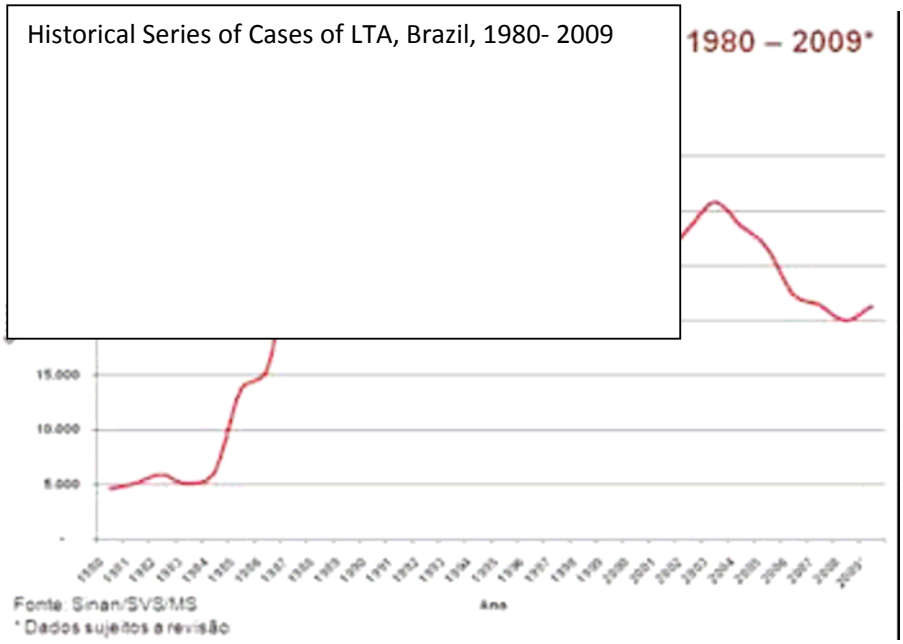
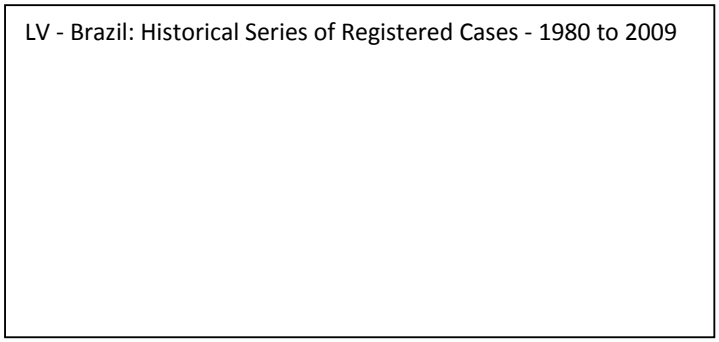


Fig. 6 – Evolution in Brazil



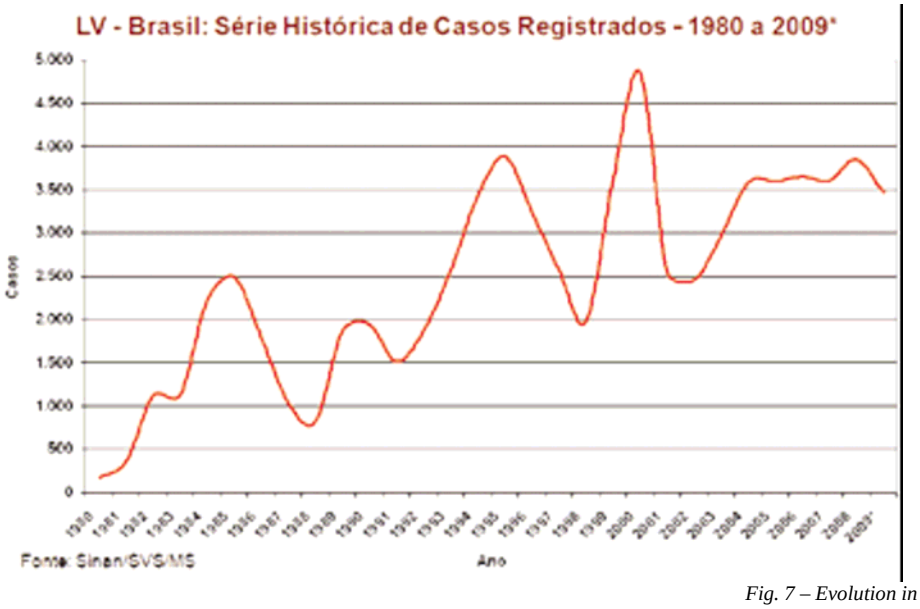


Fig. 7 – Evolution in Brazil

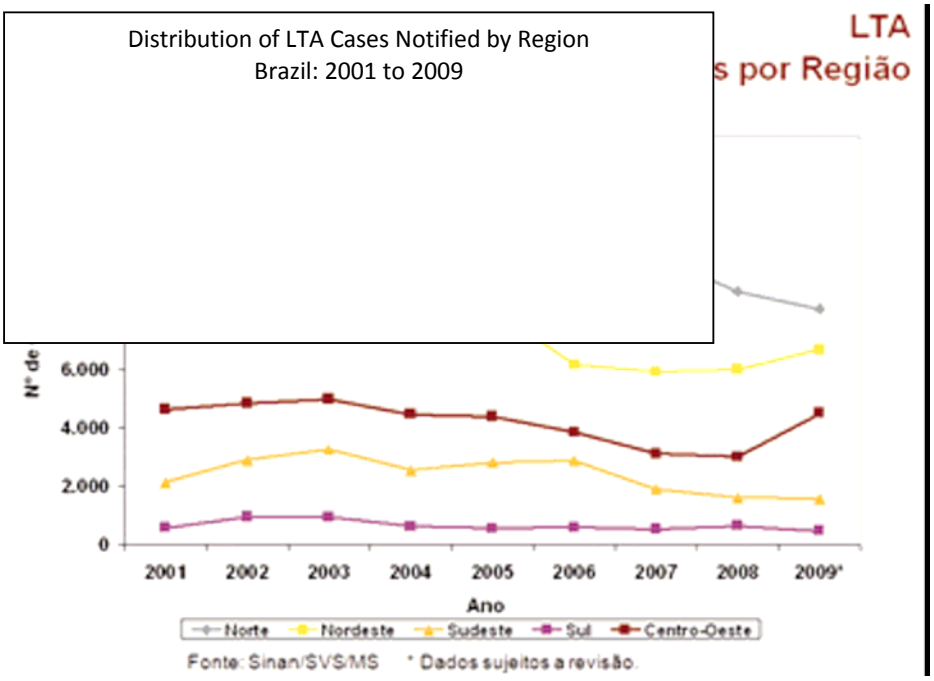


Fig. 8 – Distribution of Cases

Cases of LV Notified by Region 2001 to 2009

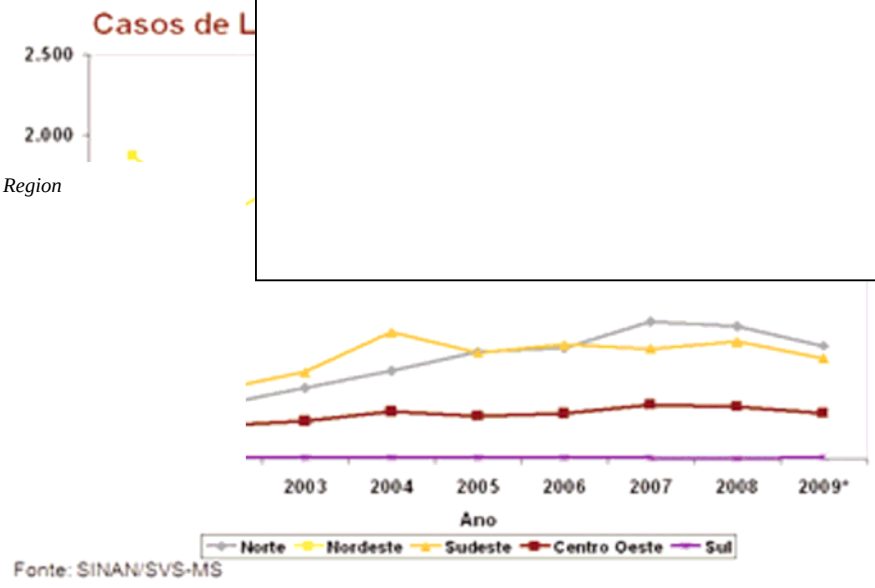


Fig. 9 – Cases Notified by Region

LTA

Cases per Municipalities

Average of Cases 2005-2007 Cases 2008

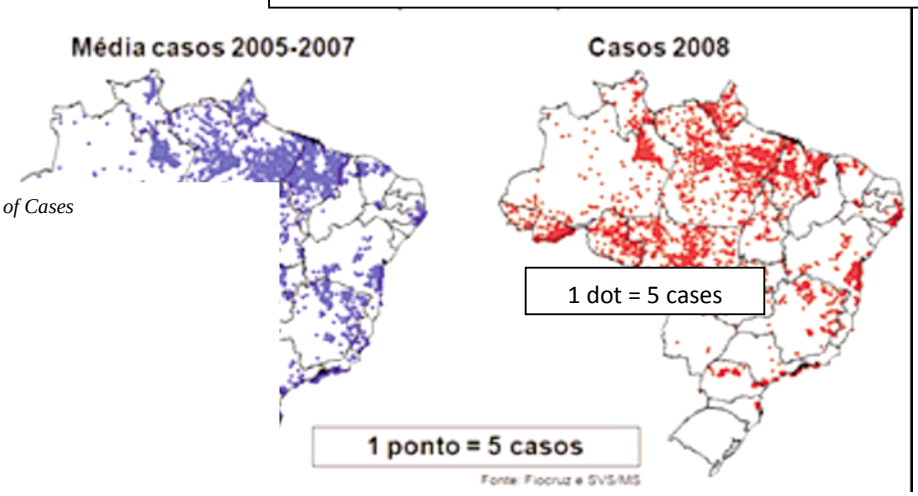


Fig. 10 – Distribution of Cases

LV

Stratification of the Municipalities According to Transmission Profile of LV – Brazil, 2006 - 2008

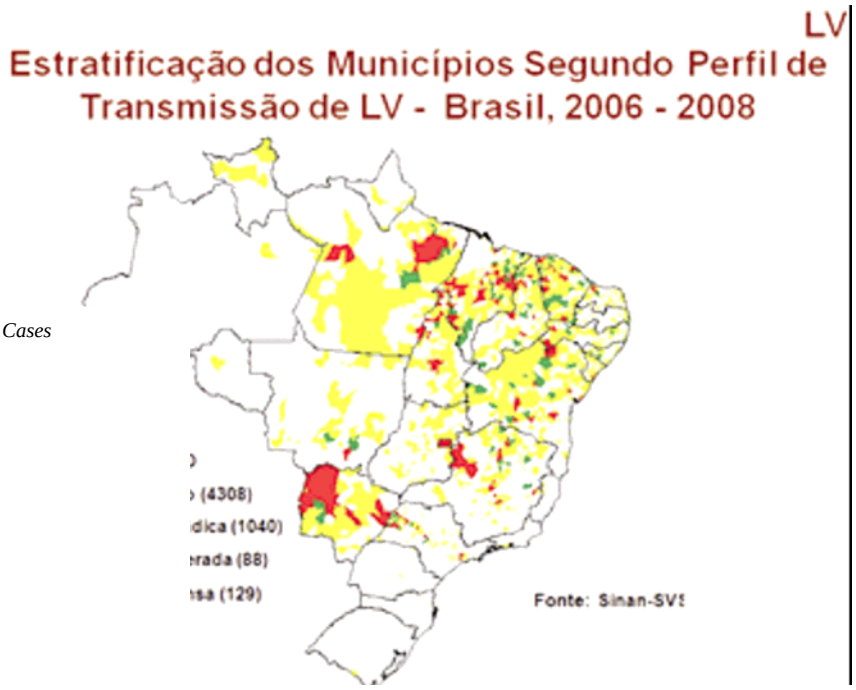


Fig. 11 – Distribution of Cases

5.3 Malaria

A disease caused by four species of protozoa of the genus *Plasmodium (P. falciarum, P. vivax, P. malariae and P. ovale)* present in 110 countries. It is the main cause of death in Sub-Saharan Africa, killing approximately 3,000 children per day. Figure 12 shows the distribution of cases in the country. The areas of risk are shown in figure 13. Treatment is currently being done with drugs based on chloroquine and more recently with artemisin. Two new combination using artesunate + mefloquine and artesunate + amodiaquine have been recommended as first class treatment.

It is worth highlighting that there are several public and private institutions which are investing intensely on researches about malaria. In this context, it can no longer be considered a neglected disease. Yet, in Brazil we still count on a limited number of researches working in this area, above all with regards to the basic research on *P. vivaz.*

Number of cases. Brazil, 1960 to 2009

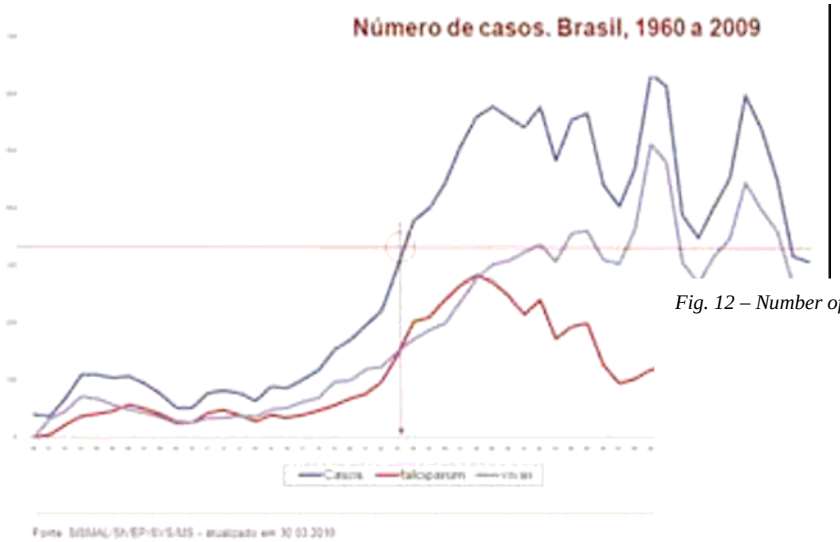


Fig. 12 – Number of Cases

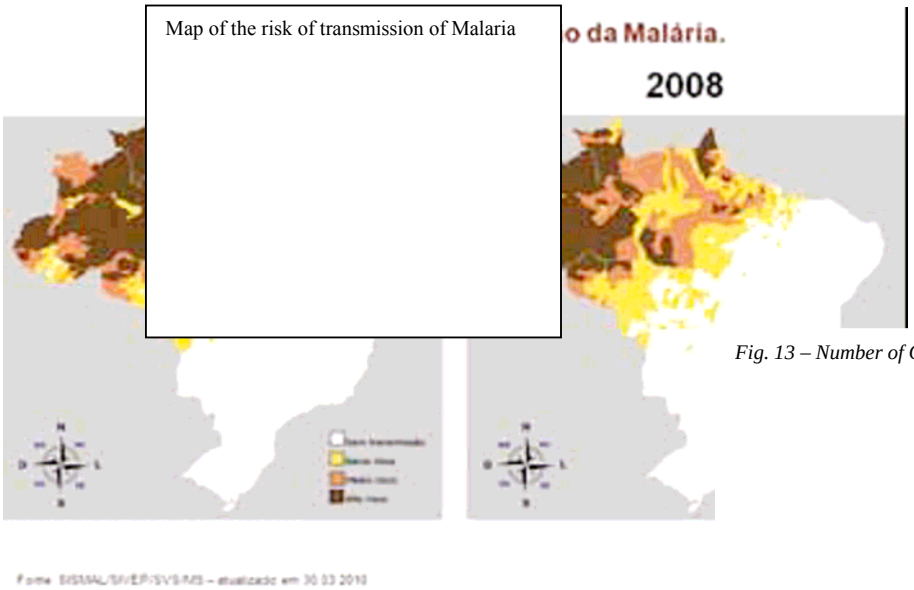


Fig. 13 – Number of Cases

5.4 Filariasis

In the case of the onchocerciasis, caused by *Onchocerca volvulus,* it is believed that there are 18million people infected, above all in Africa. In the case of the lymphatic filariasis caused by *Wuchereria bancrofti*, we estimate the existence of 120 million people infected. About these two diseases conveyed by simulium and culicidae we don´t even have precise data about the incidence and the prevalence in the country. We know that the onchocerciasis (on the skin) seems to be common among Indians and populations in the Northern frontier of the Amazonian region, but we do not have concrete data

about the subject. As we also do not have data about mansonelliasis, which according to some evidence may be responsible for corneal opacity (not at all similar to onchocerciasis) in certain areas of the Amazonia.

5.5 Mycobacteriosis (Leprosy and Tuberculosis)

Leprosy is a curable chronic infectious disease caused by *Mycobacterium leprae,* an obligate intracellular pathogen which infects, predominantly the Schwann cells in the nerve and the macrophages on the skin. The disease is ancient and has been present in humanity since the first civilized settlements. One of the problems which affect patients until today is the stigma, which for centuries lead to compulsory isolation in hospitals or lepers. The disease is practically eliminated in developed countries, but it is a public health problem in poor or developing countries like in the case of Brazil and India which alone answer to 80% of the new cases in the world. Several times, the disease presents itself epidemiologically in light clusters in pockets of poverty. The distribution of cases in Brazil (figure 14) is heterogeneous and although the rate of prevalence today runs around 17 cases per 100,000 inhabitants, there are regions in Pará, Maranhão, Bahia, Minas Gerais and Goiás with numbers ten times higher than the national average. The lack of knowledge and the lack of primary attention to health, render the disease the biggest cause of non-traumatic incapacity, because a late diagnosis in patients can cause important and long lasting impairment of the peripheral nerves which lead to deformity. Normally, leprosy affects young adults (25-40 years old) and due to the prolonged effects, in most of the cases, irreversible, is considered to be of an elevated morbidity rate. Common injuries such as ulcers on numb feet, and the “hands like hooks” or the “fallen feet” are serious problems and it is estimated that about 30% of patients with leprosy develop some kind of incapacity. The late diagnosis also indicates a fragility of the health systems, and in further analysis, indicates the lack of long term investments in methods for specific and sensitive identification diagnosis for the tracking of populations under risk, like the family members of the carrier of the disease who have a greater chance of contracting the illness. It has been estimated that 6-8% of the household contacts of the sick, develop the disease in a period of 5 years.

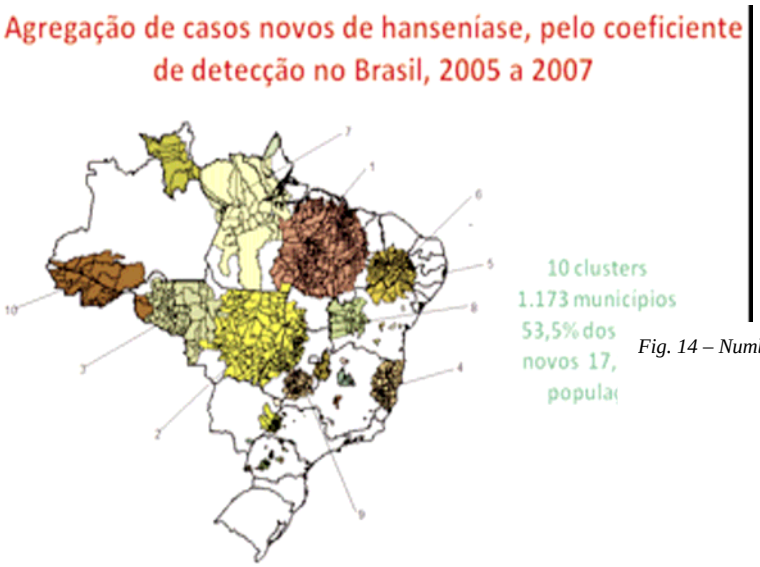


Fig. 14 – Number of Cases

In the beginning of the 80´s, with the adoption by the WHO of a new therapeutic scheme composed of 3 medications, the reaction was one of euphoria among health ministries and secretaries, with regards to eliminating the illness. Curiously, the optimism went beyond the public health environment and reached the scientific communities and the financing organizations from NGOs to foundations that assist research all over the world. The investments in basic and applied research fell drastically with the assurance of the elimination of the disease. The number of new cases is stable with a small decrease over the last 5 years. Since the introduction of polychemotherapy, for over 25 years, the number of new patients of leprosy ranged from about 400,000 cases and today about 300,000 cases are registered suggesting that maybe some basic issues regarding the immunopathogenesis and the transmission of the disease might not be resolved.

Leprosy is a forgotten disease with little investment and affects patients in the poorest regions of the world. These patients are many times, due to the late

diagnosis, deformed or disfigured and are now incapacitated for the rest of their lives. Therefore, basic and applied research on low cost diagnosis methods or even on vaccines is necessary for an adequate management within the public health.

Tuberculosis (TB) has been cause for worry throughout human history, not only with regards to

its potential to claim lives, but also due to its aspect of transmission and infectivity. Despite being a curable and preventable disease, its long term drug treatment (6 months) and the discovery that the vaccine with BCG avoids severe cases only in children, in the last decades, it has been noticed that the interruption of the transmission and propagation process of TB has not occurred. With the objective of containing the global increase of TB, since 1993, the DOTS strategy was proposed by WHO, which is based on the diagnosis of pulmonary TB by means of smear of sputum and the treatment in a shortened scheme containing rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB). Nevertheless, even with the adoption of the DOTS strategy in over 80% of the countries, at a worldwide level, the load of TB has remained high, especially in the regions where the prevalence of TB/HIV, multidrug resistant TB and of new lineages of M.tb(M.Beijing) is elevated. In 2007, the WHO estimated the existence of 9.27 million new cases of TB, which represents a significant increase when taken into consideration the 8.3 million in the year 2000; about 1.3 million deaths among HIV negative, 456,000 additional deaths among HIV positives, and about 500,000 cases of multidrug resistant TB (MDR-TB), among these, only 30,000 (8.5%) were diagnosed and 3681 (less than 1%) of the patients received treatment in accordance to international orientations. (WHO Report 2009). In the last years the dissemination of M.tb Beijing in Asia and Eastern Europe has been reported, associated to MDR and more recently, to the appearance of TB cases extremely resistant to drugs (XDR), defined as cases in which those isolated from people with TB are resistant to isoniazid and rifampicin (MDR-TB) as well as being resistant to any one of the flouroquinolones drugs and to at least one of the three injectable second-line drugs, amikacin, kanamycin or capreamycin (CDC, 2006). **The XDR-TB is raising the prospect of virtually incurable TB cases worldwide.** The absence of new vaccines, new medications and new diagnosis tests for TB have been identified as one of the key factors for the perpetuation of the disease in the planet, aside from other factors such as social inequalities, the advent of AIDS, and the aging of the population (WHO Report 2008). **In this worldwide TB scenery, the development of new diagnostic, preventive and therapeutic approaches has received elevated priority.** (Young et al. 2008).

Rate of TB Incidence. Brazil and Federated Units, 2008

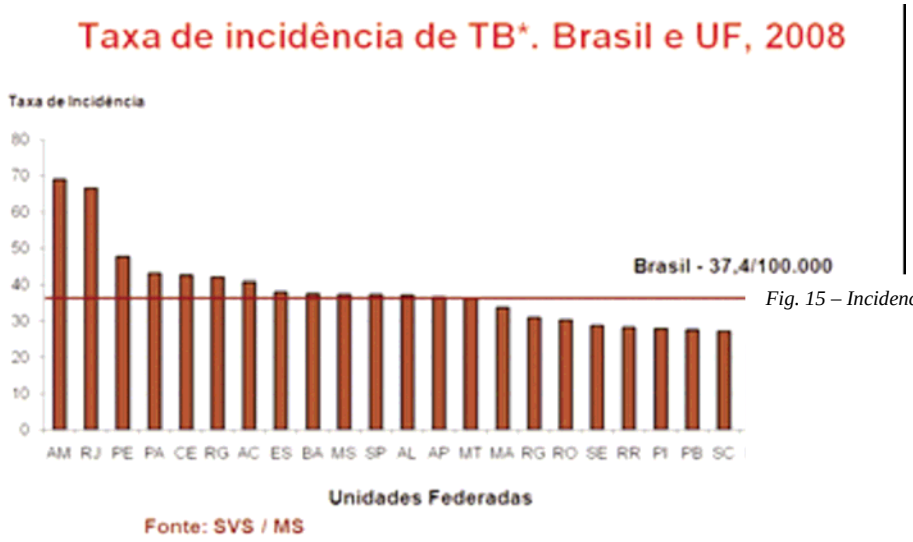


Fig. 15 – Incidence rate

Brazil is the 18th country in the ranking of the 22 countries which contain 80% of the global load of TB. The estimated prevalence is of 50million people infected with the bacillus of TB, occupying the 4th place in the causes of death by infectious diseases, and currently it's the main cause of death among people infected with HIV, even with the HAART (Highly Active Anti Retroviral Treatment) supplied to HIV infected people since 1997. Despite the generalization of DOTS since 1998, the incidence of TB continues to increase in some regions, and 30% of the cases of TB are diagnosed in hospitals, where TB control activities do not exist, where TB-MDR is prevalent and where 80% of the deaths by tuberculosis occur, the majority associated to infections by HIV and other co morbidities. In the year of 2007, 83,089 cases of active tuberculosis were notified, of which 59,166 were new cases of pulmonary tuberculosis (more than 15 years), among the 7,334 cases of TB/HIV notified, the mortality rate was 3.4 times higher (15.9%; 1166/7334) than the general mortality rate (4.6%; observed among cases of notified TB cases), especially in metropolitan areas and areas related to the late diagnosis in hospitals. Recently the Technical Advisory Committee on TB of the Ministry of Health established a priority agenda in researches on TB. Figure 15 shows the incidence of tuberculosis in the various states while figure 16 shows the mortality rate.

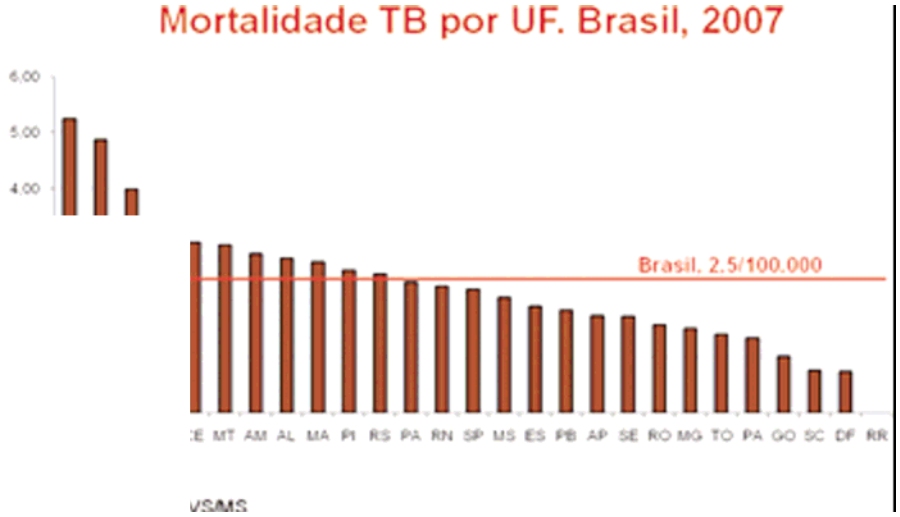


Fig. 16 – Incidence rate

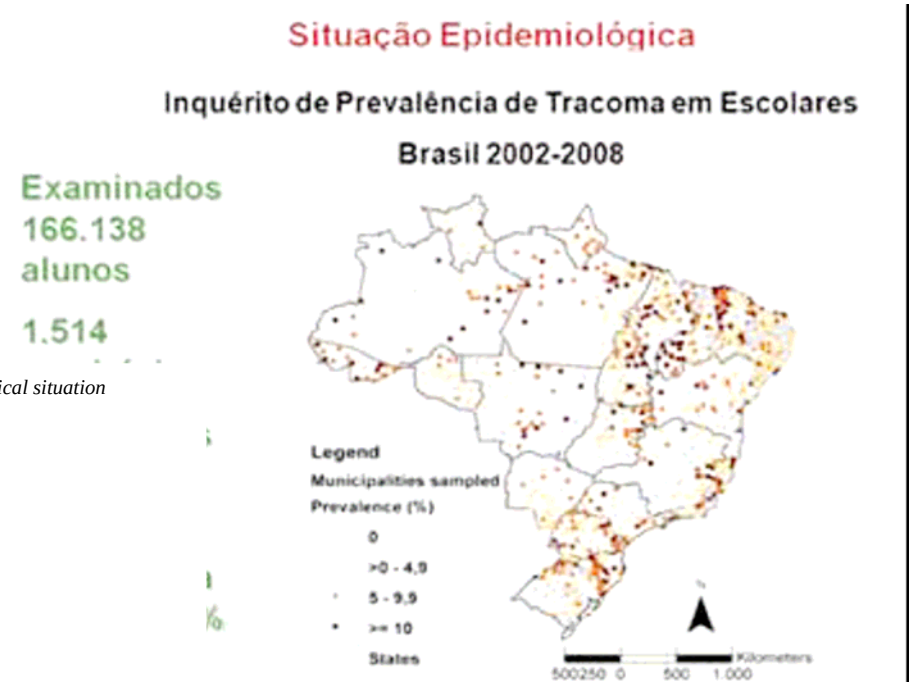


Fig. 17 – Epidemiological situation

5.6 Chlamydiosis and Rickettsial disease

Trachoma is a disease caused by *Chlamidia Trachomatis* which affects about 84 million people, of which around 8 million present serious visual deficiency. In Brazil, the Chlamydia is poorly studied. The two most important species are the *Chlamydia trachomatis* and the *C. pneumonia*. The

first one causes a series of diseases such as trachoma, lymphogranuloma venereum and especially cases of masculine a feminine urethritis and cases of cervicitis, where it becomes very dangerous due to the possibility of causing pelvic inflammatory disease, ectopic pregnancy and being transmitted to the fetus at the time of birth. It is a STD greatly disseminated in Brazil.

The second species, C. pneumonia is responsible for 5 – 15% of the pneumonias of the community, and in the primary infection affects mainly children between 5 and 15 years of age. Currently it has also been associated to possibly having a role in cardiac problems such as aortic stenosis facilitating the degenerative and fibrotic process, as well as in other similar clinical cases. This species is even less studied.

The rickettsiosis are infectious diseases of cosmopolitan distribution, caused by obligate intracellular bacteria transmitted by mites, ticks, lice and fleas which occur, with the exception of the epidemic typhus, in small outbreaks and isolated cases.

Although nowadays, under taxonomic aspects, they should be considered as a group of diseases caused strictly by proteobacteria of the subgroup α 1 (rickettsiae of the group of spotted fever and of the typhus and the ehrlichias), *Bartonella* spp. and *Coxiella burnetti*, respectively, proteobacteria of the subgroup α 2 and the proteobacteria group ?? continue to be studied in the fields of rickettsiologia.

The spotted fever, the epidemic typhus and the typhus of savannahs caused respectively by rickettsiae of the spotted fever group, *R. prowazekii* and *Orienta tsutugamushi* are considered the most important rickettsiosis due to the elevated mortality rate in the absence of specific treatment. Aside from the Rocky Mountain Spotted Fever and the Brazilian Spotted Fever (FMB) caused by *R. rickettsii,* the rickettsiosis of the spotted fever are present in several geographic areas of the world. Taking into consideration the several species, responsible for a variety of diseases, with varied clinical presentations, the spotted fever caused by the complex *R. conorii,* for example, is known in Europe and in Africa as the Mediterranean Spotted Fever, even though other subspecies are described and cause diseases in other regions like Asia, Africa, India, Israel, Italy and Russia.

In Brazil, the spotted fever caused by *R. rickettsii* is the most prevalent and known rickettsiosis, even

though there are reports on confirmed and suspected cases of recrudescent typhus, endemic typhus, ehrlichiosis, typhus transmitted by cat flea and rickettsiosis varicelliform, aside from the Q fever and the bartonellosis, and two new rickettsiosis caused by different rickettsiae of the spotted fever group in the states of Bahia and São Paulo.

The first publication on FMB was registered in 1929, but there is evidence of the knowledge of the disease by the population of the interior of the country before 1900. Therefore, although known for more than eight decades, especially in the Brazilian Southeast Region, FMB only became a disease of compulsory notification in October 2001 by the Ministry of Health Ordinance number 1,943, of 10/18/01, and since then the number of notified cases has increased with more than 650 cases confirmed, and with an average of mortality of 27% (Brazil´s Ministry of Health, 2008).

Of the confirmed and notified cases of FMB until the end of 2009, the majority of the cases occurred in the states of the Southeast Region and in the state of Santa Catarina. The infection is seasonal, with a greater number of cases of spotted fever happening between the months of June and October, corresponding to the increase of the activities of ticks and to the concomitant greater contact of man with these arthropods.

FMB, most of the times, occur as isolated cases, but the disease may occur in members of the same family or in groups of individuals who work in a common activity as occurred in the outbreak of Itaipava, Petrópolis and Rio de Janeiro in 2005, when it was possible to identify *R. rickettsii* in blood and tissue samples of patients.

As a traveler´s disease, the spotted fever is being considered, according to data from the GeoSentinel Surveillance network, one of the most important traveler´s diseases in the last two decades, especially among travelers coming from South Africa, a fact which can be confirmed when in 2008 *R.conorii* was identified in biological samples of a South-African patient, who died, with the suspicion of hemorrhagic fever caused by arenaviruses in Brazil.

With regards to the other rickettsiae, considering the most ample concept previously defined, it is important to bring attention to the growing increase of bartenellosis in the world and also in Brazil, a

country where children are frequently hospitalized with the diagnosis of lymphoproliferative disorders and adult patients present cat-scratch disease associated with meningoencephalitis and endocarditis. With the feline being considered the biggest reservoirs, studies performed in the last years have demonstrated the ample dispersion of the agents, with 27% to 90% of the analyzed cats with

molecular evidence of infection by *Bartonella* spp in different areas of the territory of Rio de Janeiro.

Recently with the molecular identification of *Coxiella burnetii*, a Q fever agent, for the first time in Brazil in patients in the state of Rio de Janeiro, it was possible to increase the number of rickettsiae submitted to epidemiological vigilance, considering, nevertheless, as occurs with the other rickettsiae, the lack of awareness of health professionals about the possibility of the occurrence of these zoonoses, as well as the inexistent support towards the research of a group of diseases which, although do not determine a quantitative impact in the opinion of public health, present an elevated mortality rate in the absence of an early diagnose and treatment, especially with regards to FMB.

5.7 Dengue

Dengue is an acute febrile illness which occurs in the tropics, being caused by four serotypes of the Dengue virus of the genus Flavivirus (Flaviviridae family). It is prevalent both in the rural areas as well as urban areas. The transmission occurs through mosquitoes of the genus *Aedes*, mainly *A. aegypti* and *A.albopictus.* Figure 18 shows the prominence of A. aegypti. Data from the WHO show that approximately 2.5 billion people are is areas of risk and that each year around 50 million cases of dengue are registered. Today the disease is endemic in 100 countries. In Brazil more than 10 million cases were registered since 1986 when dengue began its spread in the country (fig 19). Three serotypes can be found in Brazil, Dengue 1, Dengue 2 and Dengue 3. Dengue can be found in most of the states of Brazil, of which, in 2008, 9,7% of the cases occurred in the North Region, 33% in the Northeast, 46,9% in the Southeast, 8,1% in the Midwest and 2,3% in the South. All the serotypes have been associated with dengue classic fever and hemorrhagic fever (fig. 20) yet the epidemics with the greater number of severe cases occur when the serotypes of Dengue 2 and Dengue 3 predominated. **There are currently no antiviral drugs** which are

effective with the Dengue virus. **Neither are there drug therapies which can alter the course of the disease.** This does not mean that good early medical actions do not alter the course of the disease. Much to the contrary, well controlled intravenous hydration substantially modifies the course of the severe disease. It is uncertain, nevertheless, which are the patients who develop the severe disease and which patients will better benefit from invasive medical measures and hospitalization, since during an epidemic, the care for an enormous universe of individuals is extremely difficult. There are still doubts about the best way to classify the patients with the aim of obtaining a rational therapeutic approach. The *Aedes aegypti* is the main insect vector of the dengue among us. It's an insect with a strictly urban behavior, and it is very rare to find its eggs or larvae in reservoirs of water in the forests. In average, an Aedes aegypti lives around 30 days and the female can lay up to 150 to 200 eggs at a time. Once with the dengue virus, the female will becomes a permanent vector of the disease and it's believed that there is a probability of 30 to 40% of chances of its offspring already being born infected. The epidemiological importance of this ovarian transmission is yet uncertain. Therefore the need for studies such as, **the development of new specific diagnostic methods which are faster and more efficient, new therapeutic approaches, the development of vaccines** are certainly a priority for the country, as is **the intensification of epidemiological and entomological studies, researches dedicated to social and climatic issues, among others, related to the emergency of the dengue, deserve to be further studied.**

Municipalities Infested by *Aedes aegypti*

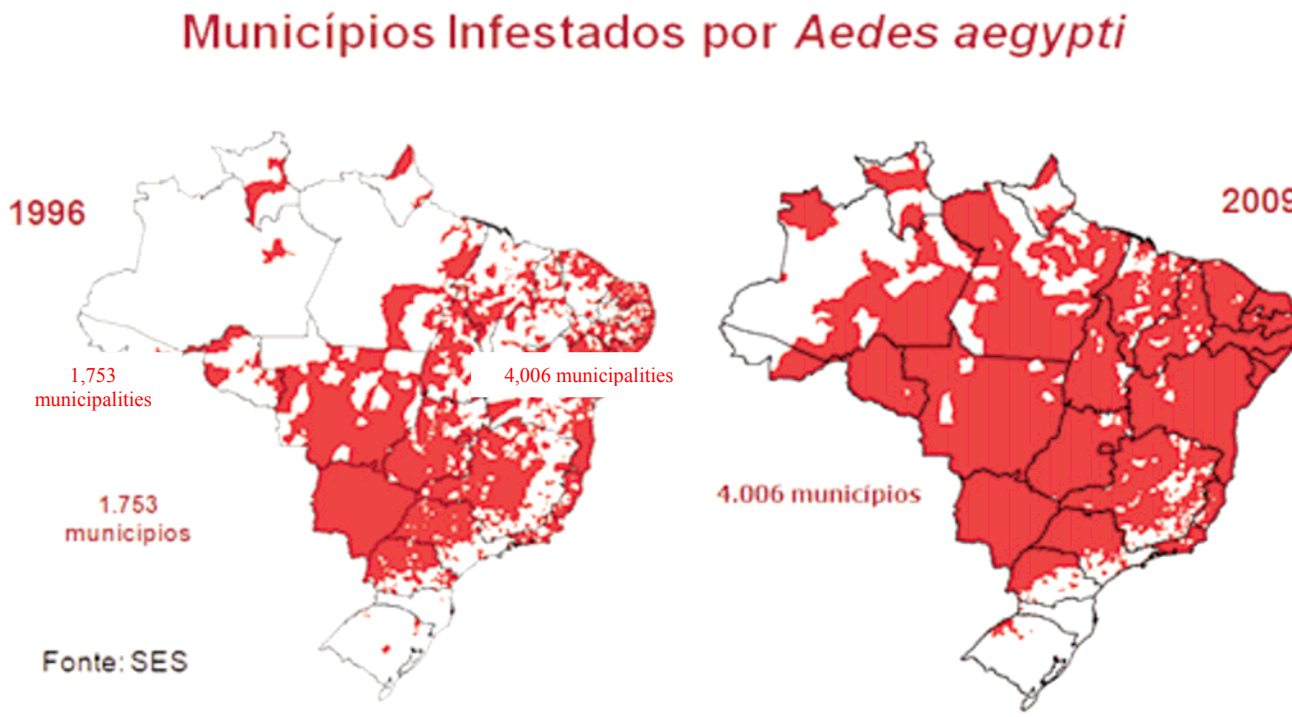


Fig. 18 – Situation of the Municipalities

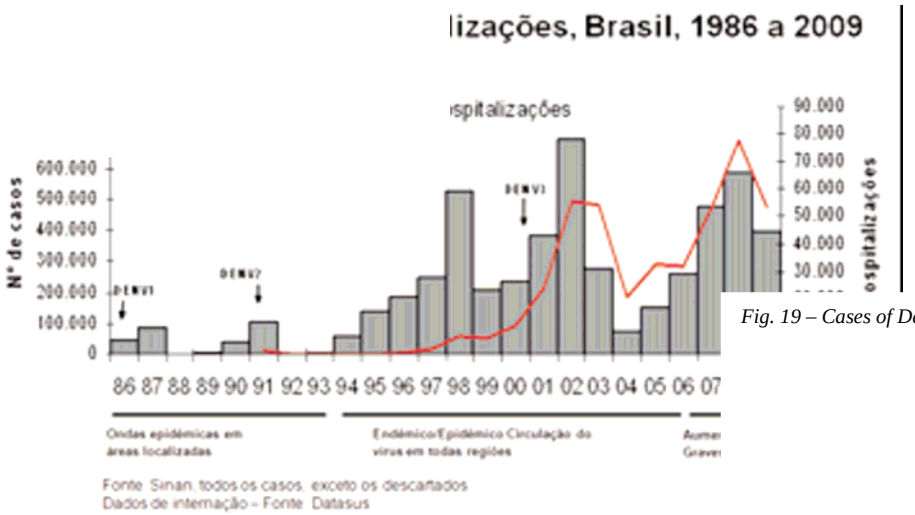


Fig. 19 – Cases of Dengue

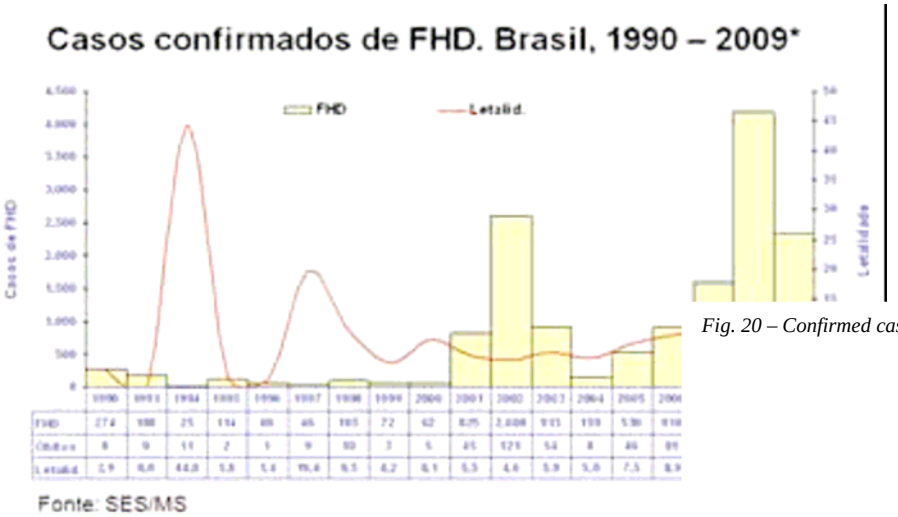


Fig. 20 – Confirmed cases

5.8 Yellow Fever and Other Arboviruses

The yellow fever is also caused by a virus of the Flaviridae family (genus Flavivirus). The yellow fever virus is being transmitted in South America in its wild form mainly by mosquitoes of the genus *Haemagogus* and *Sabethes* and in Africa of the genus *Aedes* ; the monkeys are the hosts. In both continents, the urban form, without cases in America, have as the vector the *A. aegypti*. The WHO estimates that around 200,000 people are infected annually with about 30,000 deaths per year. The epidemiological data indicate an increase of the disease as of 1980, which is the reason why it has been designated as a re emergent disease. (fig 21)

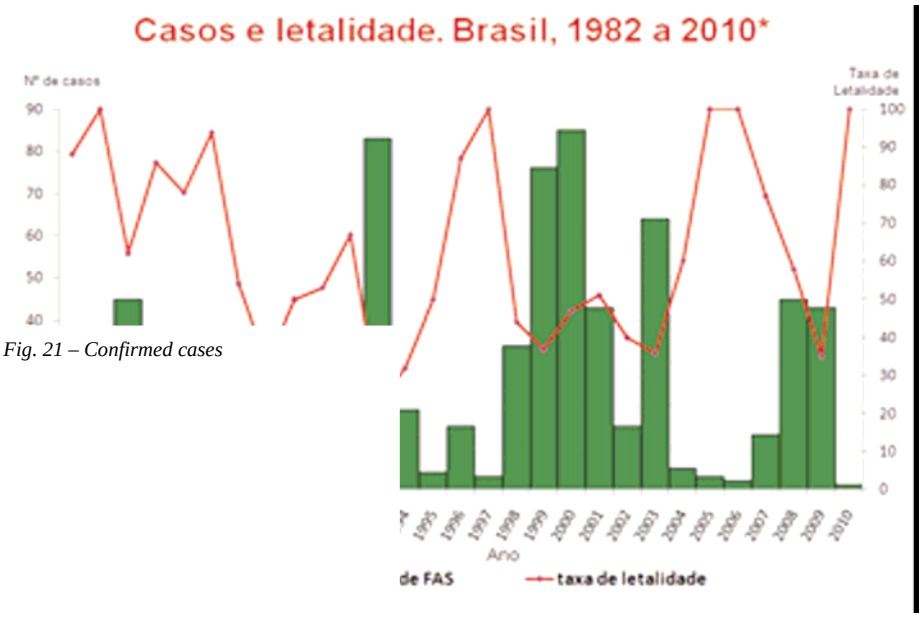


Fig. 21 – Confirmed cases

In Brazil mortality has been elevated, in the last 20 years it has ranged at about 45%, with occurrences of outbreaks every two to three years. The expansion of the transmission areas in the last five years in Brazil and in the Southern Cone has become evident in the recent epidemics described in Argentina, Paraguay and Brazil. In our country, the states of Goias, Pará and Minas Gerais are the ones who notify the greater number of cases. Yet, the occurrences of outbreaks in 2008 and 2009 in the states of Rio Grande do Sul and São Paulo, in areas with over 50 years without transmissions of yellow fever, show that the force of the transmission of yellow fever grows and emerges each year, moving towards the coast, which is the most populated region of Brazil and has a low vicinal coverage (~20%); these episodes actually had great repercussion in the media. In this scenery, it becomes necessary that new studies be developed **with the objective of understanding the current epidemiological situation, the climatic and environmental alterations in the genesis of the expansion of yellow fever, and also, in view of the cases of visceralization from the 17D vaccine, that researches be performed on the immunological and genetic aspects related to the vaccine and to the immunized population; and finally, the study of phylogenetic characteristics is needed in order to understand the molecular epidemiology of the viral yellow fever.**

There are yet another dozen arboviruses of great importance in public health and some of them are prevalent in Brazil. As such, the Fever of ORO caused by an Orthobunyavirus of the Bunyaviridae Family, is transmitted by the other parasites

Culiciudes paraensis and, after dengue, is the arbovirus with the greatest number of cases, with an estimate in the last 40 years of more than 500,000 cases of arbovirus in the Brazilian Amazonia alone. The disease has expanded to other countries of the Northeast of South America with epidemics of ORO fever being registered in Peru, Panama and Trinidad and Tobago. The main picture is that of a disease "dengue simile", but it is frequent to perceive cases of meningitis and more rarely of encephalitis.

The encephalitis caused by arbovirus is another example of arboviruses that occur in Brazil, with great importance to the Rocio and the Encephalitis Saint Louis. Both viruses are flavivirus (related to the Dengue and Yellow Fever virus) which cause encephalitis. The Saint Louis Encephalitis virus has caused outbreaks of encephalitis in North America and most recently in Argentina. In Brazil, cases of the viruses have been confirmed in the Amazonia mainly in the state of Pará and in the state of São Paulo, although the cases presented fever "dengue simili" and meningitis.

The East, West and Venezuelan equine encephalitis are alphavirus of the Togaviridae family, transmitted by mosquitoes of the genus Culex and have birds as their primary hosts. Humans and equines are terminal hosts. These antiviruses have displayed considerable prevalence of antibodies in the Amazonian population, and epizootics in the Amazonia, Northeast, Pantanal and Brazilian Southeast have been described. Of these, the equine encephalitis of the East is the most distributed. Another important Alphavirus is the Mayaro virus which is the one that causes the Mayaro fever an exanthematic disease which affects human populations living in the Amazonia and the Midwest. The disease curiously presents the same wild cycle of the yellow fever, having mosquitoes of the genus Haemagogus and monkeys as links in the transmission chain. The occurrence of this disease has been used as an alert for the circulation of yellow fever due to having the same transmitters. The Mayaro fever causes a disease that progresses with fever, headache, rash, myalgia, arthalgia and joint swelling. It is similar to the Chikungunya fever, an emergent arbovirus which

spread in the Old World and caused epidemics in Italy.

Several other arboviruses associated with acute fever of the “dengue simile” type have been described especially in the Amazonia and on a smaller scale, in the states of São Paulo. The most prevalent are the Ilhéus virus, Caraparu, Catu, Guaroa and Tacaiuma. Other less prevalent are the Maguari and the Tucunduba virus, this last one has been associated to cases of encephalitis in the Amazonia. All these viruses have in common that they are endemic, but with an episodic and sporadic circulation among humans, but with the disorganized occupation of the Amazonia they can eventually become urbanized as happened with the ORO virus, with which all of them, except the Ilhéus virus, are associated.

These sceneries provide unique opportunities for studies and researches to be developed about the mechanisms of expansion of the ORO fever, the Saint Louis encephalitis and other arboviruses, aiming towards understanding the possible association of the occupancy of the Amazonia and the disorganized urbanization with the emergence of other arboviruses. Equally interesting is the study of the molecular epidemiology of these arboviruses through a genetic and phylogenetic characterization of viral isolates. In conclusion, the eco-epidemiologic study is essential for the understanding of how these arboviruses maintain themselves in nature.

5.9 Rabies

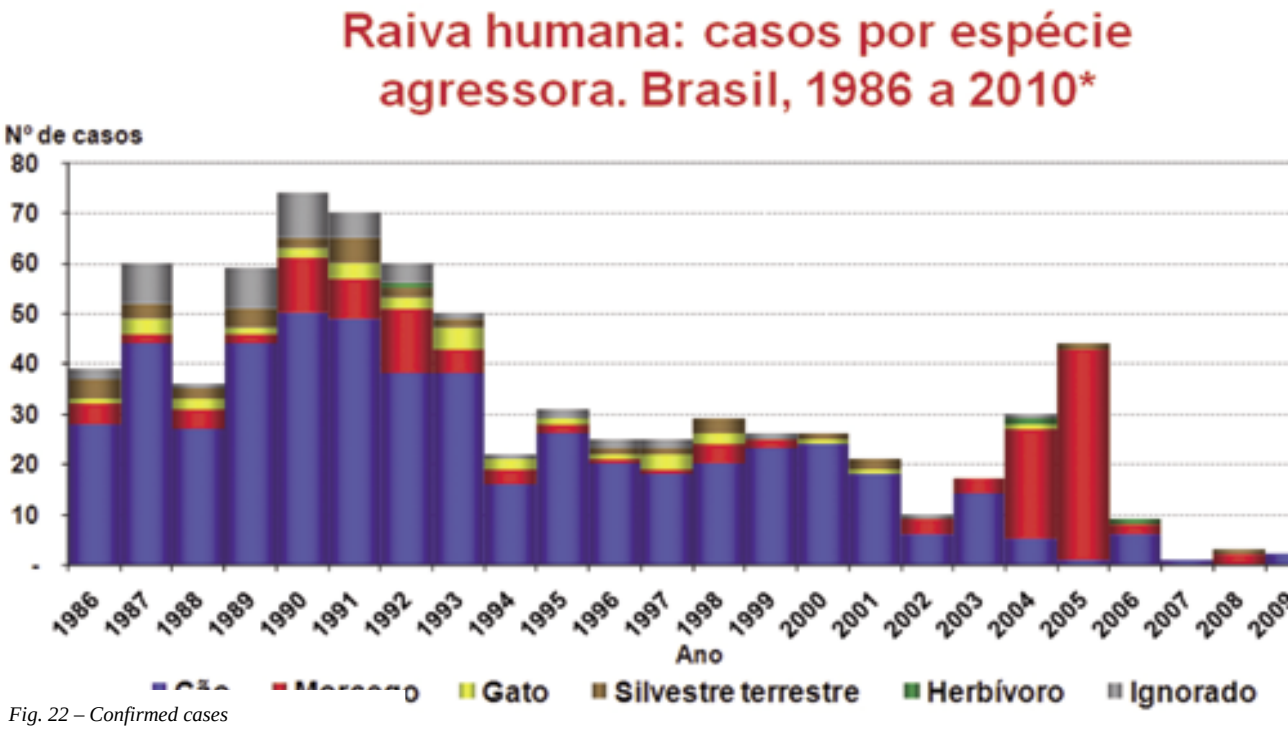


Fig. 22 – Confirmed cases

F ses of human Rabies in Brazil.

Since ancient times, rabies represents a serious public health problem and maybe, best represents the prototype of neglected infections disease. In fact, WHO estimates that around 10 million accidents occur each year that results in the need for post-exposure treatment, and more, approximately more than 10,000 deaths by rabies occur in the world, mainly in Asia. In Brazil, rabies transmitted by dogs has been controlled not having had any cases in the urban areas registered in years. Nevertheless, the control of the urban cycle resulted in the emergence of a new and grave problem, the rabies transmitted by bats, especially by vampire bats (more from vampire Desmodus rotundus) but also from frugivorous and insectivorous bats infected by spillover. Recent outbreaks of rabies transmitted by *D.rotundus* have been registered in Pará and Maranhão, but isolated cases also occur in other regions. In addition, the losses of farm animals to rabies transmitted by bats

are enormous. Therefore, the development of researches aiming towards: **the understanding of the eco-epidemiology of rabies in the savage cycle, the mechanisms associated with the emergence of rabies by bats, the role of deforestation in the genesis of transmission by bats, the biomolecular, phylogenetic and evolutionary studies, the development of more sensitive and specific techniques for the diagnosis in living, new therapeutic approaches**, among others, represent issues which deserve financial support.

5.10. Hantavirus

Two clinical syndromes are caused by the Hantavirus (genus Hantavirus, of the Bunyaviridae family), virus transmitted by excreta (feces, urine and saliva) of rodents of the Cricetidae and Muridae family, they are the hemorrhagic fever with renal syndrome and the Hantavirus cardiopulmonary syndrome (HCPS). The first one occurs in the old world and the HCPS in the New World. Since the description of HCPS in the USA in 1993, the occurrence of the disease has increased drastically. Brazil today has more than 1250 cases of HCPS and falls behind only to Argentina with regards to the notification of cases, and mortality rate ranges above 50%. On the other hand in Brazil, there is a great limitation on specific diagnosis, which results in the lack of reagents being produced in Brazil, and a small number of laboratories with the adequate level of biosafety NB needed (NB3) for the performance of studies of these viruses, which results in the delay of the development of knowledge for this viruses. Therefore, the performance of researches for the development of fast tests, self-sufficiency in reagents for use in public health laboratories, molecular epidemiology, pathogenesis, factors associated with the emergence of these viruses, the role of plantations in the environmental imbalance generating a large quantity of transmitters, etc, is important to allow for a better understanding of the natural history of these diseases in Brazil. Figures 23 and 24 show the distribution of cases in its totality in Brazil.

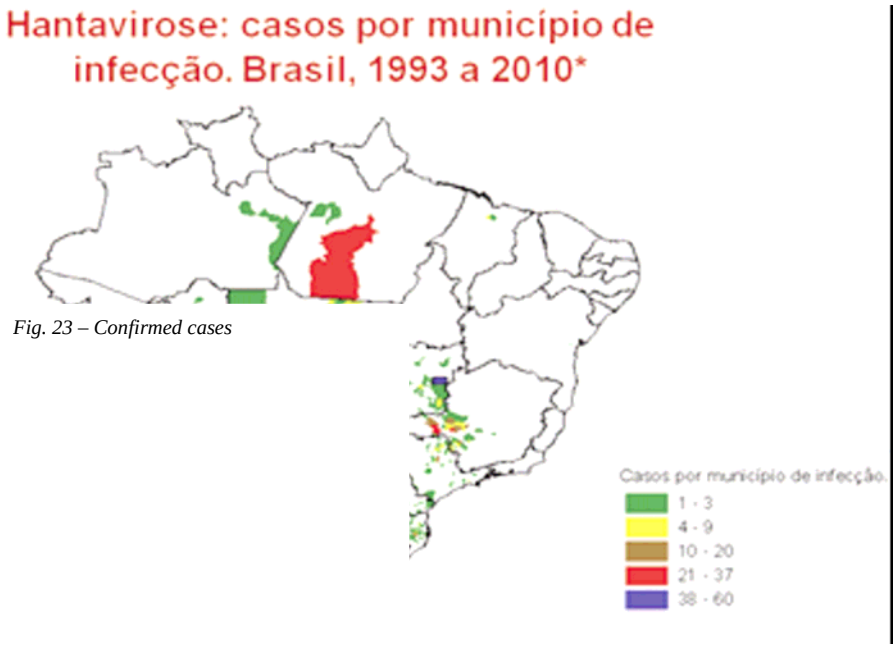


Fig. 23 – Confirmed cases

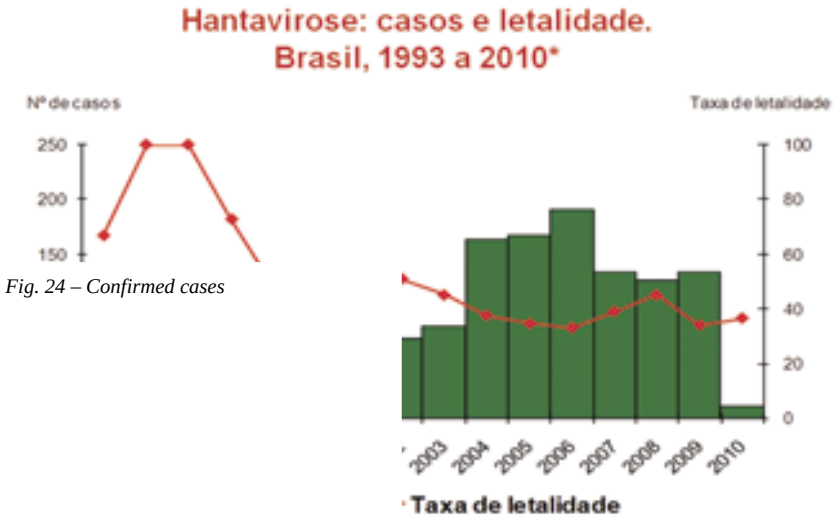


Fig. 24 – Confirmed cases

5.11 Viral hepatitis

Viral hepatitis are infectious disease whose agents have in common a primary tropism for the liver. Five viruses are recognized as etiological agents of these different human hepatitis: the hepatitis virus A (HAV), B (HBV), C (HCV), D or Delta (HDV) and E (HEV). HAV and HEV are transmitted in a fecal-oral way and the HBV, HCV and HDV through parenteral transmission. Most of the acute viral hepatitis are asymptomatic, showing an evolution normally benign, with low mortality. Nevertheless, in the dependency of the implied agent and the immunogenetic characteristics of the host, the hepatitis B, C and D can progress to a fulminating state, to chronicity or to cancer of the liver.

Hepatitis A presents a worldwide distribution, and the main means of contagion is fecal-oral transmitted through water and from contaminated food, and the stability of HAV in the environment and the large quantity of viruses present in the feces of the infected individual highly contributes to this. It is characterized as the most frequent acute viral hepatitis in the world.

The infections by the hepatitis B virus remain as a serious problem of public health in the whole world due to this agent being an important determinant of grave types of acute or chronic diseases of the liver.
According to the World Health Organization approximately two billion people were infected by the HBV, and in the world there are approximately 325 million chronic patients, with 1 to 2 million deaths per year. The virus is transmitted by horizontal means, affecting children older than five years of age and adults – through sexual, parenteral and cutaneous mucosa – and by vertical means, from mother to son, reaching children from the perinatal period up to five years of age. In Brazil, we can find the three patterns of endemicity in the Brazilian Amazon, for example the endemicity by HBV is not uniform, where we can find areas of elevated endimicity in the valleys of the river Juruá, Purus and Madeira in the Western Amazon and in the valley of the river Tapajós in the Eastern Amazon, and areas of low and medium endemicity in the valleys of the river Xingu, Trombetas and Tocantins and in the great capitals like Belém and Manaus.

Hepatitis C is normally asymptomatic and is considered by many the current most important chronic infectious disease in the world, it is estimated that there are around 170 million infected in the world, with 3-4 million chronic patients in Brazil. Hepatitis C is the most important cause of liver transplantation worldwide and in Brazil. The last international consensus supports the classification of

the variables of HCV into six genotypes (1 to 6). The genotype HCV influences the response to antiviral treatment in the progression of the disease. Data on the distribution of HCV in the North region is still scarce. Nevertheless, in the majority of the Brazilian regions the genotype 1 predominates – which are difficult to be treated.

Hepatitis D or Delta occurs in endemic areas of hepatitis B, seeing that the delta virus depends on the B virus in order to be infectious, it is estimated that there exists 18 million infected in the world, in which the biggest prevalence are found in the south of Italy and in a few areas of the ex-USSR and Africa aside from the Amazon basin. In the Amazonia a genotype (genotype III) prevails and has been associated with outbreaks of high morbidity and mortality. The survivors usually evolve rapidly to chronic hepatitis and cirrhosis.

Hepatitis E has an epidemiology and clinical course similar to that of the hepatitis A. It is an important cause of outbreaks which can develop into severe states of the illness. There is evidence that it is a zoonosis and that the pigs are the main hosts of HEV. In Brazil, infections have been registered but, despite the deficient sanitary conditions in several regions, an outbreak has never been registered.

5.12. Viral gastroenteritis

Rotavirus

Acute gastroenteritis is one of the main causes of morbidity and mortality in the world, constituting a big problem for public health. It is estimated that there are more than 700 million cases annually of diarrhea among children under the age of 5. In Brazil, although the rate of infant mortality is getting smaller since the last decade, the number of hospitalizations due to diarrhea remains at a stable level of 350,000 to 400,000 hospitalizations per year.

The rotaviruses (RVs) are classified into seven groups from A-G. Those from the group A (RVs-A) are the most important epidemiologically and responsible for 40% of the gastroenteritis cases which lead to hospitalizations among children under the age

of five, resulting in 611,000 deaths annually, especially in countries under development. The age

group between 6 and 24 months is the most vulnerable and the most associated with episodes of severe diarrhea. Acute diarrhea happens abruptly and can dehydrate the patient rapidly. In general, these situations are associated with the most important epidemiologically, serotypes/genotypes: G1P[8], G2P[4],G3P[8], G4P[8] and G9P[8]. Therefore, the use of molecular methods for the genetic characterization of these genotypes aiming not only towards the characterization of the structural genes (VP1-VP4, VP6 and VP7) but also non structural genes (NSP1-NSP5), becomes very important for a better understanding, especially after the introduction of the vaccine against the rotavirus in Brazil in March 2006 (Rotarix®, monovalent, human origin of the P[8]G1 type, GlaxoSmithKline).

Another type of rotavirus that deserves being highlighted is the RVs-C, normally associated to cases of infant diarrhea of self-limited course, with a possible transmission by pigs. However, the incidents of infection by this group in humans is underestimated, because in general the diagnosis method utilized for its detection is the polyacrymide gel electrophoresis (EGPA), instead of the chain reaction mediated by polymerase preceded of reverse transcription (RT-PCR) and the electronic microscopy, which hinders its detection. Therefore, only a study focused specifically on the detection and characterization of RVs-C as the cause of gastroenteritis in the hospitalized infant population will show us its real prevalence, and thus enlarging our knowledge about the participation of these agents in these episodes.

The RVs also cause infections in animal and, therefore, are seen as potential reservoirs for the genetic/antigenic diversity of the human rotaviruses; consequently the study on animal rotavirus is considered the key to acquire a better understanding of the evolution and the ecology of the rotavirus. Several studies are being developed in this area, mainly based on the genetic sequencing of the samples, opening a great range of discussions about the occurrence or not of heterologous infection.

Another agent which has been taking on great importance due to its association to gastrointestinal disorders, is the Picobirnavirus (PBVs), even though its pathogenicity is still not well defined. They are small bi or tri segmented viruses, non-enveloped with

double stranded RNA identified in feces of humans and symptomatic and asymptomatic animals. Base on the sequence of the RdPd gene, the human PBVs are classified in genogroups I and II.

Based on such facts, it is intended to implement new technologies and scientific methodologies which will supply knowledge that will assist in the evaluation of the impact and in the perspectives of the national immunization program anti RV, effectively contributing to the actions of the Ministry of Health.

Norovirus, sapovirus and human astrovirus

Other viruses are associated to gastroenteritis, with special attention to the norovirus group considered to be responsible for more than 90% of the explosive outbreaks of non-bacterial diarrhea, leading to the occurrence of about 200,000 deaths, especially among children under the age of 5 who come from developing countries. The sapovirus and the human astrovirus are also related to outbreaks, recently being associated to hospitalizations and sporadic cases together with the norovirus.

The studies involving these agents in Brazil are still limited, being restricted to a few localities in the Southeast Region (Rio de Janeiro, São Paulo and Espírito Santo), Midwest (Goiás and Brasília), Northeast (Bahia and Pernambuco) and North (Pará), related especially to detention and, in a few, to molecular characterization. The positive rate found for norovirus ranged from 6.6% to 39.7%. In the years of 2009/2010, an expressive increase in number of cases of gastroenteritis caused by norovirus was observed, and the first outbreaks were detected in transatlantic ships in Santos, Salvador and Búzios. In Belem, in hospital vigilance, it was verified that there was a significant increase in the circulation of these agents attaining a positive rate of above 60% in a few months of this biennium.

Therefore, **an intensive vigilance both in hospitals as in outpatient clinics becomes necessary in order to best define the circulation of these virus, as well as a genetic characterization of the circulating types, viewing to associate them to the most severe cases observed. The establishment of faster yet sensitive techniques is necessary in order to supply results in the shortest period of time and thus assist in the therapeutic conduct to be ministered to the patient, and in the case of hospitalized**

children, assist in the measures of prevention and control, to avoid the dissemination of these agents.

5.13 Paracoccidioidomycosis and other profound mycosis

The paracoccidioidomycosis, also known by *Disease Lutz-Spendore-Almeida* and South American blastomycosis is a pulmonary disease caused by the *Paracoccidioides brasiliensis* fungus. The indigenous cases of paracoccidioidomycosis occur exclusively in countries of South America and Central America, in tropical and subtropical regions, particularly in Brazil, in Colombia, in Venezuela and in Argentina. It consists in the most important systemic mycosis in Brazil, which includes the biggest endemic area of the world, with prominent prevalence in the South, and Midwest Regions, of which the State of São Paulo is one of. In severe cases, mortality is estimated between 2 and 23% reaching 30% if associated to AIDS. For the amount of premature death it provokes, especially in specific social segments such as the rural workers, paracoccidioidomycosis represents a serious problem of public health.

Paracoccidioidomycosis predominates in the rural zones of Brazil and affects mainly the farmers who work the land where the fungus is present. The infection is initiated through the inhalation of infectious spores. In Brazil, the highest number of incidents occurs in São Paulo, Rio de Janeiro and Minas Gerais. The cases reported out of the endemic areas are of patients who visited or lived for some time in a Latin American country. The infection by the *paracoccidioides brasiliensis* is acquired in the first two decades of life, with a peak incidence between the ages of 10 and 20. The evolution into a disease in uncommon in these decades, and it occurs more in adults between 30 and 50 years of age, as a reactivation of the endogenous latent focus and depends on factors related to both the infectious agent as the host. The majority of the cases of paracoccidioidomycosis occur in individuals of the male gender, smokers and chronic alcoholics whose hygienic, nutritional and socioeconomic conditions are precarious. These individuals are usually rural workers who, due to their activity, stay in direct contact with the earth and the vegetables.

In a general aspect, this disease is not subject to national epidemiological vigilance; but in a few

Brazilian states, Paracoccidioidomycosis is part of the list of diseases which demand compulsory notification. In Brazil it is the mycosis which causes the greatest number of deaths, being considered as the defining condition of AIDS.

The average coefficient of mortality by paracoccidioidomycosis as the basic cause of death in Brazil, between 1980 and 1995 was of 1.45 deaths per 1,000,000 inhabitants. The greatest proportion of deaths in this period (29.86%) occurred in the state of São Paulo. In the state of Paraná, between 1980 and 1998, this coefficient was of 3.48 deaths per 1,000,000 inhabitants.

Between 1985 and 2005, there were 1,950 deaths in the state of São Paulo where the paracoccidioidomycosis was mentioned as the cause of the death. In this period, the average coefficient of mortality was of 2.73 deaths per 1,000,000 inhabitants (ref; SANTO Augusto Hasiak. Tendency of mortality related to paracocciodioidomycosis, state of São Paulo, Brazil, 1985 to 2005: study utilizing multiple causes of death. *Rev. Panam Salud Publica* 2008, volu.23, n.5, pp 313-324). The figure below compares the number of deaths where the paracoccidioidomycosis is the basic cause of death or the related disease.

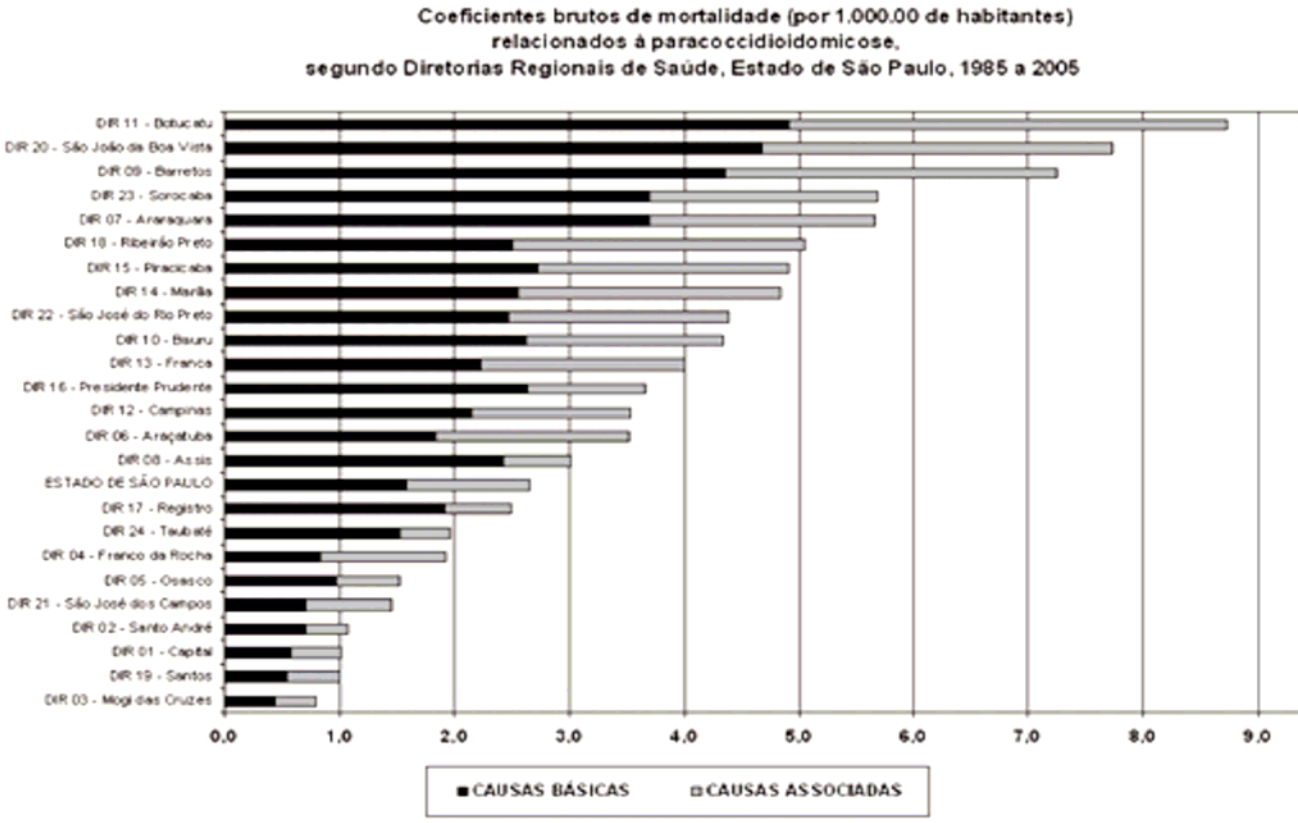


Fig. 25 – Gross coefficient of deaths (per 1,000,000 inhabitants) related to paracoccidioidomycosis according to regional health authorities (DIR), in the state of São Paulo, Brazil from 1985 to 2005 (Source: Santos AH, 2008; Revista Panamericana de Salud Publica 23, pp 313-324).

success of the therapy depends not only on the utilized antifungal, but also on the level of dissemination of the injuries and the immunological capacity of the patient.

The regression of the clinical changes is observed between one and six months after the beginning of the treatment. Nevertheless, the eradication of the fungus on the tissue takes a long time, and the ill should be examined periodically through clinical and complementary exams, in order to evaluate if the regression of the symptoms and the disappearance of the active injuries occurred or not.

There is yet a group of infections by fungi that deserve attention, as is the case of (a) Chromoblastomycosis, a frequent disease in the tropical and subtropical regions, common among rural workers and caused by fungi of the genus Fonsecaea, Phialophora, Cladophialophora and Rhinocladiella, (b) Sporotrichosis is a cutaneous or subcutaneous mycosis, with a sub-acute or chronic evolution in most of the cases, it usually affects the skin and the lymphatic vessels near the injured area. All the forms of sporotrichosis in man are causes by a single species, the fungus *Sporothrix schenckii*, the state of Rio de Janeiro suffers a relevant epidemic outbreak since 1998. (c) The profound mycosis or Invasive Fungi Infections (IFIs) has become an important public health problem, especially in Intensive Care Units (ICUs). Among the important species we have Candida spp., *Aspergillus* spp and *Cryptococcus neoformans.*

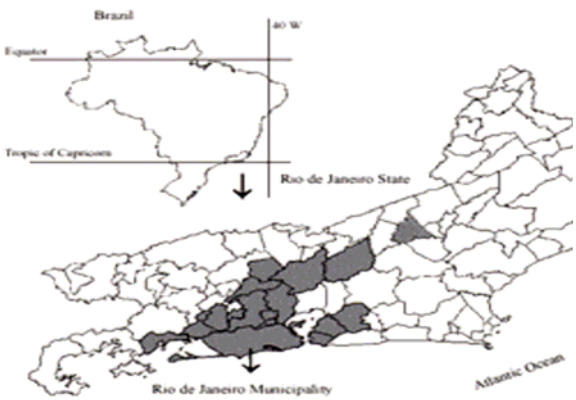


Fig. 26 –Map of the state of Rio de Janeiro showing the municipalities (dark areas) where cases of human and feline sporothicosis were identified (sourch: Schubach et al, 2005; Emerging Infectious Diseases 11, pp.1952 – 1954).

The main classes of antifungals comprise the polyene, the azoles, thiocarbamates, allylamines, morpholinic derivates, 5-fluorocytosine, griseofulvin and echinocandins. Yet, the therapeutic arsenal is limited due to problems of selectivity, toxicity and the resistance profile of the fungi, to the antifungals available. Currently the drugs commonly used in the antifungal therapy are the polyene and the azole agents and in the therapy for cases of invasive mycosis the chemotherapeutic weapons are even m ore limited, where the most indicated drugs are amphotericin B, itraconazole and voricinazole. Even though amphotericin B has been considered the standard golden drug for these infections, its use has

been limited due to its high level of hepatotoxicity and nephrotoxicity.

5.14. Toxins

Poisonous animals compose a large set of serpents, scorpions, spiders, caterpillars, bees, lizards, frogs, stingrays, mollusks, anemone, platypus, certain ants and even birds with the capacity of producing and inoculating in their victims a poisonous secretion. Given the vast distribution of these animals especially in tropical and subtropical regions, the extensive number of accidents and the complexity of the clinical case that it causes, the poisoning from venomous animals is a global problem of great importance to public health (Gutierrez et al, 2006).

Poisoning by serpents constitutes, particularly, a grave problem to public health due to its high incidence, and the seriousness of the poisoning depends on different genus of serpents that inhabit specific environments. It is estimated that more than 500 thousand cases of ophidism occur in the world and approximately 130 thousand deaths (26%) per year. A great part of these deaths occur due to the lack of specific anti-venom, to the delay in its application or due to the incorrect use of the product. In these cases, according to the World Health Organization (2007), the part of the population that is most affected is constituted predominantly by adult farmers and their children, who work in poor rural communities of countries under development in Africa, Asia, Latin America and Oceania. Figure 27 illustrates the situation of ophidism in the world.

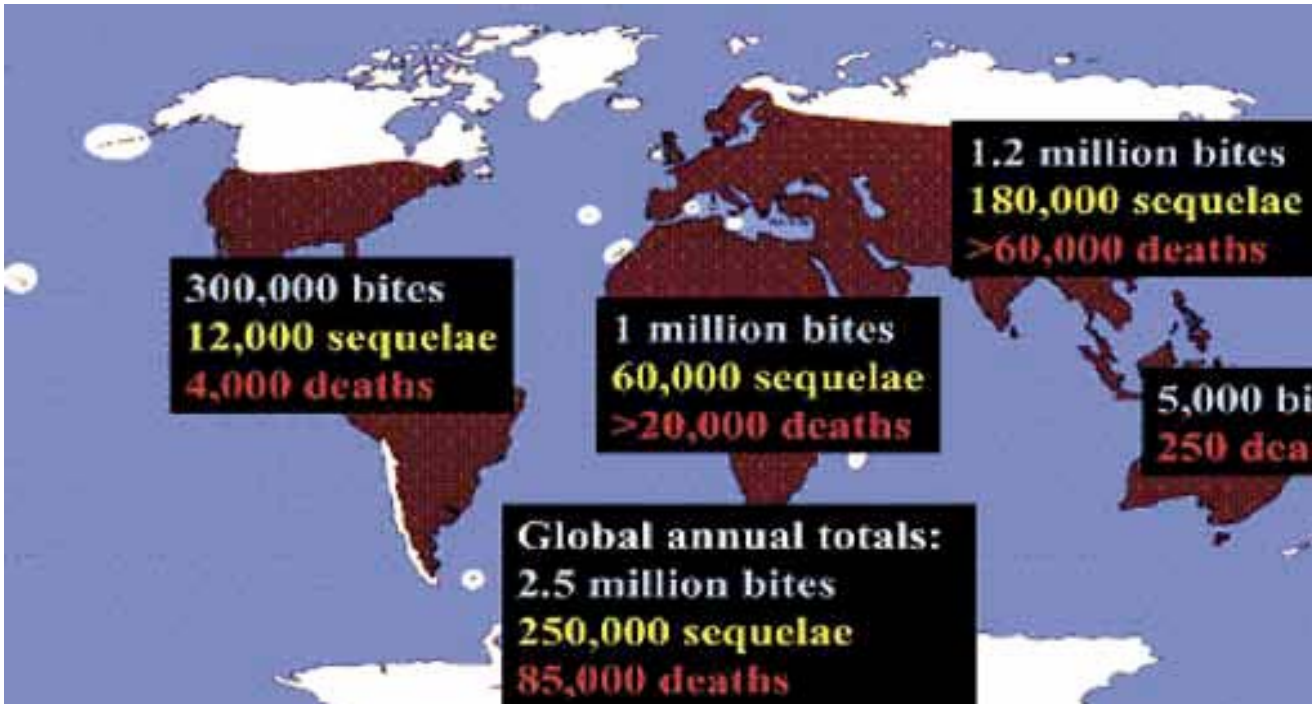


Fig. 27 –Estimated regional and global morbidity and mortality from snakebite, from Gutiérrez et al. 2010. Toxicon, in press.

In general terms, in accidents by other venomous animals, this same population is the one which is most exposed to risks. Therefore, such accidents fulfill the criteria of "neglected tropical disease" seeing that they exclusively affect poor people and people who lack political power in the rural areas of tropical countries with a low per-capita income (Kinhauser, 2003). Consequently, the World Health Organization recently incorporated ophidism to its list of neglected diseases. (www.who.int/neglected_diseases/diseases/en)

We highlight as well that such circumstance provides a bigger exposure of these people to the risk of contact with the most diverse types of poisonous animals. In other words, poisoning by venomous animals constitutes a case of environmental and occupational disease, which would require a greater attention from national and regional authorities of the health sector (Gutiérrez et al, 2010). Just as occurs with other neglected diseases, the poisoning by these venomous animals has received very little attention from the health authorities, from the pharmaceutical industries and even from funding agencies in several parts of the world. Nonetheless, WHO´s global alert has attracted the attention of governmental and non-governmental authorities, anti-venom producers and research groups, for a bigger interest on the discussion and the search for solutions for this theme. (World Health Organization, 2007; Williams et al., 2010).

Similar to the cases of other diseases and public health problems, coping with the complex problematic resulting from the poisoning by venomous animals requires an integrated performance by different actors in order to promote specific actions.

Poisoning by Venomous Animals – Situation in Brazil

Brazil has a very diverse poisonous fauna, including most of the animals indicated above which cause a great number of poisoning, constituting a devastating situation of neglected diseases. A recent study by the Toxicological Information Center of the state of Rio Grande do Sul (CIT-RS), about the incidence of the diverse and different types of accidents with poisonous animals, indicated the occurrence of 61,172 notifications of accidents in the period of 1980 – 2005 only in this State! The study indicates that as of 1984 there was an exceptional increase in the number of accidents with poisonous animals surpassing, in some decades of the 90´s, the registry of accidents with medications (Abella et al., 2006).

The monitoring and cataloguing of the cases of accidents caused by the great number of venomous species in Brazil, have been continuously registered by the Information System for Notifiable Diseases (SINAN) of the Secretary of Health Surveillance of the Ministry of Health and are summarized below in tables 1 and 2.

Table 1 – Accidents caused by venomous animals in Brazil in the year 2008.

ACCIDENTS CAUSED BY VENOMOUS ANIMALS – DATA FROM 2008*

	TOTAL DATA BRAZIL			
ACCIDENTS CAUSED BY	TOTAL NUMBER OF CASES	CASES PER MILLION INHABITANTS	DEATHS	LETHALITY %
1 Serpents	26,156	130	119	0.50
2 Spiders	20,993	110	19	0.10
3 Scorpions	37,862	220	87	0.23

4 Caterpillars	3,968	20	5	0.10
Lonomia	592	___	2	0.30
5 Bees	5,605	30	13	0.23
TOTALS	94,584	510	243	0.1-0.5%

* Source: SINAN/SVS/MS - Electronic Epidemiological Report, June 2009.

It is worth mentioning that due to the characteristics of the occurrences and the difficulty of diagnosis, there is a known under-notification of accidents by poisonous animals in Brazil. Nevertheless, the data supplied by SINAN/SVS of the Ministry of Health for the year of 2008, show an elevated number of occurrences: around 95 thousand that year. As Table 2 shows, such accidents affect the population of all the regions, being responsible for 243 deaths notified in 2008. Table 2 is a comparison of the types of accidents caused by venomous animals in the regions of the country.

ACCIDENTS CAUSED BY VENOMOUS ANIMALS – DATA FROM 2008*

		Serpents	Spiders	Scorpions	Caterpillars	Bees
BRAZIL	Number of accidents	26,156	20,993	37,862	3,968	5,605
	Cases per million inhabitants	130	110	220	20	30
	Deaths	119	19	87	5	13
	Lethality%	0.5	0.1	0.23	0.1	0.23
ACCIDENTS PER REGION			CASES PER MILLION INHABITANTS			
North region		520	27	136	7	14
Northeast region		130	10	326	2	20
Midwest region		150	20	100	4	20
Southeast Region		80	55	201	15.00	31
South region		110	557	36	80	58

* Source: SINAN/SVS/MS - Electronic Epidemiological Report, June 2009.

The data on the tables indicate that the main accidents which result in poisoning cases in Brazil are caused by serpents, scorpions and spiders (Ministry of Health, 1998). Yet, as can be seen, there has been an increase in the last years, of the number of occurrences of accidents caused by bees and

caterpillars. With regards to the types of poisoning and the most affected regions of the country:

a) Serpents: The most critical situations are in the Northeast with 25% of the accidents, 41 deaths per year (34% of the country´s) and the highest index of lethality, 0.64%. Yet, the North region, with the highest proportion of cases of ophidism with regards to population (520 accidents/million inhabitants), has an aggravated situation due to the difficulty of locomotion and communication, generating insufficient level of notifications with regards to accidents and to lethality indexes. The Midwest region also, despite the lower number of cases notified, has been presenting an elevated index of lethality (0.61% of the cases).

b) Scorpions: Registering almost 38 thousand cases per year, the scorpion is the cause of the highest number of accidents by poisonous animals. Once again, the Northeast region stands out with the highest incidence with regards to population and a high index of deaths. Scorpion poisoning is also elevated with a high index of deaths in the Southeast region, hitting mainly children.

c) Spiders and Caterpillars: Accidents with such organisms are most frequent in the South region, with emphasis on the attacks by spiders in Paraná where accidents by the spider of the genus Loxosceles predominates. In Rio Grande do Sul and Santa Catarina, between 1997 and 2005, 1009 accidents produced by the caterpillar of the Lonomia obliqua species were registered, of which 984 occurred in Rio Grande do Sul, with grave hemorrhagic situation resulting in five deaths, at a lethality rate of 0.5% (Abella et al.,2006). As of 1989, the accidents provoked by the caterpillars have taken on endemic proportions (Duarte et al., 1990), when in the year 2005 alone, 127 accidents were registered in Rio Grande do Sul, in which the levels of lethality were considered 3-6 times higher than those observed in poisoning by serpents (Diaz, 2005; Abella et al.,2006).

d) Bees: They produce several types of accidents in all the regions of the country, both in the countryside as well as in urban areas, occasionally with elevated lethality, especially among children.

6. PRIORITIES IN RESEARCH SUPPORT IN THE CONTEXT OF THIS PROGRAM

6.1. Chagas Disease

- Screening on a large scale for new drugs and chemotherapy in a centralized way;
- Pre-clinical development of substances with established anti-parasitic activity;
- Experimental models;
- Criteria of cure;
- Ample biological characterization of the six strains of Trypanosoma cruzi established in 2009;
- Adaptation of the vectors to the home.

6.2. Leishmaniasis

- Screening on a large scale for new drugs and chemotherapy;
- Pre-clinical development of substances with established anti-parasitic activity;
- Vectors: molecular identification, Eco-epidemiology; Diversity of phlebotominae;
- Cryptic parasitism in leismaniasis on man and dog;
- Early diagnosos.

6.3. Malaria

- All aspects of Plasmodium vivax;
- Establishment of Brazilian colonies of vectors.

6.4. Filariasis

- All aspects.

6.5. Chlamydiosis and Pathogenic Rickettsial

- All aspects.

6.6. Pathogenic Mycobacteria

- Screening on a large scale for new drugs and chemotherapy;
- Pre-clinical development of substances with established anti-parasitic activity;
- Experimental models;
- Early Diagnosis;
- Studies of Immunopathogenesis.

6.7. Paracoccidioidomycosis and other profound mycosis

- Screening on a large scale for new drugs and chemotherapy;
- Pre-clinical development of substances with established anti-parasitic activity;
- Experimental models;
- Diagnosis.

6.8. Diseases caused by viruses

- Modernization in the production of anti-viral vaccines;
- Expansion of clinical centers capable of testing anti-viral vaccines;
- Development and nationalization of fast methods of diagnosis;
- Studies on the proof of the efficiency and safety of new insecticides in the countryside;
- Factors which predict the severity of the infection by the dengue virus;
- Definition of factors associated to the pathophysiogeny of the disease;
- Screening and pre-clinical development of ne anti-viral drugs;
- Immunopathological response to the vaccine for Yellow fever;
- Identification and characterization of new arbovirus;
- Identification of reservoirs of the rabies virus
- Study on the immunological response to the rabies vaccine;
- Early diagnose of the rabies infection;
- All the aspects related to the hantaviruses;

- Hepatocellular carcinoma etioepidemiologia and other liver tumors in Brazil;

- Resistance of Hepatitis B virus to antiviral therapy;

- Domestic and wild reservoirs for the hepatitis E virus in the Amazonia;

- Seroepidemiologic and biomolecular pattern of the hepatitis virus in indigenous communities of the Amazonia;

- Phylogeny of the Hepatitis D virus prevalent of Brazil.

6.9. Toxins

- Natural sources of new toxins of plants, animals and water organisms;

- Identification and production of toxin recombinant epitopes;

- Capacitating and training of human resources for research and for health care teams to mend for people in accidents who have become permanently incapacitated due to serious illness complications in consequence of poisoning by venomous animals;

- Involvement from organizations of local communities in the prevention and handling of problems utilizing educational methods and publication of preventive procedures.

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