PROTOCOL FOR SCREENING, DIAGNOSIS AND TREATMENT OF CHAGAS DISEASE IN PREGNANT LATIN AMERICAN WOMEN, THEIR NEWBORNS AND OTHER CHILDREN

Programme for Congenital Chagas Disease Prevention and Control of in Catalonia
Subdirectorate-General for Epidemiological Surveillance and Public Health Emergency Response

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1. INTRODUCTION

Chagas disease remains an important public health problem. According to the World Health Organization, about 8 million people worldwide, mostly in Latin America, are estimated to be infected with *Trypanosoma cruzi*. In nonendemic countries such as our own, Chagas disease is observed in infected individuals coming from endemic countries, or in newborns from nonendemic countries but to mothers infected with the disease (congenital transmission).

With the purpose of ensuring the surveillance and control of Chagas disease, the Programme for Congenital Chagas Disease Prevention and Control in Catalonia was launched in the year 2010, coordinated by the Ministry of Health, and including the diagnosis, control, follow-up and treatment of congenital Chagas disease targeted to pregnant women and their children. The *Protocol for screening and diagnosing Chagas disease in pregnant Latin American women and their newborns* was developed in 2010 in the context of the mentioned Programme. This document was the result of joint effort on the part of healthcare professionals with expertise in the disease, different scientific societies and professionals of the Ministry of Health of the Government of Catalonia, with the support of the Working Group on Nonendemic Countries and the WHO's Department for the Control of Neglected Tropical Diseases.

In addition to continuing on the same lines as the first edition, the Protocol presented herein offers an update on different clinical, diagnostic and epidemiological surveillance aspects based on the experience and evidence gained during these 8 years of the Programme for Congenital Chagas Disease Prevention and Control in Catalonia. Over these years, the public health dimension of the Programme has been reinforced, with the participation of numerous professionals pertaining to the healthcare system and community health agents, in an attempt to lessen the impact of the vertical transmission of Chagas disease in Catalonia.

The first part of this document describes the clinical aspects of Chagas disease. The appearance of the disease has been relatively recent in our setting; however, thanks to the information afforded in both healthcare and community contexts in recent years, Chagas disease is no longer a neglected and unknown disease in Catalonia.

Over the last years, advances and experience gained in our setting referred to the diagnosis of Chagas disease have led to consensus on the use of direct molecular methods, as described in the present Protocol. Likewise, the compilation of epidemiological data on the prevalence of the infection and the incidence of cases of the disease has improved greatly thanks to the surveillance and reporting of information contemplated in the setting of the Programme for Congenital Chagas Disease Prevention and Control in Catalonia on the part of the professionals belonging to the Working Group on Congenital Chagas Disease. In this regard, and in order to improve control, family and community care physicians have been enrolled in the effort, since they are among the healthcare professionals closest to the patients.

A fundamental aspect derived from this document and the application of the Programme is the multidisciplinary nature of the effort. The challenge facing the public health surveillance and healthcare system is coordination of the professionals in different specialties, such as gynecologists, microbiologists, midwives, primary care and hospital pediatricians, physicians specialized in family and community care medicine, nurses, specialists in infectious diseases, epidemiologists and community health agents, who all work together with the aim of achieving the established objectives.

The present Protocol intends to be an eminently practical document, offering healthcare professionals the essential elements needed for the screening of pregnant women. The Protocol also hopes to contribute to the early detection and treatment of cases of Chagas disease in the pediatric population – newborns and other children in Catalonia – with the ultimate purpose of improving maternal and child health in Catalonia.

2. CHAGAS DISEASE

2.1 Description

Chagas disease is a parasitic disease caused by *Trypanosoma cruzi*. The disease is usually transmitted by hematophagic triatomines such as *Triatoma infestans*, which transmit the parasite on defecating upon the skin or mucous membranes when biting to feed on blood. The parasites penetrate the body through any wound in the skin or mucous membranes when the individual touches or scratches the site of the insect bite. Transmission can also occur through contaminated blood transfusion or organ transplants; vertically from an infected mother to her fetus; or by the consumption of food contaminated with the parasite.[1]

2.2 Epidemiology

The disease is endemic in South American countries (except the islands of the Caribbean): Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Nicaragua, Mexico, Panama, Paraguay, Peru, Suriname, Uruguay and Venezuela. It is particularly prevalent in the centre and south of Bolivia, north-western Argentina, the south of Peru, western Paraguay, part of Ecuador, Nicaragua, El Salvador and southern Mexico (Figure 1). In the year 2010, the estimated prevalence rate of Chagas disease ranged from 0.03% in Brazil to 6.1% in Bolivia.[2] The prevalence has changed thanks to campaigns designed to fight the vector, which have been implemented in the different countries, and which have made it possible to either eliminate vector-borne transmission or reduce it significantly in some areas.[3,4]

Chagas disease is an emergent disorder in areas without vector-borne transmission.[5] In Europe, in 2009 there were an estimated 68,000 to 122,000 people infected with *T. cruzi*, with an underdiagnosis rate of between 94–96%.[6] A recent meta-analysis on the presence

of Chagas disease in Europe has evidenced a prevalence of 4.2% among the Latin American population.[7]

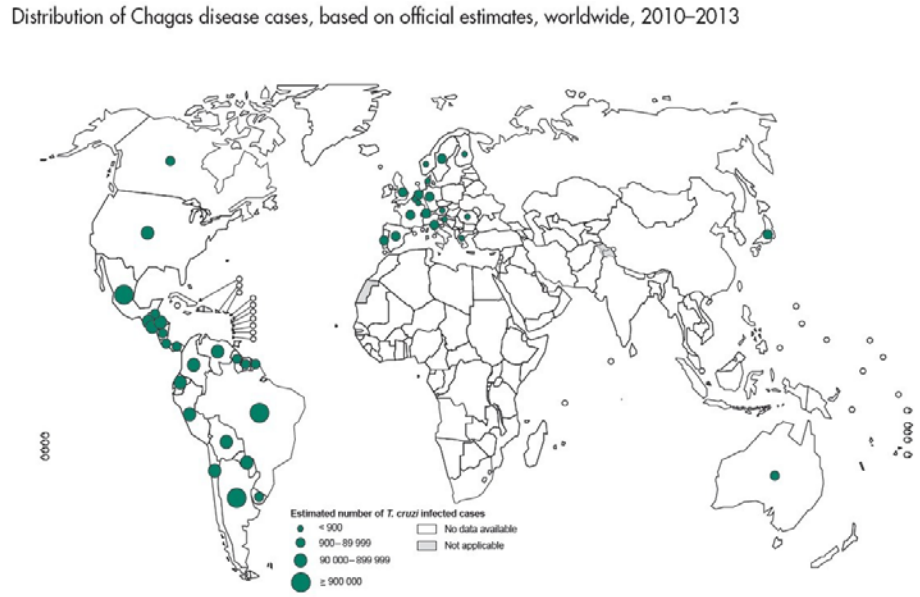
Migratory flows have been the cause of this phenomenon, which is important due not because of the number of cases of Chagas disease but also due to the possibility of *T. cruzi* transmission through nonvector-borne mechanisms such as blood transfusion, organ transplantation, and mother-to-child transmission during pregnancy and childbirth.[8] For these reasons, some European countries have introduced screening programmes in blood banks and also in transplantation programmes.[8]

With regard to congenital transmission, studies conducted in our setting indicate a prevalence of Chagas disease among pregnant women of 3.4% in the Latin American population overall, and of 27.7% in those from Bolivia.[9]

In other nonendemic countries, the vertical transmission rate varies between 0-7%.[10] Studies in endemic countries reveal vertical transmission rates similar to those found in nonendemic countries (between 1.7–5%).[11-14]

The growing presence of immigrants from endemic regions, the importance of early detection of the infection,[15] the great effectiveness of treatment in newborns[10] and the cost-effectiveness of a congenital transmission control programme[16] have been the main reasons for launching the Programme for Congenital Chagas Disease Prevention and Control in Catalonia in the year 2010. Indeed, Catalonia has been one of the first regions in Europe to introduce such a vertical transmission control programme from a public health perspective.[17]

Figure 1. **Distribution of cases of *Trypanosoma cruzi* infection in the world (WHO 2010-2013).**



Source: Neglected Tropical Diseases. A Statistical Update – Latest Data Available. World Health Organization. Available from:

http://www.who.int/neglected_diseases/NTD A_statistical_update_latest_data_available.pdf

2.3 Clinical aspects

Chagas disease develops in two phases: acute and chronic. The acute phase is characterized by few and generally nonspecific symptoms.[1] As a result, the disorder in most cases goes unnoticed or is confused with other diseases. In the symptomatic chronic phase, however, the complications may be severe and can prove fatal, particularly in the presence of cardiac alterations.[18]

2.3.1 *Acute phase*

The acute infection or primary infection may be characterized by an initial local inflammatory reaction at the penetration site (chagoma) and regional lymphadenitis. Other systemic manifestations are (in descending order of frequency): headache, paleness, muscle pain, dyspnea, edemas, abdominal pain, cough, hepatomegalia, rash, painful nodules, splenomegalia, vomiting, diarrhea and anorexia. When penetration takes place through the conjunctiva, the patient may develop unilateral periorbital edema and conjunctivitis (Romana's sign).[19] Other more severe presentations are in the form of acute myocarditis or meningoencephalitis. Myocarditis is seen in 3% of the infected individuals, particularly in children under 5 years of age. The symptoms comprise chest pain and signs of heart failure, and the chest X-rays can evidence an increase in the cardiac silhouette. The electrocardiogram (ECG) can reveal alterations of cardiac rhythm, atrioventricular block, low-voltage QRS complexes and negative T-waves.[18] Cases of meningoencephalitis are characterized by fever, seizures, paralysis and coma.[20] The most severe forms of the disease are associated to nutritional deficiencies, immune suppression (acquired immunodeficiency syndrome [AIDS]), an age of under 5 years and outbreaks of oral transmission that are believed to be related to higher parasite burdens.[20,21] In our setting, and with the exception of sporadic cases of transmission through transplants and of congenital transmission, acute phase Chagas disease is very unlikely, due to the absence of the transmitting vector.[5]

2.3.2 *Chronic phase*

If the acute infection has not received etiological treatment, Chagas disease progresses to the chronic phase within 2–3 months. The **chronic infection** may remain latent during decades or even for life (indeterminate form of the disease), or it may have an impact upon some target organ (symptomatic form) – depending on the characteristics of Chagas disease in the originating geographical region.[22]

1. **Indeterminate form**: between 60–70% of all infected individuals remain asymptomatic for life. In this form of Chagas disease the patients show:
   - no signs or symptoms of the disease;
   - positive serological test results or a confirmed parasitological diagnosis;
   - normal conventional ECG findings, and
   - normal chest or digestive tract (esophagus and colon) radiographic findings.

   The infection may become reactivated concomitant to some severe disease or under conditions of intense immunosuppression associated to organ transplantation or AIDS.[23]

2. **Symptomatic form**: this form manifests in approximately 30–40% of the cases. The symptomatic infection may be characterized by cardiac and digestive disorders and autonomic dysfunction causing alterations of the sympathetic and parasympathetic nervous system, with the involvement of target organs such as the heart and gastrointestinal system (mainly esophagus and colon). Over the long term, chronic inflammation results in fibrosis of the affected organs. The origin of this tissue damage is explained by both direct pathogenic action of the parasite and by destructive action mediated through other mechanisms such as exposure to the specific and nonspecific immune response, or microvascular disease.[24]

The **cardiac form** is the main symptomatic form of Chagas disease. This is potentially the most severe form of the disease, and can give rise to heart failure, alterations in cardiac rhythm and sudden death.[25] It tends to manifest between 15-30 years after the start of the acute phase in the form of dilated cardiomyopathy, which can lead to heart failure, arrhythmias or aneurysms that favor the development of thromboembolism. The most common arrhythmias are sinus bradycardia, conduction block (right bundle block, left hemiblock, atrioventricular block), negative T-waves, multifocal or polymorphic ventricular extrasystoles, ventricular tachycardia (torsades de pointes) and ventricular fibrillation.[26] The chest X-rays may show an increase in cardiac silhouette. Echocardiography in turn shows dilatation of the cavities, apical aneurysms and fragmental akinesis or hypokinesis of posteroinferior-intramural predominance (secondary to fibrosis).[27]

Below the equator, between 5-10% of all infected individuals present the **digestive form** of the disease,[28] while above the equator the digestive lesions are very infrequent and very incipient.[29]

Gastrointestinal involvement is generalized and is caused among other mechanisms by local damage to the autonomic neuronal system. Nevertheless, the sum of peristaltic discoordination, altered sphincter function and mechanical distension due to the dry luminal contents causes the esophagus and colon to be the most affected areas of the digestive tract.[30]

With regard to esophageal involvement, which is more common in central Brazil, the initial symptoms are usually difficulty in progression of the food bolus, with retrosternal pain and discomfort, while the more advanced stages are characterized by regurgitation and reflux. In the region of the Andes, colon involvement is more frequent than esophageal disease, with generally initial involvement of the sigmoid and rectum. Although megacolon may remain asymptomatic in many cases, the most common manifestation is constipation.[29]

Other symptoms may be meteorism, abdominal discomfort and bloating, and fecalomas. Depending on the geographical setting, megacolon, megaesophagus and heart disease may be associated, and it has been estimated that up to 30% of all patients with gastrointestinal involvement also have cardiomyopathy due to Chagas disease.[1]

In some cases the **nervous system** may be affected. The neurovegetative system is the primarily affected component in such situations. Meningoencephalitis is the most common form of presentation in situations of reactivation due to severe immune suppression, particularly in the context of AIDS.[31] In **HIV-positive patients**, the central nervous system (CNS) disorders present in 75% of the patients become predominant and sometimes exclusive, and have a greater incidence than cardiac problems, which are found in over 40% of patients.[32] In patients with immune depression secondary to leukemia or immunosuppressive therapies, among others, myocarditis has been reported in 60% of the cases, and meningoencephalitis in up to 45%.[33]

2.4 Diagnostic tests

In order to confirm the diagnosis of *T. cruzi* infection, consistent epidemiological antecedents must be present (possible contact with *T. cruzi*), with serological or parasitological confirmation of infection. However, the presence of clinical manifestations is not mandatory, due to the large proportion of asymptomatic patients or individuals with nonspecific symptoms (chronic phase, indeterminate form of Chagas disease). A distinction can be made between infection (epidemiological evidence and laboratory tests indicating the presence of the parasite) and actual disease (appearance of symptoms).[30]

The diagnosis can be established using **direct methods** such as parasitological tests which microscopically identify the parasite or isolate it from culture, the detection of DNA based on molecular methods such as polymerase chain reaction (PCR), or **serological or indirect methods** that detect the humoral immune response to the infection.

- **Microscopic identification** of the parasite in blood can be made using a recent blood drop and also (albeit with lesser sensitivity) using the thick drop smear technique following giemsa staining. All these methods allow visualization of the parasite in the trypomastigote phase. The positive predictive value of the test is dependent upon the degree of parasitemia. Parasite concentrating techniques such as the micromethod or microhematocrit technique and the Strout method increase the yield of the test compared with the thick drop smear procedure.[34-36] These are the methods of choice for establishing the diagnosis in the acute phase of the disease or in cases of reactivation.[1] At present, they are not advised as diagnostic methods in the chronic phase of Chagas disease, though they are indicated for the detection of *T. cruzi* in newborns.[37] In the case of tissue biopsies, and following histological staining, the parasites are observed in amastigote phases.

  Isolation of the parasite can be made from blood or biopsies. Cultures are made in Novy-MacNeal-Nicolle medium or Liver Infusion Tryptose (LIT) medium, among others.[38,39] In this case the parasite is observed in the epimastigote phase of its life cycle. Xenodiagnosis is currently only used in research.[40]

  The **molecular methods** include qualitative and quantitative or real-time PCR.[41] In comparison with other direct parasitological techniques, PCR is more sensitive and rapid in detecting *T. cruzi*, and in the case of real-time PCR (RT-PCR), the technique is able to quantify the parasitic burden.[42-45] In small children, although the diagnostic technique of choice is still based on conventional parasitological and serological methods,[46,47] PCR testing is able to identify those patients that are infected, in contrast to serology, which in the first months of life is unable to

distinguish between passive antibodies (of maternal origin) and proprietary antibodies. Therefore, the use of PCR during the first months of life may help to ensure the early identification of eventual cases of congenital transmission of the disease.[48] This technique is currently already being used in clinical practice. In any case, there are many different techniques with different levels of sensitivity that require internal quality controls and validation of the test methodology.[47]

- The **serological methods** are based on the determination of the presence of antibodies against specific antigens: indirect hemagglutination (IHA), indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA) techniques or chemiluminescence immunoassay (CLIA) procedures, among others.[49–52] The sensitivity levels of the different ELISA and CLIA tests range from 98–100%, with specificity levels of 97-100%.[53,54] Taking into account the high sensitivity of the commercially available serological tests, a single screening test may suffice to discard the disease.[54] Nevertheless, in view of the reduction in positive predictive value, it may be advisable to confirm serological testing with a second test involving different antigens, in order to establish the definitive diagnosis.[55] In the event of discrepancies, a third technique is required.[56]

Once Chagas disease has been diagnosed, an anamnesis and physical examination in search of alterations of the target organs are indicated in all cases. The **diagnosis of cardiac involvement** initially must be made using ECG and chest X-rays, and an echocardiographic study is moreover advised. If anomalies are detected, the patient can be subjected to Holter ECG monitoring, exercise testing, angiography and isotopic techniques, or the methods indicated by the Department of Cardiology.[27]

Screening for digestive involvement is based on the esophagogram and an opaque enema to assess colon disease. Complementary studies can be made using fibrogastroscopy.[57]

2.5 Treatment

The drug of choice is benznidazole. If this drug is contraindicated, or in the event of side effects, nifurtimox can be prescribed. Both of these drugs must be requested as foreign medication.[58] Their administration reduces the severity and duration of the acute disease, and either eliminates or lowers parasitemia. The effectiveness of the existing treatments is inversely proportional to the evolutive degree of the disease. In this regard, effectiveness is very high in the first year of life and in the acute phase of Chagas disease, but decreases over time after infection.[59,60] No satisfactory treatment is available for the chronic phase of the disease. Depending on the region of origin, some studies report a parasitological healing rate of 21% in treated adults.[61] Other studies have shown treatment in this phase appears to slow progression of the disease.[62] The results of the BENEFIT trial in patients with advanced chronic Chagas disease cardiac disease indicate that while benznidazole is able to reduce parasitemia, it is unable to lessen progression of the disease after 5 years.[63] This reinforces the notion that antiparasitic drug treatment must be started as soon as possible, before irreversible structural damage has occurred. Such treatment consequently should also be offered in the early chronic phase of Chagas disease.[58] Another study in women of child-bearing potential has shown etiological treatment before pregnancy to reduce the percentage of vertical transmission of *T. cruzi*.[64] These data underscore the need for early therapy.

Etiological treatment must be provided in all cases diagnosed in individuals under 18 years of age, and in cases of reactivation of the disease. In individuals between 18-50 years of age treatment is advised particularly in women of child-bearing potential, in order to avoid vertical transmission of the disease. The possibility of treatment can be offered after the fourth decade of life, evaluating each case on an individualized basis.[65] Apart from

etiological treatment, symptomatic therapy also improves the course of the disease.

Characteristics of treatment with **benznidazole**:

- Administration is in the form of two or three doses during 60 days after meals, with a maximum of 300 mg/day.
- Dosing:
  - < 15 years of age and < 40 kg: the dose is 5–7 mg/kg/day. In nursing children under one year of age with no other disease conditions, the dose can be up to 10 mg/kg/day.[55,66,67]
  - > 40 kg or > 15 years of age: the dose is 5 mg/kg/day.[55]
  - In cases of meningoencephalitis, the recommended dose is 25 mg/kg/day.[55]
- Contraindications: pregnant and nursing women, patients with liver or kidney failure, and severe neurological, digestive, skin or hematological disease. Patients allergic to imidazoles.
- Adverse events: the most common are digestive, skin or neurological disorders, which can manifest in 30% of the patients.[68] In order to descending frequency, adverse events comprise gastrointestinal symptoms; hypersensitivity reactions, such as dermatitis with rash, generalized edema, fever, muscle and joint pain; polyneuropathy, paresthesias and polyneuritis. Less frequent adverse events are bone marrow suppression with thrombocytopenic purpura and agranulocytosis (the latter being the most severe manifestation). The drug should be suspended in the event of bone marrow suppression or severe hypersensitivity reactions (Stevens-Johnson syndrome). The effects are reversible following drug withdrawal or dose reduction.
- Children tolerate the medication better than adults. In the case of intolerance to the daily drug dose, the duration of treatment can be prolonged in order to lessen the daily amount. However, it must be taken into account that prolonging the treatment can result in temporarily slowed weight gain in nursing children,

secondary to the anorexia which benznidazole may produce.[69]

- Follow-up includes control laboratory tests during the treatment period: at least one at the start, and another half-way through treatment in order to discard possible adverse events such as agranulocytosis due to benznidazole. In the case of adults, annual serological follow-up testing is recommended during the first 5 years, though follow-up is conditioned to the previous duration of the infection (see Table 1) and the territorial setting of origin (seronegative conversion being faster in the northern regions of the Amazon).

  Follow-up of children includes control laboratory tests in the second week of treatment and every four weeks for the full duration of therapy, and whenever symptoms appear. Annual serological testing is to be repeated until seronegative conversion is confirmed – this taking between 1–7 years, depending on the geographical region of origin and the age of the patient.[60] If necessary, the patient should be referred to the cardiologist for follow-up.

Table 1. Percentage healing rate (based on conventional serological test titers) in individuals with Chagas disease according to the years of evolution of the infection in South America.

Years of infection	< 1 year*	1-12 years**	Adults***
Percentage healing rate	100%	62%	21%
Time to negative conversion of the serological tests	< 1 year	4 years	5 years

* Schijman *et al*. [59]
** Sosa *et al*. [60]
*** Viotti *et al*. [61]

Characteristics of treatment with **nifurtimox**:

- Administration is in the form of three doses during 60 days after meals.
- Dosing:
  - In adults the dose is 8-10 mg/kg/day.

- In children the dose is up to 15 mg/kg/day.[66]

- Adverse events are more common with benznidazole.[70] In decreasing order of frequency, they comprise digestive symptoms (40–100%): weight loss, vomiting, anorexia, abdominal discomfort; central nervous system disorders (60–70%): irritability, sleep disturbances, disorientation, tremor; peripheral nervous system disorders (25%): dose-dependent polyneuropathy, paresthesias and polyneuritis; psychosis and hallucinations (10%) that are difficult to treat; and generalized weakness sensation. The effects are reversible following drug withdrawal or dose reduction.
- Children suffer side effects less often than adults.
- Follow-up includes control laboratory tests during the period of treatment.

  In the case of adults, annual serological follow-up testing is recommended during the first 5 years, though follow-up is conditioned to the previous duration of the infection.

  Follow-up of children includes control laboratory tests in the second week of treatment and every four weeks for the full duration of therapy, and whenever symptoms appear. Annual serological testing is to be repeated until seronegative conversion is confirmed – this taking between 1–7 years, depending on the geographical region of origin and the age of the patient.

Treatment of adverse events

The patient should receive an explanation of the possible adverse events before treatment is started, since they often lead to suboptimal therapy adherence. In the case of mild or moderate adverse events, treatment can be added in the form of analgesics (paracetamol) or an antiallergic drug (dexchlorpheniramine, ebastine, etc.), at variable doses and durations depending on the type and intensity of the symptoms (a pediatric formulation is available for children over two years of age). In the case of serious adverse events, the medication should be suspended and reintroduction should be considered provided the

benefits outweigh the risks – with the possibility of simultaneously adding other drugs to control the symptoms.

2.6 The situation in Catalonia

During the first decade of this century, the presence of people from endemic regions has grown exponentially in Catalonia. In the year 2009 there were 369,940 people originating from endemic regions in Catalonia.[71] Since 2010 the trend has inverted, though in 2014 there were still 253,850 people living in Catalonia holding citizenships from some of the 21 countries in which Chagas disease is endemic.[71] In addition to these data, consideration is also required of those people who have been born in endemic countries but hold Spanish citizenship or citizenships from other European countries. Overall, in the year 2014, the presence of a total of 449,595 people originating from endemic countries was registered.[71] On applying the prevalence rates corresponding to each country to this population,[6] the number of people infected with *T. cruzi* in our territory in 2014 is estimated to be between 12,000–20,000.

Direct vector-borne transmission of the disease is not possible in Catalonia, due to the absence of the natural vector. The risk of infection through contaminated blood or organs has been subjected to control since 2005, when the Blood and Tissue Bank of Catalonia (BSTC) started systematic screening tests in donors.[72] A study carried out by the BSCT in 2008 revealed a *T. cruzi* infection seroprevalence rate of 0.62%.[73] The detected cases include individuals that have lived in endemic areas, even though they were not born there. A similar study conducted in Madrid revealed a prevalence of 0.8%.[74]

The Programme for Congenital Chagas Disease Prevention and Control in Catalonia[75] was launched in the year 2010 with the purpose of ensuring the surveillance, control and treatment of the children from *T. cruzi*-postive mothers.

During the first four years of the Programme (2010–2013), a total of 25,072 pregnant

women from endemic regions gave birth in Catalonia.[76] Of these, 487 were diagnosed with Chagas disease during pregnancy.[77] Lastly, 18 cases of congenital transmission of the parasite have been identified, and the congenital transmission rate was 1.6% in 2012 and 6% in 2011.[77] This is consistent with the different studies made in nonendemic countries, with reported vertical transmission rates of between 0–7%.[10]

The prevalence rates of Chagas disease in pregnant women from endemic areas that gave birth in Catalonia between 2010–2013 was 1.9% overall and 11% among Bolivian women.[77]

In parallel to the above, control has been made of the other children of these women, with a reported control rate that has increased from 5% in 2010 to 54% in 2012. In this respect, 9 cases of *T. cruzi* infection have been detected in other children under 18 years of age of seropositive women.[77]

The estimated coverage rate of the Programme has increased from 69% in 2010 to 88% in 2013.[77]

3. PROTOCOL FOR SCREENING, DIAGNOSIS AND TREATMENT OF CHAGAS DISEASE IN PREGNANT LATIN AMERICAN WOMEN, THEIR NEWBORNS AND OTHER CHILDREN

3.1 Target population

Pregnant women:

1. Originating from one of the 21 countries with endemic Chagas disease
2. Mother originating from endemic countries, though with the patient being born in Catalonia
3. Stays lasting over one month in endemic regions with presence of the disease vector

The screening in pregnant women, their newborns and other children are graphically displayed in Figures 2 and 3.

3.2 Screening for T. cruzi *infection*

3.2.1 *Pregnant women without* T. cruzi *serological control*

Screening is to be performed by serological testing which should be included in the control tests of the first three months of pregnancy between gestational weeks 8 and 12. If the first visit of the pregnant woman takes place beyond week 12, testing for Chagas disease should be included in the first tests requested, as is done with the rest of the serological pregnancy control tests.

The screening serological tests should be based on techniques of great sensitivity in detecting antibodies with native or recombinant antigens (ELISA or chemiluminescence), since they are easy to perform in the conventional laboratory, sensitive, and afford

objective readings. The commercial products used must comply with current European legislation and should offer well specified technical performances. Such serological testing is made in the laboratories where ASSIR tests are performed, or in the centres where the pregnancy is being controlled.

If the first test proves negative, the patient should continue with the routine clinical control of pregnancy. The result of the test (positive or negative) must be reflected in the case history and patient card of the pregnant woman.

3.2.2 *Pregnant women with previous* T. cruzi *serological control*

If the pregnant woman has already undergone serological testing for the diagnosis of Chagas disease in Catalonia, such testing should be repeated in the following cases:

1. In a woman with a previous negative serological test result, testing is to be repeated if she has spent over one month in endemic regions with presence of the disease vector.
2. In a woman with a previous positive serological test result, repetition of testing is advised in the event of a new pregnancy, independently of whether previous treatment for Chagas disease has been received or not.

3.3 Diagnosis of Chagas disease

In the event of a positive screening test, diagnostic confirmation based on serological testing is required.

It is advisable for such testing to involve ELISA [53] or CLIA [52,78] with an antigen different from that used in the screening test.

In the event of discrepancy between the screening and diagnostic confirmation tests, a third decisive test different from the previous tests is indicated. It is advisable for this test to be performed with a new blood sample.

3.4 Management of T.cruzi-*infected pregnant women*

When the tests confirm that a woman is infected with *T. cruzi*, an evaluation of her clinical condition is required in order to establish the form of the disease (indeterminate, cardiac, digestive or others). Depending on the stage of pregnancy, an electrocardiogram (ECG) is indicated, with the postponement of radiological techniques. It is advisable for follow-up and evaluation to be made in the infectious or tropical diseases clinic of the reference hospital, followed by referral to the corresponding specialist, if applicable.

Pregnancy should not be made particularly complicated. Routine control is applicable, though it is advisable to ensure the obstetric visit. If the woman presents symptoms of the disease, the pregnancy should be referred according to the existing risk to the care level already established by the pregnancy monitoring protocol in force in Catalonia.[79] The degree of severity is particularly established by the presence of heart disorders, requiring pertinent patient referral as already established and following clinical criterion.

3.5 Management of T. cruzi-*infected adult women*

Although pregnant women constitute the target population of this Programme, serological testing to detect *T. cruzi* infection is advised in all women of child-bearing potential originating from endemic countries.

Once *T. cruzi* infection has been detected, the asymptomatic woman must be controlled on an annual basis in order to identify the appearance of symptoms. An anamnesis is required, particularly oriented to cardiac or gastrointestinal problems, together with a clinical

examination and annual ECG study. These controls are made in the primary care setting by family physicians (general practitioners), or in tropical disease reference centres by physicians with expertise in Chagas disease.

The treatment of infected adults is controversial, since the existing studies do not indicate high effectiveness. Some studies show that parasitemia decreases with treatment, and progression of the disease therefore can be slowed. Furthermore, in women of child-bearing potential the vertical transmission rate in posterior pregnancies is seen to decrease.[64,80,81] It is advisable to offer adult women treatment once the nursing period has ended.

3.6 Management and control of other children from T. cruzi-positive women

At the time of confirmation of a positive diagnosis in the mother, the family physician, the midwife monitoring the pregnancy or the paediatrician must ensure the diagnosis and control of her other children under 18 years of age living in Catalonia, using the pertinent serological tests (Figure 3). If these children are not controlled or if correct control has not been confirmed, they should be referred to the paediatrician or family physician corresponding to their healthcare area, conditioned to age. In the case of children over 18 years of age or living outside Catalonia, the pertinent controls related to Chagas disease should be made by the reference physician in each case.

It is advisable to follow the same screening scheme as in the pregnant women (Figures 2 and 3).

In the event of a positive diagnosis, treatment is to be started in children under 12 years of age, with the offering of therapy after this age.[60] The recommended treatment consists of benznidazole at the required dosage, or nifurtimox in the case of contraindications or adverse events of the former drug. Both drugs are of foreign origin and require individualized authorization. Since 2018 a paediatric (0–2 years of age) presentation of benznidazole has been available.[82]

3.7 Management of newborns of T. cruzi-*positive women*

3.7.1 *Neonatal examination*

Most infected newborns do not present symptoms (79% of all newborns with a positive diagnosis have remained asymptomatic during the period 2010–2012 in Catalonia).[77] Consequently, routine neonatal care is indicated,[83] with performance of the diagnostic tests detailed below.

The rest of newborns may exhibit the symptoms specified in Table 2. These are nonspecific symptoms that can also appear in other congenital transmission diseases belonging to the so-called TORCH group (toxoplasmosis, rubella, syphilis, varicella, cytomegalovirus, *herpes simplex*, HIV). Clinical manifestations of congenital Chagas disease may appear gradually. Clinical controls during the first weeks of life are therefore required. It is necessary to determine the degree of involvement, which may be serious in the presence of cardiac, neurological or respiratory disorders. Referral to other healthcare services is dictated by clinical criteria, following the clinical paths already established in routine clinical practice.[83]

Table 2. Warning signs in newborns of T. *cruzi*-infected women

- Apgar score < 5 at 1 min / < 7 at 5 min
- Low birth weight: < 2500 g
- Fever (> 37.5°C) or hypothermia (< 35°C)
- Adenopathies
- Splenomegalia
- Hepatomegalia
- Jaundice
- Skin bleeding (petechiae)

- Edemas / anasarca
- Hyporesponsiveness to stimuli
- Signs or symptoms of meningoencephalitis
- Signs or symptoms of myocarditis
- Respiratory distress:
  - **Chest X-rays**: lung infiltrates characteristic of pneumonia with a possible diffuse and homogeneous reticular-granular pattern, and air bronchogram
- Laboratory test criteria:
  - Lymphocytosis (> 24,000 cells/mm^3)
  - Lymphopenia (< 10,000 cells/mm^3)
  - Anemia
  - Hypoalbuminemia
  - Proteinuria
  - Transaminase elevation

3.7.2*Diagnostic tests during the first month of life*

When the newborn is one month old, at least one of two parasitological tests should have been made: microhematocrit or PCR.

- **Microhematocrit**

  The microhematocrit technique is advised at birth as a direct parasitological test only in those centres with experience in the use of this technique.

  The sample must be collected as soon as possible during the first days of life, and should be sent to a laboratory with expertise in reading the test. The reading is to be made in the first 24 hours after sample collection.

  The following actions must be taken according to the results of the microhematocrit test (Figure 3):

  - Microhematocrit with positive result: treatment is to be started regardless of the PCR test result.

- Microhematocrit with negative or no result: infection cannot be ruled out, and routine control should be continued, with PCR testing at one month of age or serological testing at 9–12 months of age.

Form of sample collection: blood can be collected from the heel or a peripheral vein, but not from the umbilical cord, since the presence of maternal blood may yield a false positive result.

- **Polymerase chain reaction (PCR) technique**

Polymerase chain reaction (PCR) testing of the newborn is recommended at four months of age in order to avoid detecting remnant DNA from parasites in the mother in the first days of life of the newborn, which could yield a false positive result. A negative PCR result could also be obtained during the first days due to the fact that there is still a low parasite burden in blood.

If the amount of blood in the sample is smaller than the minimum amount required for the test (depending on the type of PCR), repeat sampling is indicated.

The following actions must be taken according to the results of the PCR test (Figure 3):

- Positive PCR result at one month of age: treatment should be started.
- Negative PCR result at one month of age: continue routine control, with serological testing at 9–12 months of age.
- PCR with indeterminate result or insufficient sample: repeat testing until a definitive result is obtained.
- Positive or negative PCR result before one month of age: wait and repeat testing from one month of age.
- If symptoms consistent with Chagas disease are observed at birth, and after discarding other possible disorders, a positive PCR test – even if performed before one month of age – will dictate the treatment strategy.

3.7.3 *Serological tests after 9–12 months of age*

Enzymoimmunoassay (EIA) or CLIA can be used, as in the case of the mother. Serological control should be made with one test and, if found to be positive, testing should be repeated with a second serological test involving a different antigen.

It is advisable to perform the test between 9–12 months of age in order not to detect antibodies of maternal origin, though in some cases such antibodies may take longer in disappearing. It is not advisable to wait beyond 12 months of age, because in the case of congenital transmission of the disease, the earlier the start of treatment the greater the chances of cure.

In the case of discrepant results between the two tests, or if the result is indeterminate with values close to the cut-off, the control should be repeated after two months, before starting treatment.

The following actions must be taken according to the results of the serological tests (Figure 3):

- Positive serological testing after 9–12 months: testing should be repeated with a serological test involving a different antigen.
  - Positive second serological test: treatment should be started.
  - Negative second serological test or with indeterminate result (values close to cut-off): wait two months and then repeat the test.
- Serological test with indeterminate result at 9–12 months: wait two months and then repeat the same test.
- Negative serological test at 9–12 months: negative case.

In the case of an uncontrolled pregnancy, serological testing of the mother is required, and if the maternal diagnosis is confirmed after childbirth, it is advisable to perform PCR testing in the newborn from one month of age, or serological testing from 9 months of age.

3.7.4 *Treatment of infected newborns*

Treatment is to be started in any of the following cases:

- Positive microhematocrit test
- Positive PCR test from one month of age
- Two positive serological tests involving different antigens from 9 months of age

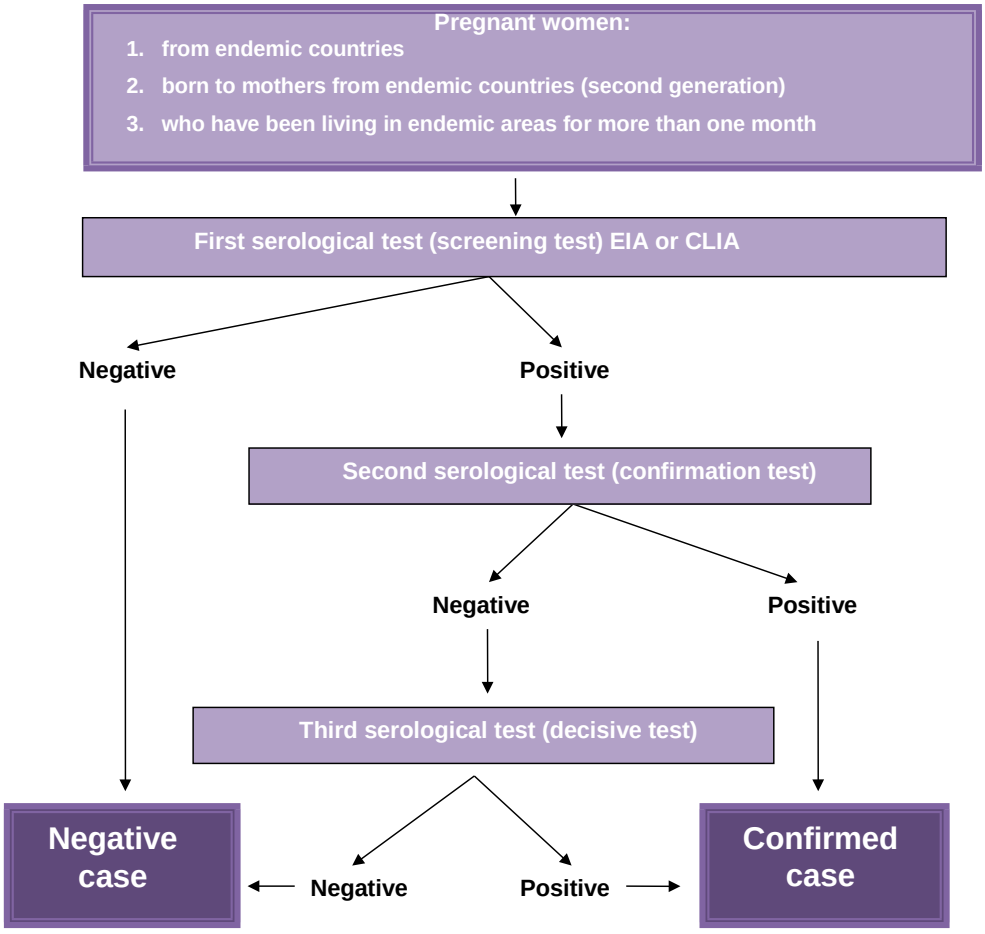
In the case of severe symptoms, and after discarding other infectious diseases, the decision to prescribe treatment depends on the criterion of the supervising physician.

The treatment recommended for Chagas disease comprises oral benznidazole at a dose of 5–7 mg/kg/day during 60 days, divided into 2-3 doses or, in the case of contraindications or side effects of this drug, nifurtimox can be administered at a dose of 10 mg/kg/day in 2–3 doses during 60 days. Both drugs are of foreign origin and require individualized authorization. Since 2018 a pediatric presentation of benznidazole has been available.[82]

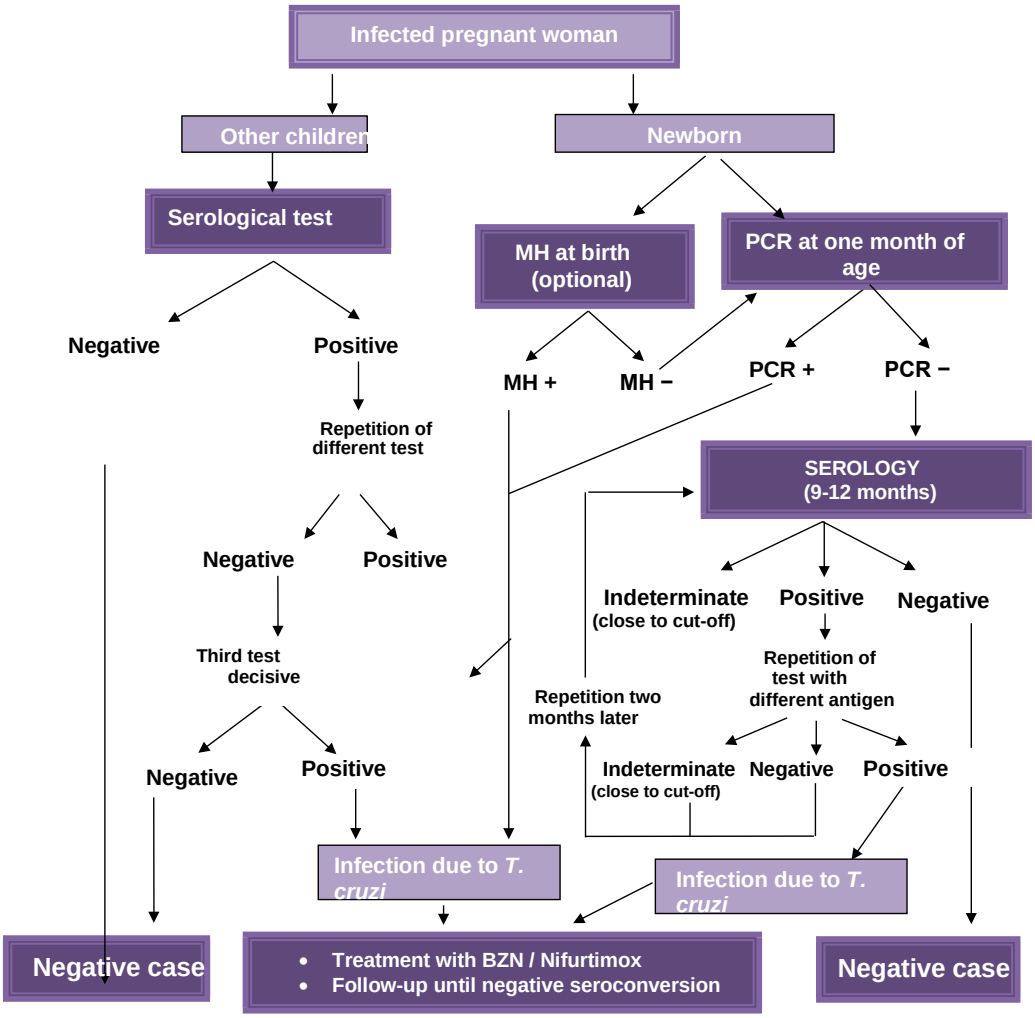
3.7.5 *Follow-up of infected newborns*

The follow-up of newborns in which treatment has been started includes control laboratory tests in the second week of treatment and every four weeks for the full duration of therapy, or whenever symptoms or adverse events appear. Annual serological testing is to be repeated until seronegative conversion is confirmed – this taking between 1–7 years, depending on the geographical region of origin. A cardiological study (ECG / echocardiography) is also recommended during follow-up.

3.8 Figure 2. Screening for pregnant women



3.9 Figure 3. Screening for newborns and their siblings from* T. cruzi-*positive mothers



MH: microhematocrit; **PCR**: polymerase chain reaction; **BZN**: benznidazole

4. EPIDEMIOLOGICAL SURVEILLANCE SYSTEMS OF THE PROGRAMME FOR CONGENITAL CHAGAS DISEASE PREVENTION AND CONTROL OF IN CATALONIA

Epidemiological surveillance of congenital Chagas disease is a key element for the control of the disorder. The main objectives of epidemiological surveillance are:

1. Proceed in the detection, treatment and follow-up of the infection in newborns and their siblings of infected mothers.
2. Monitor information and analyse data obtained in order to identify patterns in the disease.
3. Evaluate the Programme for Congenital Chagas Disease Prevention and Control in Catalonia using the established indicators.
4. Periodically provide reporting of results obtained from the applied control strategies.
5. Train and provide support for professionals in contact with patients and the laboratory staff.

The epidemiological surveillance clinical paths of reported cases may vary depending on the region, conditioned to the usual clinical paths for case referral and professionals involved. The implicated centres (laboratory, ASSIR, hospital, primary care) and the ASPCAT jointly guarantee a reporting and follow-up clinical path adapted to each area, with the purpose of ensuring the control, treatment and follow-up of newborns and other children of all pregnant women with a positive diagnosis, as well as the reporting of all cases to the ASPCAT (Figure 4).

Epidemiological surveillance of congenital Chagas disease is based on:

1. The **Microbiological Reporting System of Catalonia**
2. The **Voluntary Case Registry of Congenital Chagas Disease in Catalonia**
3. The **Newborn Registry**
4. The **Working Group** of the Programme for Congenital Chagas Disease Prevention and Control in Catalonia

4.1 Microbiological Reporting System of Catalonia

The Microbiological Reporting System of Catalonia (SNMC) is a basic healthcare information system that forms part of the Epidemiological Surveillance Network of Catalonia, and is composed of the global public and private hospital and out-hospital microbiology laboratories of Catalonia. The system compiles the periodic statements on microorganisms that cause acute infectious diseases and the antimicrobial resistance reports corresponding to certain microorganisms of relevance in the public healthcare setting.

According to Decree 203/2015,[84] creating the Epidemiological Surveillance Network of Catalonia and regulating the reporting system on reportable diseases and epidemic outbreaks, *T. cruzi* and all microorganisms reported to the SNMC are subject to mandatory microbiological reporting.

4.2 Voluntary Case Registry of Congenital Chagas Disease in Catalonia

The Voluntary Case Registry of Congenital Chagas Disease in Catalonia (RVMC) compiles all cases of positive-*T. cruzi* pregnant women and their newborns and other children reported in Catalonia. This registry is integrated within the Epidemiological Repository of Catalonia (REC), which compiles clinical and epidemiological data on diseases subject to surveillance in Catalonia.

The RVMC is composed of two interconnected electronic registries:

1. Primary registry: Each case corresponds to the pregnancy of a woman with a positive diagnosis (if one same woman has had two or more pregnancies since the start of the Programme, each case constitutes an independent case in the registry). Identifying, demographic, diagnostic and clinical–epidemiological data on the woman are collected, together with the information referred to the newborn of that pregnancy and to the other children of that same woman (Annex 1).

   The following variables are entered in this registry:

   Identifying information: Patient identification code, case number, case history number, identifying information on the father.

   Demographic information: Date of birth, age, gender, city / town of residency, district, province, healthcare region.

   Diagnostic information: Reporting healthcare centre, reporting physician, diagnostic tests, diagnostic laboratory, reporting date, date of diagnosis, timing of diagnosis (before and during pregnancy, delivery, postpartum, previous pregnancy).

   Clinical and epidemiological information: Country of origin, year of arrival, form of the disease, immunosuppressive disease, treatment history, expected delivery date, pregnancy outcome (delivery, fetal loss, lost case), type of fetal loss, reason for loss.

   Follow-up information on the rest of children: Other children living in Catalonia, age, other controlled children, other positive children, serological findings (negative, positive, not controlled), comments.

   Follow-up information on a newborn: Delivery date, delivery hospital, patient identification code / first and last names / case history number, parasitological tests at birth, parasitological tests at one month of age, serological tests from 9 months of age, negative seroconversion date, centre of follow-up, final outcome (negative, positive, pending, lost), reason for loss.

2. Secondary registry: Each case corresponds to newborn or other children diagnosed with *T. cruzi* infection, or the children of pregnant women with a positive diagnosis reported to the registry (Annex 2).

   The following variables are entered in this registry:

Identifying information: Patient identification code, patient identification code of the mother, case number, case history number, type of case (newborn, other children).

Demographic information: Date of birth, age, gender, country of birth, city / town of residency, district, province, healthcare region.

Diagnostic information: Parasitological tests at birth, parasitological tests at one month of age, serological tests, reporting date, date of diagnosis, reporting healthcare centre, reporting physician, diagnostic laboratory, follow-up centre, age at diagnosis (in months).

Clinical and epidemiological information: Symptoms at birth or after birth, hospital admission, treatment, date of start of treatment, date of end of treatment, adverse reactions, treatment adherence, negative serological tests, date of negative serological tests, comments.

4.3 Newborn Registry

The Newborn Registry is managed from the Subdirectorate-General for Epidemiological Surveillance and Public Health Emergency Response of the Secretariat for Public Health Secretariat. Since the year 1993, data has been entered to this registry from the Programme for early neonatal detection of congenital metabolic disorders. This is a registry with almost 100% coverage of the live births in both the maternal centres of the Public Integrated Healthcare System of Catalonia (SISCAT) and the private centres. The compilation, analysis, interpretation and disclosure of the indicators affords more objective knowledge of the characteristics of mothers and newborns in Catalonia, with a view to planning, adopting decisions and adequately managing the health policies and programmes from a public health perspective.

The variables of this registry which are used for the epidemiological surveillance of Chagas disease are: nationality of the pregnant woman, city / town of residency, delivery hospital, maternal age, number of previous deliveries, neonate gender.

4.4 Working Group

The Working Group on the Programme for Congenital Chagas Disease Prevention and Control of in Catalonia is composed of professionals from different specialties: midwives, microbiologists, obstetricians, gynecologists, pediatricians, family physicians, specialists in infectious diseases, epidemiologists and community health agents. These healthcare professionals constitute the references of the different centres that collaborate in the Programme and are in charge of the control, diagnosis, reporting and follow-up of cases (pregnant women, newborns and their siblings) in their respective reference areas.
Their participation in the Working Group is voluntary, and each professional has a defined role in the epidemiological surveillance of the disease.

- **Midwives:** The midwives are responsible for the screening of pregnant women, preferably during the first three months of pregnancy, in the ASSIR centres. They are in charge of the following:
    1. Screening of risk pregnancies.
    2. Compilation of data and supervision of the control of the other children living in Catalonia.
    3. Referral to the reference pediatrician of other children of *T. cruzi*-positive pregnant woman that are not controlled.

4. Completion and submission to the ASPCAT of the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive pregnant women, their newborns and other children* (Annex 1).

- **Microbiologists or parasitologists**: These professionals are in charge of the diagnosis, reporting to the ASPCAT of the positive cases detected in pregnant women, newborns or other children to the SNMC, and of the conduction of follow-up tests in newborns and other children up until negative seroconversion.
- **Obstetricians or gynecologists**: These professionals are in charge of the pertinent controls of pregnant women with a positive diagnosis, and of informing the paediatricians of the risk of congenital transmission to the newborn.
- **Paediatricians**:
  - **Controls of other children of *T. cruzi*-positive women**: The paediatricians are in charge of requesting serological controls of other children under 15 years of age of the positive pregnant women living in Catalonia and who have not been subjected to serological control. Control preferably should take place in the course of pregnancy.
    - In the case of a positive diagnosis, the pediatrician is to complete the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive newborns and other children* (Annex 2), and must report it to the ASPCAT.
    - In the case of a negative diagnosis, the pediatrician is to complete the section "Follow-up of other children" of the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive pregnant women, their newborns and other children* (Annex 1), and must report it to the ASPCAT.
  - **Control of a newborn**: From the time of delivery, the hospital paediatricians are in charge of guaranteeing that the parasitological tests of a newborn are

made at birth (microhematocrit) or at one month of age (PCR testing). Serological testing of the baby from 9 months of age can be made both in the hospital and in the primary care centres.

- In the case of a positive diagnosis, the pediatrician is to complete the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive newborns and other children* (Annex 2), and must report it to the ASPCAT.
- In the case of a negative diagnosis, the pediatrician is to complete the section "Follow-up of newborns" of the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive pregnant woman, their newborns and other children* (Annex 1), and must report it to the ASPCAT.

➢ **Family physicians:**

- **Control of other children of *T. cruzi*-positive mothers**: The family physicians are in charge of requesting serological controls of the other children aged 15 years or older of the positive pregnant women living in Catalonia and who have not been subjected to serological control. Control preferably should take place in the course of pregnancy.
  - In the case of a positive diagnosis, the family physician is to complete the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive newborns and other children* (Annex 2), and must report it to the ASPCAT.
  - In the case of a negative diagnosis, the family physician is to complete the section "Follow-up of the other children" of the *Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi *pregnant woman, their newborns and other children* (Annex 1), and must report it to the ASPCAT.

- **Control and follow-up of *T. cruzi*-positive mothers**: The family physicians must conduct the annual controls of mothers with a positive diagnosis in order to detect possible symptoms related to the disease, administer treatment once nursing has ended, and control the possible side effects.

- **Specialists in infectious diseases or experts in tropical medicine**: These professionals are in charge of the follow-up of *T. cruzi*-positive pregnant women, their newborns and other children, if required. They can provide support or substitute the functions of paediatricians, midwives and family physicians in the control and treatment of mothers with a positive diagnosis, the follow-up and control of newborns and other children, and the reporting of cases to the ASPCAT.

- **Community health agents**: These agents are in charge of redirecting newborns living in Catalonia and who have not been subjected to control to the healthcare network, and of providing support.

4.5 Reporting of cases to the ASPCAT

All the information compiled by the RVMC is obtained from the Working Group references through the cases reported to the SNMC and from the three epidemiological forms available for the reporting of cases with a positive diagnosis:

4.5.1 *Microbiological reporting to the Microbiological Reporting System of Catalonia*

In the event of any case of *T. cruzi* infection detected in pregnant women or individuals under 18 years of age, based on the established diagnostic criteria, the microbiologist must report the case to the ASPCAT via the SNMC.[85] If the information on the pregnancy is not available, those women of child-bearing potential and a positive diagnosis

must be reported.

The variables to be recorded are: identifying information of the case (patient identification code, city / town of residency, country of origin, pregnant woman), microbiological data (diagnosis, microorganism, sample and diagnostic technique) and information on the reporting centre (centre, centre of origin of the sample, and requesting physician).

4.5.2 *Epidemiological data*

The epidemiological data of the cases are compiled from the references of the Working Group through the following epidemiological forms:

1. ***Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive pregnant women, their newborns and other children***

   This includes basic information about the pregnant woman with a positive diagnosis, the presence and control of other children living in Catalonia, and the birth and control of the newborn resulting from this pregnancy (Annex 1).

   It is divided into three parts: the first part collects information on the current pregnancy; the second on the control of the other children; and the third on the follow-up of the newborn resulting from this pregnancy.

2. ***Epidemiological form for cases of Chagas disease. Follow-up of* T. cruzi-*positive newborns and other children***

   This is addressed to paediatricians or family physicians, and should only be completed in the event of a diagnosis of Chagas disease in a newborn or other children. This form collects data on the symptoms, treatment and follow-up of the

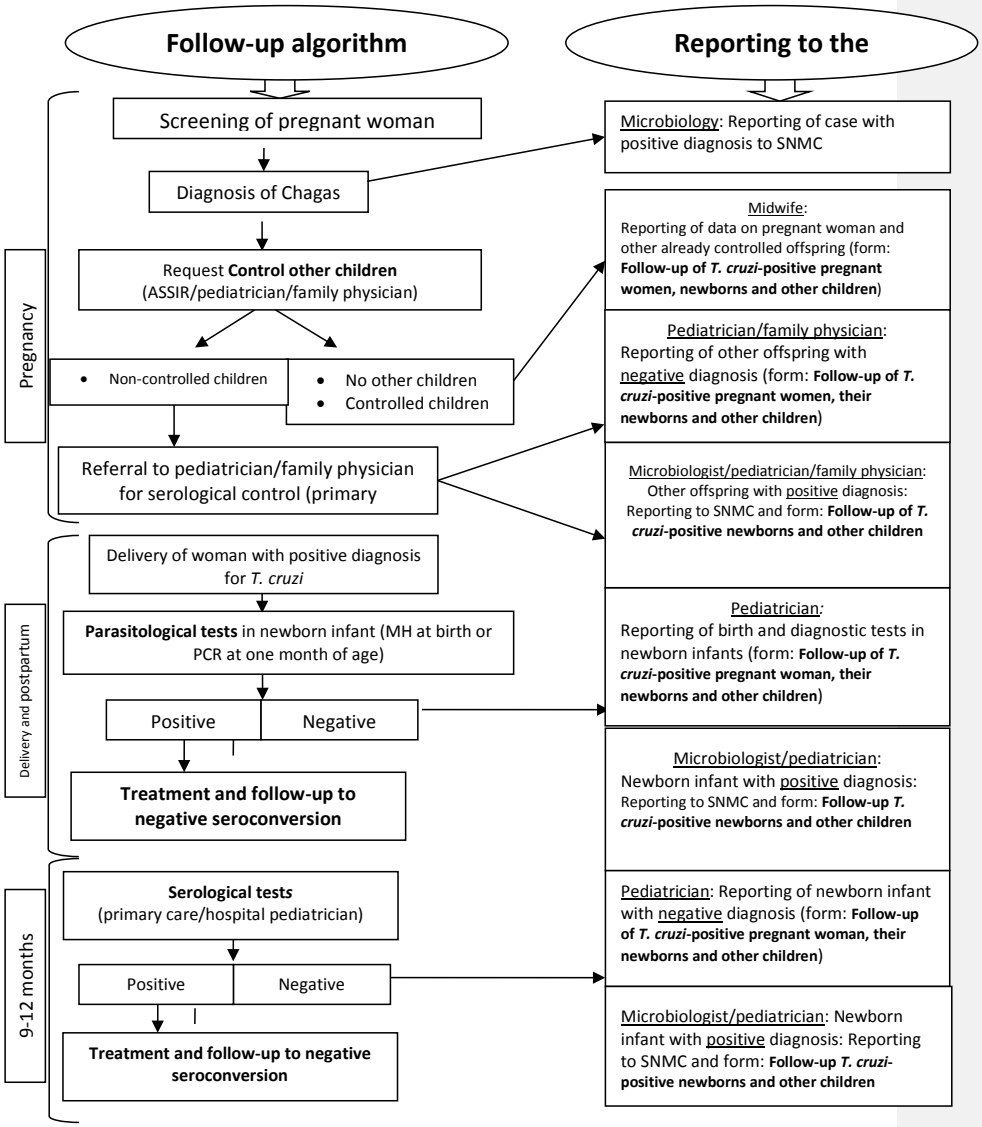
cases with a positive diagnosis (Annex 2).

3. ***Annual coverage reporting sheet of the Programme for the ASSIR centres***

   This sheet is used to collect the data on annual coverage of the Programme for each ASSIR centre (Annex 3). It includes the annual number of first visits of pregnant women originating from endemic areas due to Chagas disease, serological test requests for *T. cruzi* and positive diagnoses of *T. cruzi* infection.

The epidemiological forms are to be sent preferably by encrypted e-mail (chagas@gencat.cat), and the message should specify the reference centre and physician. If an e-mail cannot be sent, the other reporting options may be: telephone (935 513 662 / 935 513 680), fax (935 517 506) or conventional mail (Programa de prevenció i control de la malaltia de Chagas congènita a Catalunya, Sub-direcció General de Vigilància i Resposta a Emergències de Salut Pública, Agència de Salut Pública de Catalunya, Departament de Salut, Generalitat de Catalunya, C/ Roc Boronat, 81–95, 08005 Barcelona).

4.5.3 *Figure 4. Algorithm for surveillance and control of congenital Chagas disease in Catalonia*



5. EVALUATION INDICATORS OF THE PROGRAMME FOR CONGENITAL CHAGAS DISEASE PREVENTION AND CONTROL IN CATALONIA

With the data collected from the RVMC, three indicators of use in evaluating the Programme for Congenital Chagas Disease Prevention and Control in Catalonia are calculated:

1. Programme coverage rate
2. Chagas disease prevalence rate observed in the pregnant population
3. Congenital transmission rate

5.1 Programme coverage rate

The annual coverage rate of the Programme is defined as the number of pregnant women originating from endemic areas screened in one year with respect to the total women from endemic regions that have become pregnant that same year.

This indicator is calculated as follows:

- The numerator represents the number of *T. cruzi* serological test requests made in one year in all the ASSIR centres in Catalonia and in the hospitals in those cases in which the pregnant women have been controlled only in the hospital.
- The denominator represents the number of first visits of pregnant women from the 21 countries endemic for Chagas disease to the ASSIR centres in Catalonia and to the hospitals in those cases in which the pregnant women have only been controlled in the hospital.

The number of serological test requests and the number of first visits are to be compiled once a year from each ASSIR centre using the ***Annual coverage reporting sheet of the Programme for the ASSIR centres*** (Annex 3).

5.2 Observed prevalence rate

The observed prevalence rate is defined as the number of cases diagnosed with Chagas disease per 100 deliveries in the pregnant population originating from endemic areas.

- The numerator represents the number of newborns of mothers with a diagnosis of Chagas disease recorded in the RVMC in one year.
- The denominator represents the number of newborns in Catalonia of mothers from endemic areas in one year.

The data corresponding to the numerator are obtained from the RVMC, while the data of the denominator are obtained from the Newborn Registry of the Subdirectorate–General for the Surveillance and Response to Public Health Emergencies.

5.3 Congenital transmission rate

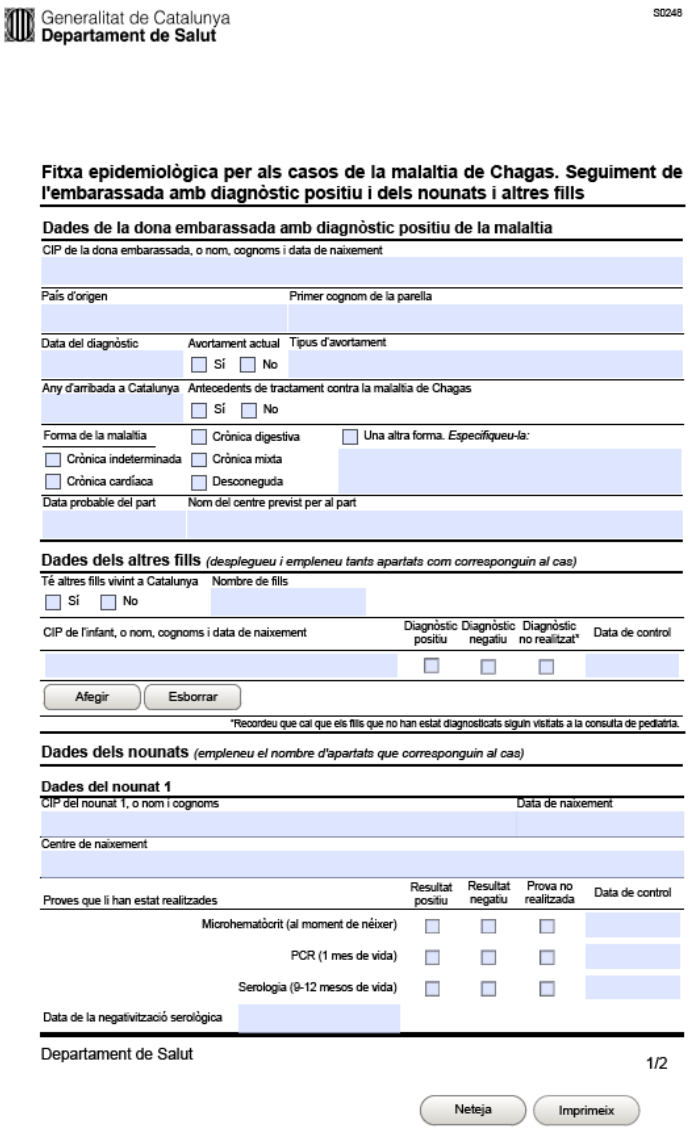
The annual congenital transmission rate is defined as the number of newborns congenitally infected with *T. cruzi* with respect to the total newborns controlled in one same year. The rates are calculated in the population originating from endemic areas and in the population of Bolivian origin.

- The numerator represents the number of newborns with a positive diagnosis for *T. cruzi* born in one year of mothers with a diagnosis of Chagas disease recorded in the RVMC.

- The denominator represents the number of newborns in one year of mothers diagnosed with *T. cruzi* infection recorded in the RVMC and that have completed follow-up.

6. ANNEXES

Annex 1. *Epidemiological form for cases of Chagas disease. Follow-up of T. cruzi-positive pregnant woman, their newborns and other children*



Generalitat de Catalunya
Departament de Salut

S0248

Fitxa epidemiològica per als casos de la malaltia de Chagas. Seguiment de l'embarassada amb diagnòstic positiu i dels nounats i altres fills

Dades de la dona embarassada amb diagnòstic positiu de la malaltia

CIP de la dona embarassada, o nom, cognoms i data de naixement

País d'origen | Primer cognom de la parella

Data del diagnòstic | Avortament actual ☐ Sí ☐ No | Tipus d'avortament

Any d'arribada a Catalunya | Antecedents de tractament contra la malaltia de Chagas ☐ Sí ☐ No

Forma de la malaltia ☐ Crònica digestiva ☐ Una altra forma. *Especifiqueu-la:*
☐ Crònica indeterminada ☐ Crònica mixta
☐ Crònica cardíaca ☐ Desconeguda

Data probable del part | Nom del centre previst per al part

Dades dels altres fills *(desplegueu i empleneu tants apartats com corresponguin al cas)*

Té altres fills vivint a Catalunya ☐ Sí ☐ No | Nombre de fills

CIP de l'infant, o nom, cognoms i data de naixement	Diagnòstic positiu	Diagnòstic negatiu	Diagnòstic no realitzat*	Data de control
	☐	☐	☐	

Afegir | Esborrar

*Recordeu que cal que els fills que no han estat diagnosticats siguin visitats a la consulta de pediatria.

Dades dels nounats *(empleneu el nombre d'apartats que corresponguin al cas)*

Dades del nounat 1

CIP del nounat 1, o nom i cognoms | Data de naixement

Centre de naixement

Proves que li han estat realitzades	Resultat positiu	Resultat negatiu	Prova no realitzada	Data de control
Microhematòcrit (al moment de néixer)	☐	☐	☐	
PCR (1 mes de vida)	☐	☐	☐	
Serologia (9-12 mesos de vida)	☐	☐	☐	

Data de la negativització serològica

Departament de Salut 1/2

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Dades dels nounats *(empleneu el nombre d'apartats que correspongui al cas)*

Dades del nounat 2

CIP del nounat 2, o nom i cognoms	Data de naixement

Centre de naixement

Proves que li han estat realitzades	Resultat positiu	Resultat negatiu	Prova no realitzada	Data de control
Microhematòcrit (al moment de néixer)	☐	☐	☐	
PCR (1 mes de vida)	☐	☐	☐	
Serologia (9-12 mesos de vida)	☐	☐	☐	

Data de la negativització serològica

Dades del nounat 3

CIP del nounat 3, o nom i cognoms	Data de naixement

Centre de naixement

Proves que li han estat realitzades	Resultat positiu	Resultat negatiu	Prova no realitzada	Data de control
Microhematòcrit (al moment de néixer)	☐	☐	☐	
PCR (1 mes de vida)	☐	☐	☐	
Serologia (9-12 mesos de vida)	☐	☐	☐	

Data de la negativització serològica

Dades del metge o metgessa i del centre declarant

Nom i cognoms del metge o metgessa	Telèfon de contacte

Nom del centre sanitari	Data de la declaració

Observacions

A012v01-18

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canalsalut.gencat.cat

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Annex 2. *Epidemiological form for cases of Chagas disease. Follow-up of T. cruzi-positive newborns and other children*

Generalitat de Catalunya
Departament de Salut

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Fitxa epidemiològica per als casos de la malaltia de Chagas. Seguiment dels nounats i altres fills amb diagnòstic positiu

Dades del nounat o d'un altre fill amb diagnòstic positiu de la malaltia

CIP

En el cas de no tenir CIP, cal emplenar les dades següents de l'infant:

Inicials | Data de naixement | Sexe ☐ Home ☐ Dona

Dades de la mare amb diagnòstic positiu

CIP

En el cas de no tenir CIP, cal consignar les dades següents de la mare:

Nom i cognoms

Clínica del nounat o d'un altre fill amb diagnòstic positiu

Pacient asimptomàtic ☐ Sí *(passeu a Proves diagnòstiques)* ☐ No *(especifiqueu-ne les manifestacions)*

Data d'inici dels símptomes

Signes generals	Signes d'afectació del SNC	Signes cardíacs
☐ Febre o hipotèrmia ☐ Hepatomegàlia	☐ Irritabilitat	☐ Cardiomegàlia a la RX de tòrax
☐ Esplenomegàlia ☐ Destret respiratori	☐ Depressió neurològica	☐ Alteracions a l'ECG
☐ Altres. *Especifiqueu-los:*	☐ Altres. *Especifiqueu-los:*	☐ Altres. *Especifiqueu-los:*

Proves diagnòstiques realitzades al nounat o un altre fill amb diagnòstic positiu

Prova	Tècnica	Positiva	Negativa	No realitzada	Data
Microhematòcrit		☐	☐	☐	
Una altra prova		☐	☐	☐	
Serologia 1		☐	☐	☐	
Serologia 2		☐	☐	☐	
Serologia 3		☐	☐	☐	

A015-V02-11

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Dades sobre el tractament

Nom del centre sanitari | Hospitalització ☐ Sí ☐ No | Data d'inici | Data de finalització

Tractament	Pauta		Dosi total
☐ Benznidazole		mg/kg	
☐ Nifurtimox		mg/kg	

Reaccions adverses del tratament

☐ No
☐ Sí *(marqueu el que correspongui)*

☐ Dermatològiques
☐ Cefalea
☐ Anorèxia
☐ Astènia
☐ Altres. *Especifiqueu-les:*

☐ Febre
☐ Artràlgies
☐ Leucopènia

Compliment del tratament

☐ Correcte
☐ Irregular. Nre. de dosis perdudes:
☐ Abandonament del tractament Data
☐ Suspès per causes mèdiques Data
☐ Altres. *Especifiqueu-ho:*

Conclusió final del cas

☐ Curació (negativització serològica)
☐ Mort per la malaltia de Chagas
☐ Mort per altres causes. *Especifiqueu-les:*
☐ Perdut
☐ Altres. *Especifiqueu-ho:*

Dades del metge o metgessa i del centre declarant

Nom i cognoms del metge o metgessa | Telèfon de contacte

Nom del centre sanitari | Data de declaració

Observacions

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***Annex 3**. Annual coverage reporting sheet of the Programme for the ASSIR centres*

Generalitat de Catalunya
Departament de Salut

Notificació de la cobertura anual del Programa de cribratge de la malaltia de Chagas congènita per a centres ASSIR

Dades de la notificació

Any de cobertura | Data de notificació

Nom i cognoms de la persona responsable | Telèfon de contacte

Dades del centre ASSIR

Nom del centre

Adreça del centre (nom de la via, núm., pis, porta, CP, localitat)

Dades de la cobertura anual del Programa

Concepte	Nombre total
Peticions de serologia de *Trypanosoma cruzi*	
Primeres visites de gestants originàries de zones endèmiques de la malaltia de Chagas	
Diagnòstics positius d'infecció per *Trypanosoma cruzi* en dones gestants	

Observacions

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Comentat [BFH1]: L'enllaç no funciona