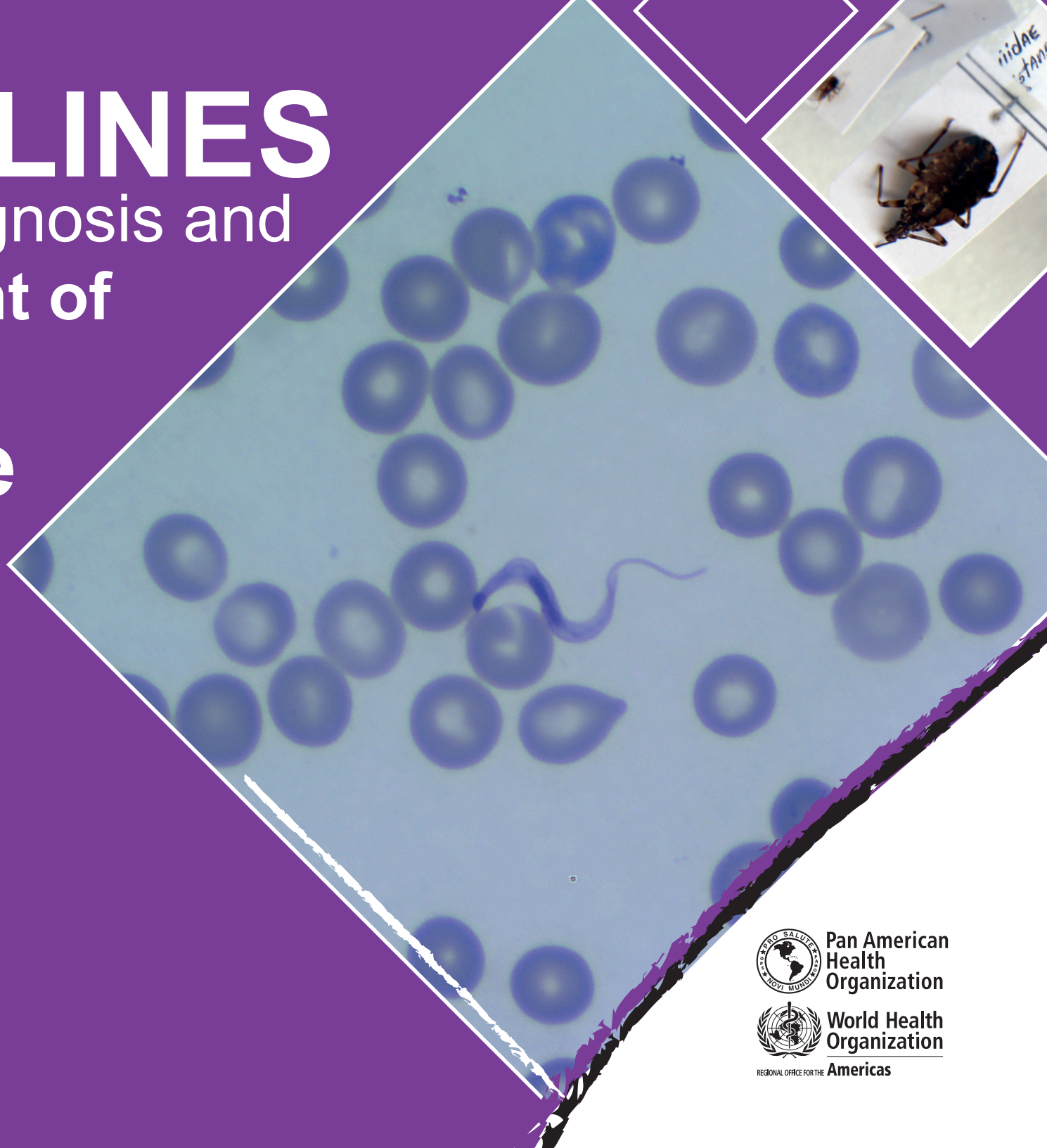
GUIDELINES
for the Diagnosis and Treatment of Chagas Disease



Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas

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for the Diagnosis and

Treatment of

Chagas Disease

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Preface

This document is a valuable working tool for anyone who works in the health networks of Latin American countries. It describes the most recent basic and fundamental guidelines for the diagnosis and treatment of American trypanosomiasis (Chagas disease) based on the evidence published to date, and is now being put into the hands of all interested parties by the Pan American Health Organization (PAHO).

The work carried out by a team of Chagas disease specialists in coordination with experts in the GRADE methodology (*Grading of Recommendations Assessment, Development and Evaluation*), provides the highest guarantees and scientific credibility, giving health workers and patients clinical knowledge that is based on the most up-to-date and reliable evidence and knowledge available.

Chagas disease is a neglected infectious disease that affects between six and eight million people in the Americas. Current estimates indicate that there are roughly 28,000 new acute cases each year, and nearly 65 million people live at continuous risk of contracting the disease by vector-borne transmission, blood or congenital transmission, or food-borne transmission. For these reasons, PAHO recognizes that there are substantial needs in terms of increasing access, coverage, and quality of care within national health care systems, mainly in primary care networks.

This document is without question a significant contribution to the training of new health workers. We hope that it will effectively contribute to basic and refresher training for all healthcare personnel in the public and private sectors, and that it will help standardize the required knowledge and procedures for the diagnosis and treatment of this endemic parasitosis.

These guidelines were developed as part of the Chagas-related commitments made by the PAHO Directing Council in Resolution CD55.R9 (2016): Plan of Action for the Elimination of Neglected Infectious Diseases and Post-Elimination Actions, 2016-2022.

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The Pan American Health Organization (PAHO) would like to thank the group that developed these guidelines for the tremendous work, quick response, and commitment they demonstrated in this process. We would like to especially recognize the following doctors: Roberto Chuit, Jaime Altcheh, Alejandro Luquetti, Faustino Torrico, and Juan Carlos Villar, for sharing their extensive expertise on the subject; Ariel Izcovich, Juan Criniti, Ana Marcela Torres, and Ludovic Reveiz, for methodological coordination; and Roberto Salvatella and Luis Castellanos for promoting this initiative. The full list of members of the development group can be found in Annex 1.

We would also like to thank the international expert panel that helped formulate the recommendations, for their special support in providing useful recommendations for the management of Chagas disease.

Special thanks go to Argentina's National Academy of Medicine, particularly its Institute of Epidemiology, for offering to host the working meetings throughout the entire guideline development process and providing many of the facilities that made this work possible.

We also want to thank the PAHO/WHO Representative Office in Argentina for all its support during the process.

Executive summary

Rationale

Chagas disease (American trypanosomiasis) is caused by the flagellate protozoa *Trypanosoma cruzi*, which is primarily transmitted (more than 80% of recorded infections) by *hemiptera* insects, which are triatomines that have different names in different places in the Americas: "*vinchucas,*" "*pitos*," "*chirimachas*," "kissing bugs," etc. Within this subfamily of hematophagous insects, most cases of Chagas disease are attributable to the following household species: *Rhodnius prolixus, Triatoma dimidiata*, and *Triatoma infestans* (1).

Other modes of transmission are: blood transfusions from *T. cruzi*-infected donors (nearly 20% of infections; due to lack of universal screening of donors to rule out Chagas disease in blood banks); transplacental congenital infection, which is found in 2% to 6% of newborns of infected pregnant mothers; through consumption of *T. cruzi*-contaminated food; and other potential modes of transmission such as organ transplantation, accidental contact with wild zoonotic cycles, and laboratory accidents.

With an annual incidence of 28,000 cases in the Region of the Americas, it is estimated that Chagas disease affects around six million people and causes nearly 12,000 deaths each year (compared to 45,000 in the 1980s and 23,000 in the 1990s). It is calculated that around 65 million people are at risk of contracting the disease. Recent estimates of the burden of Chagas disease in Latin America indicate that its annual health cost is approximately US$500 million, with 770,000 years of life lost from premature death or disability-adjusted life years (DALYs) (2, 3).

Although significant progress has been made in prevention and control (4), medical care of people infected by *T. cruzi* has lagged for many years due to the diagnostic and therapeutic problems caused by this systemic parasitosis.

There is a need for evidence-based guidelines that offer detailed information on the situation that currently characterizes the diagnosis and treatment of American trypanosomiasis.

Objectives

This document focuses on making recommendations for the diagnosis and treatment of Chagas disease, an infection caused by *Trypanosoma cruzi*, the protozoan agent of a systemic parasitic disease.

Methodology

These clinical practice guidelines were prepared following the WHO handbook for guideline development (5). A multidisciplinary development group was formed, comprised of thematic experts, epidemiologists, methodologists, and users. Since there were no existing guidelines that could be adapted, the guidelines were developed from scratch. Searches were conducted to find systematic reviews and primary studies up to August 2017 in online databases (PubMed, EMBASE, Cochrane) and through manual searches. Later, the evidence summary and profiles were prepared using the GRADE approach (*Grading of Recommendations Assessment, Development and Evaluation*). The recommendations were graded by an expert panel on Chagas disease. The guidelines were peer-evaluated according to subject area and methodology. All expert panel and development group participants signed conflict of interest statements that were analyzed by the guidelines coordination team.

Recommendations

This document provides recommendations for the diagnosis and treatment of adult and pediatric patients. The following recommendations pertain to individuals with: 1) suspected Chagas disease; 2) exposure to Chagas disease; 3) diagnosis of chronic Chagas disease; and 4) diagnosis of acute Chagas disease.

The recommendations marked with an asterisk (*) have been selected as key recommendations for the implementation process.

Recommendation Grade	No.	Summary
What is the best diagnosis strategy for patients with suspected chronic *T. cruzi* infection (one or two serological techniques)?		
Conditional	1	In patients diagnosed with suspected chronic *T. cruzi* infection, use of the "diagnostic gold standard" is suggested, i.e. the combining of two serological tests with antigens that detect different antibodies against *T. cruzi* (ELISA, HAI, or IIF) plus a third test if there are conflicting results, in order to make a definitive diagnosis, which is better than a single serological technique. Quality of evidence on diagnostic accuracy: High/moderate ⊕⊕⊕◯
What is the best diagnostic strategy in the context of seroepidemiological surveys to identify patients with chronic Chagas disease?		
Strong	2	Use of the ELISA or ICT test is recommended for population studies on the prevalence of Chagas disease. Quality of evidence on diagnostic accuracy: High/moderate ⊕⊕⊕◯ *The strong recommendation is based on high certainty that both ELISA and ICT, as single tests, are easier to use in this scenario.*
What is the best diagnostic method for screening Chagas disease in hemotherapy services?		
Strong	3	Use of the ELISA test (highly sensitive kits) or CMIA is recommended to screen Chagas disease in hemotherapy services. Quality of the evidence: High/moderate Alta/moderada ⊕⊕⊕◯
How useful are the diagnostic methods in patients with suspected acute *T. cruzi* infection (congenital or recent)?		
Strong	4	In patients with suspected acute *T. cruzi* infection, it is recommended to perform direct parasitological tests (microhematocrit and direct observation) and any subsequent serological follow-up (acute congenital infection, starting at 8 months of age; seroconversion for other transmission modes). Quality of the evidence: Moderate ⊕⊕⊕◯
What is the safest, most effective therapeutic intervention for adult patients with chronic *T. cruzi* infection and no specific organ damage?		
Conditional	5	In adult patients with chronic *T. cruzi* infection and no specific organ damage, trypanocidal therapy is suggested. Quality of the evidence: Low ⊕⊕◯◯

Recommendation Grade	No.	Summary
What is the safest, most effective therapeutic intervention for pediatric patients with *T. cruzi* infection?		
Strong	6	In children with Chagas disease (chronic infection), trypanocidal therapy is recommended over no treatment. Quality of the evidence on parasiticidal effect: Moderate ⊕⊕⊕◯ *The strong recommendation is based on potential benefits in the context of a potentially catastrophic epidemiological situation.*
What is the safest, most effective therapeutic intervention for girls and women of childbearing age with *T. cruzi* infection?		
Strong	7	In women of childbearing age with Chagas disease (chronic infection), trypanocidal therapy is recommended over no treatment. Quality of the evidence: Moderate ⊕⊕⊕◯
What is the safest, most effective therapeutic intervention for adult patients with chronic *T. cruzi* infection and specific organ damage?		
Conditional	8	In adults with chronic *T. cruzi* infection who have suffered specific organ damage, we suggest NOT prescribing trypanocidal therapy. Quality of the evidence: Moderate ⊕⊕⊕◯
What is the safest, most effective therapeutic intervention for patients with acute /congenital *T. cruzi* infection?		
Strong	9	In patients with acute /congenital *T. cruzi* infection, trypanocidal therapy is recommended. Quality of the evidence on parasiticidal effect: Moderate ⊕⊕⊕◯ *The strong recommendation is based on potential benefits in the context of a catastrophic clinical situation.*
Of the available drugs, what is the best therapeutic intervention for patients with acute or chronic Chagas disease who are prescribed trypanocidal therapy?		
Conditional	10	In patients with acute or chronic Chagas disease who are prescribed trypanocidal therapy, either benznidazole or nifurtimox is suggested. Quality of the evidence: Very low ⊕◯◯◯

Introduction

Evidence-informed guidelines are currently one of the most useful tools to improve public health and clinical practice, offer interventions with solid efficacy testing, prevent unnecessary risks, use resources rationally, reduce clinical variability, and overall, improve health and ensure quality care, which is the raison d'être of health systems and services.

Guideline development using the methodology proposed by the GRADE Working Group (*Grading of Recommendations Assessment, Development and Evaluation*), is based on rigorous systematic reviews and the development of evidence tables and profiles. In addition to analyzing the quality of the evidence, the GRADE methodology includes the effectiveness of the recommended interventions and the balance between the desirable and undesirable consequences of these interventions, issues such as the values and preferences of the individuals or populations that benefit from them, the use of resources to implement the recommendations, and costs to the health system, among others.

This document, which follows the GRADE methodology, offers health professionals guidelines for managing patients with Chagas disease. Part one provides the theoretical framework, with details on the scope and objectives of the guidelines and the target population. In part two, the methodology used to develop the guidelines is described. Part three poses questions and offers recommendations to respond to them, supported by a summary of the panel's judgments. Part four contains strategies for updating and implementing the guidelines. The last section has additional information on the guideline development process (detailed description of the questions in PICO format, summary of findings tables, GRADE "from evidence to recommendations" tables with a subgroup analysis, and tables related to the validity of surrogate outcomes), as well as the list of members of the development group.


Photo: PAHO/WHO

I. Foreword

Chagas disease (American trypanosomiasis) is a neglected disease that is primarily known by clinicians for the difficulties and limitations involved in its diagnosis and etiological treatment.

When symptoms are suggestive of Chagas disease in its various stages, clinical suspicion or diagnosis is very infrequent, even in endemic areas. Among many other reasons, this is due to the insufficient training and information that doctors and health workers receive on this subject. Simply resorting to laboratory studies to confirm a diagnosis presents difficulties (availability, carrying out the study, and the resulting laboratory report), and it can be difficult to accurately interpret the results vis-à-vis the progression of the symptoms being analyzed.

In general, doctors and health workers know little or nothing about when etiological treatment is indicated and the results that can be expected, which leads to centralized referral of patients from their area of residence to specialized centers in urban capitals, with serious socioeconomic consequences for individuals and their families and communities.

The objective of these evidence-informed guidelines is to spell out the basic indications for the diagnosis and treatment of Chagas disease, in order to clarify the procedures and methods currently available for the proper care of people infected by *T. cruzi.*

Scope and users

These clinical practice guidelines provide evidence-informed recommendations for adult and pediatric patients exposed to or with a suspected or confirmed diagnosis of Chagas disease.

The recommendations are for health professionals (pediatricians, general practitioners, family doctors, gynecologists and obstetricians, among others) in charge of patients with Chagas disease.

The document is intended to be used by decision-makers and members of government agencies to facilitate the implementation process.

These guidelines do not include patient assessment and management issues related to pathophysiological symptoms and processes stemming from disorders and lesions associated with confirmed Chagas disease.

Theoretical framework and rationale

Chagas disease (American trypanosomiasis) is a chronic systemic vector-borne parasitosis that is endemic to the Americas but now has spread throughout the continent and even to other parts of the world due to the migration of populations infected by its agent, *Trypanosoma cruzi* (6).

In the Region of the Americas, an estimated six million people are infected (compared to about 30 million in 1990), with between 29,000 and 30,000 annual cases of vector-borne transmission (vs. 700,000 annual cases in 1990), plus some 8,000 annual cases of vertical transmission. Presently, about 70 million people (120 million in 1990) live in conditions that put them at risk of contracting the disease (7, 2). Between 20% and 30% of infected people develop lesions and cardiac or digestive disorders as a consequence of trypanosome infection (8). The estimated annual cost of treating these patients, often without a complete diagnosis, is US$627 million, with approximately 806,170 DALYs each year (3).

The 21 endemic countries of the Americas have launched a prevention and control response based on South-South cooperation between the countries (9): the Sub-regional Initiatives for Prevention, Control, and Treatment of Chagas disease (Southern Cone, Andean countries, Central America/Mexico, and Amazonian countries), together with the Technical Secretariat of PAHO, have made significant efforts to control household transmission of *T. cruzi* through its insect vectors (hematophagous triatomines [Order: Hemiptera] living in household habitats) and to screen blood bank donors to prevent transmission through blood transfusions.

In connection with WHO Resolution WHA66.12 (2013) (10), PAHO Resolution CD49.R19 (2009) (11) on neglected diseases, and PAHO Resolution CD50.R17 (2010) "Strategy and Plan of Action for Chagas Disease Prevention, Control and Care" (12), significant progress has been made in prevention and control: 17 of the 21 endemic countries have interrupted household vector-borne transmission of *T. cruzi* in part or all of their territories (13) and the national health systems of the 21 endemic countries have implemented universal screening to detect Chagas disease in blood donors (14).

Currently, Resolution CD55.R9, "Plan of Action for the Elimination of Neglected Infectious Diseases and Post-Elimination Actions 2016-2022," adopted by the 68th Session of the WHO Regional Committee for the Americas in 2016 (15), represents the framework of reference for the prevention, control, and treatment of Chagas disease among all neglected diseases.

Although the annual incidence and prevalence rates have fallen as a result of prevention and control measures and overall improvements to quality of life, the situation is troubling in terms of care, since it is estimated that only 1% of people infected by *T. cruzi* each year receive timely, proper diagnosis and treatment, due to a multitude of problems: ignorance on the part of health workers, the fact that it is a silent disease that affects rural populations, national health systems that rarely or never take regional diseases into consideration, or lack of access to diagnosis and treatment. Some progress has been made, but much remains to be done (16).

The purpose of these guidelines, developed by experts brought together by PAHO and using the GRADE methodology, is to serve as reference material that will contribute to more and better care for people infected by *Trypanosoma cruzi*.

Objectives and target population

These clinical practice guidelines were developed for the following purpose: describe the strategies, resources, and available capacities for the diagnosis, treatment, and follow-up of patients with Chagas disease in Latin America and the rest of the world.

How to use these guidelines

Each clinical question is followed by a group of recommendations and good practices with indications for the management of Chagas disease. Each recommendation shows the quality of the evidence based on the GRADE system:

Judgment	Description
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕◯	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low ⊕⊕◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low ⊕◯◯◯	Any estimate of effect is very uncertain.

Furthermore, the strength of each recommendation is indicated based on the GRADE system:

Strength of recommendation	Meaning
Strong for an intervention	The desirable effects clearly outweigh the undesirable effects. RECOMMENDED
Conditional or weak for an intervention	The desirable effects probably outweigh the undesirable effects. SUGGESTED
Conditional or weak against an intervention	The undesirable effects probably outweigh the desirable effects. NOT SUGGESTED
Strong against an intervention	The undesirable effects clearly outweigh the desirable effects. NOT RECOMMENDED

II. Methodology

This section is adapted from the evidence-informed guidelines template that can be found in the directive for strengthening national evidence-informed guidelines programs (17).

Composition of the development group

Thematic experts in Chagas disease were part of the development group. Annex 1 lists all members of the group.

Three groups participated in the development of the guidelines: First, the coordinating group (members of PAHO), which was in charge of organization, direction, and coordination; second, the group of experts, who were selected from well-known professionals with experience in the diagnosis, management, and treatment of Chagas disease and were responsible for: 1) devising relevant questions that should be answered; 2) helping the methodological team find and select evidence that would be used to answer the questions; 3) formulating recommendations to respond to the questions; 4) participating in the process of drafting the final document. Finally, the group of methodologists was selected at the request of specialized areas of PAHO and was in charge of: 1) providing methodological support to the group of experts when the questions were being formulated; 2) performing systematic reviews of the literature in order to compile the evidence required to answer the questions; 3) summarizing the evidence; 4) providing methodological support to the group of experts in order to formulate the recommendations; and 5) participating in the process of drafting of the final document.

Declaration of conflicts of interest

All members of the development group, the panel of experts, and the individuals that supported the experts and participated in the external review, signed a declaration of conflict of interest. The general coordinators of the guidelines reviewed all of the declarations to determine if there were any conflicts that could affect value judgments and recommendations. All of these individuals indicated that they had no conflicts of interest regarding the formulation of recommendations, are not involved as investigators in any current clinical trials on the disease, and have not received donations or gifts from any interest groups. In general, no conflicts were found that would bias the guideline recommendations. The analysis of conflicts appears in Annex 2.

Declaration of editorial independence

PAHO provided support during the development of this document to ensure the transferability and applicability of its content in a clinical setting. The guideline development group was independently responsible for scientific research and for formulating the recommendations.

Definition of the scope and objectives of clinical practice guidelines

PAHO defined the scope and objectives of these guidelines so that they would serve as support for health professionals and enable them to provide uniform medical care with quality, equity, and efficiency. After reviewing the pertinent literature, the development group drafted a document with the main topics and subtopics, objectives, background information, and the rationale for developing these clinical practice guidelines; heterogeneity in clinical practice was taken into consideration, as was the availability of new evidence, existence of new therapeutic options, the insufficient use of resources, and quality problems in practice derived from health care. The topics that are covered as well as those not covered, the guidelines' target population, and the key clinical aspects were also defined.

The objective of these guidelines is to update, organize, and assess PAHO's recommendations on the diagnosis and treatment of Chagas disease in order to encourage technical and scientific interaction on this issue in the countries of the Region.

This document gives the Member States and their partners the best available evidence for making decisions aimed at reducing the incidence, prevalence, morbidity, and mortality from Chagas disease, and contribute to the control of this neglected disease as a public health concern.

Decision on *de novo* development or adaptation

The quality and clinical relevance of existing guidelines was analyzed and it was determined that none of them could be adapted. It was therefore decided to develop the guidelines from scratch.

Formulation of clinical questions

The development group comprised of thematic experts and epidemiologists reviewed the relevant clinical aspects that should be addressed and formulated specific questions using the PICO format (population, intervention, comparison, and outcomes). The questions were formulated at an in-person meeting in Buenos Aires on 4 April 2017. The PICO questions can be found in Annex 3.

Identification and grading of the outcomes of clinical practice guidelines

The development group conducted an outcome prioritization exercise to determine which outcomes are significant and should be included. Clinical outcomes on safety, effectiveness, and quality of life were identified and prioritized, along with those that were important to patients.

Each outcome was classified as "critical," "important non-critical," and "unimportant" to patients, based on a scale of nine units as proposed by the GRADE group (18-20).

Evidence search and summary

Systematic reviews

The methodological team performed modified rapid systematic reviews for the purpose of compiling all evidence available to respond to the formulated questions. The search was structured in stages. In the first stage, the purpose was to find clinical practice guidelines and systematic reviews that answered questions that were the same or similar to those outlined in this document, in order to extract primary studies. All guideline citations and systematic reviews recovered were recorded and all potentially relevant primary studies were assessed, based on their title, to determine which should be included. The second stage of the search was designed to find primary studies that were not included in the guidelines and systematic reviews in the first stage. The inclusion of all relevant publications identified as primary studies was assessed. In the third stage, a list with all selected publications was sent to the group of experts who were asked to determine whether any relevant additional literature existed, besides the references that were found.

All studies identified by title and considered potentially relevant were simultaneously analyzed by two methodologists to decide if they should be included.

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All studies identified by title and considered potentially relevant were simultaneously analyzed by two methodologists to decide if they should be included. Any disagreements were resolved through discussion.

The universal search terms (for all stages and questions) were: (Chagas disease OR trypanosomiasis).

Depending on the stage and question, the following terms were added: "systematic;" "guidelines;" ("sensitivity" OR "specificity" OR "accuracy"); "randomized."

The criteria for selecting the studies were as follows:

- For diagnostic method accuracy: cross-sectional studies that compared the diagnostic method(s) with a reference technique (gold standard).
- For prevalence: observational studies that reported on prevalence.
- For efficacy and safety of therapeutic interventions: randomized controlled trials and prospective or retrospective observations that included a control group comprised of patients from the same initial population.
- For baseline risks: observational studies that reported on the risk of developing the outcome in question.

The publications considered relevant were synthesized in summary-of-findings tables following the GRADE assumptions (19, 20). To this end, the group of methodologists extracted and analyzed the information contained in the aforementioned publications as follows:

- To summarize the accuracy of the diagnostic methods, they extracted (when available) the rate of true positives, true negatives, false positives, and false negatives of each primary study. They meta-analyzed the results (sensitivity and specificity) through a bivariate model using the "reitsma" function of the R-package mada (21).
- To summarize the efficacy and safety of therapeutic interventions, the group meta-analyzed the relative risks with Review Manager Software (RevMan, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen), using the Mantel-Haenszel statistical method. In cases where it was not possible to obtain relative risks (e.g., no control group), we calculated the median or average incidence of each relevant outcome in each evaluated arm, as applicable.
- To summarize the baseline risks and prevalence rates, we used the median or average baseline risks or prevalence rates observed in the control arms of the studies with two arms or the median or average baseline risks or prevalence rates described in the observations of an arm, as applicable.

Evaluation of certainty in the body of evidence

The group of methodologists evaluated the evidence through the studies, separating the information by outcome evaluated, based on the criteria suggested by the GRADE Working Group (22). We define "certainty of the evidence" as our confidence that the desirable and undesirable consequences are within an interval that clearly justifies a recommendation in favor of or against a given intervention or management strategy (23).

Going from evidence to recommendations

To move from evidence to recommendations, the group of methodologists devised forms to facilitate the process (*evidence-to-decision frameworks*) based on the recommendations of the GRADE Working Group (24, 25). These forms included: 1) the question formulated in PICO format; 2) the summary of findings table constructed with the evidence that was found; 3) information on patient values and preferences; 4) information on the use of resources and costs; 5) information related to the feasibility of using the intervention, and equity.

The group of methodologists conducted a bibliographic search to identify additional relevant information pertaining to each of these aspects. The expert panel assessed the compiled evidence when discussing and defining the components that ultimately influenced each recommendation.

The group of experts issued a judgment for each aspect relevant to the recommendation to respond to each question. This judgment was made by group consensus and, if no consensus could be reached, the issue was decided by a show of hands. The results of each vote were recorded.

Based on the decisions made for each relevant aspect, the group of experts defined the recommendations. To do so, they had to decide on the direction (in favor of or against the intervention) as well the strength of the intervention (strong or weak), following the GRADE guidelines (25). As with the individual components, the strength and direction of each recommendation were decided by consensus; if it was not possible to reach a consensus, the decision was made by a show of hands, and the results of each vote were recorded. To define a recommendation as strong, at least 80% of the panel members needed to agree; if that percentage could not be reached, the recommendation was defined as conditional.

The GRADE methodology has two grades of strength for a recommendation: "strong" and "weak" (or "conditional"). After considering the balance between risks and benefits, the quality of the evidence, patient values and preferences, and the Latin American context, the strength of each recommendation was determined based on the following structure:

This situation led the panel, in some scenarios, to propose strong recommendations even in the absence of evidence with a moderate or high degree of certainty.

Strength of the recommendation	Meaning
Strong for an intervention	The desirable effects clearly outweigh the undesirable effects. RECOMMENDED
Conditional or weak for an intervention	The desirable effects probably outweigh the undesirable effects. SUGGESTED
Conditional or weak against an intervention	The undesirable effects probably outweigh the desirable effects. NOT SUGGESTED
Strong against an intervention	The undesirable effects clearly outweigh the desirable effects. NOT RECOMMENDED

The process of defining the strength of a recommendation included a lengthy discussion by the expert panel on the difficulty of conducting studies that contribute reliable information on the efficacy and safety of diagnostic and therapeutic interventions for Chagas disease. Due to the nature of the disease, clinical consequences may manifest decades after the time when the patients were infected by the parasite, so conducting controlled studies with sufficient follow-up is difficult and may even be unfeasible. This situation led the panel, in some scenarios, to propose strong recommendations even in the absence of evidence with a moderate or high degree of certainty.

Finally, it was verified that the expert panel agreed with the suggested recommendations and that these recommendations reflected the participants' views. At the meeting of the expert panel, a majority vote was obtained in the first round in each case.

Incorporation of issues related to costs, patient preferences, equity, and implementation

A review of the literature was conducted to identify studies that described issues related to costs, patient preferences and values, and the social aspects of Chagas disease. The information was summarized in narrative form and was included in the considerations.

If it was not possible to find evidence on these issues, the judgments were based on the experience and perceptions of members of the expert panel.

Inclusion of external evaluator observations

These clinical practice guidelines were independently reviewed by peer experts in methodology and thematic content.

III. Recommendations

Photo: PAHO/WHO

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What is the best strategy for diagnosing patients with suspected chronic *T. cruzi* infection?

Evidence summary

Interventions considered

Taking into account the available technologies, the expert panel determined that the interventions to be considered were: 1) enzyme-linked immunosorbent assay (ELISA): 2) immunochromatographic test (ICT); 3) chemiluminescent microparticle immunoassay (CMIA); and 4) diagnostic gold standard, i.e., the combining of two positive serological tests (ELISA, hemagglutination inhibition assay [HAI], or indirect immunofluorescence [IIF]), and potentially a third test if the results are conflicting, in order to make a definitive diagnosis.

Summary of the findings

Several studies on accuracy were identified that evaluate these diagnostic tests using the diagnostic gold standard of two positive serological tests. The degree of certainty regarding accuracy was high in the case of ELISA and CMIA, and moderate in the case of ICT. It should be pointed out that with both the ELISA and ICT tests, there is significant variability in the sensitivity intervals described in the individual studies, which appears to be based on the technique used in the case of ELISA, but is not so clearly explained in the case of ICT. In the absence of studies that directly evaluate the effect of diagnostic interventions on clinically relevant outcomes, this effect was estimated based on a model that considered the accuracy of the different interventions, the prognosis of untreated patients, and the effect of trypanocidal treatment. In this regard, the uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term organ damage (see Annex 9) resulted in a "low" degree of certainty regarding the effect of the different diagnostic interventions on clinical outcomes. The panel stressed that accurately identifying *T. cruzi*-infected individuals has other relevant benefits, such as reducing the risk of vector-borne or vertical transmission, which are difficult to quantify in this scenario.

Benefits and harms

Compared to the diagnostic gold standard, all of the diagnostic interventions evaluated are associated with harm related primarily to incorrectly classifying patients as healthy (false negatives), who would then remain exposed to the harmful effects of the disease if they do not receive treatment. With a prevalence of 26.3% (considered high for residents of an endemic area), the rate of patients who were incorrectly diagnosed as healthy would be 7 (CI 95%: 5 9) per 1,000 with ELISA, 17 (CI 95%: 11-24) per 1,000 with ICT, and 2 (CI 95%: 1-7) per 1,000 with CMIA. In addition, with a prevalence of 3.1% (as observed in blood donors in Argentina), the rate of patients incorrectly diagnosed as healthy would be 1 (CI 95%: 1-1) per 1,000 with ELISA, 2 (CI 95%: 1-3) per 1,000 with ICT, and less than 1 (CI 95%: 0-1) per 1,000 with CMIA (Annex 4, SoF 1-3). The results that compare the different diagnostic tests against each other suggest, with moderate to high certainty, that there are no substantial differences between the tests in terms of sensitivity (Annex 4, SoF 4-5).

Use of resources

Taking primarily into account the direct costs of the different interventions evaluated, and considering issues related to their use (quantity of reagents consumed due to the volume of tests requested), the panel judged that compared to the diagnostic gold standard, the ELISA test could entail moderate savings, while either of the other two interventions (ICT or CMIA) could entail a moderate increase in costs and accessibility problems due to the complexity and need for equipment and human resources.

Usability and impact on equity

The panel judged that implementation of the ELISA and ICT tests would likely have a positive impact on equity (reduced inequity), since both interventions are easier to use than the diagnostic gold standard in settings where there are disadvantaged populations. On the other hand, the CMIA test could potentially increase inequity, since it is an intervention with restricted access.

Balance between benefits and negative aspects

The panel concluded that the negative consequences that a smaller number of patients would be exposed to from having been incorrectly diagnosed (false negatives and false positives) outweighed the potential economic advantages and equity resulting from the use of the ELISA or ICT tests instead of the diagnostic gold standard.

Details on the expert panel's judgments can be found in Annex 5 (frameworks 1-3).

Additional considerations

- In contexts where resources or access to diagnosis are limited, ELISA could be administered as a single test. In the event of a positive result, the diagnosis should be confirmed by other tests before initiating treatment.
- The results of the analysis of the diagnostic accuracy of commercially available techniques (Annex 6) suggests that there could be significant variability between them (especially in the ELISA test), which should be taken into account when implementing these types of strategies.

1 Recommendation

It is suggested using the diagnostic gold standard, rather than ELISA, ICT, or CMIA as single isolated tests for patients with suspected chronic *T. cruzi* infection (conditional recommendation, based on a moderate-high degree of certainty regarding the accuracy of the different techniques evaluated).

What is the best method or strategy for screening Chagas disease in population studies?

Evidence summary and panel judgments

Interventions considered

Taking into account the available technologies, the expert panel determined that the interventions to be considered were: 1) ELISA; 2) ICT; 3) CMIA; and 4) the diagnostic gold standard, i.e., a combination of two serological tests (ELISA, HAI, or IIF) and potentially a third if the results are conflicting.

Summary of the findings

Several studies on diagnostic accuracy were identified that evaluate the above techniques, using as a reference the diagnostic gold standard of two positive serological tests. The degree of certainty regarding accuracy was moderate in the case of ELISA and ICT, and high in the case of CMIA. However, since there were no studies that directly evaluate the effect of the diagnostic interventions on clinically relevant outcomes, this effect was estimated based on a model that considered the accuracy of the different interventions, the prognosis of untreated patients, and the effect of trypanocidal treatment. The uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term organ damage (see Annex 9) led to the determination that certainty regarding the effect of the different diagnostic interventions on clinical outcomes was "low." The panel stressed that accurately identifying individuals infected by *T. cruzi* has other relevant benefits, such as reducing the risk of vector-borne or vertical transmission, which are difficult to quantify in this scenario.

Benefits and harms

Compared to the diagnostic gold standard, all of the diagnostic interventions evaluated are associated with harm, related primarily to incorrectly classifying patients as healthy (false negatives), who would then continue to be exposed to the harmful effects of the disease if they do not receive treatment. With a prevalence of 26.3% (considered high for residents of an endemic area), the rate of patients incorrectly diagnosed as healthy would be 7 (CI 95%: 5 9) per 1,000 with ELISA, 17 (CI 95%: 11-24) per 1,000 with ICT, and 2 (CI 95%: 1-7) per 1,000 with CMIA. In addition, with a prevalence of 3.1% (as observed in blood donors in Argentina), the rate of patients incorrectly diagnosed as healthy would be 1 (CI 95%: 1-1) per 1,000 with ELISA, 2 (CI 95%: 1-3) per 1,000 with ICT, and less than 1 (CI 95%: 0-1) per 1,000 with CMIA (Annex 4, SoF 1-3). The results that compare the different diagnostic tests against each other suggest, with moderate to high certainty, that are no substantial differences between them in terms of sensitivity (Annex 4, SoF 4-5).

Use of resources

Taking primarily into account the direct expenses of the different evaluated interventions, and considering aspects related to their use (quantity of reagents consumed due to volume of tests requested), the panel judged that compared to the diagnostic gold standard, the ELISA test could potentially entail substantial savings, while either of the other two interventions (ICT or CMIA) could involve a moderate increase in costs.

Usability and impact on equity

The panel judged that implementation of either the ELISA or ICT test would likely have a positive impact on equity (reduced inequity), since both interventions are easier to use than the diagnostic gold standard in contexts where there are technical disadvantages. On the other hand, the CMIA test could potentially increase inequity, since it is an intervention with restricted access.

Balance between benefits and negative aspects

In the context of seroepidemiological surveys, the panel concluded that the ease of use (ELISA and ICT) and lower cost (ELISA) of the interventions outweighed the negative consequences of incorrectly classifying a smaller number of screened patients.

Details on the expert panel's judgments can be found in Annex 5 (frameworks 1-3).

2 Recommendation

It is recommended using the ELISA or ICT test in population studies on the prevalence of Chagas disease (strong recommendation, based on a moderate-high degree of certainty on the accuracy of the different interventions evaluated). The strong recommendation is based on the fact that there is a high degree of certainty that both the ELISA and ICT, as single tests, are easier to implement in this scenario.

What is the best method or strategy for screening Chagas disease in hemotherapy services?

Evidence summary and panel judgments

Interventions considered

Taking into account the available technologies, the expert panel determined that the interventions to be considered were: 1) ELISA; 2) ICT; 3) CMIA; and 4) diagnostic gold standard, i.e., the combining of two serological tests (ELISA, HAI, IIF) and potentially a third if the results are conflicting.

Summary of the findings

Several studies on diagnostic accuracy were identified that evaluate the interventions using as a reference the diagnostic gold standard of two serological tests. The degree of certainty regarding accuracy was moderate in the case of ELISA and ICT, and high in the case of CMIA. In this scenario, in which the most relevant outcome is preventing transfusion transmission, the certainty regarding the accuracy of the complementary methods was considered an appropriate surrogate outcome.

Benefits and harms

Compared to the diagnostic gold standard, all of the interventions evaluated are associated with harm, related primarily to incorrectly classifying patients as healthy (false negatives), which would result in a greater likelihood of transfusion transmission of the disease. With a prevalence of 3.1% (estimated population prevalence in blood donors in Argentina), the rate of patients incorrectly diagnosed as healthy would be 1 (CI 95%: 1-1) per 1,000 with ELISA, 2 (CI 95%: 1 3) per 1,000 with ICT, and less than 1 (CI 95%: 0-1) per 1,000 with CMIA (SoF 1-3). The results that compare the different diagnostic tests against each other suggest, with moderate to high certainty, that there are no substantial differences between them in terms of sensitivity (SoF 4, 5). The panel stressed that there is significant variability in the accuracy of the different commercial ELISA kits (Annex 6), but hemotherapy services are frequently able to procure highly sensitive kits and are part of diagnostic quality control networks.

Use of resources

Taking primarily into account the direct expenses of the different interventions evaluated, and considering issues related to their use (quantity of reagents consumed due to the volume of tests requested), the panel judged that compared to the diagnostic gold standard, the ELISA and CMIA tests could potentially entail substantial savings, while the ICT could entail a moderate increase in costs.

Usability and impact on equity

In this scenario where the interventions in question would be implemented in hemotherapy services, the panel considered that there are no relevant factors regarding usability or equity issues.

Balance between benefits and negative aspects

The panel placed high value on preventing transfusion transmission of the disease, which is why it considered that the CMIA, diagnostic gold standard, and ELISA tests could be implemented (ELISA would only be used if high sensitivity kits can be obtained). Furthermore, in this scenario where a very large number of tests have to be conducted, they recommended that the advantages of administering a single test (ELISA or CMIA) would be highly relevant in terms of resource savings.

Details on the expert panel's judgments can be found in Annex 5 (frameworks 1-3).

3 Recommendation

It is recommended using ELISA (highly sensitive kits) or CMIA for screening chronic *T. cruzi* infection in hemotherapy services (strong recommendation, based on a high-moderate degree of certainty on the effects of the intervention).

q.4

What is the best diagnostic strategy for patients with suspected acute *T. cruzi* infection transmitted congenitally or otherwise?

Evidence summary and panel judgments

Interventions considered

Taking into account the available technologies, the expert panel determined that the interventions to be considered were: 1) direct parasitological examinations (microhematocrit and direct observation); 2) hemocultures; and 3) diagnostic gold standard, i.e., serological follow-up (ELISA, HAI, IIF) in the case of suspected congenital infection, starting at 8 months of age; or seroconversion, in the case of suspected acute infection with another mode of transmission.

Summary of the findings

Several studies of diagnostic accuracy were identified that evaluate the interventions in question using as reference the diagnostic gold standard of serological follow-up. The degree of certainty regarding accuracy was low when comparing direct observation with the diagnostic gold standard, and moderate when comparing the microhematocrit test or hemocultures with the diagnostic gold standard. Despite uncertainty (low certainty of the evidence) regarding the magnitude of the treatment's impact on the risk of long-term organ damage (see Annex 9), existing information on the accuracy of the tests in this scenario (moderate certainty that the available tests have very low sensitivity) was considered an appropriate surrogate outcome.

Benefits and harms

Compared to the diagnostic gold standard, all of the interventions evaluated are associated with harm, related primarily to incorrectly classifying patients as healthy (false negatives), which would result in a greater likelihood of long-term organ damage as a consequence of incorrect diagnosis. With a prevalence of 4.7% (congenital transmission resulting from combining several studies in meta-analysis), the rate of patients incorrectly diagnosed as healthy would range from 8 to 34 per 1,000 with the microhematocrit test, 9 (CI 95%: 3 23) per 1,000 with direct observation, and 21 (CI 95%: 13-30) per 1,000 with hemocultures (Annex 4, SoF 6-8).

Use of resources

Considering that direct parasitological tests are low-cost and accessible, the panel judged that using it in lieu of the diagnostic gold standard would entail savings by lowering direct costs. However, the negative consequences of incorrectly diagnosing patients as healthy could entail significant indirect costs, which led to the conclusion that the interventions' impact on costs is difficult to estimate.

Usability and impact on equity

The panel determined that the use of simple, accessible diagnostic tests (microhematocrit and direct observation) in lieu of other more complex tests (serological follow-up or hemocultures) could potentially reduce inequity.

Balance between benefits and negative aspects

The panel concluded that the negative consequences that a significant number of patients would be exposed to from having been incorrectly diagnosed (false negatives) outweighed potential economic advantages, as well as the equity that would result from using direct parasitological tests as a single isolated test, instead of combining these techniques with the diagnostic gold standard.

Details on the expert panel's judgments can be found in Annex 5 (Framework 4).

Additional considerations

- Some studies suggest that in asymptomatic patients with suspected congenital transmission (child of a mother who is a carrier of *T. cruzi*), the parasitemia peak could occur 20-30 days after birth, which means that the serial use of parasitological tests could improve the detection of infected individuals.
- Given the low sensitivity of direct parasitological tests, in patients with suspected non-congenital acute infection, the use of serial parasitological tests could increase the detection of infected individuals.
- The recommendation is valid for immunosuppressed patients with suspected reactivation.

4 Recommendation

It is recommended direct parasitological tests (microhematocrit and direct observation) and subsequent serological follow-up (acute congenital infection, starting at 8 months of age; seroconversion for other transmission modes) in patients with suspected acute *T. cruzi* infection (strong recommendation, based on moderate degree of certainty on the effects of the intervention).

Should trypanocidal treatment be prescribed for adults with chronic *T. cruzi* infection and no specific organ damage?

q.5

Evidence summary and panel judgments

Summary of the findings

Several observational studies were found that describe the impact of trypanocidal treatment on clinically relevant outcomes such as death or the development of heart disease. A single randomized study describes the intervention's efficacy in this subpopulation and presents the short-term negativization of parasitemia as the sole outcome. In addition, there are randomized studies that evaluate the negativization of parasitemia in adults with specific organ damage and serological negativization in pediatric patients. In terms of the intervention's negative aspects, four randomized studies were included on the subject of interrupting treatment due to adverse effects in patients with Chagas disease in general.

The overall certainty in the body of evidence was deemed low (very low with regard to mortality; low with respect to the development of heart disease and serological negativization; moderate with regard to the negativization of parasitemia; and high with regard to interruption of treatment because of adverse effects) due to the risk of bias (observational studies), imprecision, and inconsistency.

Benefits and harms

The analyzed body of evidence shows that trypanocidal treatment could reduce the risk of the long-term development of heart disease (OR, 0.38; CI 95%: 0.18 0.78). It is not possible to determine the impact on mortality, since the certainty of the evidence regarding this outcome was very low. The intervention probably substantially increases the likelihood of negativizing short-term parasitemia (RR, 1.44; CI 95%: 1.21 1.72) and possibly long-term serology (OR, 3.32; CI 95%: 1.4-7.8). The treatment is associated with an increase in the risk of adverse effects, leading to interruption of treatment (RR, 5.71; CI 95%: 2.46-13.29), with an average incidence of 3.33% in the control arm and 16.20% in the intervention arm. Only a minority of the adverse effects associated with the intervention are classified as serious (Annex 4, SoF 9). The panel considered that the vast majority of well-informed patients would potentially place more value on the potential benefits of the intervention than the negative aspects, including adverse effects and the stigma of being seen as sick as a result of accepting the treatment.

Use of resources

The panel assumed that the direct costs of the treatment are not excessive. Given the potential savings from less development of specific organ damage, the panel judged that the intervention is probably associated with moderate savings.

Usability and impact on equity

The panel agreed that there is a disadvantaged population (socioeconomically and geographically) that has a greater likelihood of benefiting if it receives trypanocidal treatment (the likelihood of suffering specific organ damage appears to be greater in this subpopulation). However, this group of patients is less likely to have access to treatment.

Balance between benefits and negative aspects

The panel concluded that the reduction of the parasitic burden and the potentially substantial benefits in terms of clinically relevant outcomes (specific organ damage) outweighed the negative aspects of the intervention (severe or serious adverse effects that are exceptional, and stigmatization).

Details on the expert panel's judgments can be found in Annex 5 (Framework 5).

Additional considerations

- Some patients and physicians may give more weight to the negative aspects of the intervention (adverse effects, stigmatization) than to potential benefits and may choose to not follow treatment. We suggest engaging in a joint decision-making process to discuss the potential benefits and harms of the intervention.
- In immunosuppressed patients (HIV coinfection, transplantation, immunosuppressive treatments), the potential benefits could be considerably greater: prevention of flare-ups (observed average rate of reactivation of 27.86%; Annex 7) and the consequences thereof. This should be explained when making the decision.
- Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
- Patients should be periodically monitored on a regular and ongoing basis.

5 Recommendation

It is suggested prescribing trypanocidal treatment for adult patients with chronic *T. cruzi* infection and no specific organ damage (conditional recommendation, based on low certainty regarding the effects of the intervention).

Should trypanocidal treatment be prescribed for children with chronic *T. cruzi* infection?

q.6

Evidence summary and panel judgments

Summary of the findings

Two randomized studies were found that describe the impact of trypanocidal treatment on different outcomes. Only one of them evaluates the development of heart disease (such as electrocardiographic abnormalities), but no events are reported in either of the two arms. The other efficacy outcomes are serological negativization and the negativization of parasitemia.

Although the certainty of the evidence on parasitemic and serological negativization and adverse effects was deemed moderate, the overall certainty in the body of evidence was deemed low due to imprecision and indirect information, since there was no information on the intervention's direct impact on clinically relevant outcomes (death or the development of specific organ damage).The level of certainty on the validity of the evaluated efficacy outcomes (negativization of parasitemia and serology) as surrogates for clinically relevant outcomes (development of heart disease or death) is low, due to the absence of reliable evidence on the association between the two and the potential magnitude of such association (Annex 9).

Benefits and harms

The body of evidence analyzed shows that trypanocidal treatment may substantially increase the likelihood of negativizing serology (RR, 2.41; CI 95%: 1.16 5.02) and parasitemia (RR, 1.69; CI 95%: 1.33-2.16). This could lead to significant benefits in terms of reducing specific organ damage. No increase in the risk of adverse effects was observed (RR, 0.55; CI 95%: 0.22-1.41) (Annex 4, SoF 10). The panel considered that the vast majority of well-informed patients would place more value on the potential benefits of the intervention than on its negative aspects, including adverse effects (apparently less frequent than in adults) and the stigma of being seen as sick as a result of accepting the treatment.

Use of resources

The panel assumed that the direct costs of the treatment are not excessive. Given the potential savings from less development of specific organ damage, the panel judged that the intervention is probably associated with moderate savings.

Usability and impact on equity

The panel agreed that there is a disadvantaged population (socioeconomically and geographically) that has a greater likelihood of benefiting if it receives trypanocidal treatment (the likelihood of suffering specific organ damage appears to be greater in this subpopulation). However, this group of patients is less likely to have access to treatment.

Balance between benefits and negative aspects

The panel accepted that a reduction in the parasitic burden and the potentially substantial benefits of clinically relevant outcomes (specific organ damage) outweighed the intervention's negative aspects (adverse effects, stigmatization). Despite the aforementioned limitations in the body of evidence, the panel decided to make a strong recommendation, with the understanding that this does not strictly adhere to the methodology used to develop the guidelines (GRADE methodology). The reasons for this decision are explained below:

- The significant impact on surrogate outcomes (negativization of serology and parasitemia) suggests that there are probably long-term clinical benefits even in the absence of direct tests (there are no studies with long-term follow-up).
- The intervention is probably not associated with significant adverse effects.
- Chagas disease is endemic to a significant part of Latin America and severely affects a large proportion of the population, especially people at socioeconomic and geographical disadvantage. In this context, even in the absence of reliable evidence on the benefits of the treatment, population measures have been adopted and are being adopted to improve the situation (e.g., programs to detect and treat Chagas disease in the field). The panel suggest that a conditional recommendation could be interpreted in a way that could endanger the adequate development and continuity of these measures.
- The experts all agree that serological negativization implies adequate therapeutic response.

Details on the expert panel's judgments can be found in Annex 5 (Framework 6).

Additional considerations

- Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
- Patients should be periodically monitored on a regular and ongoing basis.

6 Recommendation

It is recommended prescribing trypanocidal treatment for children with chronic *T. cruzi* infection (strong recommendation, based on moderate certainty regarding the parasiticidal effects (negativization of antibodies) and low certainty regarding the intervention's effects on clinical outcomes). The strong recommendation is essentially based on the experts' consensus that serological negativization is equivalent to a therapeutic response.

Should trypanocidal treatment be prescribed to prevent vertical transmission in girls and women of childbearing age with chronic *T. cruzi* infection?

q.7

Summary of evidence and panel judgments

Summary of the findings

Although the population of girls and women of childbearing age is included in the subpopulations evaluated in other questions in this document (adults with and without specific organ damage or children), the panel considered that, in this scenario, there is an additional potential benefit in terms of preventing vertical transmission. Therefore, to answer this question, the panel focused on that outcome and the possible adverse effects on mothers and newborns. Four comparative observational studies were found that describe the impact of trypanocidal treatment on the probability of vertical transmission of Chagas disease. There is also a study that evaluates the vertical transmission rate in 15 women with chronic Chagas disease who had been treated with benznidazole or nifurtimox (26). In terms of the intervention's negative aspects, six randomized studies were included that describe withdrawal from the treatment due to adverse effects in patients with Chagas disease in general, and four observational studies were included that report adverse fetal effects.

Overall certainty in the body of evidence was deemed moderate despite having come from observational studies, since a major effect was observed.

Benefits and harms

The body of evidence analyzed shows that trypanocidal treatment probably substantially decreases the likelihood of vertical transmission (OR, 0.07; CI 95%: 0.02 0.3). The treatment was associated with an increased risk of adverse effects that lead to withdrawal from treatment, but no adverse fetal or neonatal effects (Annex 4, SoF 11) were observed. The panel recommended that all or nearly all well-informed women and girls would place more value on the potential benefits of the intervention than on its negative aspects.

Use of resources

The panel assumed that the direct costs of the treatment are not excessive. Given the potential savings from a lower rate of congenital transmission, the panel judged that the intervention is probably associated with moderate savings.

Usability and impact on equity

The panel agreed that there is a disadvantaged population (socioeconomically and geographically) that is more likely to benefit if it receives trypanocidal treatment (the likelihood of suffering specific organ damage appears to be greater in this subpopulation). However, this group of patients is less likely to have access to treatment.

Balance between benefits and negative aspects

The panel considered that the possibility of significantly reducing vertical transmission outweighed the negative aspects of the intervention (adverse effects).

Details on the expert panel's judgments can be found in Annex 5 (Framework 7).

Additional considerations

- Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
- The treatment is administered exclusively to women of childbearing age who are not pregnant, and pregnancy must be ruled out before initiating trypanocidal treatment.
- Girls and women should be periodically monitored on a regular and ongoing basis.
- Chagas disease should be included among the vertically transmitted diseases that should be monitored in women of childbearing age.

7 Recommendation

It is recommended prescribing trypanocidal treatment in girls and women of childbearing age with chronic *T. cruzi* infection (strong recommendation, based on moderate certainty regarding the intervention's effects).

Should trypanocidal treatment be prescribed for adults with chronic *T. cruzi* infection and specific organ damage?

q.8

Evidence summary and panel judgments

Summary of the findings

One randomized study was found that describes the impact of trypanocidal treatment on clinically relevant outcomes (death or the development of heart disease) and negativization of parasitemia. In terms of the intervention's negative aspects, four randomized studies were included that describe withdrawal from treatment due to adverse effects in patients with Chagas disease in general.

The overall certainty in the body of evidence was deemed moderate due to imprecision (moderate regarding death and the progression of heart disease, and high with regard to the negativization of parasitemia and withdrawal due to adverse effects).

Benefits and harms

The body of evidence analyzed shows that trypanocidal treatment most likely does not have a significant impact on death (OR, 0.94; CI 95%: 0.78 1.14) or the progression of heart disease (OR 0.88; CI 95%: 0.67-1.15), and probably increases the negativization of parasitemia evaluated through PCR (RR, 1.98; CI 95%: 1.7.5-2.24). The treatment is associated with an increased risk of adverse effects that leads to withdrawal (RR, 5.71; CI 95%: 2.46-13.29), with an average incidence of 3.33% in the control arm and 16.20% in the intervention arm. Only a minority of the adverse effects related to the intervention were classified as serious (Annex 4, SoF 12). The panel considered that there was probably significant variability in the patients' assessment of the intervention's effects: some may give greater weight to the possibility, regardless of how small, of obtaining benefits, while the majority would potentially prefer not to be exposed to the adverse effects of the intervention.

Use of resources

In the absence of significant benefits in terms of clinically relevant outcomes, the panel considered adequate that prescribing treatment in this patient subgroup could potentially result in a moderate increase in costs.

Applicability and impact on equity

The panel estimated that the resources used to treat patients with specific organ damage could be allocated to other populations with a greater probability of obtaining benefits.

Balance between benefits and negative aspects

The panel concluded that the negative aspects of the intervention (adverse effects, increased costs, greater inequity) outweighed potential marginal benefits in terms of the progression of heart disease and mortality. The panel rated the strength of the recommendation as conditional, considering the close balance between benefits and harms, and potential variability in patient values and preferences.

Details on the expert panel's judgments can be found in Annex 5 (Framework 8).

Additional considerations

- Some patients and physicians may give more weight to the potential benefits (regardless of how small) and choose to follow treatment. We suggest engaging in a joint decision-making process to discuss the potential benefits and harms of the intervention.
- In immunosuppressed patients (HIV coinfection, transplantation, immunosuppressive treatments), the potential benefits could be considerably greater: prevention of flare-ups (observed average rate of reactivation of 27.86%; Annex 7) and the consequences thereof). This should be explained when making the decision.
- Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
- Patients should be periodically monitored on a regular and ongoing basis.
- A comprehensive therapeutic approach where these patients will receive adequate therapeutic support for heart disease is assumed.

8 Recommendation

It is not recommended prescribing trypanocidal treatment for adult patients with chronic *T. cruzi* infection and specific organ damage (conditional recommendation, based on moderate certainty regarding the effects of the intervention).

Should trypanocidal treatment be prescribed for patients with acute/congenital *T. cruzi* infection?

q.9

Evidence summary and panel judgments

Summary of the findings

Acute *T. cruzi* infection has been treated with available drugs since the 1960s and 1970s. In the early stages, impressive benefits were observed in terms of symptomatic improvement (expert observation) and negativization of serology (a study published in 1969 that compared the serological evolution of 151 patients with acute *T. cruzi* infection who were treated with benznidazole or a placebo), which made antiparasitic drugs the therapeutic standard in this scenario. For this reason, the body of the available evidence only includes a few comparative studies that report impressive benefits in terms of outcomes related to parasitic burden. In addition, there are several observations in a single arm that describe a very high incidence of negativization of parasitemia and serology compared to what could be expected in patients who did not receive timely treatment (close to 0%).

The overall certainty in the body of evidence was deemed moderate with regard to the negativization of serology because of a risk of bias (observational studies or clinical trials with serious methodological problems) and the very large magnitude of the observed effect. However, the certainty in the overall body of evidence was very low, since we cannot find comparative studies (trypanocidal compared to a control) that describe the intervention's effect on clinical outcomes. The level of certainty regarding the validity of the evaluated outcomes (negativization of parasitemia and serology) as surrogates for clinically relevant outcomes (development of heart disease or mortality) is low, due to the absence of reliable evidence on the association between the two and the potential magnitude of such association (Annex 9).

Benefits and harms

The body of evidence analyzed shows that trypanocidal treatment most likely substantially increases the probability of negativizing parasitemia (negativization rate between 74.7% and 89.6%) and serology (RR, 25.5; CI 95%: 2.7 3.7; negativization of serology rate, 50.3%-60%). These effects could entail significant benefits in terms of reducing the development of specific organ damage (Annex 4, SoF 13). Furthermore, the panel considered that the treatment in this scenario probably has a positive impact on symptomatic control, although this outcome is not sufficiently evaluated in the above studies. Serious adverse effects were exceptional (see Annex 8). The panel agreed that acute Chagas disease infection is potentially catastrophic, since it is associated with a high mortality rate of nearly 5% (27), and because nearly 100% of untreated patients progress to the chronic phase. Therefore, the panel judged that the potential benefits of the treatment are significant. It recommended that the vast majority of well-informed patients would possibly place more value on the potential benefits of the intervention than its negative aspects.

Use of resources

The panel judged that the direct costs of the treatment are not excessive. Given the potential savings from less development of specific organ damage, the panel determined that the intervention is probably associated with significant savings.

Usability and impact on equity

The panel agreed that there is a disadvantaged population (socioeconomically and geographically) that is more likely to benefit if it receives trypanocidal treatment (the likelihood of suffering specific organ damage appears to be greater in this subpopulation). However, this group of patients is less likely to have access to treatment.

Balance between benefits and negative aspects

The panel interpreted the observed results on the negativization of parasitemia and serology as surrogate markers of potential benefits in terms of clinically relevant outcomes (death, chronic infection, specific organ damage) in the context of a potentially catastrophic clinical situation. Therefore, it acknowledged that the possibility of obtaining these benefits outweighed the intervention's negative aspects (adverse effects, stigmatization).

Details on the expert panel's judgments can be found in Annex 5 (Framework 9).

Additional considerations

- Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
- Patients should be periodically monitored on a regular and ongoing basis.

9 Recommendation

We recommend prescribing trypanocidal treatment for patients with acute / congenital *T. cruzi* infection (strong recommendation, based on moderate certainty regarding the parasiticidal effects of the intervention (negativization of antibodies) and on very low certainty regarding the effect on clinical outcomes). The strong recommendation is based on the possibility of obtaining benefits in the context of a catastrophic clinical situation.

What is the best option for patients who will begin trypanocidal treatment?

q.10

Evidence summary and panel judgments

Interventions considered

Given the available medications and the panel members' experience with these drugs, the alternatives considered were: 1) benznidazole; 2) nifurtimox.

Summary of the findings

In the context of acute *T. cruzi* infection, we did not find any randomized studies that directly compare the two interventions.

The overall certainty in the body of evidence was deemed very low, since the information comes from observational studies that did not adjust for confounding variables.

In the context of chronic *T. cruzi* infection, we found one controlled study and several observations where treatment arms that received benznidazole and nifurtimox were included.

The overall certainty of the evidence was deemed low or very low due to a risk of bias and imprecision, since most of the information comes from observational studies.

Benefits and harms

The body of evidence analyzed shows that both benznidazole and nifurtimox have been used in several research studies that support the recommendations formulated to answer questions 5 to 9. However, the certainty in the body of evidence in terms of comparing the two drugs is very low, so there is uncertainty regarding differences in their relative efficacy (Annex 4, SoF 14, 15). In terms of adverse effects, based on the evidence that was found (Annex 8) and the panel members experience, it was determined that there are no substantial differences between the two drugs. However, it was stressed that each drug has different side

effect profiles: nifurtimox is associated with weight loss and adverse psychiatric effects, while benznidazole is associated with cutaneous and neurological reactions.

Use of resources

Both pharmacotherapies have a similar direct cost.

Balance between benefits and negative aspects

The panel based the recommendation on the existing uncertainty regarding differences in the efficacy of the evaluated interventions.

Details on the expert panel's judgments can be found in Annex 5 (Framework 10).

Additional considerations

- There are studies underway that will provide new pharmacokinetic data for identifying the most appropriate timing and dosage regimens.

10 Recommendation

It is suggested prescribing either benznidazole or nifurtimox to patients with Chagas disease (acute or chronic infection) who will follow trypanocidal treatment (conditional recommendation, based on very low certainty regarding differences in the effects of the evaluated pharmacotherapies).

Updating the guidelines

The recommendations made in these guidelines should be updated in the next four years or sooner if there is new evidence that would change the recommendations formulated herein.

IV. Implementation plan

Actors responsible for implementing the clinical practice guideline recommendations

1. Recognition and use of the guidelines -- the National Health System Directorates (NHS) in each country.
2. Dissemination of the guidelines -- administrative and technical units of the SNS health institutions.
3. Availability of materials -- the offices of primary care authorities and the respective focal points at other levels.
4. Dissemination of the guidelines with the support of the Directorates -- health education and training institutions.

Implementation barriers

- Human resources
- Awareness of the guidelines
- Lack of supplies
- Access

Implementation strategies

- Training
- Development of materials
- Digital reminders in clinical histories
- Support policies
- Electronic systems to support decision-making
- Auditing and feedback
- Traditional distribution
- Administrative support

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ANNEXES

Annex1

Development group

To develop evidence-based guidelines for the diagnosis and treatment of Chagas disease, a multidisciplinary team was created to help formulate recommendations following the highest methodological standards.

Thematic team

- Dr. Roberto Chuit, Director of the Epidemiology Institute of the National Academy of Medicine, (Buenos Aires, Argentina).
- Dr. Alejandro Luquetti, Former head of the Laboratory for Research on Chagas Disease, Hospital das Clínicas, Goiás Federal University (Goiania, Brazil).
- Dr. Jaime Altcheh, Director of the Parasitology and Chagas Disease Unit, Dr. R. Gutiérrez Children's Hospital (Buenos Aires, Argentina).
- Dr. Faustino Torrico, Director of the Chagas Disease Platform, University of San Simón (Cochabamba, Bolivia).
- Dr. Juan Carlos Villar, Associate Professor, Faculty of Health Sciences, Preventive Cardiology Group, Autonomous University of Buracamanga; Research associate, Department of Research, Child Heart Foundation, Institute of Cardiology, Bogotá (Colombia).
- Dr. Roberto Salvatella, Regional Advisor on Chagas Disease, PAHO/WHO.

Methodological team

- Dr. Ariel Izcovich, Clinical Medicine Unit, Hospital Alemán de Buenos Aires.
- Dr. Juan Martín Criniti, Clinical Medicine Unit, Hospital Alemán de Buenos Aires.

Expert panel

Name	Specialty	Position	Affiliation
Ariel Izcovich	Clinical physician	Methodological team	Hospital Alemán de Buenos Aires
Juan Martín Criniti	Clinical physician	Methodological team	Hospital Alemán de Buenos Aires
Roberto Chuit	Cardiologist/epidemiologist	Thematic team	National Academy of Medicine (Argentina)
Alejandro Luquetti	Immunologist	Thematic team	Laboratory for Research on Chagas Disease Hospital das Clínicas Goiás Federal University (Brazil)
Jaime Altcheh	Pediatrician	Thematic team	Director of the Parasitology and Chagas Disease Unit, Dr. R. Gutiérrez Children's Hospital, (Buenos Aires, Argentina)
Faustino Torrico	Cardiologist	Thematic team	University of San Simón, Cochabamba (Bolivia)
Juan Carlos Villar	Preventive cardiologist / Clinical epidemiologist	Thematic team	Autonomous University of Buracamanga and Child Heart Foundation, Institute of Cardiology (Colombia)
Roberto Salvatella	Medical parasitologist/ Public health expert	Thematic team	PAHO/WHO

Annex2

Summary of Conflicts of Interest

The following table summarizes the analysis of the conflict of interest declarations signed by each member of the development group, as well as the decision made by the leaders.

Name	Role in the guidelines	A. Specific and/ or nonspecific personal financial interest	B. Specific and/or nonspecific nonpersonal financial interest	C. Personal nonfinancial interest	D. Specific and/or nonspecific personal financial interest of a family member	Any other circumstances that could affect the person's objectivity or independence in the process?
Ariel Izcovich	Methodologist	No	No	No	No	No
Juan Martín Criniti	Methodologist	No	No	No	No	No
Roberto Chuit	Expert	No	No	No	No	No
Alejandro Luquetti	Expert	No	No	No	No	No
Jaime Altcheh	Expert	No	No	No	No	No
Faustino Torrico	Expert	No	No	No	No	No
Juan Carlos Villar	Expert/ Methodologist	No	No	No	No	No
Roberto Salvatella	Expert	No	No	No	No	No

Annex3

PICO Questions

Diagnosis

What is the best diagnostic strategy for patients with suspected chronic *T. cruzi* infection?

1

- **Population:** Adults or children with suspected *T. cruzi* infection.
- **Assay index:** ELISA with total or recombinant antigen, immunochromatography (ICT), chemoluminescence (CMIA).
- **Diagnostic gold standard:** The combining of two serological tests with antigens that detect different antibodies against *T. cruzi* (ELISA, HAI, or IIF), and a third test if the results are conflicting, in order to make a definitive diagnosis.
- **Outcome:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), true positives (TPs), false positives (FPs), true negatives (TNs), false negatives (FNs).

What is the best diagnostic strategy in the context of seroepidemiological surveys to identify patients with *T. cruzi* infection?

2

- **Population:** Adults or children living in an area where Chagas disease is endemic.
- **Assay index:** ELISA with total or recombinant antigen, immunochromatography, chemoluminescence.
- **Diagnostic gold standard:** The combining of two serological tests with antigens that detect different antibodies against *T. cruzi* (ELISA, HAI, or IIF), and a third test if the results are conflicting, in order to make a definitive diagnosis.
- **Outcome:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), TPs, FPs, TNs, FNs.

What is the best diagnostic method for screening Chagas disease in hemotherapy services?

3

- **Population:** Blood donors.
- **Assay index:** ELISA with total or recombinant antigen, immunochromatography, chemoluminescence.
- **Diagnostic gold standard:** The combining of two serological tests with antigens that detect different antibodies against *T. cruzi* (ELISA, HAI, or IIF), and a third test if the results are conflicting, in order to make a definitive diagnosis.
- **Outcome:** Transfusion transmission, TPs, FPs, TNs, FNs.

4 What is the best diagnosis method for patients with suspected acute *T. cruzi* infection (congenital or acute phase)?

- **Population:** Adults, children, or newborns with suspected acute or congenital Chagas disease.
- **Assay index:** Direct parasitology (fresh, Strout and/or microhematocrit concentration methods, slide smear, thick blood film); indirect parasitology (hemoculture, xenodiagnosis, inoculation in susceptible animal).
- **Diagnostic gold standard:** Serological follow-up, seroconversion.
- **Outcome:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), TPs, TNs, FPs, FNs.

Treatment

5 What is the best therapeutic intervention for adult patients with chronic Chagas disease and no specific organ damage?

- **Population:** Adults with chronic *T. cruzi* infection and no specific organ damage (heart disease or gastrointestinal pathology).
- **Intervention:** Trypanocidal treatment.
- **Comparator:** Absence of trypanocidal treatment.
- **Outcomes:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), negativization of parasitemia (percentage of patients with negative parasitemia in 1 2 months), negativization of serological tests (percentage of patients with negative serological tests in 2-3 years), adverse effects.

6 What is the best therapeutic intervention for pediatric patients with chronic Chagas disease?

- **Population:** Children with chronic *T. cruzi* infection.
- **Intervention:** Trypanocidal treatment.
- **Comparator:** Absence of trypanocidal treatment.
- **Outcomes:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), negativization of parasitemia (percentage of patients with negative parasitemia in 1-2 months), negativization of serological tests (percentage of patients with negative serological tests in 2-3 years), adverse effects.

7 What is the best therapeutic intervention for girls and women of childbearing age with chronic *T. cruzi* infection?

- **Population:** Women of childbearing age with chronic *T. cruzi* infection.
- **Intervention:** Trypanocidal treatment outside of pregnancy.
- **Comparator:** Absence of trypanocidal treatment.
- **Outcomes:** Vertical transmission, adverse fetal effects (this analysis is in addition to what is included in other questions related to adult patients with chronic Chagas disease).

8 What is the best therapeutic intervention for adult patients with chronic *T. cruzi* infection and specific organ damage?

- **Population:** Adults with diagnosis of chronic Chagas disease and specific organ damage (heart disease or enteropathy).
- **Intervention:** Trypanocidal treatment.
- **Comparator:** Absence of trypanocidal treatment.

- **Outcomes:** Mortality, specific organ damage (progression of heart disease or enteropathy, depending on the study definition), negativization of parasitemia (percentage of patients with negative parasitemia in 1-2 months), negativization of serological tests (percentage of patients with negative serological tests in 2-3 years), adverse effects.

9 What is the best therapeutic intervention for patients with acute/congenital infection?

- **Population:** Patients with acute *T. cruzi* infection.
- **Intervention:** Trypanocidal treatment.
- **Comparator:** Absence of trypanocidal treatment.
- **Outcomes:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), negativization of parasitemia (percentage of patients with negative parasitemia in 1-2 months), negativization of serological tests (percentage of patients with negative serological tests in 2-3 years), adverse effects.

10 What is the best therapeutic intervention for patients with Chagas disease who will receive trypanocidal treatment?

- **Population:** Adults or children with diagnosis of acute or chronic Chagas disease.
- **Intervention:** Benznidazole.
- **Comparator:** Nifurtimox.
- **Outcomes:** Mortality, specific organ damage (development of heart disease or enteropathy depending on the study definition), negativization of parasitemia (percentage of patients with negative parasitemia in 1-2 months), negativization of serological tests (percentage of patients with negative serological tests in 2-3 years), adverse effects.

Annex4

Summary of Findings (SoF)

Summary of Findings (SoF) Table 1

ELISA compared to the diagnostic gold standard

Pooled sensitivity: 0.97 (CI 95%: 0.96-0.98) | **Pooled specificity:** 0.98 (CI 95%: 0.97-0.99)

Test results	Number of results per 1,000 patients tested (CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Overall prevalence in blood donors in Argentina[51]	Prevalence 26.3% Median prevalence rported in studies conducted in an endemic area[1-4,6-9]			
True positives	**30** (30 - 30)	**255** (252 - 257)	7,650 (48)[1-48]	⨁⨁⨁⨁ HIGH[a,b]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[49,50,c]
False negatives	**1** (1 - 1)	**8** (6 - 11)			Depending on prevalence, between 0 and 1 more patients per 1,000 will develop specific organ damage in 10 years, as a result of incorrect diagnosis.[49,50,c]
True negatives	**951** (942 - 955)	**723** (716 - 727)	54,670 (48)[1-48]	⨁⨁⨁⨁ HIGH[b,d]	Patients will not receive treatment or undergo more complementary studies.
False positives	**18** (14 - 27)	**14** (10 - 21)			The majority of patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.

CI: confidence interval.

Explanations

a. Sensitivity interval observed in studies with low risk of bias: 53%-99%. However, the differences appear to be explained by the results observed in the different tests evaluated (see Annex 6).
b. Although we recommended that most of the studies included in the analysis had a high risk of bias, we decided not to downgrade certainty for this reason, since the sensitivity test conducted with only studies with low to moderate risk (*n = 17*) produced results similar to the overall estimate (sensitivity of 95.9% and specificity of 98.7%).
c. Estimate modeled from the baseline risk observed by Sabino et al.[49] and the relative effect of the treatment obtained in the study by Viotti et al.[50]
d. Specificity interval observed in the studies with low risk of bias: 81%-100%. However, the differences appear to be explained by the results observed in the different tests evaluated (see Annex 6).

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Summary of Findings (SoF) Table 2

ICT compared to the diagnostic gold standard

Pooled sensitivity: 0.94 (CI 95%: 0.91-0.96) | **Pooled specificity:** 0.97 (CI 95%: 0.96-0.98)

Test results	Number of results per 1,000 patients tested(CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Seen typically in patients with suspected Chagas disease	Prevalence 26.3% Seen typically in people living in an endemic area			
True positives	**29** (28 - 30)	**246** (239 - 252)	4,540 (19)[1-19,a]	⨁⨁⨁◯ MODERATE[b,c]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[20,21,d]
False negatives	**2** (1 - 3)	**17** (11 - 24)			Depending on prevalence, between 0 and 3 more patients per 1,000 will develop specific organ damage in 10 years, as a result of incorrect diagnosis.[20,21,d]
True negatives	**944** (933 - 951)	**718** (710 - 723)	10,581 (19)[1-19,a]	⨁⨁⨁⨁ HIGH[c]	Patients will not receive treatment or undergo more complementary studies.
False positives	**25** (18 - 36)	**19** (14 - 27)			The majority of patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.

CI: Confidence interval.

Explanations
a. Approximate number.
b. Interval of sensitivities observed in studies with a low to moderate risk of bias: 54%-99%. This variability cannot be completely explained by the results observed in the different tests evaluated (Annex 6).
c. Only 3 of the 19 studies included were considered as having a high risk of bias, and a sensitivity analysis in which only studies with low to moderate risk (*n = 16)* were included produced results similar to the overall estimate (sensitivity, 93.6%; specificity, 97.6%).
d. Estimate modeled from the baseline risk observed by Sabino et al.[21] and the relative effect of the treatment obtained in the study by Viotti et al.[20]

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Summary of Findings (SoF) Table 3

CMIA compared to the diagnostic gold standard

Pooled sensitivity: 0.99 (CI 95%: 0.97-1.00) | **Pooled specificity:** 0.98 (CI 95%: 0.91-0.99)

Test results	Number of results per 1,000 patients tested (CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Seen typically in patients with suspected Chagas disease	Prevalence 26.3% Seen typically in people living in an endemic area			
True positives	**31** (30 - 31)	**261** (256 - 262)	1095 (7)[1-7]	⨁⨁⨁⨁ HIGH[a]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[8,9,b]
False negatives	**0** (0 - 1)	**2** (1 - 7)			Depending on prevalence, between 0 and 1 more patients per 1,000 will develop specific organ damage in 10 years, as a result of incorrect diagnosis.[8,9,b]
True negatives	**948** (877 - 964)	**721** (667 - 733)	9744 (7)[1-7]	⨁⨁◯◯ LOW[c,d]	The patients will not receive treatment or undergo more complementary studies.
False positives	**21** (5 - 92)	**16** (4 - 70)			The majority of patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.

CI: confidence interval.

Explanations

a. Although we recommended that most of the studies included in the analysis had a high risk of bias, we decided not to downgrade certainty due to bias risk, since the analysis of sensitivity that only included studies with low to moderate risk (*n = 2*) produced results similar to the overall estimate (sensitivity, 97.9%).
b. Estimate modeled from the baseline risk observed by Sabino et al.[9] and the relative effect of the treatment obtained in the study by Viotti et al.[8]
c. Specificity was 91.5% in the study subgroup (*n = 2*) with a low to moderate risk of bias.
d. Observed specificity interval: 73%-99%.

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Summary of Findings (SoF) Table 4

ELISA compared to ICT

Pooled sensitivity ELISA: 0.97 (CI 95%: 0.96-0.98) | **Pooled specificity ELISA:** 0.98 (CI 95%: 0.96-0.99)

Pooled sensitivity ICT: 0.91 (CI 95%: 0.86-0.94) | **Pooled specificity ICT:** 0.95 (CI 95%: 0.90-0.97)

Test results	Number of results per 1,000 patients tested (CI 95%)				Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Seen typically in patients with suspected Chagas disease		**Prevalence 26.3%** Seen typically in people living in an endemic area				
	ELISA	ICT	ELISA	ICT			
True positives	**30** (30 - 31)	**28** (27 - 29)	**256** (252 - 259)	**239** (225 - 247)	684 (5)[1-5]	⨁⨁⨁⨁ HIGH	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[6,7,a]
	2 more TPs in ELISA		17 more TPs in ELISA				
False negatives	**1** (0 - 1)	**3** (2 - 4)	**7** (4 - 11)	**24** (16 - 38)			Depending on prevalence, for every 1,000 patients evaluated with ELISA instead of ICT, between 0 and 3 fewer will develop specific organ damage in 10 years as a result of incorrect diagnosis.[6,7,a]
	2 fewer FNs in ELISA		17 fewer FNs in ELISA				
True negative	**950** (935 - 958)	**919** (871 - 944)	**722** (711 - 729)	**699** (663 - 718)	713 (5)	⨁⨁⨁◯ MODERATE[b]	The patients will not receive treatment or undergo more complementary studies.
	31 more TNs in ELISA		23 more TNs in ELISA				

Test results	Number of results per 1,000 patients tested (CI 95%)				Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Seen typically in patients with suspected Chagas disease		**Prevalence 26.3%** Seen typically in people living in an endemic area				
	ELISA	ICT	ELISA	ICT			
False positives	19 (11 - 34)	50 (25 - 98)	15 (8 - 26)	38 (19 - 74)			The majority of the patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.
	31 fewer FPs in ELISA		23 fewer FPs in ELISA				

CI: Confidence interval

Explanations
a. Estimate modeled from the baseline risk observed by Sabino et al.[7] and the relative effect of the treatment obtained in the study by Viotti et al.[6]
b. Confidence interval of 95%, which includes benefits with ELISA and no benefits.

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Summary of Findings (SoF) Table 5

ELISA compared to CMIA

Sensitivity of one ELISA study: 0.98 (CI 95%: 0.94-0.99) | **Specificity of one ELISA study:** 0.96 (CI 95%: 0.93-0.98)

Sensitivity of one CMIA study: 1.00 (CI 95%: 0.97-1.00) | **Specificity of one CMIA study:** 0.89 (CI 95%: 0.4-0.92)

<table>
<tr><th rowspan="3">Test results</th><th colspan="4">Number of results per 1,000 patients tested (CI 95%)</th><th rowspan="3">Number of participants (studies)</th><th rowspan="3">Certainty of the evidence (GRADE)</th><th rowspan="3">Comments</th></tr>
<tr><th colspan="2">Prevalence 3.1%
Seen typically in patients with suspected Chagas disease</th><th colspan="2">Prevalence 26.3%
Seen typically in people living in an endemic area</th></tr>
<tr><th>ELISA</th><th>CMIA</th><th>ELISA</th><th>CMIA</th></tr>
<tr><td rowspan="2">True positives</td><td>30 (29 - 31)</td><td>31 (30 - 31)</td><td>258 (248 - 262)</td><td>263 (255 - 263)</td><td rowspan="4">161
(1)[1]</td><td rowspan="4">⨁⨁◯◯
LOW[a,b]</td><td>The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[2,3,c]</td></tr>
<tr><td colspan="2">1 less TP in ELISA</td><td colspan="2">5 fewer TPs in ELISA</td></tr>
<tr><td rowspan="2">False negatives</td><td>1 (0 - 2)</td><td>0 (0 - 1)</td><td>5 (1 - 15)</td><td>0 (0 - 8)</td><td rowspan="2">Depending on prevalence, for every 1,000 patients evaluated with CMIA instead of ELISA, between 0 and 1 fewer will develop specific organ damage in 10 years as a result of incorrect diagnosis.[2,3,c]</td></tr>
<tr><td colspan="2">1 more FN in ELISA</td><td colspan="2">5 more FNs in ELISA</td></tr>
</table>

Test results	Number of results per 1,000 patients tested (CI 95%)				Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 3.1% Seen typically in patients with suspected Chagas disease		**Prevalence 26.3%** Seen typically in people living in an endemic area				
	ELISA	CMIA	ELISA	CMIA			
True negatives	**932** (898 - 951)	**859** (811 - 893)	**709** (683 - 723)	**653** (617 - 680)	238 (1)	⨁⨁⨁◯ MODERATE[a]	The patients will not receive treatment or undergo more complementary studies.
	73 more TNs in ELISA		**56 more TNs in ELISA**				
False positives	**37** (18 - 71)	**110** (76 - 158)	**28** (14 - 54)	**84** (57 - 120)			The majority of the patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.
	73 fewer FPs in ELISA		**56 fewer FPs in ELISA**				

CI: Confidence interval

Explanations
a. The one study that evaluates this comparison has a spectrum bias.
b. Confidence interval of 95%, which includes the benefits of the ELISA and CMIA tests.
c. Estimate modeled from the baseline risk observed by Sabino et al.[3] and the relative effect of the treatment obtained in the study by Viotti et al.[2]

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Summary of Findings (SoF) Table 6

Microhematocrit compared to the diagnostic gold standard

Sensitivity interval: 0.28-0.82 | **Specificity interval:** 0.90-0.90

Test results	Number of results per 1,000 patients tested (CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 4,7% Congenital transmission (combination of several studies in meta-analysis)[5]	**Prevalence 50%** Higher rate of congenital transmission observed (pregnant women with acute infection) in all studies included in the systematic[5] review			
True positives	13 - 39	138 - 412	46 (2)[1,2,1]	⨁⨁⨁◯ MODERATE[a,b]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[3,4,c]
False negatives	8 - 34	88 - 362			Depending on prevalence, between 7 and 72 more patients per 1,000 will develop specific organ damage as a consequence of incorrect diagnosis.[3,4,c]
True negatives	854 - 854	448 - 448	173 (1)[2,2]	⨁⨁⨁⨁ HIGH[b]	The patients will not receive treatment or undergo more complementary studies.
False positives	99 - 99	52 - 52			The majority of the patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.

CI: Confidence interval
Explanations
a. Significant variability between the two studies included.
b. Small sample.
c. Estimate modeled from the baseline risk observed by Sabino et al.[4] and the relative effect of the treatment obtained in the study by Viotti et al.[3]

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Summary of Findings (SoF) Table 7

Direct observation compared to the diagnostic gold standard

Sensitivity of a single study: 0.80 (CI 95%: 0.51-0.94) | **Specificity of a single study:** cannot be calculated

Test results	Number of results per 1,000 patients tested (CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 4,7% Congenital transmission (combination of several studies in meta-analysis)[4]	**Prevalence 50%** Higher rate of congenital transmission observed in all studies included in the systematic[4] review			
True positives	**38** (24 - 44)	**400** (255 - 470)	15 (1)[1]	⨁◯◯◯ LOW[a,b]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[2,3,c]
False negatives	**9** (3 - 23)	**100** (30 - 245)			Depending on prevalence, between 2 and 20 more patients per 1,000 will develop specific organ damage within 10 years, as a consequence of incorrect diagnosis.[2,3,c]
True negatives	**0** (0 - 0)	**0** (0 - 0)		-	
False positives	**953** (953 - 953)	**500** (500 - 500)			

CI: Confidence interval

Explanations
a. The one study that evaluates this intervention has a spectrum bias.
b. The confidence interval of 95% includes very high and low sensitivities.
c. Estimate modeled from the baseline risk observed by Sabino et al.[3] and the relative effect of the treatment obtained in the study by Viotti et al.[2]

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Summary of Findings (SoF) Table 8

Hemocultures compared to the diagnostic gold standard

Sensitivity of a single study: 0.55 (CI 95%: 0.36-0.73) | **Specificity of a single study:** 1.00 (CI 95%: 0.97-1.00)

Test results	Number of results per 1,000 patients tested (CI 95%)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Prevalence 4,7% Congenital transmission (combination of several studies in meta-analysis)[4]	**Prevalence 50%** Higher rate of congenital transmission observed in all studies included in the systematic[4] review			
True positives	**26** (17 - 34)	**276** (180 - 365)	16 (1)[1]	⨁⨁⨁◯ MODERATE[a]	The majority of patients will receive antiparasitic treatment and approximately 5% will develop specific organ damage in the following 10 years.[2,3,b]
False negatives	**21** (13 - 30)	**224** (135 - 320)			Depending on prevalence, between 4 and 45 more patients per 1,000 will develop specific organ damage within 10 years, as a consequence of incorrect diagnosis.[2,3,b]
True negatives	**953** (926 - 953)	**500** (486 - 500)	186 (1)[1]	⨁⨁⨁⨁ HIGH	The patients will not receive treatment or undergo more complementary studies.
False positives	**0** (0 - 27)	**0** (0 - 14)			The majority of the patients will undergo more complementary studies. Probably only a very small minority will end up receiving unnecessary antiparasitic treatment.

CI: Confidence interval.

Explanations
a. CI 95% includes moderate and low sensitivities.
b. Estimate modeled from the baseline risk observed by Sabino et al.[3] and the relative effect of the treatment obtained in the study by Viotti et al.[2]

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Summary of Findings (SoF) Table 9

Treatment in adults with no specific organ damage

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Mortality	2,328 (5 observational studies)[1-5,a]	⨁◯◯◯ VERY LOW[b,c]	OR 0.57 (0.21-1.51)	Population study	
				39 per 1,000[a]	**16 fewer per 1,000** (31 fewer to 19 more)
Development of myocardiopathy	1,173 (5 observational studies)[1,3,5-7,a]	⨁⨁◯◯ LOW[b]	OR 0.38 (0.18-0.78)	Population study	
				138 per 1,000[a]	**81 fewer per 1,000** (110 fewer to 27 fewer)
Early negativization of parasitemia (1-2 months)	260 (1 RCT)[8,d]	⨁⨁◯◯ LOW[e,f]	RR 1.44 (1.21-1.72)	Population study	
				657 per 1,000[d]	**289 more per 1,000** (138 more to 473 more)
Negativization pf parasitemia (end of treatment) evaluated with: PCR	1,175 (1 RCT)[11]	⨁⨁⨁◯ MODERATE[h]	RR 1.98 (1.75-2.24)	Population study	
				335 per 1,000	**328 more per 1,000** (251 more to 415 more)
Negativization of serology (2-3 years) Adults	1,787 (4 observational studies)[1,3-5,d]	⨁⨁◯◯ LOW[b]	OR 3.32 (1.40-7.88)	Population study	
				199 per 1,000[d]	**253 more per 1,000** (59 more to 463 more)
Negativization of serology (2-3 years) Pediatric patients	447 (2 RCT)[12,13]	⨁⨁◯◯ LOW[i,j,k]	RR 2.41 (1.16-5.02)	Population study	
				229 per 1,000[d]	**229 per 1,000[d]**
Withdrawal from treatment due to adverse effects	3,697 (4 RCT)[8-11]	⨁⨁⨁⨁ HIGH	RR 5.71 (2.46-13.29)	Population study	
				33 per 1,000[g]	**157 more per 1,000** (49 more to 409 more)
Serious adverse effects	2,911 (2 RCT)[10,11]	The incidence of (any) serious adverse effects with benznidazole was from 8.3% to 10%. The most frequent effects were: skin rashes (4.1%), gastrointestinal symptoms (4.1%), neuropathies (1.8%), and leukopenia (1.0%).			

CI: Confidence interval; RCT: Randomized controlled trial; OR: Odds ratio; RR: Relative risk.

Explanations
a. Average rate of events in the control arm of the included studies. Median follow-up: 15 years.
b. Heterogeneity in the estimates in studies with doubtful clinical relevance.
c. The confidence interval includes the possibility of clinically relevant benefits and harms.
d. Average rate of events in the control arm of the included studies.
e. Does not properly clarify random selection and random assignment.
f. Limited number of patients.
g. Average rate of events in the control arm of the included studies. Median follow-up: 4 years.
h. Estimate from the BENEFIT study that included patients with specific organ damage, which led to downgrading certainty due to indirect information.
i. Small number of patients
j. Heterogeneity in the estimates in primary studies.
k. Indirect information is assumed given that the intervention's effect could differ between adults and children.

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Summary of Findings (SoF) Table 10

Treatment in children

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Negativization of serology (2-3 years)	447 (2 RCT)[1,2,d]	⨁⨁⨁◯ MODERATE[c,e]	**RR 2.41** (1.16-5.02)	Population study	
				229 per 1,000[d]	**323 more per 1,000** (37 more to 922 more)
Progression or development of myocardiopathy	129 (1 RCT)[1,a]	⨁⨁◯◯ LOW[b,c]	Not estimable	Population study	
				0 per 1,000	**0 less per 1,000** (0 less to 0 less)
Early negativization of parasitemia (1-2 months)	106 (1 RCT)[2,d]	⨁⨁⨁◯ MODERATE[c]	**RR 1.69** (1.33-2.16)	Population study	
				176 per 1,000[d]	**122 more per 1,000** (58 more to 205 more)
Withdrawal from treatment due to adverse effects	235 (2 RCT)[1,2,f]	⨁⨁⨁◯ MODERATE[g]	**RR 0.55** (0.22-1.41)	Population study	
				95 per 1,000[f]	**43 fewer per 1,000** (74 fewer to 39 more)

CI: Confidence interval; RCT: Randomized controlled trial; RR: Risk ratio.

Explanations
a. Average rate of events in the control arm of the study by Andrade et al. Average follow-up: 6 years.
b. Limited follow-up time.
c. Small number of patients.
d. Average rate of events in the control arm of the included studies.
e. Heterogeneity in the study estimates.
f. Average rate of events in the arm control of the included studies. Median follow-up: 5 years.
g. The confidence interval includes the possibility of clinically significant benefits and harms.

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Summary of Findings (SoF) Table 11

Treatment in girls and women of childbearing age

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Vertical transmission	735 (4 observational studies)[1-4]	⨁⨁⨁◯ MODERATE[d]	OR.07 (0.02-0.30)	Low	
				20 per 1,000[a]	**19 fewer per 1,000** (20 fewer to 14 fewer)
				High	
				50 per 1,000[b]	**46 fewer per 1,000** (49 fewer to 34 fewer)
				Population study	
				147 per 1,000	**135 fewer per 1,000** (143 fewer to 98 fewer)
Adverse fetal effects	0 (observational studies)[1-4]	-	-	None of the analyzed studies reports adverse fetal effects in women who received antiparasitic treatment.	
Withdrawal from treatment due to adverse effects: adults	3,697 (4 RCT)[5-7,9]	⨁⨁⨁⨁ HIGH	RR 5.71 (2.46-13.29)	Population study	
				33 per 1,000[c]	**157 more per 1,000** (49 more to 409 more)
Withdrawal from treatment due to adverse effects: children	235 (2 RCT)[8,10,f]	⨁⨁⨁◯ MODERATE[e]	RR 0.55 (0.22-1.41)	Population study	
				95 per 1,000[c]	**43 fewer per 1,000** (74 fewer to 39 more)

CI: Confidence interval; RCT: Randomized controlled trial; OR: Odds ratio; RR: Risk ratio.

Explanations

a. Rate of events reported in: Martins-Melo FR, Lima MS, Ramos AN Jr, Alencar CH, Heukelbach J. Prevalence of Chagas Disease in Pregnant Women and Congenital Transmission of *Trypanosoma Cruzi* in Brazil: A Systematic Review and Meta-Analysis. Trop Med Int Health 2014; 19 (8): 943-957.

b. Rate of events presented in: Howard EJ, Xiong X, Carlier Y, Sosa-Estani S, Buekens P. 2014. Frequency of the Congenital Transmission of *Trypanosoma Cruzi*: A Systematic Review and Meta-Analysis. BJOG 2013; 121 (1): 22-33.

c. Average rate of events in the control arm of the included studies. Median follow-up: 4-5 years.

d. The certainty increased due to the large magnitude of the intervention's effect.

e. The confidence interval includes the possibility of clinically relevant benefits and harms.

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Summary of Findings (SoF) Table 12

Treatment in adults with specific organ damage

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Mortality	2,854 (1 RCT)[1,a]	⨁⨁⨁◯ MODERATE[b]	**OR 0.94** (0.78-1.14)	Population study	
				181 per 1,000[a]	**9 fewer per 1,000** (34 less to 20 more)
				Low	
				20 per 1,000[c]	**1 less per 1,000** (4 fewer to 3 more)
Progression of myocardiopathy	2,854 (1 RCT)[1,a]	⨁⨁⨁◯ MODERATE[b]	**OR 0.88** (0.67-1.15)	Population study	
				86 per 1,000[a]	**10 fewer per 1,000** (27 fewer to 12 more)
Negativization of parasitemia (end of the treatment) Evaluated with: PCR	1,175 (1 RCT)[2]	⨁⨁⨁⨁ HIGH	**RR 1.98** (1.75-2.24)	Population study	
				335 per 1,000	**328 more per 1,000** (251 fewer to 415 more)
Withdrawal from treatment due to adverse effects	3,697 (4 RCT)[1-4]	⨁⨁⨁⨁ HIGH	**RR 5.71** (2.46-13.29)	Population study	
				33 per 1,000[d]	**157 more per 1,000** (49 more to 409 more)
Serious adverse effects	2,911 (2 RCT)[1,2]	The incidence of all serious adverse effects from benznidazole ranged from 8.3% to 10%. The most frequent effects were: skin rashes (4.1%), gastrointestinal symptoms (4.1%), neuropathies (1.8%), and leukopenia (1.0%).			

CI: Confidence interval; RCT: Randomized controlled trial; OR: Odds ratio; RR: Risk ratio.

Explanations

a. Average rate of events in the control arm of the analyzed study. Median follow-up: 5.4 years.
b. The confidence interval includes the possibility of clinically relevant benefits and harms.
c. Annual mortality rate reported by: Cucunubá et al.: Cucunubá ZM, Okuwoga O, Basáñez MG, Nouvellet P. Increased Mortality Attributed to Chagas Disease: A Systematic Review and Meta-Analysis. *Parasit Vectors* 2016; 9: 42.
d. Average rate of events in the control arm of the analyzed study. Median follow-up: 4 years.
e. Lost to follow-up.

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Summary of Findings (SoF) Table 13

Treatment in acute infection

Results Number of participants (studies)	Relative effect (CI 95%)	Expected absolute effects (CI 95%)			Certainty	Effect
				Difference		
Negativization of serology Follow-up: 20 months Number of participants: 151 (1 observational study)[11]	**RR 25.5** (2.7-37.0)[a]	Bajo 2.7%b	**69.1%** (7.3-100.0)	**66.4% más** (4.6 more to 97.6 more)	⨁⨁⨁◯ MODERATE[c,e]	Trypanocidal treatment probably increases the likelihood of negativizing serology.
Negativization of parasitemia evaluated with: any method Follow-up: 1 year Number of participants: (16 observational studies)[1-16]	16 studies were considered (*n* = 1,087) Benznidazole: 89,66% (*n* = 466) Nifurtimox: 74.74% (*n* = 621)				-	
Negativization of parasitemia evaluated with: xenodiagnosis Follow-up: 1 year Number of participants: (14 studies)[1-7,10-16]	14 studies were considered (*n* = 1,020) Benznidazole: 87.25% (*n* = 428) Nifurtimox: 73.52% (*n* = 592) Congenital Chagas disease: Benznidazole: 77.08% Nifurtimox: 77.36%				-	
Negativization of serology Evaluated with: any method Follow-up: 2-3 years Number of participants: (21 studies)[1-8,10-18-22]	21 studies were considered (*n* = 1,600) Benznidazole: 50.33% (*n* = 540) Nifurtimox: 60.00% (*n* = 1,060)				-	
Negativization of serology Evaluated with: complement fixation Follow-up: 2-3 years Number of participants: (6 studies)[1,2,4,5,7,11]	6 studies were considered (*n* = 484) Benznidazole: 88.59% (*n* = 149) Nifurtimox: 77.96% (*n* = 335)				-	
Severe adverse effects	See attached Table (Annex 8)				-	

The risk in the intervention group (and its confidence interval of 95%) is based on the assumed risk in the comparison group and on the intervention's relative effect (and its confidence interval of 95%).

CI: Confidence interval; RR: Risk ratio.

Degrees of certainty regarding the evidence, based on the GRADE system

High: There a high level of confidence that the true effect is similar to the estimated effect.

Moderate: There is moderate confidence in the estimated effect: the true effect is probably close to the estimated effect, but there is a possibility that it is markedly different.

Low: The confidence in the estimated effect is limited: the true effect might be markedly different from the estimated effect.

Very low: There is very little confidence in the estimated effect: the true effect is probably markedly different from the estimated effect.

Explanations
a. CI 95% was estimated since there were no events in the control arm.
b. Baseline risk was estimated based on the observed effect since there were no events in the control arm.
c. Small number of events.
d. Studies of one arm.
e. Large magnitude of effect.

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Summary of Findings (SoF) Table 14

Benznidazole compared to nifurtimox in acute infection

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Impact
Negativization of parasitemia Evaluated with: any method Follow-up: 1 year	(16 studies)[1-16]	-	16 studies were considered (*n* = 1,149): Benznidazole: 89.66% (*n* = 528) Nifurtimox: 74.74% (*n* = 621)
Negativization of parasitemia Evaluated with: xenodiagnosis Follow-up: 1 year	(14 studies)[1-7,10-16]	-	14 studies were considered (*n* = 1,020): Benznidazole: 87.25% (*n* = 428) Nifurtimox: 73.52% (*n* = 592) Congenital Chagas disease: Benznidazole: 77.08% Nifurtimox: 77.36%
Negativization of serology Evaluated with: any method Follow-up: 2-3 years	(21 studies)[1-8,10-22]	-	21 studies were considered (*n* = 1,600): Benznidazole: 50.33% (*n* = 540) Nifurtimox: 60.00% (*n* = 1,060)
Negativization of serology Evaluated with: complement fixation Follow-up: 2-3 years	(6 studies)[1,2,4,5,7,11]	-	6 studies were considered (*n* = 484): Benznidazole: 88.59% (*n* = 149) Nifurtimox: 77.96% (*n* = 335)
Severe adverse effects	-	-	See Annex 8.

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Summary of Findings (SoF) Table 15

Benznidazole compared to nifurtimox in chronic infection

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with nifurtimox	Risk difference compared to benznidazole
Progression or development of myocardiopathy Observations	294 (2 observational studies)[1,2,a]	⨁◯◯◯ VERY LOW[b]	OR 0.43 (0.16-1.11)	Population study 94 per 1,000[a]	**51 fewer per 1,000** (77 fewer to 9 more)
Early negativization of parasitemia (1-2 months) Observations	226 (1 observational study)[2]	⨁◯◯◯ VERY LOW[b]	OR 1.94 (0.36-10.57)	Population study 760 per 1,000	**100 more per 1,000** (227 fewer to 211 more)
Early negativization of parasitemia (1-2 months) Randomized	53 (1 RCT)[3]	⨁⨁◯◯ LOW[c,d,e]	OR 0.10 (0.01-0.83)	Population study 84 per 1,000	**75 fewer per 1,000** (83 fewer to 13 fewer)
Negativization of serology (2-3 years) Observations	226 (5 observational studies)[2,f]	⨁◯◯◯ VERY LOW[b]	OR 1.88 (0.36-9.90)	Population study 21 per 1,000[f]	**18 more per 1,000** (13 fewer to 153 more)
Withdrawal from treatment due to adverse effects Observations	294 (4 observational studies)[1,2,a]	⨁◯◯◯ VERY LOW[b]	OR 0.85 (0.47-1.55)	Population study 195 per 1,000[a]	**24 fewer per 1,000** (93 fewer to 78 more)
Withdrawal from treatment due to adverse effects Randomized	53 (1 RCT)[3,g]	⨁⨁◯◯ LOW[b,c]	OR 0.31 (0.07-1.33)	Population study 296 per 1,000[g]	**181 fewer per 1,000** (268 fewer to 63 more)

CI: Confidence interval; RCT: Randomized controlled trial; OR: Odds ratio.

Explanations
a. Average rate of events in the control arm of the included studies. Median follow-up: 6 years.
b. The confidence interval includes the possibility of clinically relevant benefits and harms.
c. The dose of nifurtimox was less than what is usually recommended.
d. The study presents the negative rate of xenodiagnosis in the total number of analyzed samples; data is not disaggregated by patient.
e. Small number of events.
f. Average rate of events in the control arm of the included studies. Average follow-up: 10 years.
g. Average rate of events in the control arm of the included studies. Average follow-up: 30 days.

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Annex5

GRADE Tables: From evidence to recommendations

Framework 1. ELISA compared to the diagnostic gold standard

Evaluation

	Judgment	Research evidence	Additional information
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel selected the question as a priority. It considered the possibility of replacing the diagnostic standard (positivity in two serological tests, typically ELISA, HAI, and IIF) with a single test.	
Test accuracy	How accurate is the test? ○ Very inaccurate ○ Inaccurate ○ Accurate ● Very accurate ○ Varies ○ Don't know	*See Annex 4, SoF 1, 4, 5.*	There is variability in the different kits. Some have 100% sensitivity (Annex 6). The panel emphasizes that there may be variability in the results as well as the recommendations when using tests with greater or lesser accuracy.
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Depending on prevalence, between 0 and 1 more patient per 1,000 will develop specific organ damage in 10 years, as a consequence of incorrect diagnosis.	The panel stressed that there are additional effects that are difficult to quantify in this scenario, such as the impact of an incorrect diagnosis on vector-borne and vertical transmission.

	Judgment	Research evidence	Additional information
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Depending on prevalence, between 0 and 1 more patient per 1,000 will develop specific organ damage in 10 years, as a consequence of incorrect diagnosis.	The panel stressed that there are additional effects that are difficult to quantify in this scenario, such as the impact of an incorrect diagnosis on vector-borne and vertical transmission.
Certainty regarding the accuracy of the test	What is the overall certainty of the evidence regarding the accuracy of the test? ○ Very low ○ Low ○ Moderate ● High ○ No studies were included	The sensitivity and specificity interval described in the different studies varies significantly. However, this variability may be explained by the differences observed in the results of the different commercially available tests (see Annex 6.) Although the panel considered that most of the studies included in the analysis had a high risk of bias, it decided to not downgrade certainty due to risk of bias, since a sensitivity analysis that included only studies with low to moderate risk (n = 17) produced results similar to the overall estimate (sensitivity, 95.9%; specificity, 98.7%).	
Certainty regarding effects	What is the overall certainty of the evidence regarding the effects of the test? ○ Very low ● Low ○ Moderate ○ High ○ No studies were included	Confidence is low primarily because of the uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term-specific organ damage (Annex 9). For the purpose of this analysis, the estimates described by Sabino et al. (1) (25% risk of developing heart disease in 10 years in untreated patients) and Viotti et al. (2) (80% relative reduction of the risk of development or progression of specific organ damage if antiparasitic treatment is prescribed) were used to model the intervention's impact.	

	Judgment	Research evidence	Additional information
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	The judgment was based on the opinion of the experts, who considered that the existence of variability in this scenario is unlikely.	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	An incorrect diagnosis in a percentage of patients (regardless of how small) leads to harm, which is why the panel judged that the balance favors the diagnostic gold standard.	

	Judgment	Research evidence	Additional information
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Significant savings ○ Varies ○ Don't know	Abras calculates savings of US$4,516 per year in a hospital center as a consequence of using one diagnostic test (CMIA) instead of two tests (3). Pirard estimated that direct costs would be reduced by approximately one-half if one diagnostic test were used instead of two (4).	Suspected Chagas disease: In this scenario the potential absolute savings are not significant, since the number of tests to be conducted is not very large. Blood bank screening: In this scenario the savings are significant, since the number of studies to be requested is very high. Screening in seroepidemiological surveys: In this scenario the savings are significant, since the number of studies to be requested is large.
Inequity	What would be the impact on health inequity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (5): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; $p = 0.004$). • Lower overcrowding ratio (HR = 0.82 [0.70-0.97]; $p = 0.022$). • Greater social coverage (HR = 1.46 [1.01-2.09]; $p = 0.04$). • More years of education (HR = 0.88 [0.80-0.97]; $p = 0.01$).	Suspected Chagas disease: The intervention would reduce inequity because it is more accessible, and it helps people who are less likely to have access to the diagnostic standard. Blood bank screening: No impact on equity. Screening in seroepidemiological surveys: The intervention would reduce inequity because it is more accessible, facilitates the performance of these types of interventions, and increases the probability of detecting individuals who would otherwise not be diagnosed.

	Judgment	Research evidence	Additional information
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the intervention is acceptable in all of the scenarios presented.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the intervention is more easily implementable than the comparator (diagnostic gold standard) in all of the scenarios presented.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Centainty regarding the accuracy of the test	Very low	Low	Moderate	High			No studies were included
Certainty regarding effects	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should ELISA be used as the only test to diagnose suspected Chagas disease/screen for Chagas disease?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	**The PAHO panel suggests using the diagnostic gold standard before ELISA in patients with suspected Chagas disease (chronic infection)** (conditional recommendation, based on the low level of certainty on the effects of the intervention and high certainty on the accuracy of the test). **The PAHO panel recommends using ELISA before the diagnostic gold standard to screen for Chagas disease (chronic infection) in seroepidemiological surveys** (strong recommendation, based on the low level of certainty on the effects of the intervention and high certainty on the accuracy of the test). **The PAHO panel only recommends using ELISA before the diagnostic gold standard in patients screened for Chagas disease (chronic infection) in hemotherapy services when the purchased kit has a sensitivity of more than 99%** (strong recommendation, based on high certainty regarding the accuracy of the test).				
Justification	**Suspected Chagas disease:** The panel concluded that the negative consequences of incorrectly diagnosing a percentage of evaluated patients outweighed the benefits in terms of feasibility of use and increased equity. **Screening in seroepidemiological surveys:** The panel concluded that the feasibility of use and increased equity outweighed the possibility of incorrectly diagnosing some of the screened patients. The panel decided to make a strong recommendation given the uncertainty regarding the intervention's effect (it is unclear that it is significantly less effective in terms of clinically relevant outcomes) and the certainty regarding better possibilities of implementing ELISA as the only test. **Screening in hemotherapy services:** The panel gave significant weight to the reduction of costs. However, the panel emphasized the negative implications of incorrectly diagnosing a patient with Chagas disease as healthy in this scenario, which is why it decided to make the recommendation only if it can be shown that the ELISA test is particularly sensitive. The overall certainty of the evidence for this scenario was deemed high, since the most significant outcome is transfusion transmission of the infection, and the accuracy of the test is considered an adequate surrogate outcome.				

Subgroup considerations	
Implementation considerations	The variability in the different tests available at the time of implementation must be taken into consideration.
Monitoring and evaluation	
Research priorities	

Reference summary

1. Sabino EC, Ribeiro AL, Lee TH, Oliveira CL, Carneiro-Proietti AB, Antunes AP, Menezes MM, Ianni BM, Salemi VM, Nastari L, Fernandes F, Sachdev V, Carrick DM, Deng X, Wright D, Gonçalez TT, Murphy EL, Custer B, Busch MP; Chagas Study Group of the NHLBI Retrovirus Epidemiology Donor Study-II, International Component. Detection of *Trypanosoma cruzi* DNA in blood by PCR is associated with Chagas cardiomyopathy and disease severity. *Eur J Heart Fail* 2015; 17 (4): 416-23.
2. Viotti R, Vigliano C, Lococo B, Bertocchi G, Petti M, Álvarez MG, Postan M, Armenti A. Long-term cardiac outcomes of treating chronic Chagas disease with Benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; 144 (10): 724-734.
3. Abras A, Gállego M, Llovet T, Tebar S, Herrero M, Berenguer P, Ballart C, Martí C, Muñoz C. Serological Diagnosis of Chronic Chagas Disease: Is It Time for a Change? *J Clin Microbiol* 2016; 54 (6): 1566-1572.
4. Pirard M, Iihoshi N, Boelaert M, Basanta P, López F, Van der Stuyft P. The validity of serologic tests for *Trypanosoma cruzi* and the effectiveness of transfusional screening strategies in a hyperendemic region. *Transfusion* 2005; 45 (4): 554-561.
5. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.

Framework 2. ICT compared to the diagnostic gold standard

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel selected the question as a priority. It considered the possibility of replacing the diagnostic standard (two serological tests, typically ELISA, HAI, and IIF) with a single test.	
Test accuracy	How accurate is the test? ○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	*See Annex 4, SoF 2, 4*	
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Depending on prevalence, between 0 and 3 more patients per 1,000 will develop specific organ damage in 10 years, as a consequence of incorrect diagnosis.	The panel emphasized that there are additional effects that are difficult to quantify in this scenario, such as the impact of an incorrect diagnosis on vector-borne and vertical transmission.
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Depending on prevalence, between 0 and 3 more patients per 1,000 will develop specific organ damage in 10 years, as a consequence of incorrect diagnosis.	The panel emphasized that there are additional effects that are difficult to quantify in this scenario, such as the impact of an incorrect diagnosis on vector-borne and vertical transmission.

	Judgment	Research evidence	Additional comments
Certainty regarding the accuracy of the test	What is the overall certainty of the evidence regarding the accuracy of the test? ○ Very low ○ Low ● Moderate ○ High ○ No studies were included	The sensitivity and specificity interval described in the different studies varies significantly, which led to the determination of inconsistency. These differences do not appear to be explained by the results of the analysis of the different commercially available tests (Annex 6).	
Certainty regarding effects	What is the overall certainty of the evidence regarding the effects of the test? ○ Very low ● Low ○ Moderate ○ High ○ No studies were included	Confidence is low primarily because of the uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term-specific organ damage (Annex 9). For the purpose of this analysis, the estimates described by Sabino et al. (1) (25% risk of developing heart disease in 10 years in untreated patients) and Viotti et al. (2) (80% relative reduction of the risk of development or progression of specific organ damage if antiparasitic treatment is prescribed) were used to model the intervention's impact.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	The judgment was based on the opinion of the experts, who considered that the existence of variability in this scenario is unlikely.	

	Judgment	Research evidence	Additional comments
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	An incorrect diagnosis in a percentage of patients (regardless of how small) leads to harm, which is why the panel judged that the balance favors the diagnostic gold standard.	
Required resources	How large are the resource requirements (costs)? ○ High costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Significant savings ○ Varies ○ Don't know	Abras calculates savings of US$4,516 per year in a hospital center as a consequence of using one diagnostic test (CMIA) instead of two tests (3). Pirard estimated that direct costs would be reduced by approximately one-half if one diagnostic test were used instead of two (4).	The panel estimated that the direct costs of the ICT test are higher than the costs of the diagnostic standard in the majority of the contexts in which it can currently be used.

	Judgment	Research evidence	Additional comments
Inequity	What would be the impact on health inequity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ○ Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (5): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; *p* = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70-0.97]; *p* = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; *p* = 0.01).	Suspected Chagas disease: The intervention would reduce inequity because it is more accessible, and helps people who are less likely to have access to the diagnostic standard. Screening in seroepidemiological surveys: The intervention would reduce inequity because it is more accessible, facilitates the performance of these types of interventions, and increases the probability of detecting individuals who would otherwise not be diagnosed. Blood bank screening: No impact on equity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the intervention is acceptable in all of the scenarios presented.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the intervention is more easily implementable than the comparator (diagnostic gold standard) in all of the scenarios presented.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty regarding the accuracy of the test	Very low	Low	Moderate	High			No studies were included
Certainty regarding effects	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should ICT be used as the only test to diagnose suspected Chagas disease/screen for Chagas disease?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	**The PAHO panel suggests using the diagnostic gold standard before ICT in patients with suspected Chagas disease (chronic infection)** (conditional recommendation, based on the low level of certainty on the effects of the intervention and moderate certainty on the accuracy of the test). **The PAHO panel recommends using ICT before the diagnostic gold standard for population studies on the prevalence of Chagas disease (chronic infection)** (strong recommendation, based on the low level of certainty on the effects of the intervention and moderate certainty on the accuracy of the test). **The PAHO panel recommends not using ICT in patients screened for Chagas disease (chronic infection) in hemotherapy services** (strong recommendation, based on moderate certainty on the intervention's effects).				
Justification	**Suspected Chagas disease:** The panel concluded that the negative consequences of incorrectly diagnosing a percentage of evaluated patients outweighed the benefits in terms of feasibility of use and increased equity. **Screening in seroepidemiological surveys:** The panel concluded that the feasibility of use and increased equity outweighed the possibility of incorrectly diagnosing some of the screened patients. The panel decided to make a strong recommendation given the uncertainty regarding the intervention's effect (it is unclear that it is significantly less effective in terms of clinically relevant outcomes) and the certainty regarding better possibilities of implementing ICT as the only test compared to the diagnostic standard. **Screening in hemotherapy services:** The panel considered that the negative implications of incorrectly diagnosing a patient with Chagas disease as healthy in this scenario. The overall certainty of the evidence for this scenario was deemed moderate, since the most significant outcome is transfusion transmission of the infection, and the accuracy of the test is considered an adequate surrogate outcome.				
Subgroup considerations					
Monitoring and evaluation					
Research priorities					

Reference summary

1. Sabino EC, Ribeiro AL, Lee TH, Oliveira CL, Carneiro-Proietti AB, Antunes AP, Menezes MM, Ianni BM, Salemi VM, Nastari L, Fernandes F, Sachdev V, Carrick DM, Deng X, Wright D, Gonçalez TT, Murphy EL, Custer B, Busch MP; Chagas Study Group of the NHLBI Retrovirus Epidemiology Donor Study-II, International Component. Detection of *Trypanosoma cruzi* DNA in blood by PCR is associated with Chagas cardiomyopathy and disease severity. *Eur J Heart Fail* 2015; 17 (4): 416-23.
2. Viotti R, Vigliano C, Lococo B, Bertocchi G, Petti M, Álvarez MG, Postan M, Armenti A. Long-term cardiac outcomes of treating chronic Chagas disease with Benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; 144 (10): 724-734.
3. Abras A, Gállego M, Llovet T, Tebar S, Herrero M, Berenguer P, Ballart C, Martí C, Muñoz C. Serological Diagnosis of Chronic Chagas Disease: Is It Time for a Change? *J Clin Microbiol* 2016; 54 (6): 1566-1572.
4. Pirard M, Iihoshi N, Boelaert M, Basanta P, López F, Van der Stuyft P. The validity of serologic tests for *Trypanosoma cruzi* and the effectiveness of transfusional screening strategies in a hyperendemic region. *Transfusion* 2005; 45 (4): 554-561.
5. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.

Framework 3. CMIA compared to the diagnostic gold standard

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel selected the question as a priority. It considered the possibility of replacing the diagnostic standard (two serological tests, typically ELISA, HAI, and IIF) with a single test.	
Test accuracy	How accurate is the test? ○ Very inaccurate ○ Inaccurate ○ Accurate ● Very accurate ○ Varies ○ Don't know	*See Annex 4, SoF 3, 5.*	
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Depending on prevalence, between 0 and 1 more patients per 1,000 will develop specific organ damage in 10 years, as a consequence of incorrect diagnosis.	The panel emphasized that there are additional effects that are difficult to quantify in this scenario, such as the impact of an incorrect diagnosis on vector-borne and vertical transmission.
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

	Judgment	Research evidence	Additional comments
Certainty regarding the accuracy of the test	What is the overall certainty of the evidence regarding the accuracy of the test? ○ Very low ○ Low ○ Moderate ● High ○ No studies were included	Confidence in sensitivity (which panel considered to be more relevant) was HIGH.	
Certainty regarding effects	What is the overall certainty of the evidence regarding the effects of the test? ○ Very low ● Low ○ Moderate ○ High ○ No studies were included	Confidence is low, primarily because of the uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term specific organ damage (Annex 9). For the purpose of this analysis, the estimates described by Sabino et al. (1) (25% risk of developing heart disease in 10 years in untreated patients) and Viotti et al. (2) (80% relative reduction of the risk of development or progression of specific organ damage if antiparasitic treatment is prescribed) were used to model the intervention's impact.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	The judgment was based on the opinion of the experts, who considered that the existence of variability in this scenario is unlikely.	

	Judgment	Research evidence	Additional comments
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	In this scenario the panel considered that given the test's high sensitivity, the balance does not favor either the intervention or the comparator.	
Required resources	How large are the resource requirements (costs)? ○ High costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Significant savings ○ Varies ○ Don't know	Abras calculates savings of US$4,516 per year in a hospital center as a consequence of using one diagnostic test (CMIA) instead of two tests (3). Pirard estimated that direct costs would be reduced by approximately one-half if one diagnostic test were used instead of two (4)	Suspected Chagas disease: The panel judged that the costs could potentially be higher in our setting, if the CMIA test is implemented instead of the diagnostic gold standard. This conclusion was based on the low number of tests that are requested and on the quantity of reagents that would be consumed. Screening in seroepidemiological surveys: The panel judged that in this scenario, there may not be significant differences in costs. Blood bank screening: The panel judged that the implementation of CMIA instead of the diagnostic gold standard in this scenario could be associated with significant savings.

	Judgment	Research evidence	Additional comments
Inequity	What would be the impact on health inequity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ○ Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (5): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70- 0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01).	Because access to the CMIA is restricted at this time, the panel judged that the recommendation to implement this test before others could have a negative impact on equity in all of the scenarios presented.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel judged that the intervention is acceptable in scenarios of suspected Chagas disease and blood bank screening. In the context of screening in seroepidemiological surveys, the CMIA is probably not acceptable due to the complexity associated with its use.	
Feasibility	Is the intervention feasible to implement? ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	The panel concluded that implementation-related issues probably vary significantly in the different scenarios.	Suspected Chagas disease: Implementing the intervention with this objective is complicated. It would be necessary to discard many reagents due to the low volume of requests. Screening in seroepidemiological surveys: Not feasible to implement in this setting. Blood bank screening: feasible to implement in blood banks due to the quantity of required tests.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty regarding the accuracy of the test	Very low	Low	Moderate	High			No studies were included
Certainty regarding effects	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should CMIA be used as the only test to diagnose suspected Chagas disease /screen for Chagas disease?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	**The PAHO panel suggests using the diagnostic gold standard before CMIA in patients with suspected Chagas disease (chronic infection)** (conditional recommendation, based on the low level of certainty on the effects of the intervention and high certainty on the accuracy of the test). **The PAHO panel recommends not using CMIA for population studies on the prevalence of Chagas disease (chronic infection)** (strong recommendation, based on the low level of certainty on the effects of the intervention and high certainty on the accuracy of the test). **The PAHO panel recommends CMIA before the diagnostic standard in patients screened for Chagas disease (chronic infection) in hemotherapy services** (strong recommendation, based on high certainty regarding the effects of the intervention).				
Justification	**Suspected Chagas disease:** The panel concluded that the negative consequences associated with the intervention in terms of feasibility of use. **Screening in seroepidemiological surveys:** The panel accepted that the negative consequences associated with the intervention in terms of feasibility of use. The panel decided to make a strong recommendation, given the uncertainty on the intervention's effect in terms of clinically relevant outcomes and the certainty that this intervention cannot be implemented in this scenario. **Screening in hemotherapy services:** The panel gave significant weight to the reduction of costs. The overall certainty of the evidence for this scenario was deemed high, since the most significant outcome is transfusion transmission of the infection, and the accuracy of the test is considered an adequate surrogate outcome.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

Reference summary

1. Sabino EC, Ribeiro AL, Lee TH, Oliveira CL, Carneiro-Proietti AB, Antunes AP, Menezes MM, Ianni BM, Salemi VM, Nastari L, Fernandes F, Sachdev V, Carrick DM, Deng X, Wright D, Gonçalez TT, Murphy EL, Custer B, Busch MP; Chagas Study Group of the NHLBI Retrovirus Epidemiology Donor Study-II, International Component. Detection of *Trypanosoma cruzi* DNA in blood by PCR is associated with Chagas cardiomyopathy and disease severity. *Eur J Heart Fail* 2015; 17 (4): 416-23.
2. Viotti R, Vigliano C, Lococo B, Bertocchi G, Petti M, Álvarez MG, Postan M, Armenti A. Long-term cardiac outcomes of treating chronic Chagas disease with Benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; 144 (10): 724-734.
3. Abras A, Gállego M, Llovet T, Tebar S, Herrero M, Berenguer P, Ballart C, Martí C, Muñoz C. Serological Diagnosis of Chronic Chagas Disease: Is It Time for a Change? *J Clin Microbiol* 2016; 54 (6): 1566-1572.
4. Pirard M, Iihoshi N, Boelaert M, Basanta P, López F, Van der Stuyft P. The validity of serologic tests for *Trypanosoma cruzi* and the effectiveness of transfusional screening strategies in a hyperendemic region. *Transfusion* 2005; 45 (4): 554-561.
5. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.

Framework 4. Microhematocrit, direct observation, and hemocultures compared to the diagnostic gold standard

Evaluation

	Judgment	Research evidence	Additional information
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel selected the question as a priority.	
Test accuracy	How accurate is the test? ● Very inaccurate ○ Inaccurate ○ Accurate ○ Very Accurate ○ Varies ○ Don't know	*See Annex 4, SoF 6-8.*	
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Depending on prevalence, the number of patients who will develop specific organ damage as a consequence of an incorrect diagnosis will range from 7 to 72 more with the microhematocrit test, from 4 to 45 more with hemocultures, and from 2 to 20 more with direct parasitological examination.	

	Judgment	Research evidence	Additional information
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Depending on prevalence, the number of patients who will develop specific organ damage as a consequence of an incorrect diagnosis will range from 7 to 72 more with the microhematocrit test, from 4 to 45 more with hemocultures, and from 2 to 20 more with direct parasitological examination.	
Certainty regarding the accuracy of the test	What is the overall certainty of the evidence regarding the accuracy of the test? ○ Very low ○ Low ● Moderate ○ High ○ No studies were included	The certainty that the tests are inaccurate is MODERATE (imprecision) in the case of hemocultures and microhematocrit, and LOW (imprecision and risk of bias) in the case of direct parasitological examination.	
Certainty regarding effects	What is the overall certainty of the evidence on the effects of the test? ○ Very low ○ Low ● Moderate ○ High ○ No studies were included	Despite the uncertainty (low certainty of the evidence) related to the magnitude of the treatment's impact on the risk of long-term specific organ damage (see Annex 9), the existing information on the tests' accuracy in this scenario (moderate certainty that the available tests are insensitive) was considered an adequate surrogate outcome.	

	Judgment	Research evidence	Additional information
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	The judgment was based on the opinion of the experts, who considered that the existence of variability in this scenario is unlikely.	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel judged that the accuracy of the diagnostic tests evaluated is insufficient to replace the diagnostic standard (serological follow-up).	
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Significant savings ○ Varies ● Don't know	The cost of the microhematocrit and direct observation tests is low. The cost of the hemocultures test is moderate to high.	The implementation of some of the tests evaluated (microhematocrit and direct observation) instead of the diagnostic standard could potentially entail savings with regard to direct costs. However, considering the harm resulting from an incorrect diagnosis, these savings could turn into costs.

	Judgment	Research evidence	Additional information
Inequity	What would be the impact on health inequity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ○ Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (1): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70-0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01).	The implementation of simple diagnostic tests (microhematocrit and direct observation) instead of other more complex tests could potentially reduce inequity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the intervention is acceptable to the stakeholders.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the interventions are feasible to implement, especially microhematocrit tests and direct parasitological examination. The hemoculture tests require greater complexity and may not be feasible in some settings.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty regarding the accuracy of the test	Very low	Low	Moderate	High			No studies were included
Certainty regarding effects	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should microhematocrit, direct observation, or hemocultures be used as single tests (with no serological follow-up) to diagnose acute Chagas disease in the newborn of an infected mother?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention or of the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	●	○	○	○	○
Recommendation	The PAHO panel recommends serological follow-up in addition to direct parasitological tests (microhematocrit and direct observation) in patients with suspected Chagas disease **(acute congenital infection, starting at 8 months of age; seroconversion for other transmission modes)** (strong recommendation, based on moderate certainty regarding the effects of the intervention).				
Justification	The panel agreed that in the absence of accurate diagnostic tests that make it possible to determine who is sick and who is healthy, if acute Chagas disease is suspected, the standard diagnostic test should be performed, i.e. serological follow-up (starting in at 8 months of age if congenital transmission is suspected and seroconversion if other transmission modes are suspected). The panel accepted that the specificity of direct parasitological tests (practically no false positives), as well as their affordability and accessibility, which is why the panel decided to include them in the recommended diagnostic plan. Furthermore, the panel considered that the implementation of these tests could lead to early detection in some infected patients, which could be associated with benefits in terms of clinically relevant outcomes.				
Subgroup considerations					
Implementation considerations	Some studies suggest that, in asymptomatic patients with suspected congenital transmission (child of a mother who is a carrier of *T. cruzi*), the parasitemia peak could occur 20-30 days after birth, so serial parasitological testing could improve the detection of infected individuals. Given the low sensitivity of direct parasitological tests, in patients with suspected non-congenital acute infection, the implementation of serial parasitological testing could increase the detection of infected individuals. The recommendation is valid for immunosuppressed patients with suspected reactivation.				
Monitoring and evaluation					
Research priorities					

Reference summary

1. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.

Framework 5. Patients with chronic Chagas disease with no specific organ damage

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel indicated that the question was a priority.	
Desirable effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*See Annex 4, SoF 9.*	
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Annex 4, SoF 9.*	

	Judgment	Research evidence	Additional comments
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ● Very low ○ Low ○ Moderate ○ High ○ No studies were included	The information on critical outcomes comes from observational studies, with imprecision in the mortality outcome.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	Studies on patient values and preferences in this scenario were not identified. A study that evaluated the sociocultural impact of Chagas disease indicates that having the disease may be associated with a lower likelihood of getting a job, which leads to psychosocial problems that negatively impact personal and family life (4).	There was a debate on probable variability vs. probable absence of variability, which depended on the different experiences of the panel members. It was stressed that accepting treatment implies presumed existence of the disease, which in many cases is seen as a stigma. This could create variability in acceptance of the treatment, especially in adults.
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel concluded that the potential effect on reducing specific organ damage outweighed the adverse effects of the treatment.	

	Judgment	Research evidence	Additional comments
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Significant savings ○ Varies ○ Don't know	Although the estimated average annual cost of the treatment is nearly US$500 per patient, some estimates reduce the cost to US$47, depending on the required level of care. The majority of patients with no specific organ damage are from consultations at the primary care level (5, 6, 7). A cost-effectiveness study concludes that the early treatment of patients with chronic Chagas disease significantly reduces costs, by preventing complications associated with specific organ damage (8).	The level of confidence in the estimate of moderate savings is LOW, primarily because of uncertainty regarding the intervention's impact on clinically relevant outcomes. The vote was 2 to 1 in favor of savings, with 1 abstention.
Inequity	What would be the impact on health inequity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ● Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (9): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70-0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01). There are multiple barriers that impede equitable access to treatment. One of them is the heterogeneous and insufficient supply of medications to meet estimated demand (10). The additional difficulty of providing treatment to patients in areas with limited resources such as rural areas has been described (2).	There is a disadvantaged population (socioeconomically, geographically). The panel agreed that disadvantaged people are more likely to benefit if they receive treatment, but are less likely to have access to treatment.

	Judgment	Research evidence	Additional comments
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a qualitative study, barriers to distribution and access to treatment for Chagas disease were observed, including those associated with the availability of treatment: lack of systematic case-finding, little coordination between the levels of care and actors in the health system, and lack of training of the health team with respect to patient treatment and follow-up (1). Difficulties in the provision of anti-Chagas medications due to supply chain problems, lack of information on the treatment provided, deficiencies in the follow-up system, and difficulties in terms of geographical access have been described (2, 3).	It is feasible but depends on the availability of medications.

Summary of judgments

	Judgment							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know	Favors trypanocidal drugs
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know	Probably favors the placebo
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included	Probably favors the placebo
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability				Does not favor either the intervention or the comparison
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	Probably favors trypanocidal drugs
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know	Probably favors trypanocidal drugs
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know	Does not favor either the intervention or the comparison
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison

Conclusions

Should trypanocidal drugs be administered to patients with chronic Chagas disease and no specific organ damage or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Decision	**The PAHO panel suggests administering trypanocidal treatment rather than not offering any treatment to adults with Chagas disease (chronic infection) with no specific organ damage** (conditional recommendation, based on a low level of certainty on the effects of the intervention).				
Justification	The panel concluded that the possibility of obtaining substantial benefits in terms of clinically relevant outcomes (specific organ damage) weighed the risk of adverse effects. The low level of certainty of the evidence is what led to the conditional recommendation.				
Subgroup considerations	Some patients and physicians may give more weight to the negative aspects of the intervention (adverse effects, stigmatization) than to potential benefits and may choose to not follow treatment. We suggest engaging in a joint decision-making process to discuss the potential benefits and harms of the intervention. In immunosuppressed patients (HIV coinfection, transplantation, immunosuppressive treatments), the potential benefits could be considerably greater: prevention of flare-ups (observed average rate of reactivation of 27.86%; Annex 7) and the consequences thereof, which should be explained when making the decision. Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access. Patients should be periodically monitored on a regular and ongoing basis.				
Implementation considerations	Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.				
Monitoring and evaluation	Patients should be periodically monitored on a regular and ongoing basis.				
Research priorities	We recommend conducting randomized controlled trials that include this population subgroup, in addition to evaluating new drugs and new treatment guidelines. A randomized study in which benznidazole will be compared with nifurtimox and a placebo is currently in the recruitment phase (NCT02369978).				

Reference summary

1. Klein K, Burrone MS, Alonso JP, Rey Ares L, García Martí S, Lavenia A, et al. Estrategia para mejorar el acceso al tratamiento etiológico para la enfermedad de Chagas en el primer nivel de atención en Argentina. *Rev Panam Salud Pública* 2017; 41: e20.
2. Yun O, Lima MA, Ellman T, Chambi W, Castillo S, Flevaud L, Roddy P, Parreño F, Albajar Viñas P, Palma PP. Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières. *PLoS Negl Trop Dis* 2009; 3 (7): e488.
3. Manne J, Snively CS, Levy MZ, Reich MR. Supply Chain Problems for Chagas Disease Treatment. *Lancet Infect Dis* 2012; 12 (3): 173-175.
4. Storino R, Auger S, San Martino M, Urrutia MI, Jörg M. Aspectos biológicos, psicológicos y sociales de la discriminación del paciente Chagásico en Argentina. *Rev. Salud Pública* 2002; 4 (3): 258-269.
5. Moncayo A. Progress towards interruption of transmission of Chagas disease. Mem *Inst Oswaldo Cruz* 1999; 94 Suppl 1: 401-404.
6. Schenone H. Human infection by *Trypanosoma cruzi* in Chile: epidemiology estimates and costs of care and treatment of the chagasic patient. *Bol Chil Parasitol* 1998; 53 (1-2): 23-26.
7. Castillo-Riquelme M, Guhl F, Turriago B, Pinto N, Rosas F, Flórez Martínez M, Fox-Rushby J, Davies C, Campbell-Lendrum D, Gurtler RE. The Costs of Preventing and Treating Chagas Disease in Colombia. *PLoS Negl Trop Dis* 2008; 2 (11): e336.
8. Ramsey JM, Elizondo-Cano M, Sánchez-González G, Peña-Nieves A, Figueroa-Lara A. Opportunity cost for early treatment of Chagas disease in Mexico. *PLoS Negl Trop Dis* 2014; 8 (4): e2776.
9. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.
10. Costa Chaves G, Abi-Saab Arrieche M, Rode J, Mechali D, Ouverney Reis P, Vieira Alves R, et al. Estimación de la demanda de medicamentos antichagásicos: una contribución para el acceso en América Latina. *Rev Panam Salud Pública* 2017; 41: e45.

Framework 6. Children with Chagas disease

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel indicated that the question was a priority.	
Desirable effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	*See Annex 4, SoF 10.*	The panel judged the negativization of serology as evidence of a therapeutic response, and therefore described the benefits as LARGE.
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		As described in the included studies, in the panel members' experience the risk of adverse effects is significantly lower in children than in adults.
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ○ Very low ● Low ○ Moderate ○ High ○ No studies were included	There is MODERATE/HIGH confidence regarding the impact on surrogate outcomes (negativization of serology/parasitemia) due to imprecision, but the certainty on the validity of these outcomes as surrogates for clinically relevant outcomes (development of heart disease or mortality) is LOW due to the absence of studies that validate those outcomes (Annex 9).	

	Judgment	Research evidence	Additional comments
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ○ Probably no significant uncertainty or variability ● No significant uncertainty or variability	No studies on patient preferences were identified. A study that evaluated the sociocultural impact of Chagas disease indicates that having the disease may be associated with a lower likelihood of getting a job, which leads to psychosocial problems that negatively impact personal and family life (4). These results suggest that having Chagas disease is associated with stigmatization in adults, and may also occur in children.	The panel stressed that there will not be significant variability in how much patients value the outcomes. However, it stressed that accepting treatment implies accepting the disease, which in many cases is seen as a stigma. This could create variability in acceptance of the treatment, especially in adults.
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel considered that the potential benefit over clinically relevant outcomes outweighed the negative aspects of the intervention (adverse effects, burden of treatment).	

	Judgment	Research evidence	Additional comments
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Significant savings ○ Varies ○ Don't know	No cost-effectiveness studies were found that evaluate the impact of anti-Chagas treatment in children on the long-term use of resources. Based on the information on adults (5, 6, 7, 8), the panel recommended that early treatment would reduce costs due to complications of the disease in the long term. It is not possible to estimate the economic difference in net cost between treatment in childhood and the timely treatment of complications. Furthermore, the studies do not indicate a reliable rate of the incidence of preventable chronic complications with the treatment.	The panel concluded that the savings would be greater if treatment starts early: savings in terms of the possible development of specific organ damage, transfusion transmission, vertical transmission, and elimination of the role of a parasite reservoir. The level of confidence on the estimate of significant savings is LOW, primarily because of uncertainty regarding the intervention's impact on clinically relevant outcomes.
Inequity	What would be the impact on health inequity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ● Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (9): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; $p = 0.004$). • Lower overcrowding ratio (HR = 0.82 [0.70- 0.97]; $p = 0.022$). • Greater social coverage (HR = 1.46 [1.01-2.09]; $p = 0.04$). • More years of education (HR = 0.88 [0.80-0.97]; $p = 0.01$). A study that estimated the theoretical supply and demand for Chagas disease medications concludes that it is only possible for Latin American countries to adhere to the recommended treatment in 0.43% of the children (1 to 15 years) that need it (10). The additional difficulty of providing treatment to patients in areas with limited resources such as rural areas has been described (2).	There is a disadvantaged population (socioeconomically, geographically). The panel agreed that disadvantaged people are more likely to benefit if they receive treatment, but are less likely to have access to treatment.

	Judgment	Research evidence	Additional comments
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a qualitative study, barriers to distribution and access to treatment for Chagas disease were observed, including those associated with the availability of treatment: lack of systematic case-finding, little coordination between the levels of care and actors in the health system, and lack of training of the health team with respect to patient treatment and follow-up (1). Difficulties in the provision of anti-Chagas medications due to supply chain problems, lack of information on the treatment provided, deficiencies in the follow-up system, and difficulties in terms of geographical access have been described (2, 3).	It is feasible but depends on the availability of medications.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should trypanocidal drugs be administered to children with chronic Chagas disease or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or of the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Decision	**The PAHO panel recommends administering trypanocidal treatment rather than not offering any treatment to children with Chagas disease** (strong recommendation, based on moderate certainty regarding the parasiticidal effects of the intervention and low certainty regarding the effects on clinically relevant outcomes).				
Justification	The panel concluded that the possibility of obtaining substantial benefits in terms of clinically relevant outcomes (specific organ damage) outweighed the risk of adverse effects. Despite the limitations in the body of evidence, the panel decided to make a strong recommendation in this scenario, with the understanding that this does not strictly adhere to the methodology used to develop the guidelines (GRADE methodology). The reasons for this decision are explained below: • Although there is no direct evidence on the intervention's benefits in terms of clinically relevant outcomes, the significant impact on surrogate outcomes (negativization of serology and parasitemia) suggests that this is possible/probable. • The intervention is probably not associated with significant adverse effects. • Chagas disease is endemic to a significant part of Latin American and severely affects a large proportion of the population, especially people at a socioeconomic and geographical disadvantage. In this context, even in the absence of solid evidence on the benefits of the treatment, population measures have been adopted and are being adopted to improve the situation (e.g. programs to detect and treat Chagas disease in the field). The panel considers that a conditional recommendation could be interpreted in a way that could endanger the adequate development and continuity of these measures. • The experts all agree that the negativization of serology is an adequate therapeutic response.				
Subgroup considerations					

Implementation considerations	Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.
Monitoring and evaluation	Patients should be periodically monitored on a regular and ongoing basis.
Research priorities	We recommend conducting randomized controlled trials that include this population subgroup, in addition to evaluating new drugs and new treatment guidelines. We recommend conducting studies to validate intermediate outcomes (negativization of serology) as valid surrogates for clinically relevant outcomes.

Reference summary

1. Klein K, Burrone MS, Alonso JP, Rey Ares L, García Martí S, Lavenia A, et al. Estrategia para mejorar el acceso al tratamiento etiológico para la enfermedad de Chagas en el primer nivel de atención en Argentina. *Rev Panam Salud Pública* 2017; 41: e20.
2. Yun O, Lima MA, Ellman T, Chambi W, Castillo S, Flevaud L, Roddy P, Parreño F, Albajar Viñas P, Palma PP. Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières. *PLoS Negl Trop Dis* 2009; 3 (7): e488.
3. Manne J, Snively CS, Levy MZ, Reich MR. Supply Chain Problems for Chagas Disease Treatment. *Lancet Infect Dis* 2012; 12 (3): 173-175.
4. Storino R, Auger S, San Martino M, Urrutia MI, Jörg M. Aspectos biológicos, psicológicos y sociales de la discriminación del paciente Chagásico en Argentina. *Rev. Salud Pública* 2002; 4 (3): 258-269.
5. Moncayo A. Progress towards interruption of transmission of Chagas disease. *Mem Inst Oswaldo Cruz* 1999; 94 Suppl 1: 401-404.
6. Schenone H. Human infection by *Trypanosoma cruzi* in Chile: epidemiology estimates and costs of care and treatment of the chagasic patient. *Bol Chil Parasitol* 1998; 53 (1-2): 23-26.
7. Castillo-Riquelme M, Guhl F, Turriago B, Pinto N, Rosas F, Flórez Martínez M, Fox-Rushby J, Davies C, Campbell-Lendrum D, Gurtler RE. The Costs of Preventing and Treating Chagas Disease in Colombia. *PLoS Negl Trop Dis* 2008; 2 (11): e336.
8. Ramsey JM, Elizondo-Cano M, Sánchez-González G, Peña-Nieves A, Figueroa-Lara A. Opportunity cost for early treatment of Chagas disease in Mexico. *PLoS Negl Trop Dis* 2014; 8 (4): e2776.
9. Viotti R, Vigliano CA, Álvarez MG, Lococo BE, Petti MA, Bertocchi GL, Armenti AH. The Impact of Socioeconomic Conditions on Chronic Chagas Disease Progression. *Rev Esp Cardiol* 2009; 62 (11): 1224-1232.
10. Costa Chaves G, Abi-Saab Arrieche M, Rode J, Mechali D, Ouverney Reis P, Vieira Alves R, et al. Estimación de la demanda de medicamentos antichagásicos: una contribución para el acceso en América Latina. *Rev Panam Salud Pública* 2017; 41: e45.

Framework 7. Women of childbearing age with Chagas disease

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel indicated that the question is a priority. The panel agreed that in addition to the assessment of the treatment's impact on adults and children, the subgroup of women of childbearing age should be analyzed separately, since there are additional benefits and harms. This analysis considers the treatment's impact on vertical transmission and fetal or maternal adverse effects.	
Desirable effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	*See Annex 4, SoF 11.*	
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		The observed undesirable effects negatively impact mothers. The panel considers that there are no grounds for considering the possibility of adverse effects in newborns.

	Judgment	Research evidence	Additional comments
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ○ Very low ○ Low ● Moderate ○ High ○ No studies were included	The information comes from observational studies which have a higher level of confidence due to the large magnitude of the effect.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ○ Probably no significant uncertainty or variability ● No significant uncertainty or variability	No studies were found that evaluated the values and preferences of women at risk of vertically transmitting Chagas disease. A systematic review that evaluated the values and preferences of women with HIV at risk of vertically transmitting the disease shows that for the vast majority of women, it is extremely important to prevent vertical transmission, while many others focused on the adverse effects of the treatment (4).	The panel recommended that the vast majority of women prioritize preventing vertical transmission over the other outcomes evaluated.
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The panel concluded that the benefits of reducing vertical transmission outweighed the adverse effects on mothers.	

	Judgment	Research evidence	Additional comments
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Significant savings ○ Varies ○ Don't know	Two economic models demonstrate that the early treatment of congenital Chagas disease is cost-effective (5, 6). Therefore, the treatment of women of childbearing age could potentially reduce costs even more, since it would keep resources from being used in three nonexclusive scenarios: the cost associated with disease in mothers, the cost of treating children with congenital Chagas disease, and costs stemming from complications in children who do not receive early treatment.	The panel recommended that the prevention of vertical transmission probably has a significant impact on costs. Resources would primarily be saved when monitoring newborns at risk of infection and in the treatment of those who are infected.
Inequity	What would be the impact on health inequity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably Increased ○ Increased ● Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (7): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70- 0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01). A study in which a tool was designed to calculate the demand for anti-Chagas medications in 14 countries of Latin America concludes that there is a significant gap between the estimated demand for drugs and the estimated number of required treatments. According to this study, in adults over 15 years of age the availability of benznidazole would treat 0.22%-0.29% of the cases that should receive the drug in an ideal scenario (8). The additional difficulty of providing treatment to patients in areas with limited resources such as rural areas has been described (2).	There is a disadvantaged population (socioeconomically, geographically). The panel agreed that disadvantaged people are more likely to benefit if they receive treatment, but are less likely to have access to treatment.

	Judgment	Research evidence	Additional comments
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a qualitative study, barriers to distribution and access to treatment for Chagas disease were observed, including those associated with the availability of treatment: lack of systematic case-finding, little coordination between the levels of care and actors in the health system, and lack of training of the health team with respect to patient treatment and follow-up (1). Difficulties in the provision of anti-Chagas medications due to supply chain problems, lack of information on the treatment provided, deficiencies in the follow-up system, and difficulties in terms of geographical access have been described (2, 3).	It is feasible but depends on the availability of the medications.

Summary of judgment

	Judgment							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know	Favors trypanocidal drugs
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know	Probably favors the placebo
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included	Probably favors trypanocidal drugs
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability				Does not favor either the intervention or the comparison
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	Favors the trypanocidal drugs
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know	Probably favors trypanocidal drugs
Inequity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	Does not favor either the intervention or the comparison
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison

Conclusions

Should trypanocidal drugs be administered to women of childbearing age with chronic Chagas disease or is better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or of the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Decision	The PAHO panel recommends administering trypanocidal treatment rather than not prescribing any treatment to women of childbearing age with Chagas disease (strong recommendation, based on moderate certainty regarding the effects of the intervention).				
Justification	The panel concluded that the reduction in vertical transmission outweighed the risk of adverse effects. The moderate certainty in the balance between benefits and harms is what led to the strong recommendation.				
Subgroup considerations	In immunosuppressed patients (coinfection by HIV, transplantation), the potential benefits could be considerably greater: prevention of flare-ups (observed average rate of reactivation of 27.86%; Annex 7) and the consequences thereof, which should be explained when making the decision.				
Implementation considerations	Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.				
Monitoring and evaluation	Patients should be periodically monitored on a regular and ongoing basis.				
Research priorities	Promoting research on vertical transmission and the subgroups that may benefit to a greater or lesser extent.				

Reference summary

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2. Yun O, Lima MA, Ellman T, Chambi W, Castillo S, Flevaud L, Roddy P, Parreño F, Albajar Viñas P, Palma PP. Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières. *PLoS Negl Trop Dis* 2009; 3 (7): e488.
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Framework 8. Patients with chronic Chagas disease and specific organ damage

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel indicated that the question is a priority.	
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Annex 4, SoF 12.*	
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

	Judgment	Research evidence	Additional comments
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ○ Very low ○ Low ● Moderate ○ High ○ No studies were included	The overall certainty provided by randomized studies is MODERATE, due to imprecision.	The panel decided to consider only the evidence provided by randomized studies.
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ● Possibly significant uncertainty or variability ○ Probably no significant uncertainty or variability ○ No significant uncertainty or variability	Studies on patient values and preferences in this scenario were not found. A study that evaluated the sociocultural impact of Chagas disease indicates that having the disease may be associated with a lower likelihood of getting a job, which leads to psychosocial problems that negatively impact personal and family life (4).	This was debated, depending on the panel members' experience. Some argued that many patients prefer not to receive trypanocidal treatment so that they won't be exposed to the adverse effects of the intervention. The panel also concluded that many patients interpret acceptance of the treatment as a negative aspect, since they are exposed to the stigmatization associated with Chagas disease.
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel judged that in the absence of significant benefits, the balance does not favor either the intervention or the comparator.	

	Judgment	Research evidence	Additional comments
Required resources	How large are the resource requirements (costs)? ○ High costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Significant savings ○ Varies ○ Don't know	The estimated average annual cost of treating chronic Chagas cardiopathy in different countries of Latin America was between US$439.29 and US$584.25 (5-7). In patients who present cardiac complications and require care in specialized centers, the estimated cost is between	Since there were no significant benefits were observed in terms of clinically relevant outcomes, the panel accepted that prescribing treatment in this patient subgroup could lead to a moderate increase in costs.
Inequity	What would be the impact on health inequity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (7): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70- 0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01). One study concludes that the supply of anti-Chagas medications in 14 countries of Latin America would cover less than the 1% of the estimated demand in people over the age of 15 (10). The additional difficulty of providing treatment to patients in areas with limited resources such as rural areas has been described (2).	The panel considered that the resources used to treat patients with specific organ damage could be allocated to other populations with much greater probability of obtaining benefits.

	Judgment	Research evidence	Additional comments
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		It depends on the views of the healthcare professional.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In a qualitative study, barriers to distribution and access to treatment for Chagas disease were observed, including those associated with the availability of treatment: lack of systematic case-finding, little coordination between the levels of care and actors in the health system, and lack of training of the health team with respect to patient treatment and follow-up (1). Difficulties in the provision of anti-Chagas medications due to supply chain problems, lack of information on the treatment provided, deficiencies in the follow-up system, and difficulties in terms of geographical access have been described (2, 3).	It is feasible but depends on the availability of the drugs.

Summary of judgments

	Judgment							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know	Probably favors the placebo
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know	Probably favors the placebo
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included	Probably favors the placebo
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability				Probably favors trypanocidal drugs
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	Does not favor either the intervention or the comparison
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know	Probably favors the placebo
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know	Probably favors the placebo
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison

Conclusions

Should trypanocidal drugs be administered to patients with chronic Chagas disease and specific organ damage or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for the intervention or of the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Decision	**The PAHO panel suggests NOT prescribing trypanocidal treatment in patients with Chagas disease (chronic infection) and specific organ damage** (conditional recommendation, based on moderate certainty regarding the effects of the intervention).				
Justification	The panel accepted that the negative aspects of the intervention (adverse effects, increased costs, increased inequity) outweighed the marginal benefits observed. The panel considered that the balance between benefits and negative aspects did not definitively lean either way, and considered potential variability in patient values and preferences, which led to the conditional recommendation.				
Subgroup considerations	Some patients and physicians may give more weight to the potential benefits (regardless of how small) and choose to follow treatment. We suggest engaging in a joint decision-making process to discuss the potential benefits and harms of the intervention. In immunosuppressed patients (HIV coinfection, transplantation), the potential benefits could be considerably greater: prevention of flare-ups (observed average rate of reactivation of 27.86%; Annex 7) and the consequences thereof). This should be explained when making the decision.				
Implementation considerations	Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.				
Monitoring and evaluation	Patients should be periodically monitored on a regular and ongoing basis.				
Research priorities					

Reference summary

1. Klein K, Burrone MS, Alonso JP, Rey Ares L, García Martí S, Lavenia A, et al. Estrategia para mejorar el acceso al tratamiento etiológico para la enfermedad de Chagas en el primer nivel de atención en Argentina. *Rev Panam Salud Pública* 2017; 41: e20.
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Framework 9. Patients with acute/congenital Chagas disease

Evaluation

	Judgment	Research evidence	Additional comments
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel considered that the question is probably a priority.	
Desirable effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	*See Annex 4, SoF 13.*	Since no randomized controlled trials were found, studies on a single arm with at least one-year follow-up were included, which describe the negativization of parasitemia in one year or the negativization of serology in 2 3 years. No research describes the development or progression of specific organ damage or outcomes in pregnant or lactating patients.
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

	Judgment	Research evidence	Additional comments
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ● Very low ○ Low ○ Moderate ○ High ○ No studies were included	The information comes from uncontrolled observational studies.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ○ Possibly significant uncertainty or variability ● Probably no significant uncertainty or variability ○ No significant uncertainty or variability	We did not find any studies that evaluated patient values and preferences in this scenario.	The panel considered that given the possibility of preventing the chronification of Chagas disease, the vast majority of people would prefer to receive treatment.

	Judgment	Research evidence	Additional comments
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel concluded that acute Chagas infection is a potentially catastrophic situation, based on the following data: • Without treatment, 100% of patients develop the chronic phase of the disease. • The vast majority of patients present myocardial damage during the acute stage of the infection (8). • Mortality from acute Chagas disease is around 10% (8, 9). For this reason, based on the potential benefits observed in terms of the negativization of serology and parasitemia and the fact that treatment in this phase could have a positive impact on the disease's progression in these patients, the panel judged that the benefits outweigh the negative aspects of the intervention.	
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Significant savings ○ Varies ○ Don't know	Two economic models demonstrate that the early treatment of congenital Chagas disease is cost-effective (4, 5).	The panel agreed that preventing progression to the chronic phase of the disease will most likely result in moderate savings, especially considering that the direct cost of trypanocidal drugs is not high.

	Judgment	Research evidence	Additional information
Inequity	What would be the impact on health inequity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	The panel agreed that there is a disadvantaged population: people who are less likely to access diagnostic interventions due to socioeconomic and geographical differences. A study that evaluated the impact of socioeconomic conditions on the natural evolution of chronic Chagas disease indicated that the following variables are good markers of disease progression (7): • Less time living in an endemic area: Hazard ratio (HR) = 0.97 [0.96-0.99]; p = 0.004). • Lower overcrowding ratio (HR = 0.82 [0.70- 0.97]; p = 0.022). • Greater social coverage (HR = 1.46 [1.01-2.09]; p = 0.04). • More years of education (HR = 0.88 [0.80-0.97]; p = 0.01). There are multiple barriers that impede equitable access to treatment. One of them is the heterogeneous and insufficient supply of medications to meet estimated demand (7). The additional difficulty of providing treatment to patients in areas with limited resources such as rural areas has been described (2).	There is a disadvantaged population (socioeconomically, geographically). The panel agreed that disadvantaged people are more likely to benefit if they receive treatment, but are less likely to have access to treatment.

	Judgment	Research evidence	Additional information
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In a qualitative study, barriers to distribution and access to treatment for Chagas disease were observed, including those associated with the availability of treatment: lack of systematic case-finding, little coordination between the levels of care and actors in the health system, and lack of training of the health team with respect to patient treatment and follow-up (1). Difficulties in the provision of anti-Chagas medications due to supply chain problems, lack of information on the treatment provided, deficiencies in the follow-up system, and difficulties in terms of geographical access have been described (2, 3).	It is feasible but depends on the availability of the drugs.

Summary of judgments

	Judgment							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know	Favors trypanocidal drugs
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know	Probably favors the placebo
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included	Favors the placebo
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability				Probably favors trypanocidal drugs
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	Favors trypanocidal drugs
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know	Probably favors trypanocidal drugs
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know	Does not favor either the intervention or the comparison
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	Probably favors trypanocidal drugs
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	Does not favor either the intervention or the comparison

Conclusions

Should trypanocidal drugs be administered to patients with acute/congenital Chagas disease or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or of the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Decision	**The PAHO panel recommends administering trypanocidal treatment over not prescribing treatment in patients with acute/congenital Chagas disease** (strong recommendation, based on a very low level of certainty on the effects of the intervention).				
Justification	The panel understood that trypanocidal treatment in this scenario could be associated with significant benefits in the context of a catastrophic situation, since mortality in this phase (acute) is high (nearly 5%), even when trypanocidal treatment is received, and 100% of the patients who are not treated progress to the chronic phase. Therefore, considering that severe adverse effects of the treatment are exceptional, the strong recommendation is based on the context of a very low level of certainty regarding the effects of the intervention.				
Subgroup considerations					
Implementation considerations	Medications and healthcare services must be ensured, particularly for populations that are disadvantaged in terms of access.				
Monitoring and evaluation	Patients should be periodically monitored on a regular and ongoing basis.				
Research priorities					

Reference summary

1. Klein K, Burrone MS, Alonso JP, Rey Ares L, García Martí S, Lavenia A, et al. Estrategia para mejorar el acceso al tratamiento etiológico para la enfermedad de Chagas en el primer nivel de atención en Argentina. *Rev Panam Salud Pública* 2017; 41: e20.
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Framework 10. Benznidazole compared to nifurtimox

Evaluation

	Judgment	Research evidence	Additional information
Problem	Is the problem a priority? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The panel considered that the question is probably a priority.	
Desirable effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Annex 4, SoF 14, 15.*	Since no randomized controlled trials were found on patients with acute Chagas disease, studies on a single arm with at least one-year follow-up were included, which describe the negativization of parasitemia in one year or the negativization of serology in 2 3 years. There are very few cohorts that compare one treatment with another. The development or progression of specific organ damage is not described. No study describes the outcomes in pregnant or lactating patients
Undesirable effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Depending on the panel members' experience with each drug, nifurtimox is associated with weight loss and psychiatric effects and benznidazole is associated with cutaneous and neurological reactions.

	Judgment	Research evidence	Additional information
Certainty of the evidence	What is the overall certainty of the evidence on the effects? ● Very low ○ Low ○ Moderate ○ High ○ No studies were included	For acute Chagas disease, the information comes from uncontrolled observational studies. For chronic Chagas disease, observational and randomized studies with a risk of bias and indirect information were used.	
Values	Is there significant uncertainty or variability in how much people value the main outcomes? ○ Significant uncertainty or variability ● Possibly significant uncertainty or variability ○ Probably no significant uncertainty or variability ○ No significant uncertainty or variability	Studies on patient preferences in this scenario were not found.	It was recommended that patients may value the specific toxicological profile of the two drugs differently.
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	In the absence of reliable evidence that suggests the benefits of one intervention over the other, the panel based its judgment on the toxicological profile of the two drugs, which it considered to be similar.	

	Judgment	Research evidence	Additional information
Required resources	How large are the resource requirements (costs)? ○ High costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Significant savings ○ Varies ○ Don't know	Both drugs have a similar cost.	
Inequity	What would be the impact on health inequity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably Increased ○ Increased ○ Varies ○ Don't know	The panel considered that if both drugs are available, prescribing either alternative would not have an impact on equity.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No studies were identified that analyze the use of treatment with benznidazole compared to nifurtimox. The feasibility of prescribing one pharmacotherapy or the other will depend on the availability of the drugs.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence	Very low	Low	Moderate	High			No studies were included
Values	Significant uncertainty or variability	Possibly significant uncertainty or variability	Probably no significant uncertainty or variability	No significant uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Required resources	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Significant savings	Varies	Don't know
Inequity	Reduced	Probably reduced	Probably no impact	Probably Increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Conclusions

Should benznidazole or nifurtimox be used for acute/chronic Chagas disease?

Type of Decision	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for the intervention or of the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Decision	**The PAHO panel suggests prescribing either benznidazole or nifurtimox without distinction in patients with Chagas disease (acute or chronic infection)** (conditional recommendation, based on the very low level of certainty regarding the effects of prescribing one drug over the other).				
Justification	Given the uncertainty resulting from the analysis of the available evidence for this comparison, the panel agreed that both drugs have proven to be effective and have a similar toxicological profile.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

Annex6

Analysis of diagnostic method accuracy by commercial test

			Overall analysis		Number of studies
Assay	Test	Laboratory	Sensitivity	Specificity	
ELISA	Abbot	Abbot	97,9	98,8	5
ELISA	Adlatis	Adlatis	99,1	51,2	1
ELISA	Bioelisa	Biokit	98,5	99	3
ELISA	Bioelisacruzi	Biolab	98,3	98,8	4
ELISA	Biomanguinhos	Biomanguinhos	100	93,3	1
ELISA	Biozyma	Lemos	97,7	96,9	1
ELISA	Biozima	Polychaco	100	94,6	1
ELISA	BLK	BLK	97,6	100	1
ELISA	Celisa	Cellabs	100	100	1
ELISA	Chagas ELISA	Ebram	97,6	97,7	1
ELISA	Chagas III	Bios Chile	95,3	96	4
ELISA	Chagatek	Lemos	97,7	92,2	4
ELISA	Chagatest	Wiener	95,5	95,2	6
ELISA	Dia Kit	Gador	99,6	99,1	1
ELISA	Elisacruzi	Biomerieux	99	94,8	3

Assay	Test	Laboratory	Overall analysis		Number of studies
			Sensitivity	Specificity	
ELISA	GenCell	Gencell	95.1	94.5	1
ELISA	Gull	Gull	100	98.5	1
ELISA	Hemagen	Hemagen	99.3	96.7	2
ELISA	Hemobio	Embrabio	99.8	96	2
ELISA	IgG-ELISA	Novatec	100	87.5	1
ELISA	IICS	IICS	98.8	98.1	1
ELISA	Imuno-Elisa	Wama	99.5	96.5	1
ELISA	IVD	IVD	100	93	1
ELISA	Ortho	Ortho	98.3	99.4	3
ELISA	Pharmatest	Pharmatest	53.3	99.9	1
ELISA	Premier	Meridian	91.6	99.9	3
ELISA-r	Chagatest V3	Wiener	89	98.5	6
ELISA-r	Fiocruz	Biomanguinhos	97	99.3	2
ELISA-r	Gold Elisa	Gold Elisa	100	99.3	1
ELISA-r	Pathozyme	Omega	99.2	97.6	2
HAI	Biochagas	Bioshop	84.8	98.1	1
HAI	Cecon	Cecon	93.4	91.4	2
HAI	Chagas-HAI	Ebram	91.9	85.5	3
HAI	Chagatest	Wiener	86.9	99.2	6
HAI	Fiocruz	Biomanguinhos	44.2	96.6	1
HAI	Hemacruzi	Biolab	96.7	98.5	4
HAI	Hemagen	Hemagen	93.3	90.3	2
HAI	Imuno-HAI	Wama	98.2	96.3	2
HAI	Imunoserum	Lemos	96.9	93.8	2
HAI	Salk	Biotec São Paulo	93.5	97.1	1
HAI	Trilab	Trilab	71.5	97.7	1

Assay	Test	Laboratory	Overall analysis		Number of studies
			Sensitivity	Specificity	
ICT	AB rapid	Bioline	88	100	1
ICT	Chagas Detect	Inbios	94.2	97.5	7
ICT	Chagas Quick	Cypress	92.9	93.2	1
ICT	Check Chagas	Wiener	90.2	98.4	3
ICT	Immunocomb	Orgenics	97.3	94	1
ICT	Onsite	CTK	92.9	94.3	2
ICT	Operon	Operon	90.2	94	5
ICT	SD-Chagas	Standard Diagnostics	90.6	94	1
ICT	Serodia	Furijibio	94.2	94.8	1
ICT	Stat-Pak	Chembio	94.7	98.5	17
CMIA	Architect	Abbot	98.9	92.8	3
CMIA	Prism	Abbot	100	99.9	1
CMIA	Immulite	Siemens	100	88.7	1
IFI	Immunocruzi	Biolab	96.4	89.8	6
PA	ID-Chagas		96.2	98.9	3
PA	Serodia		100	97.7	1

Annex7

Reactivation of Chagas disease in immunosuppressed patients

Trypanocidal drugs compared to placebo for secondary prophylaxis for Chagas disease			
Evaluation of certainty	Summary of findings		
Number of participants (studies) Follow-up	Study event rates (%)		Impact
	With placebo	With trypanocidal drugs	
Reactivation			
92 observational studies[1-92]	Observed prevalence of reactivation (parasitemia) with no prophylaxis: immunosuppressed patients (total, without HIV), 27.86%; liver transplant, 1.76%; bone marrow transplant, 23.33%; kidney transplant, 27.27%; heart transplant, 30.89%; HIV/AIDS, 39.58%. Death from reactivation: heart transplant, 1.71%. Observed prevalence of reactivation with prophylaxis: heart transplant, 100%; steroid therapy, 0%.		

CI: Confidence interval.

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Annex8

Adverse effects of nifurtimox and benznidazole

Adverse effects based on duration of treatment and drug used in acute or chronic disease

Duration	Treatment	Acute	Chronic	Total
< 30 days	Benznidazol	0% 0/189	6.51% 76/1,168	4.94% 76/1,537
	Nifurtimox	0% 0/71	–	0% 0/71
31 a 60 days	Benznidazol	0% 0/61	10.82 116/1,072	10.24% 116/1,133
	Nifurtimox	2.91% 11/378	18.52% 25/135	7.02% 36/513
61 a 90 days	Benznidazol	–	8.33% 119/1,429	8.33% 119/1,429
	Nifurtimox	0.98% 4/407	1.67% 1/60	1.07% 5/467
> 90 days	Nifurtimox	–	14.29% 44/308	14.29% 44/308

Nifurtimox adverse effects according to dose used

Dose (mg/kg/day)	Acute	Chronic	Total
≤ 10	2.65% 4/151	16.67% 25/150	9.63% 29/301
11 - 20	0.68% 2/294	17.62 34/193	7.39% 36/487
> 20	2.19% 9/411	10.38% 11/106	3.87% 20/517

Dose (mg/kg/día)	Acute	Chronic	Total
5	0% 0/91	8.54% 264/3,091	8.30% 264/3,182
7.5	0% 0/52	1.56% 1/64	0.86% 1/116
> 7.5	-	8.95% 46/514	8.95% 46/514

Adverse effects of nifurtimox and benznidazole by age group

Age (years)	Acute	Chronic	Total
≤ 12	1.44% 11/765	3.24% 6/185	1.79% 17/950
> 12	10.95% 350/3,195	10.33% 4/30	10.98% 354/3,225

Annex 9

Analysis of the validity of negativization of serology and parasitemia as surrogates for clinically relevant outcomes

The inclusion of the outcome "negativization of serological tests" was a topic of discussion, since it concerns a surrogate outcome. Considering that a large number of studies only measure this outcome or use it as a primary outcome, the group of experts decided to include it. The evidence was analyzed to substantiate the relationship between this outcome and clinically relevant outcomes; the analysis compared the probability of specific organ damage in the subgroup of patients with and without negativization, as well as the effect of antiparasitic treatment on these subgroups (see below). Based on this analysis, it was concluded that the quality of the evidence that supports the use of "serological negativization" as a surrogate for clinically relevant outcomes is between low and very low, so this outcome was included in the summary tables, but was regarded as indirect.

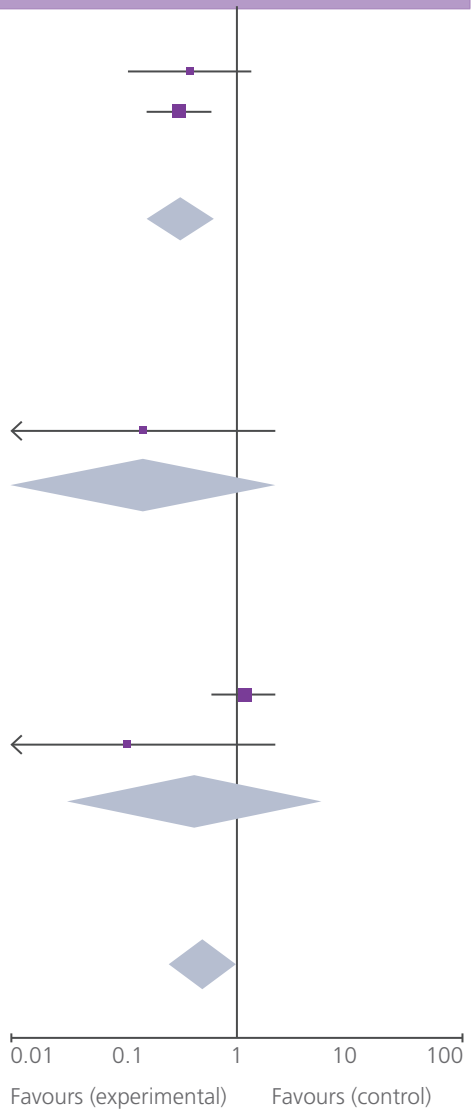
Analysis of the negativization of serology as a surrogate outcome:
Effect of the treatment on different outcomes

Study	Negativization of serology (RR)	Persistence of positive serology (RR)	Death (RR)	Cardiopathy (RR)	Clinical deterioration (RR)	ECG (RR)
Fabbro de Suasnábar D, Arias E, Streiger M, Piacenza M, Ingaramo M, Del Barco M, Amicone N. "Evolutive behavior towards cardiomyopathy of treated (nifurtimox or benznidazole) and untreated chronic chagasic patients." *Rev Inst Med Trop São Paulo* 2000; 42 (2): 99-109	1.38	0.35	0.64	–	0.45	0.46
Fabbro DL, Streiger ML, Arias ED, Bizai ML, del Barco M, Amicone NA. "Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe city (Argentina), over a mean follow-up of 21 years: parasitological, serological and clinical evolution." *Rev Soc Bras Med Trop* 2007; 40 (1): 1 10	43.2	0.63	–	0.23	–	0.45
Sosa Estani S, Segura EL, Cura E, Velázquez E, Prado N. Evolución clínica y serológica en niños en fase indeterminada de la infección por *Trypanosoma cruzi*, tratados con benznidazol. Seguimiento de 7 años. *Medicina* 1999; 55 (supl III): 17-18.	16.5	0.77	–	–	–	
Viotti R, Vigliano C, Lococo B, Bertocchi G, Petti M, Álvarez MG, Postan M, Armenti A. "Long-term cardiac outcomes of treating chronic Chagas disease with Benznidazole versus no treatment: a nonrandomized trial." *Ann Intern Med* 2006; 144 (10): 724 734.	2.5	0.9	0.25	–	0.3	0.33
Viotti R, Vigliano C, Armenti H, Segura E. "Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up." *Am Heart J* 1994; 127 (1): 151-162.	3.1	0.86	0.53	–	0.2	0.23

Study	Negativization of serology (RR)	Persistence of positive serology (RR)	Death (RR)	Cardiopathy (RR)	Clinical deterioration (RR)	ECG (RR)
Coura JR, De Abreu LL, Willcox HP, Petana W. "Estudo comparativo controlado com emprego de benznidazole, nifurtimox e placebo, na forma crônica da doença de Chagas, em uma área de campo com transmissão interrompida. I. Avaliação preliminar". *Rev Soc Bras Med Trop* 1997; 30 (2): 139-144.	–	–	–	–	–	
De Andrade AL, Zicker F, De Oliveira RM, Almeida Silva S, Luquetti A, Travassos LR, Almeida IC, De Andrade SS, De Andrade JG, Martelli CM. "Randomised trial of efficacy of Benznidazole in treatment of early *Trypanosoma cruzi* infection." *Lancet* 1996; 348 (9039): 1407-1413.	12.5	0.44	–	–	–	
Gallerano RR, Sosa RR. "Interventional study in the natural evolution of Chagas disease. Evaluation of specific antiparasitic treatment. Retrospective-prospective study of antiparasitic therapy." *Rev Fac Cien Med Univ Nac Córdoba* 2000; 57 (2): 135 162.	32.4	0.98	0.16	–	–	
Silveira. "Avaliação a Longo Prazo Do Tratamento Específico Da Doença de Chagas". PhD thesis. Faculty of Medicine, University of Brasilia, 2000.	3.7	0.85	1.12	–	–	

Clinically relevant outcomes in patients with and without negativization of serology

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio Weight	Risk Ratio M - H, Random, 95% CI
1.2.1 Cardiopathy						
Machado - de - Assis 2012	3	8	54	80	22.7%	0.56(0.22, 1.38)
Sabino 2015	26	188	79	257	35.0%	0.45(0.30, 0.67)
Sosa Estani 1999	0	0	0	0		Not estimable
Subtotal (95% CI)		**196**		**337**	**57.6%**	**0.47(0.32, 0.67)**
Total events	29		133			
Heterogeneity. $Tau^2 = 0.00$; $Chi^2 = 0.17$, df = 1(P = 0.68); $I^2 = 0\%$						
Test for overall effect: Z = 4.08 (P < 0.0001)						
1.2.2 Clinical deterioration of group (Kushnir)						
Viotti 2006	0	24	23	177	4.9%	0.15 (0.01, 2.42)
Subtotal (95% CI)		**24**		**177**	**4.9%**	**0.15 (0.01, 2.42)**
Total events	0		23			
Heterogeneity. No applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.2.3 ECG changes						
Pinto 2013	15	47	37	132	32.6%	1.14 (0.69, 1.88)
Viotti 1994	0	44	36	386	4.9%	012. (0.01, 1.89)
Subtotal (95% CI)		**91**		**518**	**37.5%**	**0.51 (0.04, 5.79)**
Total events	15		73			
Heterogeneity. $Tau^2 = 2.33$; $Chi^2 = 3.26$, df = 1(P = 0.07); $I^2 = 69\%$						
Test for overall effect: Z = 0.55 (P = 0.59)						
Subtotal (95% CI)		**311**		**1032**	**100.0%**	**0.57 (0.30, 1.09)**
Total events	44		229			
Heterogeneity. $Tau^2 = 0.28$; $Chi^2 = 11.29$, df = 4 (P = 0.02); $I^2 = 65\%$						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: $Chi^2 = 0.63$, df = 2 (P = 0.73), $I^2 = 0\%$						



Experimental: patients who negativized serology; control: patients who did not negativize serology.

Annex10

Etiological treatment of Chagas disease

American trypanosomiasis (Chagas disease) (*Trypanosoma cruzi*)

Acute cases

First option: Benznidazole, patients ≤ 40 kg: 7.5-10 mg/kg/po/d; patients > 40 kg, 5-7 mg/kg/po/d. In both fractional cases 2 to 3 daily doses for 60 d.

Second option: Nifurtimox, patients ≤ 40 kg: 10-15 mg/kg/po/d; patients > 40 kg, 8-10 mg/kg/po/d. In both fractional cases 2 to 3 daily doses for 60 d.

Congenital cases

First option: Benznidazole, 10 mg/kg/po/d in 2 to 3 daily doses for 60 d.

Other options: Nifurtimox, 10-15 mg/kg/po/d in 2 to 3 daily doses for 60 d.

Recent chronic infection

Benznidazole, patients that weigh ≤ 40 kg, 7.5mg/kg/po/d. Patients that weigh > 40 kg, 5 mg/kg/po/d. In both fractional cases 2 to 3 daily doses for 60 d. Any children ≤ 12 years of age with a recent chronic infection and patients with a late diagnosis of chronic infection require a complete comprehensive evaluation and a formal prescription from the attending physician.

Reference

1. Pan American Health Organization. Treatment of Infectious Diseases. PAHO: Washington DC, 2016; pp 317.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