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Planning and Assessment
Public Health
Chagas Protocol

36

Protocol for screening and diagnosing Chagas disease in pregnant Latin American women and their newborns

Generalitat de Catalunya
Departament de Salut

(PD)

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1. FOREWORD

1. FOREWORD

The protocol for screening and diagnosing Chagas disease in pregnant Latin American women and their newborns is the result of a joint effort by the Ministry of Health and a group of healthcare professionals who are experts in the disease. The initiative was supported throughout by the World Health Organization's Department of Control of Neglected Tropical Diseases (NTD). This document reflects the efforts to reach a consensus in the identification of the most suitable measures at the current time to limit the impact of vertical transmission of Chagas disease in Catalonia.

The first part of the document includes a summary of aspects and key characteristics of this imported disease. As Chagas disease has appeared only recently in Catalonia, most healthcare professionals in the region have little knowledge of it.

Similarly, it is particularly difficult in the current situation to obtain epidemiological data on the prevalence of the infection and the incidence of cases of the disease. This is due to the fact that we still do not have systems or pathways for disease notification and data collection that enable us acquire reliable, quality information.

The initiation of screening for pregnant women from Latin American countries in which Chagas disease is endemic is based on the principle of cost-effectiveness. The aim is to implement a series of measures that can be complemented by other measures of a more general scope in the future.

This protocol is essentially a practical document, which provides healthcare professionals with essential information needed to screen the selected population. The screening is expected to lead to the detection and early treatment of cases of the disease in the vulnerable population.

One of the challenges of establishing this protocol was to reach consensus on the laboratory tests that should be used to detect and confirm a *T. cruzi* infection. This is understandably difficult, as some of the diagnostic standards for this disease are currently being revised and validated. Nevertheless, we are convinced that as the procedures and pathways become more clearly defined, marked progress will be made.

From the perspective of public health, it is essential to define and ensure pathways for collecting and transmitting information. To progress in the prevention and control of this disease it is crucial to have access to data that enable us to assess the extent of the problem, assess the impact of the measures that are applied and enable the protocol to be updated. Hence, the epidemiological form that is presented at the end of this document is a key tool for collecting data and its subsequent analysis.

Finally, public health protocols offer guidelines for establishing and standardising measures that require the involvement and collaboration of professionals in various fields. We trust that in this case the tool will help to attain the proposed objective

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2. INTRODUCTION

2. INTRODUCTION

The prevention, treatment and control of Chagas disease in non-endemic areas such as Catalonia and Spain in general is one of the new challenges for the health system and for public health surveillance in these environments. There has been an increase in the detection of cases of this disease in Catalonia, which is directly related to the social and demographic changes that have occurred in this area in the last ten years. Consequently, in recent years, the study of this disease and related interventions have been considered a priority by the professionals who are most involved in the prevention and treatment of tropical diseases, imported diseases, travel medicine and migrant health.

Various studies that have been carried out by teams of professionals in clinical practice, microbiology and public health in recent years have helped to develop the knowledge, priorities and intervention measures required to tackle this disease. In addition, these studies have produced data on the extent of the disease and the characteristics of those affected. The results have highlighted the significance of the problem. Thus, Chagas disease is now the main priority in migrant health. Some measures have begun to be adopted to detect and control it, which include systematic screening of blood banks to avoid transmission through blood.

The protocol presented here represents a further step forward in this respect, and will become a leading strategy in Catalonia. It has been supported by a working group made up of non-endemic countries and by WHO's Department of Control of Neglected Tropical Diseases. We are convinced that we are working in the right direction and that a joint effort by various areas of the healthcare network and community support for this disease will lead to health and quality of life improvements for a large sector of our population.

For all of the above reasons, Catalonia is in a privileged position in Europe and in the world to contribute considerably to advances in the prevention, diagnosis and treatment of this disease and its complications, and can assume a certain role in leadership and promotion
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4. CHAGAS DISEASE

4. CHAGAS DISEASE

4.1 Description

Chagas is a parasitic disease caused by infection with *Trypanosoma cruzi*. There are two groups of *T. cruzi*, called I and II, which have different epidemiological, pathogenic and clinical characteristics and respond differently to treatment.[1] The vectors are *blood-sucking triatomine bugs*, such as *Triatoma infestans*. They transmit the parasite when they defecate on a person's skin or mucous membranes whilst feeding on the person's blood. The parasite enters the organism through skin breaks or mucous membranes when the individual touches or scratches the bite. In addition, it can be transmitted through blood transfusions or transplants of infected organs, vertically from an infected mother to a foetus, or through the ingestion of contaminated food. Estimates of the rate of vertical transmission situate it at between 4% and 7% in certain risk groups in Catalonia,[2] and as high as 12% in some countries of origin.[3, 4]

4.2 Epidemiology

The disease is endemic in continental areas of North, Central and South America, particularly in central and southern Bolivia, northwestern Argentina, southern Peru, western Paraguay, part of Ecuador, Nicaragua, El Salvador and the south of Mexico (Figure 1). Of the two main groups of *T.cruzi*, group I is predominant to the north of the Amazon, whilst group II is more extensive in the southern area. The estimated prevalence rate ranges from 0.06% in Uruguay to 28.8% in Bolivia, according to data from the end of the 1990s.5 The prevalence has decreased considerably due to efforts to eliminate the vector that have been made in various countries. According to studies in Catalonia, the prevalence among pregnant women is 3.4% in the Latin American population and 27.7% in the Bolivian population.[2]

Table 1. Distribution of Chagas disease in North, Central and South America. WHO, 1996

4.3 Clinical aspects[1,6]

The disease comprises two phases. The acute phase has few symptoms, so it is not detected in most cases or is mistaken for other pathologies. The complications in the chronic phase may be serious and can lead to death, particularly in cases of heart disorders.

Acute phase

The acute infection or primary infection has few, generally non-specific symptoms. It may lead to an initial local inflammatory reaction in the inoculation site (the chagoma), and regional lymphadenopathy. Other systemic symptoms are, by order of frequency: cefalea,

headache, pallor, myalgia, dyspnoea, oedema, abdominal pain, cough, hepatomegaly, rash, painful nodules, splenomegaly, vomiting, diarrhoea and loss of appetite. When the inoculation is in the conjunctiva, unilateral periorbital oedema may develop and conjunctivitis (Romaña sign). Other more serious presentations are acute myocarditis (in 3% of the infected population, and particularly children under 5) or meningoencephalitis. In the case of myocarditis, symptoms may include chest pain and signs of heart failure and chest x-rays may reveal an enlarged heart silhouette. An electrocardiogram (ECG) shows abnormal heart rhythm, atrioventricular block, low voltage QRS complexes and negative T waves. Cases of meningoencephalitis involve fever, seizures, paralysis and coma. The most serious forms occur in cases of nutritional deficit, immunosuppression (AIDS), children under 5 years old and outbreaks of oral transmission, which tend to be associated with inoculations of higher parasite load.

Chronic phase

If the cause of the acute infection is not treated, in two to three months the disease will become chronic. The **chronic infection** may remain latent for decades or even during the patient's entire life (indeterminate form) or it may affect a target organ, depending on the characteristics of the Chagas disease in the geographic area of origin in question. Although both group I and group II can lead to heart problems, only *T. cruzi* from group II is associated with digestive problems.

1. Indeterminate form: This appears in approximately 60% of infected people. In this form of the disease, patients present:[7]
a) positive serological tests or confirmation of a parasitological diagnosis; b) the absence of signs or symptoms of disease; c) normal standard electrocardiograms; d) normal x-ray images of the heart, oesophagus and colon. The infection can be reactivated with a concomitant serious illness or in conditions of severe immunosuppresion due to organ transplant or AIDS

2. Symptomatic form: This form occurs in around 40% of cases. Symptomatic infection may involve heart or digestive disorders, and autonomic dysfunction that causes sympathetic and parasympathetic nervous system disorders, which, in turn, affect target organs such as the heart and the digestive system (mainly the oesophagus and the colon). In the long-term, the chronic inflammation causes fibrosis of the affected organs. This tissue damage is due to the direct pathogenic effect of the parasite and a destructive effect mediated by autoantibodies and other mechanisms, such as changes in microcirculation.

Around 10-30% of patients present the **cardiac form**. It is the most potentially serious disorder and can cause heart failure, abnormal heart rhythm and sudden death. It usually appears 15-30 years after the acute phase in the form of dilated cardiomyopathy, which can lead to heart failure and arrhythmias that may be associated with thromboembolisms. The most frequent arrhythmias are sinus bradycardia, electrical conduction blocks (right bundle branch block, anterior hemiblock and atrioventricular block), negative T waves, multifocal or polymorphic ventricular extrasystoles, ventricular tachycardia (torsade de pointes) and ventricular fibrillation. Chest x-rays reveal enlargement of the heart silhouette.

Electrocardiograms show cavity dilation, apical aneurysm, and hypokinesia or partial akinesia that mainly affects the postero-inferior, intramural area (by fibrosis).[8]

Below the Amazonian area, 5-10% of infected people have the **digestive form**,[9, 10] whilst to the north of the Amazon, digestive lesions are rare and incipient. Digestive disorders affect the entire digestive tract and are caused by local lesions of the autonomic nervous system, among other mechanisms. However, due to the combination of uncoordinated peristalsis, sphincter function disorders and mechanical distension due to dry contents, the oesophagus and the colon are the two most affected areas. Esophageal disorders are most frequent in central Brazil. The initial symptoms tend to be difficulty in moving the food bolus, with discomfort and retrosternal pain. In advanced phases, the symptoms are regurgitation and reflux. The colon is affected more frequently than the oesophagus in Andean countries. The sigmoid colon is initially affected in general, as well as the rectum in a high percentage of cases. Although megacolon may be asymptomatic in a high proportion of cases, the most frequent symptom is constipation. Other symptoms include meteorism, abdominal pain, abdominal distension and fecaliths. Depending on the geographic area, megacolon, megaesophagus and cardiopathy may be associated and it is estimated that up to 30% of patients with digestive disorders also present chagasic myocardiopathy.

In some cases, **nervous system disorders** may appear. The main nervous disorder is that of the autonomous nervous system. Meningoencephalitis is the most frequent form of presentation in cases of reactivation caused by severe immunosuppression, particularly in patients with AIDS.

The disease may be reactivated in **immunosuppressed** patients. In **HIV positive** patients, the CNS disorders that are present in 75% of such cases become predominant and sometimes exclusive, and have a greater incidence than cardiac disorders, which are found in over 40% of patients. Myocarditis has been found in 60% of patients who are immunosuppressed due to leukaemia and immunosuppressive therapies, among other reasons. Meningoencephalitis has been found in up to 45% of immunosuppressed patients.[6]

4.4 Diagnostic Tests

The diagnosis of Chagas disease can be made through direct or indirect parasitological tests (which isolate the tripomastigote) and serological methods.

- **Direct** parasitological tests include fresh-blood tests, the less sensitive thick blood film, thin blood film and blood smears. The predictive value of these tests depends on the degree of parasitaemia. Consequently, direct methods are the diagnosis of choice in the acute stage of the disease or in cases of reactivation. When the parasitaemia is low, which is common in the chronic phase, blood concentration methods are recommended (e.g. microhaematocrit or the Strout method).

- Of the **indirect** parasitological tests, biopsy cultures are usually carried out in Novy-MacNeal-Nicolle medium, and blood cultures in Liver Infusion Tryptose (LIT) medium, among others. Currently, xenodiagnosis is only used in research. Molecular methods include qualitative, quantitative or real-time PCR.[11, 12] These PCR methods under study can increase the sensitivity of the detection, the rapid characterisation of *T. cruzi* and the quantification of the parasite load, among other advantages. Currently, studies are being undertaken to provide standardised and validated tests in the near future.

- The **serological** methods are based on determining the presence of antibodies against specific antigens: indirect haemagglutination, indirect immunofluorescence, ELISA techniques and Western blot transfer, among others. Given the limited positive predictive value, serological disease confirmation requires two methods that use different antigens to make a definitive diagnosis. If there is a discrepancy, a third technique must be used. In addition, false positive results may arise due to infection with *Leishmania spp*, particularly visceral leishmaniasis, and, more rarely, infections with *Trypanosoma rangeli*, *Treponema pallidum or Plasmodium spp*.

A case history must always be taken and a physical examination carried out to discover whether there are any disorders of the target organs. The **diagnosis of cardiac disorders** must initially be made by means of ECG studies and chest X-rays, and echocardiography is recommended. If an anomaly is detected, the patient can undergo other tests such as ECG with a Holter monitor, ergometry, angiography, isotope tests or any others indicated by cardiology departments.

Screening for digestive disorders is carried out by means of an oesophagogram and a barium enema for colon evaluation. Additional tests can be undertaken by means of gastroscopy.[13, 14]

To confirm a diagnosis of Chagas infection, there must be epidemiological risk factors (possibility of contact with *T. cruzi*) and serological or parasitological confirmation of the infection. Clinical symptoms are not required, as there is a high frequency of asymptomatic patients or patients with non-specific symptoms (chronic phase, indeterminate form). We can distinguish between infection (epidemiological risk factors and laboratory tests) and disease (appearance of symptoms).

4.5 Treatment[1-3]

The drug of choice is **benznidazole**. If this is contraindicated or if side effects occur, *nifurtimox* can be used. Both drugs are available as foreign medication. Their administration reduces the duration and severity of the acute disease and eliminates parasitaemia. The effectiveness[15] of the available treatments is inversely related to the evolution time. The drugs are highly effective in the first year of life and in the acute phase, whilst their effectiveness decreases with the length of the infection. There is no satisfactory treatment for the chronic phase. Some studies found that the parasites were eliminated in 25% of adults treated in the chronic phase, depending on the region of origin. Other studies have shown that treatment in this phase seems to slow down the progression of the disease[16]. The cause of the disease must always be treated in cases of patients under 12 years old or when the infection is reactivated. From 12 to 40 years old, treatment should be offered. Once patients are over 40, treatment is optional and depends on the patient-doctor decision. In addition to etiological treatment, symptomatic treatment also improves the evolution of the disease.

Characteristics of treatment with benznidazole:

- The drug should be administered after food in 2 or 3 doses a day for 60 days, up to a maximum of 300 mg/day.

- Dosage:
  - < 15 years and < 40 kg: benznidazole 7.5-10 mg/kg/day.
  - > 40 kg and/or > 15 years: benznidazole 5 mg/kg/day.

- In cases of meningoencephalitis, the recommended dosage is 25 mg/kg/day.
- In premature infants or newborns with comorbidity, the treatment should begin at 5 mg/kg/day. If the newborn does not present leukopenia or thrombocytopenia after three days of treatment, the dose should be increased to 10 mg/kg/day. In full-term newborns of an appropriate weight with no other pathologies, the initial dose can be 10 mg/kg/day.

- Contraindications. Pregnant women and breastfeeding mothers, patients with liver failure and serious neurological, digestive, cutaneous or blood disease, allergy to imidazole.

- Side effects. The most frequent side effects are digestive, cutaneous or neurological, and may appear in 20-40% of patients. By order of frequency, they are: digestive symptoms; symptoms of hypersensitivity: dermatitis with rashes, generalised oedema, fever, arthralgia and myalgia; polyneuropathies, paresthesia and polyneuritis. More rarely, bone marrow depression: thrombocytopenic purpura and agranulocytosis (which is the most severe side effect). The drug should be withdrawn if bone marrow depression occurs or serious symptoms of hypersensitivity arise (Stevens-Johnson syndrome). The effects are reversible with drug withdrawal or dose reduction.

- Children are more tolerant of the medication than adults. In case of intolerance to the daily dose of the drug, the treatment period can be lengthened to reduce the quantity.

- The follow-up includes control analyses throughout the treatment. In adults, a serological test should be carried out annually for the first 5 years, although the length of the follow-up will depend on the previous duration of the infection (see Table 1) and the region of origin. Seroconversion is faster in the area north of the Amazon.

- In children, follow-up involves control analyses in the second week of treatment and every 4 weeks throughout the treatment or at any time that symptoms appear. Serological tests must be carried out annually until a negative result is obtained. Depending on the geographic region of origin, this could take from 1 to 7 years.

Table 1. Elimination of parasites in people who have been infected by *T.cruzi*, by year of evolution in South America.

Years of infection	< 1 year	< 12 years	> 12 years
Percentage of patients cured	100%	60%	8-25%
Time until a negative serological result	< 1 year	5-7 years	10-15 years

Characteristics of treatment with nifurtimox:

- The drug is administered after meals in 3 doses/day for 60 days.
- Dosage:
  - In adults, the dose is 8-10 mg/kg/day.
  - In children, the dose can reach up to 15 mg/kg/day.
- Side effects are more frequent than with benznidazole.[17] They are, by order of frequency: digestive symptoms (40-100%): weight loss, vomiting, lack of appetite, abdominal discomfort; symptoms of central nervous system disorders (60-70%): irritability, difficulty sleeping, disorientation, tremors; peripheral nervous system disorders (25%): dose-dependent polyneuropathies, paresthesia and polyneuritis; psychosis and hallucinations (10%) that are difficult to handle; general feeling of weakness. The effects can be reversed by withdrawing the drug or reducing the dose.
- Side effects are less frequent in children.
- The follow-up includes control analyses that are carried out throughout the treatment. In the case of adults, serological tests should be performed annually for the first 5 years, although the follow-up will depend on the length of the infection before treatment.
- The follow-up of children includes control analyses that are carried out in the second week of treatment and then every 4 weeks whilst the treatment lasts or at any time that symptoms appear. The serological tests should be repeated annually until negative results are obtained, which could take between 1 and 7 years, depending on the geographic region of origin.

4.6 Situation in Catalonia

Due to migratory movements, the population of Catalonia includes around 334,000 people from endemic countries (Catalan Health Service Central Register of People with Healthcare Coverage). As the disease has an average prevalence of 3.4% in Latin American countries (except the Caribbean islands), we can estimate that around 11,000 people are infected by *T.cruzi* in Catalonia.

Direct vector transmission cannot occur in Catalonia, as there are no triatomines in the region. The possibility of infection through blood or infected organs has led to the Blood and Tissue Bank of Catalonia screening donors for this disease. Studies have shown a seroprevalence of infection by *T. cruzi* of 0.62%.[18] Some cases have been detected among people who have lived in endemic areas, but were not born there. A similar study carried out in Madrid showed a prevalence of 0.8%.[19]

Studies carried out in Catalonia show that the rate of vertical transmission is between 4% and 7%.[2] The fertility rate is 40 to 45/1,000 women. Therefore, the number of pregnancies in Latin American women (except women from the Caribbean) could be close to 7,700 per year, of which approximately 230 women could be infected. The number of newborns per year who are infected with *T.cruzi* in Catalonia could therefore range between 9 and 16. From 10% to 40% of these newborns will present symptoms. Hence, 1 to 6 children could be born with congenital Chagas disease per year.

5. PROTOCOL FOR SCREENING IN PREGNANT WOMEN

5. PROTOCOL FOR SCREENING IN PREGNANT WOMEN

5.1 Target population

Pregnant women who:

1. are from Latin America (except the Caribbean islands)
2. have a Latin American mother, even if the patient was born here (except mothers from the Caribbean islands)
3. have spent longer than 1 month in any Latin American country (except the Caribbean islands)

The screening protocol is shown graphically in Figure 2.

5.2 Screening for *T.cruzi* infection in pregnant women

Screening should be carried out by means of a serological test that is included in the normal analyses for the first trimester of a pregnancy, between 8 and 12 weeks gestation. If the first pregnancy check-up occurs after 12 weeks gestation, the serological test for Chagas should be included in the first analysis that is requested for the patient, along with the rest of the routine serological tests.

The serological screening test should consist of an ELISA with complete antigen (conventional ELISA), as this is a sensitive, objective test that can easily be performed in a standard laboratory. The commercial products that are used must comply with current European legislation and have well-specified technical features. The sensitivity of the various features ranges from 98% to 100%, whilst the specificity varies between 97% and 100%. A sample with the following characteristics should be collected: 2 ml of serum (5 ml of blood) centrifuged in serum separator tubes. This serological test should be carried out in the laboratories that usually undertake analyses for the Sexual and Reproductive Health Services (ASSIR).

If the first test is negative, the patient should continue with normal pregnancy check-ups. The negative test result should be recorded in the patient's medical history and in her pregnancy records.

5.3 Diagnosis of Chagas disease

If the screening test is positive, a second serological test must be carried out to confirm the diagnosis. The experts consider that this test should be objective and involve a different antigen from that used in the screening test. The use of recombinant ELISA isproposed. The sensitivity and specificity of this test range between 97% and 100%.

If there is discrepancy between the screening test and the test to confirm the diagnosis (which occurs in 65% of the tests, according to data from the Blood and Tissue Bank of Catalonia), a third deciding test should be carried out. The experts recommend that this be an indirect immunofluorescence assay, although other tests with similar performance can be selected, according to the expertise of the laboratories. The sensitivity of the indirect immunofluorescence assay is 95%, and its specificity is 100%. However, its interpretation depends on the expertise of the technician and therefore it should be carried out in a specialised centre. In exceptional cases, additional serological tests should be performed to reject the possibility of cross-reactions with other infections.

Only a small number of screening tests will be positive, but there is a high probability that a third, deciding test will be needed, which must be carried out by trained personnel. This third test should be carried out in a qualified laboratory with expertise in this area. The laboratory in which the first screening test is performed must ensure that a pathway is established to transfer the samples to the appropriate laboratory. Thus, a second blood sample does not need to be taken, as the deciding tests are carried out with the serum from the first sample.

5.4 Healthcare for pregnant women with *T.cruzi* infections

When tests confirm that a woman has a *T.cruzi* infection, her clinical status should be assessed to evaluate the form of the disease (indeterminate, cardiac, digestive or other). Depending on the stage of gestation, an ECG should be carried out, but radiological tests should be postponed. The study and follow-up can be carried out by the primary care doctor (or an internist at the referral hospital). The patient can then be referred to the corresponding specialist, if necessary.

There is no reason for the pregnancy to involve particular complications. The usual pregnancy check-ups should be carried out, and the patient should also see her obstetrician. If the patient shows signs of suffering from the disease, she should be referred to the level of care established in the Protocol for monitoring pregnancy, in accordance with the risk involved in the case.[20] The severity of the disease shall be determined by cardiopathy in particular and clinical criteria shall be used to refer patients to the established facilities.

5.5 Healthcare for Newborns of mothers with *T.cruzi* infections

5.5.1 Neonatal examination

Most (between 60% and 90%) infected newborns will not have any clinical symptoms. In these cases, the newborn should be cared for in the same way as usual,[21] although the diagnostic tests described below should be carried out.

The remaining infected newborns may have the symptoms shown in Table 2, which can appear gradually. Therefore, clinical check-ups should be carried out during the first few weeks of life, to determine the seriousness of the problem. Cases are considered severe when there are cardiac, neurological or respiratory disorders. Referral to other healthcare facilities shall be determined by clinical criteria, according to the pathways that are already established in standard clinical practice.[22]

5.5.2 Diagnostic tests in newborns

According to the group of experts' recommendations, the following tests should be performed on the newborn:

1. Microhaematocrit. Blood can be taken from the heel or from any other part except the umbilical cord, due to the possibility of confusion with the mother's blood. The sample should be extracted as soon as possible and sent to a laboratory with staff who are experts in interpreting the test. Tests should be performed as soon as possible: always within 48 hours of blood sampling and, ideally, within the first 24 hours. If the microhaematocrit is positive, treatment should begin.

2. Serological tests. These could be ELISA assays, as in the case of the mother. They should be carried out when the infant is 9 months old, to avoid the presence of the mother's antibodies. If the serological test at 9 months is positive, the child should be treated for *T.cruzi* infection.

The use of PCR to diagnose Chagas disease in general, and congenital infection in particular, is currently being standardised and validated.

Microhaematocrit samples can be taken in any hospital, but the technique and the interpretation must be performed by experts. To carry out this test, total blood must be extracted with heparin (between 2 and 5 ml of blood). The samples must be analysed within 48 hours and should be carried out in the referral maternity hospitals in the region

that are level II-III. An effective pathway should be established to transfer the sample quickly or, if this is not possible, to carry out a newborn check-up soon after discharge.

In cases of pregnancies that have not been monitored, serological tests should be performed on the mother and microhaematocrit on the newborn at the time of birth. Subsequently, if the diagnosis of the mother is confirmed, the child's clinical check-ups should continue and serological tests should be carried out at 9 months. The monitoring process can be coordinated by the newborn's regular pediatrician.

5.5.3 Treatment of infected newborns

Treatment should be initiated in any of the following cases:

- Newborns with symptoms of the disease
- Positive parasitological tests or microhaematocrit
- Positive serological test at 9 months

The treatment of Chagas disease is benznidazole taken orally at a dose of 10 mg/kg/day for 60 days, divided into two or three doses or, in cases of contraindication or side effects, nifurtimox at 10 mg/kg/day in two or three doses for 60 days. Both are foreign drugs that require individual authorisation. There is no pediatric formulation, so the dose has to be prepared by hand.

There is no contraindication for breastfeeding, as long as the mother is not receiving treatment with benznidazole or nifurtimox.

5.5.4 Follow-up of infected newborns

The follow-up of children who have begun treatment includes control analyses in the second week of treatment and then every 4 weeks whilst the treatment lasts or at any time that symptoms appear. The serological tests should be repeated annually until a negative result is obtained, which may take from 1 to 7 years, depending on the geographical region of origin.

In cases in which the newborn has not been initially treated, the pediatrician at the maternity hospital will be responsible for the follow-up process, which will include serological tests at 9 months. If the tests are negative, the patient can be discharged.

5.6 Healthcare for adult women infected with *T.cruzi* and for their other children

Women with asymptomatic *T.cruzi* infections should have annual check-ups to detect the appearance of symptoms. An annual case history should be taken that particularly focuses on cardiac or digestive problems, a clinical examination and an ECG. This monitoring can be carried out by the primary healthcare doctor or the internist in the referral hospital.

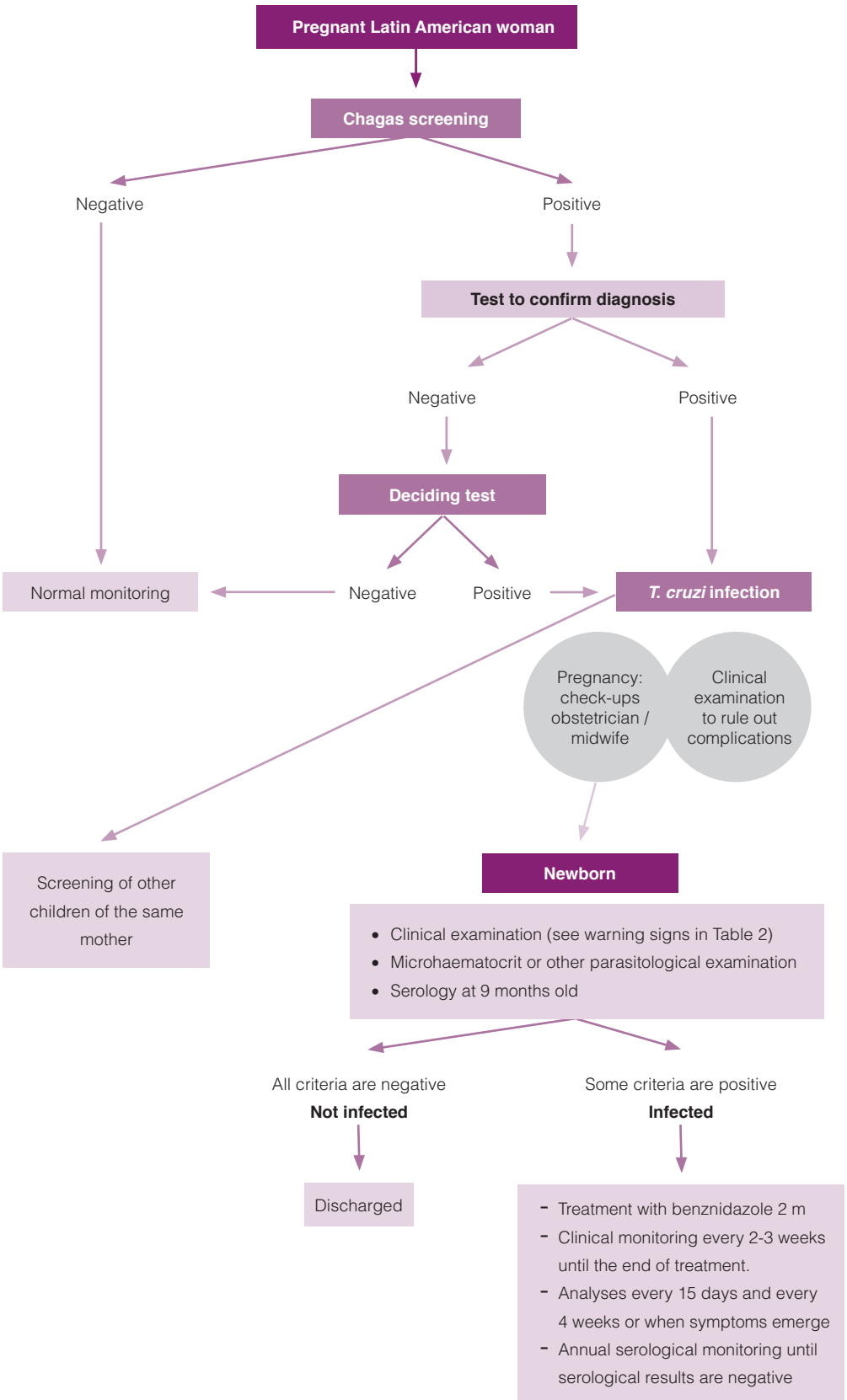
Treatment of infected adults is controversial, as existing studies show that the medication is not highly effective. Some studies show that parasitaemia decreases with the drugs and therefore they slow down the disease progression. In addition, in women of fertile age, the rate of vertical transmission may be reduced in subsequent pregnancies.
Treatment should be offered to the adult woman once she has stopped breastfeeding the infant. Diagnostic tests should be carried out on other children of the infected woman who live in Catalonia, particularly if they are infants or adolescents If they are infected,

treatment with benznidazole (or nifurtimox) should be initiated in children under 12 and offered to older children, even when there are no clinical symptoms.

Table 2. Warning signs in newborns of women with *T. cruzi* infections.

- Apgar < 5 at 1 min / < 7 at 5 min
- Low birth weight: < 2.500 g
- Fever (> 37,5 °C) or hypothermia (< 35 °C)
- Lymphadenopathy
- Splenomegaly
- Hepatomegaly
- Jaundice
- Skin haemorrhages (petechia)
- Oedemas/anasarca
- Signs of meningoencephalitis:
    - Irritability
    - Plaintive cry
    - Apathy
    - Convulsive seizure
    - Bulging fontanelle
- Signs of myocarditis:
    - Abnormal body temperature
    - Hypophonesis of heart sounds
    - Chest **X-ray**: cardiomegaly
    - **ECG**: low QRS voltages, prolonged PR or QT, sinus tachycardia with primary changes to the T wave
- Respiratory status:
    - Polypnea
    - Cyanosis
    - Bilateral symmetrical hypoventilation
    - Apathy
    - Hyporeactivity to stimuli
    - Low blood pressure (SBP < 75 mm Hg)
    - Chest **X-ray**: reduced lung volume, bell-shaped thoracic cage, diffuse and homogeneous reticulogranular pattern and air bronchogram that goes beyond the heart silhouette. In more serious cases, the lung is totally opaque and it is practically impossible to distinguish the silhouette of the heart.
- Analytical criteria:
    - Lymphocytosis (> 24,000 cel/mmc)
    - Lymphopenia (< 10,000 cel/mmc)
    - Iron deficiency anaemia
    - High ESR
    - Hypoalbuminaemia
    - Proteinuria
    - Elevated transaminases

Figure 2. Pathway of screening and diagnosis in pregnant women and newborns



6. EPIDEMIOLOGICAL SURVEILLANCE SYSTEMS

6. EPIDEMIOLOGICAL SURVEILLANCE SYSTEMS

Epidemiological surveillance (ES) is crucial to controlling Chagas disease. **The specific objectives** of ES are:

1. Support the local management of identified cases.
2. Proceed in the detection and treatment of the infection in newborns and their siblings.
3. Prevent the development of the disease in pregnant women and children, through preventive treatment.
4. Monitor the final result of the individuals under study.
5. Identify trends and risk factors, to support any interventions that are aimed at preventing new cases.
6. Monitor the process and the results of activities to control the disease so that improvements can be made.
7. Provide information about the disease to support healthcare professionals who are involved in diagnosing and following-up cases.
8. Train professionals who are in contact with patients (midwives, general practitioners, neonatologists and obstetricians) and laboratory staff.
9. Periodically provide information about the results obtained and the control strategies used.

Case definition

Confirmed Chagas disease is defined as any case in which epidemiological risk factors are present and the diagnosis is confirmed. The diagnostic criteria are as follows:

Isolation of *Trypanosoma cruzi*.

Microscopic observation of *Trypanosoma cruzi* in fresh blood tests, thick blood films, thin blood films or blood smears.

Antigen detection by PCR.

Detection of antibodies by serological tests: ELISA, indirect immunofluorescence, indirect haemagglutination or Western blot transfer (if the diagnosis is only made by means of serological tests, two methods must be applied with different antigens to make a definitive diagnosis).

In children and pregnant women (but not newborns), confirmed cases of Chagas disease are those in which the results of serological tests are positive in the screening and diagnostic confirmation stages. If there is a discrepancy between these two tests, a third assay must be carried out. If the results of this third assay are positive, the case of Chagas disease is confirmed.

In newborns, Chagas disease is confirmed if positive results are found for the microhaematocrit or for other parasitological examinations carried out on blood samples taken as soon as possible after birth, or when the serological test at 9 months old is positive.

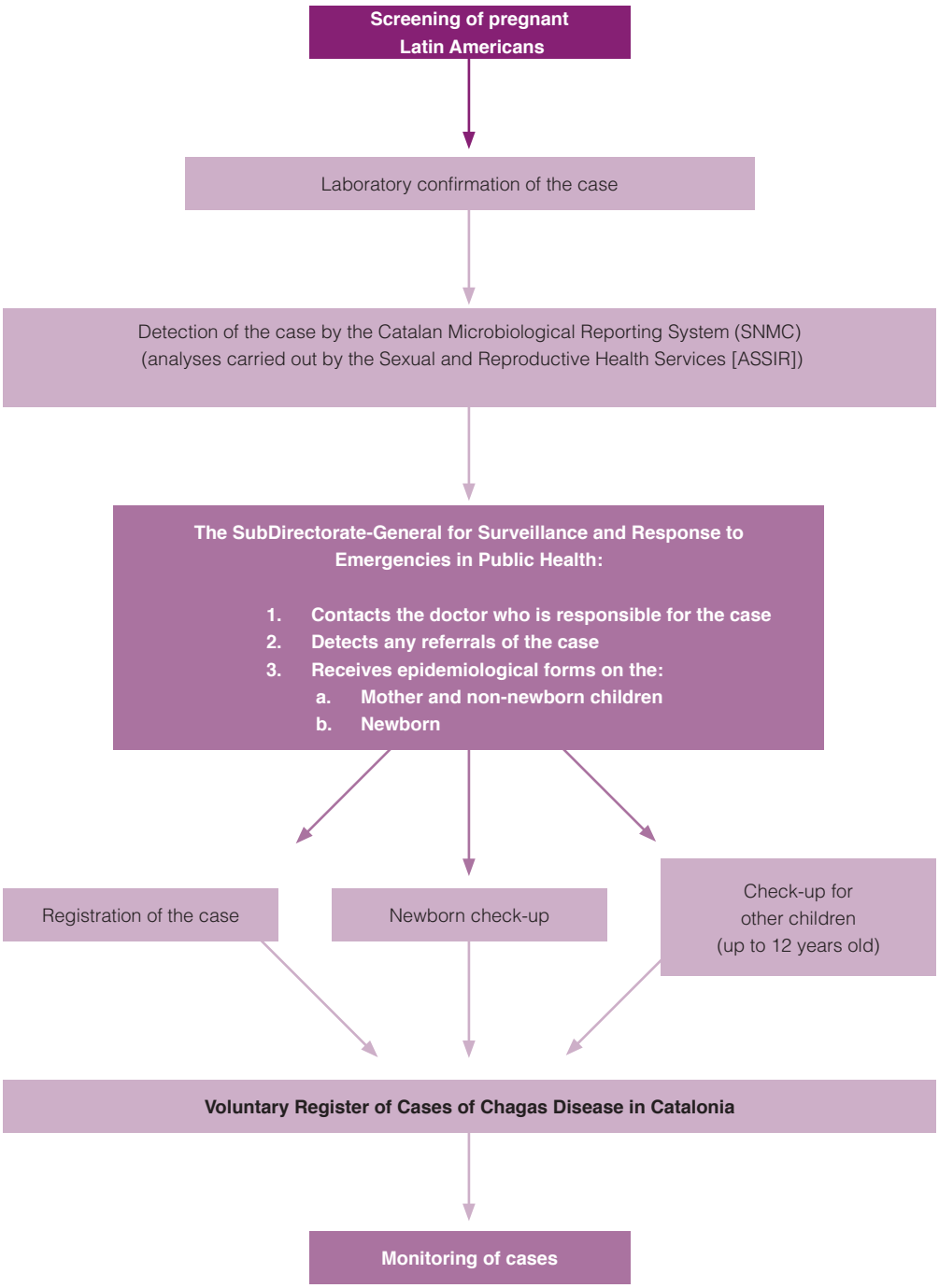
Notification of cases

The epidemiological surveillance of Chagas in Catalonia will combine active and passive surveillance systems, which will provide the information needed to create a Voluntary

Register of Cases of Chagas Disease in Catalonia, as shown in Figure 3.

Passive surveillance involves the notification of cases by microbiologists in hospital laboratories and in other centres that participate in the Catalan Microbiological Notification System (SNMC) (See Appendix 1). The basic data on the case (patient identity number [PIN], medical history, sample and diagnostic technique) are collected in the SNMC computer application.

Figure 3. Pathway for notification and monitoring of cases of Chagas disease.



Active surveillance consists in using the screening protocol to check pregnant women, their newborns and their other children detected by the SNMC. In a confirmed case of Chagas disease, the SubDirectorate-General for Surveillance and Response to Emergencies in Public Health must contact the doctor responsible for the patient and request that he/she voluntarily completes the epidemiological form for the case (Appendix 2 and Appendix 3) and sends it by post or fax (93 551 75 06) to the Subdirectorate. This Subdirectorate will manage the Voluntary Register of Cases of Chagas Disease in Catalonia, and will input, validate and analyse the information that is provided. The data collected in the epidemiological form are divided into the following variables:

- Variables that identify the patient (including the country of origin and the date of arrival in Catalonia).
- Control variables of risk factors associated with the disease (such as, for example, a record of bites by haematophage triatomines, blood transfusions, tissue or organ transplants, immunosuppressive disease, whether the patient has spent the night in an adobe house or has lived with patients with Chagas disease, whether the patient has travelled to any of the countries with endemic Chagas disease, and the area to which they have travelled).
- Variables related to the results of the tests to detect the disease (the serological screening test, the test to confirm the diagnosis and, if necessary, the deciding test).
- Variables related to the clinical status of the patient who has a laboratory-confirmed *T.cruzi* infection (if the patient is in the acute or chronic phase of the disease).
- Variables related to treatment methods, as well as the results of the treatment.
- With respect to the newborn, several variables are requested that assess the clinical status, including signs of meningoencephalitis, analytical criteria and respiratory status. Diagnostic tests on the newborn and data on the screening of other children of the same mother are collected and analysed.

The intervention of the public health services that are responsible for controlling Chagas disease is therefore initiated, once the microbiologists who participate in SNMC have reported the case. The doctor who declares the case must provide all information of use in the implementation of research and protection measures, including the full name, address and telephone number of the patient. All of the information that is collected shall be treated as confidential, in accordance with the Data Protection Act.

7. ASSESSMENT INDICATORS FOR THE NOTIFICATION SYSTEM AND THE VOLUNTARY REGISTER

7. ASSESSMENT INDICATORS FOR THE NOTIFICATION SYSTEM AND THE VOLUNTARY REGISTER

One year from the start of epidemiological surveillance, the feasibility of the Voluntary Register of Cases of Chagas Disease in Catalonia should be assessed, using the Catalan Microbiological Notification System as a source of information.

The analysis and incorporation of results provided by the Voluntary Register of Cases of Chagas Disease in Catalonia will enable us to progress in the adaptation of healthcare facilities for the population and in the establishment of technical recommendations to meet the new challenges that Chagas disease could present. Therefore, epidemiological surveillance includes as a basic element the dissemination of information to all those who need it, in order to attain more effective and dynamic preventative actions at all levels of control.

8. APPENDIX 1. LABORATORIES AND CENTRES THAT PARTICIPATE IN THE CATALAN MICROBIOLOGICAL NOTIFICATION SYSTEM (SNMC)

8. APPENDIX 1. LABORATORIES AND CENTRES THAT PARTICIPATE IN THE CATALAN MICROBIOLOGICAL NOTIFICATION SYSTEM (SNMC)

CIUTAT SANITÀRIA VALL D'HEBRON
FUNDACIÓ DE GESTIÓ SANITÀRIA HOSPITAL DE LA SANTA CREU I SANT PAU
HOSPITAL CASA MATERNITAT
HOSPITAL CLÍNIC I PROVINCIAL DE BARCELONA
HOSPITAL DE L'ESPERANÇA
HOSPITAL DEL MAR
HOSPITAL RESIDÈNCIA SANT CAMIL
HOSPITAL SANT JOAN DE DÉU (ESPLUGUES)
HOSPITAL SANT JOAN DE DÉU (MARTORELL)
HOSPITAL COMARCAL DE L'ALT PENEDÈS
HOSPITAL GENERAL DE L'HOSPITALET
HOSPITAL UNIVERSITARI DE BELLVITGE
HOSPITAL DE SANT JAUME (CALELLA)
HOSPITAL MUNICIPAL DE BADALONA
HOSPITAL UNIVERSITARI GERMANS TRIAS I PUJOL
HOSPITAL DE MATARÓ
CATLAB-CENTRE ANALÍTIQUES TERRASSA, AIE
CORPORACIÓ SANITÀRIA PARC TAULÍ
HOSPITAL DE SANT CELONI
HOSPITAL DE TERRASSA
HOSPITAL GENERAL DE CATALUNYA
HOSPITAL GENERAL DE GRANOLLERS
HOSPITAL MÚTUA DE TERRASSA
ALTHAIA
HOSPITAL DE SANT BERNABÉ
FUNDACIÓ SANITÀRIA D'IGUALADA
HOSPITAL GENERAL DE VIC
HOSPITAL DE SANT PAU I SANTA TECLA
HOSPITAL UNIVERSITARI DE TARRAGONA JOAN XXIII
HOSPITAL UNIVERSITARI SANT JOAN DE REUS
HOSPITAL COMARCAL D'AMPOSTA
HOSPITAL COMARCAL DE MÓRA D'EBRE
HOSPITAL DE TORTOSA VERGE DE LA CINTA
HOSPITAL COMARCAL DE BLANES
HOSPITAL DE FIGUERES
HOSPITAL DE SANT JAUME (OLOT)
HOSPITAL UNIVERSITARI DE GIRONA DOCTOR JOSEP TRUETA
HOSPITAL SANTA MARIA
HOSPITAL UNIVERSITARI DE LLEIDA ARNAU DE VILANOVA

9. APPENDIX 2. EPIDEMIOLOGICAL FORM FOR CASES OF CHAGAS DISEASE – MOTHER OR NON-NEWBORN CHILDREN

9. APPENDIX 2. EPIDEMIOLOGICAL FORM FOR CASES OF CHAGAS DISEASE – MOTHER OR NON-NEWBORN CHILDREN

Information about the pregnant patient or her child

Name and surname: PIN |__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Date of birth (dd/mm/yy): |__|__|__|__|__|__| Sex: 1. Male 2.Female Week of gestation |__|__|

Mother's name or PIN (if the form is for her child):

Address: Tel: |__|__|__|__|__|__|__|__|__|

Town of residence: Province: Country:

Country of birth: District/city: Nationality:

Date of arrival in Europe (dd/mm/yy): |__|__|__|__|__|__| Occupation:

Information about the doctor and centre declaring the case

Name and surname: License number: |__|__|__|__|__|

Healthcare centre: Code: |__|__|__|__|__|__|__|__|__|

Town: Province: Contact tel. number: |__|__|__|__|__|__|__|__|__|

Date of declaration (dd/mm/yy): |__|__|__|__|__|__| Week of declaration: |__|__|

Control of risk factors associated with the disease

Does the patient have children? How many?	1. Yes	2. No	Children: 1 2 3 More
Does the patient have clinical symptoms of Chagas disease?	1. Yes	2. No	
Does the patient have an immunosuppressive disease?	1. Yes	2. No	Specify which one:
Has the patient been a blood donor in Spain?	1. Yes	2. No	Specify where:
Has the patient been a live organ or tissue donor?	1. Yes	2. No	Specify which organs/tissues:

Results of the tests to detect the disease

Date of diagnosis (dd/mm/yy):
|__|__|__|__|__|__|__|

The diagnosis was made by:
1. Serology
2. Parasitological test
3. PCR

Assessment of the clinical status of the patient with laboratory-confirmed Chagas infection

Acute disease phase: |__| 1. Yes |__| 2. No In case of acute phase, date of start of symptoms (dd/mm/yy): |__|__|__|__|__|__|__|

If the disease is in the chronic phase, specify which form : |__| 1. Indeterminate |__| 2. Cardiac |__| 3. Digestive |__| 4. Others

Is treatment recommended? |__| 1. Yes |__| 2. No Possible treatment start date (dd/mm/yy): |__|__|__|__|__|__|__|

Comments:

To be completed when treatment begins

Name of health centre Medical history number:

Hospitalisation |__| 1. Yes |__| 2. No Admission date: |__|__|__|__|__|__|__| Discharge date: |__|__|__|__|__|__|__|

Treatment: Start date (dd/mm/yy): |__|__|__|__|__|__|__| End date (dd/mm/yy): |__|__|__|__|__|__|__|

1. Benznidazole

Procedure…..……

2. Nifurtimox

Procedure……

3. Others. Please specify: Adverse reactions?: |__| 1. Yes |__| 2. No

Treatment compliance:

1. Correct
2. Irregular
3. Stopped treatment (date :|__|__|__|__|__|__|__|)
4. Refused treatment
5. 1 and 3
6. 2 and 3

10. APPENDIX 3. EPIDEMIOLOGICAL FORM FOR CASES OF CHAGAS DISEASE – NEWBORN

10. APPENDIX 3. EPIDEMIOLOGICAL FORM FOR CASES OF CHAGAS DISEASE - NEWBORN

Information about the mother's at-risk newborn

Name and surname: PIN |__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Date of birth (dd/mm/yy): |__|__|__|__|__|__| Sex: 1. Male 2.Female

Mother's name or PIN:

Address: Tel: |__|__|__|__|__|__|__|__|__|

Town of residence: Province: Country:

Information about the doctor and centre declaring the case

Name and surname: License number: |__|__|__|__|__|

Healthcare centre: Code: |__|__|__|__|__|__|__|__|__|__|

Town: Province: Contact tel. number: |__|__|__|__|__|__|__|__|__|

Date of declaration (dd/mm/yy): |__|__|__|__|__|__| Week of declaration: |__|__|

Healthcare for the newborn

Asymptomatic patient: |__| 1. Yes |__| 2. No

1. Apgar < 5 at 1 min / < 7 at 5 min
2. Low birth weight: < 2.500 g
3. Fever (> 37.5°C) or hypothermia (< 35°C)
4. Lymphadenopathy
5. Splenomegaly
6. Hepatomegaly
7. Jaundice
8. Skin haemorrhages (petechia)
9. Oedemas/anasarca

Respiratory status:

1. Polypnea
2. Cyanosis
3. Bilateral symmetrical hypoventilation
4. Apathy
5. Hyporeactivity to stimuli
6. Low blood pressure (SBP < 75 mm Hg)
7. **Chest X-ray**: reduced lung volume, bell-shaped thoracic cage, diffuse and homogenous pattern and air bronchogram that extends beyond the heart silhouette. In more serious cases, the lung is totally opaque and practically impossible to distinguish from the silhouette of the heart.

Signs of meningoencephalitis:

1. Irritability
2. Plaintive cry
3. Apathy
4. Convulsive seizure
5. Bulging fontanelle

Signs of myocarditis:

1. Abnormal body temperature
2. Hypophonesis of heart sounds
3. **Chest X-ray**: cardiomegaly
4. **ECG**: low QRS voltages, prolongation of PR or QT, sinus tachycardia with primary changes to the T wave.

Diagnostic tests on the newborn

Microhaematocrit results:	1. Positive	2. Negative
PCR results:	1. Positive	2. Negative
Serological results at 9 months:	1. Positive	2. Negative

Date of confirmation of diagnosis (dd/mm/yy): |__|__|__|__|__|__|

To be completed when treatment begins

Name of health centre Medical history number

Hospitalisation |__| 1. Yes |__| 2. No Admission date: |__|__|__|__|__|__| Discharge date: |__|__|__|__|__|__|

Treatment: Start date (dd/mm/yy): |__|__|__|__|__|__| End date (dd/mm/yy): |__|__|__|__|__|__|

1. Benznidazole

Procedure.....

2. Nifurtimox

Procedure.....

3. Others. Please specify:..... Adverse reactions?: 1. Yes 2. No

Treatment compliance:

1. Correct
2. Irregular
3. Stopped treatment (date : |__|__|__|__|__|__|)
4. 1 and 3
5. 2 and 3

Conclusion of the case:

1. Cured
2. Death due to Chagas disease
3. Death due to other causes
4. Patient no longer located
5. Other. Please specify

11. REFERENCES

11. REFERENCES

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