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Combined use of two rapid tests for the conclusive diagnosis of Chagas disease: a systematic scoping review

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ABSTRACT

Objective The goal of this systematic scoping review is to collect and summarise scientific evidence regarding the validity of two simultaneous immunochromatographic tests for the conclusive diagnosis of Chagas disease. The research was informed by the following review questions: Will the use of two rapid tests be a valid method for the definitive diagnosis of Chagas disease when compared with conventional serological tests? In what type of population has the operation of two rapid tests been tried for the diagnosis of Chagas disease? What are the biomedical and public health advantages of the diagnostic method resulting from the combination of two rapid tests over the conventional serological method? Will it be a cost–benefit strategy for the diagnosis of Chagas with respect to conventional serological tests?

Design Systematic scoping review.

Setting A search of the published and unpublished literature in five databases was carried out, in order to identify, screen and select the studies included in this review.

Results 468 studies were identified, of which 46 were screened with a full-text reading, and finally, three articles were included in the review. All studies were in endemic countries with adult and paediatric populations (n=1133) and, together, they evaluated four different rapid tests. The rapid tests showed good sensitivity (97.4%–100%) and specificity (96.1%–100%) for the diagnosis of Chagas when used in combination and compared with the reference tests.

Conclusions The simultaneous use of at least two immunochromatographic rapid tests is a valid option for the definitive diagnosis of chronic Chagas in endemic rural areas, as long as there are studies that previously evaluate their performance on the areas of implementation. Therefore, this could be an alternative to the current diagnostic standard. However, additional studies are still needed in more countries in order to provide further evidence and to investigate the cost–benefit.

Strengths and limitations of this study

► A preliminary search revealed that this is the first review on this topic.
► The review follows the methodological standards of the Joanna Briggs Institute.
► A wide bibliographic search without restrictions in the databases was conducted, including grey literature.
► A critical appraisal of the studies included was carried out, following the CASPe programme.
► Due to the type of study, the risk of bias of the articles included in the review was not analysed.

INTRODUCTION

Chagas disease, also known as American trypanosomiasis, is an anthropozoonosis caused by the protozoan *Trypanosoma cruzi*.[1] Currently, this micro-organism is endemic in 21 countries in Latin America, from the south of the USA to the north of Argentina and Chile.[1] Due to the increase of population movements in the last decades, it has extended to other places of the planet, making it possible to find cases in Europe, North America, Africa, Asia and Australia,[2] being Spain the non-endemic country with the greater prevalence at a European level.[3]

According to the criteria of WHO, Chagas disease is still considered a neglected tropical disease. However, it is a disease with great and complex socioeconomic and environmental implications that makes it a health problem affecting between 6 and 7 million people worldwide.[2] It causes a global disease burden of US$627.46 million each year in health spending.[1] It is also the leading cause of cardiomyopathy and death from cardiovascular disease in people aged 30–50 in Latin America.[4]

Vectorial transmission of the disease only occurs in endemic areas and typically occurs in poor rural areas, as the vector, the infected triatomine bug, takes refuge in the tropical environment.[5] When the insect bites a person, it deposits faeces on their skin, this, when scratching the wound, can introduce the parasite in the body through the bite itself or through the mucous membranes.[1] Contagion can also occur vertically or iatrogenically

after a transplant or a blood transfusion. The latter is decreasing thanks to transfusion safety strategies, while congenital transmission is increasing, both in endemic and non-endemic countries.[6] Other less frequent forms of transmission are laboratory accidents or ingestion of contaminated food and drink.[1]

The disease has two stages, the acute stage which lasts 4–8 weeks, and is usually asymptomatic, and the chronic stage.[7] This last one presents an indeterminate phase, where the person is seropositive but does not have a clinic or, a symptomatic phase characterised by cardiac and gastrointestinal complications, which appear 10–30 years after the contagion.[1] At the moment, there are only two medicines to treat Chagas disease (benznidazole and nifurtimox) and their effectiveness decreases as time from the onset of the disease passes, so early diagnosis is important.[8]

Currently, the diagnosis in the acute and congenital phase is established with a direct visualisation of the parasite in blood or with a PCR. However, in the chronic phase the parasitaemia is low and these methods are not effective, so serological tests that detect IgG antibodies against *T. cruzi* must be performed. The most used are ELISA, indirect haemagglutination (IHA) or indirect immunofluorescence (IIF).[1] Nevertheless, the conventional realisation of these tests is not within the reach of all health centres, many times the samples have to be sent to reference laboratories,[9] with the appropriate equipment and qualified personnel. In addition, the patient must go to the medical centre at least twice (for the extraction of the blood sample and for the results). All this increases the cost of the diagnosis and also rises the risk of 'patient loss'.[10] This difficulty and delay in establishing a final diagnosis occurs mainly in rural areas of endemic regions, where the prevalence is higher.[11] Thus, American trypanosomiasis continues to be an underdiagnosed[12] and undertreated disease.

As a result, WHO places among its priorities to control Chagas disease by 2030, the 'simplify and bring up to date diagnostic algorithms to improve access and shorten time to diagnosis'.[13] With the appearance of rapid tests, which have demonstrated great sensitivity and specificity, early results can be obtained with a small sample of capillary blood, without the need for complex equipment and with simple handling.[14 15] However, according to the Pan American Health Organization's (PAHO) guidelines for the diagnosis and treatment of Chagas, rapid immunochromatography tests are indicated only for screening purposes. However, in order to establish a definitive diagnosis, a positive result must be obtained in two serological laboratory tests (ELISA, IHA, IIF) and, if there is discordance, up to a third test will be done (due to the great antigenic variability of *T. cruzi*).[16] In recent years, a new diagnostic trend has emerged in the research community which aims to find out whether the combined use of two rapid tests, which are easier to apply in remote areas, could be used as an alternative to laboratory tests. This way,

future diagnostic protocols can be established, which could be more appropriate for rural areas with scarce resources.

The objective of this systematic scoping review is to collect and summarise the scientific evidence regarding the validity of two simultaneous immunochromatographic tests for the conclusive diagnosis of Chagas.

Subheading

A preliminary search of JBI Evidence Synthesis, the Cochrane Library and PubMed was carried out to identify previous reviews of rapid test diagnostic studies for Chagas disease, and some reviews were found that reported on the accuracy of these diagnostic methods.[15 17 18] However, this proposed review is considered novel, since it is the first one in terms of studies that evaluate the simultaneous use of two rapid tests to establish a definitive diagnosis of Chagas disease.

REVIEW QUESTIONS

1. Will the use of two rapid tests be a valid method for the definitive diagnosis of Chagas disease when compared with conventional serological tests?
2. In what type of population (adult/paediatric; endemic/non-endemic areas) has the operation of two rapid tests been tried for the diagnosis of Chagas disease?
3. What are the biomedical and public health advantages of the diagnostic method resulting from the combination of two rapid tests over the conventional serological method?
4. Will it be a cost–benefit strategy for the diagnosis of Chagas with respect to conventional serological tests?

INCLUSION CRITERIA
Participants

This systematic scoping review considers studies that include samples of the human population of any age, at risk of suffering from Chagas disease and at any stage of the disease (acute/chronic). At-risk population is understood to be any person who has been for at least 1 month in an endemic area or has received a blood transfusion in the same type of area, or who has been born from a Latin American mother.[15]

Concept

This systematic scoping review considers studies that evaluate the combined use of at least two immunochromatographic rapid diagnostic tests, based on different antigen groups, for the conclusive (unscreened) diagnosis of Chagas disease. A rapid test is understood to be that which can be determined in a simple, fast (from minutes to 2 hours), economic way and which does not require complex equipment or specialised personnel.[19] In addition, studies should use as reference tests those included in the diagnostic standard established by PAHO/WHO

and which conform conventional serology: ELISA, IHA and IIF.[16 20]

Context

This systematic scoping review considers studies in endemic or non-endemic areas. Currently, Chagas is endemic in the following countries: Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guyana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay and Venezuela.[2]

Types of sources

This systematic scoping review considers cross-sectional studies with gold standard for the diagnosis of American trypanosomiasis as a reference test, but only those using a quantitative methodology.

METHODS

This systematic scoping review is developed following the methodology of the Joanna Briggs Institute for this type of work.[21]

Search strategy

The search strategy was aimed at finding both published and unpublished studies and was divided into three stages. First, an exploratory search was carried out in PubMed, only to locate the field of research and identify relevant articles whose title, abstract or keywords could be used to obtain the terms for the second, more in-depth, stage of the search. Second, a search was conducted on various health science databases to collect published and unpublished studies (grey literature) on the topic of review. Third, the bibliographic references of the literature found were searched for possible additional resources. The complete search strategy is provided in online supplemental appendix I.

Information sources

The repositories consulted were: PubMed, Scopus, ScienceDirect and Virtual Health Library; for the unpublished evidence OpenGrey was chosen.

Study selection

After searching, all documents were collected and imported into Mendeley Desktop V.1.19.4 and duplicates were immediately removed. The studies were then screened by reading the title and/or abstract. Potentially relevant articles were rescreened by reading the full text, seeking for those that met the inclusion criteria. The resulting research papers are the ones included in the present review.

Data extraction

The data of the articles chosen for the present work were extracted using the CASPe critical appraisal tool for diagnostic studies.[22] So, with the information that was extracted we will try to answer the review questions.

Data presentation

The data obtained from the search for scientific evidence are presented in a flow chart. The studies included in the review are ordered by date of publication.

Patient and public involvement

Patients or public were not involved in this study.

RESULTS

Study inclusion

We identified 463 studies through database searches and five more through other sources. After eliminating duplicates, 343 articles were screened by reading the title and/or abstract. Of these, 46 papers were rescreened by reading the full text and estimating their eligibility. Forty-three papers did not meet the inclusion criteria, so they were excluded. Details of these studies and the reasons for their exclusion can be found in online supplemental appendix II. Finally, three studies with a total of 1133 analysed human samples were included in this review. The process of selection and inclusion of studies is shown in figure 1, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses-extension for Scoping Reviews criteria.[23]

Characteristics of the studies included

A summary, of the studies chosen as sources of evidence for this review, is presented below. In addition, the most relevant data from each article are included in online supplemental appendix III.

The research by Egüez et al,[24] is a double-blind cross-sectional diagnostic study, which aims to implement the synchronous use of two rapid tests to achieve a definitive diagnosis of Chagas disease in a short time. They evaluated two immunochromatographic tests based on different antigenic compounds (Chagas Stat-Pak and Chagas Detect Plus) and compared them with three reference tests (IHA, recombinant ELISA and lysate ELISA). All patients between the ages of 1 and 59 who had attended the Reference Laboratory of the Department of Chuquisaca or the Platform for Comprehensive Care of Chagas Patients, in Sucre, Bolivia were offered to participate in the study. Thus, they recruited a sample of 342 people who had not previously received anti-Chagas treatment. The collection of blood samples was carried out in 2014, in the same session the blood test was extracted for later centrifugation of the sample in order to obtain the serum that would be used in the laboratory tests, and also the rapid tests were carried out using capillary whole blood. All participants underwent the five diagnostic tests, with three different observers (one for each rapid test and another for the conventional serological tests).

The research by Mendicino et al[25] is a double-blind cross-sectional diagnostic study, which aims to evaluate the validity of the use of two simultaneous rapid tests for the diagnosis of Chagas. They use two immunochromatographic tests (WL Check Chagas and SD BiolineChagasAb
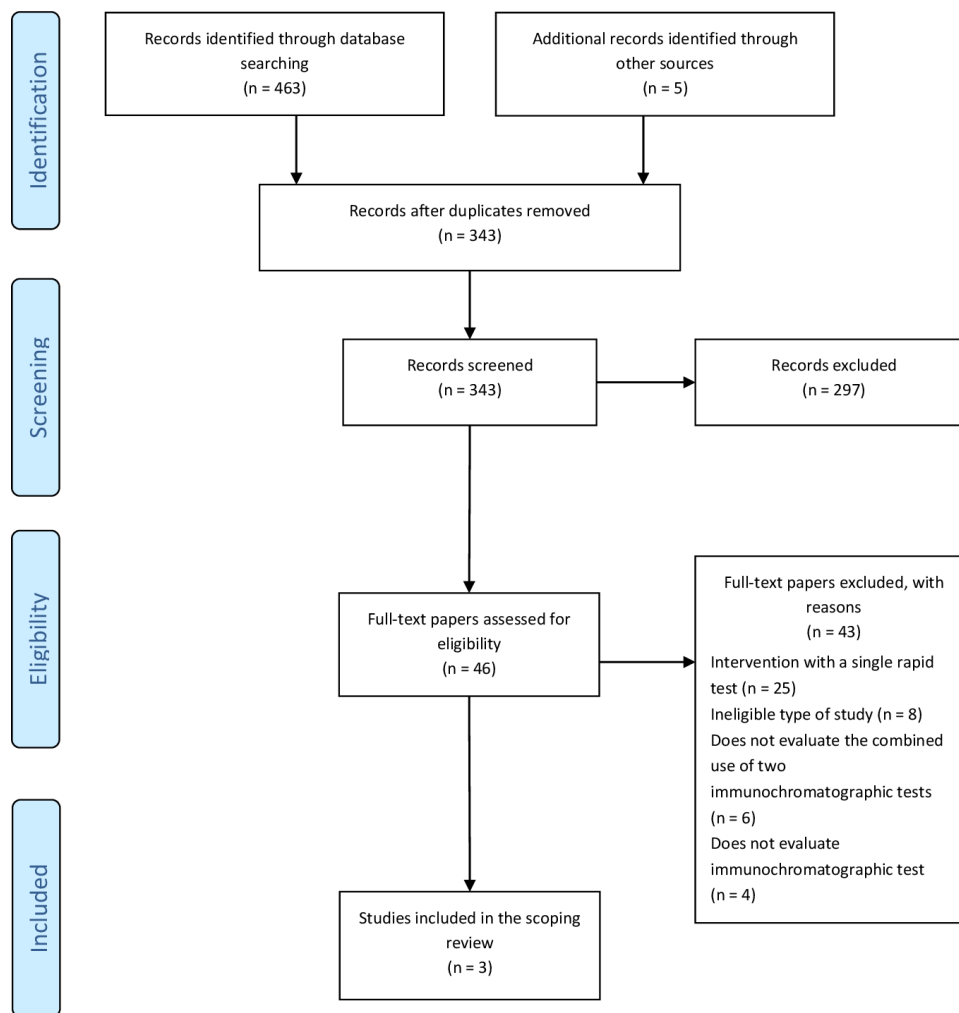
Figure 1 PRISMA flow chart of the study selection and inclusion process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Rapid) based on different *T. cruzi* antigens and compared them with the reference tests IHA, ELISA and, in discordant cases, with IIF. Participation in the study was offered to patients over 18 years old who attended health centres in the province of Santa Fe, Argentina. All the samples obtained were by venepuncture, to obtain serum after centrifugation, and all of them were submitted to the reference tests. Meanwhile, only the samples with concordant results between IHA and ELISA were used to evaluate the rapid immunochromatographic tests, which add up to a total of 106 samples from patients who had not received treatment against Chagas disease and who did not have immune diseases. For all the tests, they used the serum as a sample, two researchers were running the rapid tests.

The research by Lozano *et al*[26] is a cross-sectional diagnostic study, which aims to evaluate the algorithm for the conclusive diagnosis of chronic Chagas, based on the use of rapid tests. They use the immunochromatographic tests Chagas Stat-Pak, Chagas Detect Plus and, in case of discrepancy, WL Check Chagas (based on different antigenic compounds) and compared them with the reference tests recombinant ELISA, lysate ELISA and, in case

of discrepancy, a third ELISA was made. The participation in the study was offered to all patients older than 1 year in screening campaigns in the Gran Chaco province, Bolivia. Thus, they recruited a sample of 685 people who had never been treated for *T. cruzi* infection. The collection of blood samples was carried out in 2018, during the same session, a sample was extracted to obtain the serum by centrifugation for the serological laboratory tests and, also, the rapid tests were done using capillary whole blood. The results of the rapid tests were interpreted by a single person.

Review findings

Regarding the CASPe critical appraisal, all three articles passed the three elimination questions. Egüez *et al*'s paper[24] obtained a total score of 10/10, while Mendicino *et al*'s[25] and Lozano *et al*'s[26] papers obtained a score of 9/10, due to the fact that, in the first case, the confidence intervals of the statistical analyses are not known and, the second one does not specify the degree of blinding. In general, the results of these studies are considered valid and applicable. Therefore, it is estimated that they have internal and external validity to answer the research

questions of this review. Online supplemental appendix IV contains the results of submitting each article to the Critical Appraisal Skills Programme español (CASPe) instrument of diagnostic studies.

The total population studied (n=1133) was in a chronic phase of the disease and came from endemic areas (Bolivia and Argentina). 19.15% of the individuals (n=217) were under 15 years old and 80.85% of the individuals (n=916) were adults (≥15 years). Regarding seroprevalence, 5.99% of the paediatric sample (n=13) showed positive results, compared with 59.06% (n=541) of the adults. Overall, a Chagas prevalence of 48.90% (554/1133) was obtained.[24–26]

The investigations included a total of four different immunochromatographic rapid tests (Stat-Pak, Detect Plus, WL Check and SD BiolineChagasAb). The sensitivity and specificity of the combined use of Stat-Pak and Detect Plus was 100% and 99.3%, respectively, when compared with the reference tests.[24] The sensitivity and specificity of the combined use of WL Check and SD BiolineChagasAb was 97.4% and 100%, respectively, when compared with the reference tests.[25] The sensitivity and specificity of the combined use of Stat-Pak, Detect Plus and WL Check was 97.7% and 96.1%, respectively, when compared with the reference tests.[26]

As main conclusions, Egüez et al state that the use of two rapid tests with a minimum capillary blood sample, in an area validated for their use, should be included in the diagnostic algorithms. This alternative to laboratory tests would lead to a reliable, earlier and cheaper diagnosis (even with three rapid tests), which is beneficial for remote locations.[24]

Mendicino et al conclude that the combined use of two rapid immunochromatographic tests with serum samples is acceptable for the definitive diagnosis of Chagas disease in rural medical centres. Obtaining a rapid diagnosis with minimal equipment, although, discordant cases require a laboratory test. However, rapid tests still need to be optimised when using whole blood.[25]

Lozano et al state that a diagnostic protocol with three rapid tests may not be a good option due to its cost. The Stat-Pak test could be used alone as a diagnostic tool, and a second rapid test (Detect Plus) could be used to confirm. Therefore, they support the policy of a definitive diagnosis of Chagas in the Chaco region (or other places with similar epidemiological characteristics), based on the combined use of two immunochromatographic tests. However, further prevalence research is still needed for implementation in other geographical areas.[26]

DISCUSSION

The combined use of two rapid immunochromatographic tests to establish a definitive diagnosis of Chagas, as an alternative to conventional laboratory serology (ELISA, IHA, IIF), is a topic that has not been sufficiently studied. Consequently, only three articles were identified as eligible for the present review.[24–26] All the included

investigations were carried out in endemic regions with medium,[25] and high prevalence of the disease.[24 26] The individuals who were studied, all of them in the chronic phase, were mostly adults (80.85% ≥15 years).

In relation to the diagnosis, the Chagas guidelines recommend the agreement in at least two serological tests due to the great antigenic variability of *T. cruzi*,[16] besides, one of them has to have good sensibility and another one good specificity.[25] Currently, PAHO/WHO only recommend rapid immunochromatographic tests for the screening of Chagas disease.[16] In all the works that were reviewed, the rapid tests showed great sensitivity (97.4%–100%) and specificity (96.1%–100%), both in whole blood samples and in serum samples, when compared with the reference tests.[24–26] In view of the obtained results, all the authors agree that the simultaneous use of two immunochromatographic tests is a fast, valid and reliable method (Kappa index 0.94–0.99), which could replace the conventional laboratory serology in rural regions for the conclusive diagnosis of chronic Chagas.[24–26] Therefore, it can be included in diagnostic protocols.[24–26] It should be noted that, each author issues this statement based on the rapid tests used in their study: Stat-Pak and Detect Plus in Egüez et al;[24] WL-Check and SD BiolineChagasAb in Mendicino et al;[25] Stat-Pak, Detect Plus and WL-Check in Lozano et al.[26] Although in the latter it is stated that the Stat-Pak test could be used alone because of its good results (sensitivity 97.7% and specificity 97.4%),[26] the study[25] warns that if a test does not achieve 100% sensitivity, it would not be suitable for its use alone. Therefore, it is necessary a second test that enhances the overall sensitivity of the results,[25] being more desirable that this second test is a rapid one than one of the conventional laboratory tests.[26] In short, there is consensus that the combined use of two rapid tests can be an alternative to conventional serology for the definitive diagnosis of chronic Chagas disease in regions with scarce health resources.

However, some authors point out that the variability in the prevalence of Chagas disease that exists between different geographical areas can affect the sensitivity of the rapid tests.[27] Therefore, Egüez et al, Lozano et al warn that, prior to the implementation of rapid tests in a region, epidemiological studies should be carried out to validate their use.[24 26 28] Since, areas with less endemicity could negatively influence the performance of these tests.[26 28] Moreover, the coexistence of other infectious micro-organisms such as *Leishmania* or *Trypanosoma rangeli* could also affect the effectiveness of rapid tests.[26]

In contrast to conventional serology (necessary to confirm the diagnosis according to current regulations), which requires equipment and trained personnel,[24 26] the rapid tests are easier to use.[14] Sometimes, that makes diagnosis unfeasible in rural areas (highly endemic), which have more limited health resources.[24 26] Therefore, in many cases, patients take weeks to receive a diagnosis, with the risks of loss that this delay entails.[24–26] An even worse scenario occurs when many people are not diagnosed, the disease progresses,[24] and they do not receive

an optimal treatment for the chronic phase.[29] As an alternative, immunochromatographic tests have emerged as an option for the rapid and definitive diagnosis of Chagas disease, favouring immediate treatment and adherence.[24 25] In addition, their good tolerance makes them appropriate for diagnosis in children.[24] Consequently, it would make sense to adapt the current policy for the diagnosis of chronic Chagas disease to the reality of rural areas.[24–26]

Two of the studies that were included highlight the logistic benefits of immunochromatographic tests over conventional ones, since they do not need electricity or refrigeration, give fast results and do not require transportation to the laboratory.[24 25] In reference to the type of sample needed for the rapid tests, two of the studies used capillary whole blood samples,[24 26] while only one study used serum.[25] Serum is required as a sample for all laboratory serological tests, which involves more complex equipment and handling. In addition, a venepuncture is necessary, while for many rapid tests a small sample of capillary whole blood is enough.[30] Although some authors have pointed out that sensitivity decreases when using whole blood samples,[25] the results of Egüez et al and Lozano et al,[24 26] in agreement with other publications,[15 28] have shown that using whole blood also gives good results. The use of capillary whole blood as a sample has an advantage over serum, while it decreases the time and the material needed for the procedure because it does not require venepuncture and centrifugation to separate blood components for diagnosis.[24 25]

Regarding the price, rapid tests are more expensive than those of conventional serology, with a cost, in Bolivia, of US$4–US$7 and US$1, respectively.[24] However, according to Egüez et al, if the logistical cost of laboratory tests is taken into account, then their real cost is much higher.[10 24] Although, there is another aspect to take into account that several researchers point out, in case of discrepancy between the results of the two rapid tests, a third test would have to be done,[24–26] and this might not be a good option due to the cost.[16 26] In the present work, the discrepancies observed between the two rapid immunochromatographic tests are not very numerous (0%–6.86%).[24–26] Therefore, for Egüez et al, the increase in the cost of a third test would be acceptable, since the number of discordant results is low.[24] Therefore, rapid tests are considered as a cost-effective strategy if the logistic costs of the laboratory tests are included.[24] Likewise, Egüez et al conclude that the proposed new method of rapid tests saves on logistic resources.[10 24]

Due to its typology, the present review has some limitations, the risk of bias of the included research papers was not assessed. However, there are certain aspects of these articles that should be noted. One study[25] only included non-discordant samples among the reference tests for the evaluation of rapid tests, which may lead to bias. Furthermore, in two works[25 26] not all participants were given the same reference tests, since in the discordant cases an additional serological test was used, which can also produce bias.

The subject matter of this review is novel (first article in 2017). As a result, the number of reviewed sources of evidence is small, becoming one of the limitations of our work. Therefore, more quality research is still needed in order to generate stronger evidence. This would be the way in which we can reach firmer conclusions that could modify the current diagnostic standard.

CONCLUSIONS

The current practice, advocated by WHO, which consists of two or even three serological laboratory tests (ELISA, IHA, IIF) to confirm the diagnosis of Chagas in the chronic phase, does not facilitate either the diagnosis or the treatment of the disease in rural areas with limited resources. As an alternative to address the high Chagas prevalence in these endemic regions, immunochromatographic tests that detect anti-*T. cruzi* IgG antibodies, are positioned as an advantageous option. However, the lack of evidence about their validity, is the reason why they have not yet been included in the definitive diagnosis protocols and they are only indicated for screening. Nevertheless, with the evidence that was reviewed here, it can be concluded that immunochromatographic tests are valid for diagnosis when used simultaneously. When compared with the reference tests, they obtain high percentages of sensitivity (97.4%–100%) and specificity (96.1%–100%), which is a necessary characteristic for the confirmatory diagnostic tests. Before their use or their recommendation, previous studies on the areas of implementation should be carried on, since, the variability in the prevalence of Chagas disease and the presence of other infectious diseases can interfere negatively on immunochromatographic tests. For the time being, the simultaneous use of two immunochromatographic tests for the definitive diagnosis of chronic Chagas is recommended for areas with medium-to-high prevalence of Chagas, such as the areas of Santa Fe (Argentina), Sucre and Chaco (Bolivia) or other regions with similar epidemiological characteristics, both in the adult (≥15 years) and paediatric (≤14 years) populations. It constitutes an alternative to the current WHO diagnostic protocol for rural regions.

In cases of discordance, a third test should be used. Although the percentage of discordances among the rapid tests was low, there is no clear evidence regarding a better cost-benefit of immunochromatographic tests over conventional serology. The use of capillary whole blood as sample optimises the rapid diagnostic process.

The use of immunochromatographic tests for the definitive diagnosis of chronic Chagas disease would make it possible to take full advantage of the features of these rapid tests. The immediate diagnosis and the start of treatment would mean a much more effective control of a disease in which an early approach is crucial. In addition, because of its ease of use, the number of people who could be diagnosed would be much greater.

Recommendations for research

The lack of published papers on the subject shows how important the need for further studies is. For example, more research on diagnostic accuracy is needed to validate the use of rapid tests on other new territories with a high impact of Chagas. Also, more studies are needed to investigate the cost–benefit of rapid tests compared with conventional laboratory serology.

Recommendations for practice

In general, even when the evidence is limited, it could be suggested that the combination of two (in case of discrepancy three) immunochromatographic tests for the conclusive diagnosis of chronic Chagas, can be an alternative to the current diagnostic algorithm for endemic rural areas, always with previous field validation.

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