EVOLUTION OF CHAGAS' DISEASE IN BRAZIL. EPIDEMIOLOGICAL PERSPECTIVE AND CHALLENGES FOR THE FUTURE: A CRITICAL REVIEW

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Abstract

Aims: This paper aimed to provide a critical review of the evolution of Chagas' disease in Brazil, its magnitude, historical development and management, and challenges for the future. **Methods:** A literature search was performed using PubMed, SciELO and Google Scholar and throughout collected articles' references. Narrative analysis was structured around five main themes identified: vector transmission, control program, and transfusion, oral and congenital transmission. **Results:** In Brazil, the Chagas' disease Control Program was fully implemented in the 1980s, when it reached practically all the endemic areas, and in 1991, the Southern Cone Initiative was created, aiming to eliminate the disease transmission through eliminating the *Triatoma infestans* and controlling blood banks. As a result, the prevalence of chagasic donors in blood banks reduced from 4.4% in the 80s to 0.2% in 2005. In 2006, PAHO certified the interruption of transmission of Chagas' disease through this vector in Brazil. However, there are still challenges, such as the domiciliation of new vector species, the need for medical care of the infected individuals, the prevention of alternative mechanisms of transmission, the loss of political concern regarding the disease and, the weakening of the control program. **Conclusion:** Despite the progress towards control, there are still many challenges ahead to maintain and expand such control and minimise the risk of re-emergence.

Key words: Chagas disease, Brazil Epidemiology, Neglected Tropical Diseases, Trypanosoma cruzi, Epidemiologic Surveillance, Public Health

1. Introduction

Chagas' disease (ChD) is an infectious disease of mainly chronic characteristics, discovered in 1909 by Carlos Chagas.[1–3] It is caused by the protozoan parasite, *Trypanosoma cruzi,*[4] transmitted by hematophagous insects from the Redudiviidae family and maintained by mammalian reservoirs, such as marsupials, rodents and primates in the wild cycle, and cats, dogs and humans, in the domestic cycle.[1] Transmission mechanisms are classified as primary: vector, transfusion, oral and congenital transmission; and secondary: laboratory accidents, organ transplants, sexual transmission and others.[2,5]

ChD is an endemic disease primarily limited to the Americas and closely associated with the socio-economic development of the region. It reflects the social history and inequalities in the American continent, evidenced by the close association of higher prevalence of the vector-borne disease with poor housing conditions and low socioeconomic status.[4] It is an important endemic infection in the Americas[1] and a neglected tropical disease.[6] Moreover, there has been little funding for research and little progress in pharmacotherapy development, diagnostic methods and vaccines.[7] Only two drugs are available, benznidazole and nirfutimox and although they are effective in the early stages of the infection, treatment failures occur and drug resistance has already been identified.[7] Furthermore, treatment is long, with frequent and severe side effects and several contraindications.[3,7–9]

ChD was listed in the 2012, London Declaration on NTDs with a set of specific objectives for control and eradication goals by 2020. The London Declaration on NTDs resulted from a partnership of public and private organizations in response to the 2012 WHO Roadmap on neglected tropical diseases, and established targets for control, elimination or eradication, by 2020, of 10 NTDs (Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Soil-transmitted helminths and Trachoma, Chagas' disease, Guinea worm disease, Human African trypanosomiasis, Leprosy and Visceral Leishmaniasis). The most recent report on the progress of the initiative showed a delay in reaching the goals established by the London Declaration due to insufficient data on evaluation and progress indicators.[6]

It is estimated that six to seven million people are infected with ChD worldwide and an additional 60 million are at risk of acquiring the disease, mostly in 21 Latin American countries where it is endemic.[3,10,11] Furthermore, its confinement to the Americas has been breached with the reported spread to other continents.[3] Nonetheless, control of ChD is possible, and measures implemented in the past years have had a major impact on its prevalence and incidence in the Americas: WHO estimates a 32% decrease in new cases and a 40% decrease in the number of people at risk, between 2006 and 2010.[12]

This paper is a critical review of ChD in Brazil. Its primary transmission mechanisms are presented and followed by a review of the epidemiological scenario caused by the disease throughout modern history, the different strategies and mechanisms

implemented for its successful control and the challenges ahead due to the internationalization of human societies.

2. Methods

A literature search was performed using PubMed, SciELO and Google Scholar, and included both Portuguese and English written papers. Specific to subtopic searches were run for: vector, transfusion, oral and congenital transmission, and Chagas' disease control program. Keywords used included "Chagas disease", "Chagas disease AND Brazil", "transfusion AND Chagas disease", "Oral AND Chagas disease", "Congenital AND Chagas disease". Further manual search was performed within the reference lists of identified articles. Narrative analysis was structured around five main themes identified: vector transmission, control program and transfusion, oral and congenital transmissions.

3. Results

3.1 Vector transmission

Over 140 triatomine species are considered potential vectors for ChD, of which 52 have been described in Brazil.[2] Five species have major epidemiological importance within the domestic environment, the most important one being the *Triatoma infestans*, because of its strictly domestic habits, high capacity of infestation and infection rate.[2,13]

ChD was originally an enzooty of wild animals, but the expansion of human frontiers, the consequent invasion of native forests and modification of sylvatic environments resulted in displacement of wild animals and food scarcity for the insect vectors, interfering in the parasite's sylvatic cycle. This expansion was also frequently accompanied by poor housing conditions that offered excellent breeding sites for these insects[14], which were drawn by lights to human dwellings in search of food, and colonised domestic and peridomestic areas, feeding on humans and domestic animals.[1,5,15,16]

Even though the expansion of anthropic areas occurred in the entire American continent, domestic vector transmission does not occur in all countries.[15] Several factors are necessary for domestic transmission to occur, including the presence of infected reservoirs and intradomestic triatomine species and access of insects to humans. Thus, while poor housing conditions in most of Latin America allowed vectors to colonise the domiciles, in some countries, elements such as better housing conditions, frequent use or air conditioning and pest control prevented the colonisation and the domestic transmission of ChD.[17] Still, vector transmission accounts for most of the infections in the Western Hemisphere.[18]

In Latin America, the disease was initially limited to rural areas, marked by poverty, migrations and poor working conditions and employment practices.[16] In Brazil, regions traditionally considered as endemic for vector transmission include areas from the South, Southeast, Northeast and Midwest regions.[13] However, in Brazilian history, the

modernisation of agricultural production to meet the market needs of a globalised world and the inequalities in the old production system,[4] triggered intense rural-urban migrations after the 1950s, leading to displacement of over 40 million people from the fields to urban centres.[13] Parallel to such population mobility, there was a popularisation and expansion of haemotherapy between the 1950s and 1990s. Migrations consequently led to an increased risk for transfusion-transmitted ChD, contributed to the situation observed in the 1970s, when 20% of 100,000 new annual cases of ChD were due to transfusion transmission,[19] and leading to a change in the epidemiological profile of the disease, which was no longer restricted to rural origins and poverty.[4,13,19–21]

3.2 Chagas' Disease Control Program (ChDCP)

In the 1940s, reports regarding the severity of the illness led Brazilian authorities to seek solutions, and the first control program for ChD was established, albeit isolated and intermittent.[22,23] By the 1970s, 36% of the national territory was considered a risk area for vector transmission and the rural prevalence was estimated at 4.2%, with Minas Gerais and Rio Grande do Sul States reporting prevalence as high as 8.8%.[21,24] Furthermore, an annual incidence of 100,000 new cases nationwide was estimated, mostly caused by vector transmission, followed by transfusion transmission.[25]

It was only in 1975 that the Chagas' disease Control Program (ChDCP) was structured as a systematic nationwide programme, focusing on the elimination the main vector (*T.*

infestans) through regular household insecticide spraying. Finally, in 1983, when adequate resources were allocated, it reached most of the endemic areas in the country[2,21,23] and in 1991, with the creation of the Southern Cone Initiative (INCOSUR),[15] the pursuit towards ChD control gained momentum. The successful history of the ChDCP alongside major social, economic and cultural changes allowed the successful control of vector transmission of ChD.[23]

From 1983 to 1997, the number of municipalities with infestations of *T. infestans* were reduced by 86%, and the infection rates reduced from 8.4% to 2.9%.[21] The prevalence of chagasic infection among blood donors in the public service was also reduced, from ≥2% in the 70s, to 0.69% by 1996, and the mortality rates due to ChD in Brazil decreased from 5.2/100,000 in 1980, to 3.5/100,000 by 1997.[21] Carneiro and Antunes[23] demonstrated the efficacy of the ChDCP in the State of Minas Gerais, which resulted in the elimination of *T. infestans* and a 94.7% reduction in the prevalence of ChD among 2-6 year olds, after 10 years of intervention. Finally, in 2006 PAHO certified the interruption of ChD transmission through the *Triatoma infestans* in Brazil.[26]

However, despite the very positive milestone that such certification represents, it only demonstrates a momentary interruption in the transmission by a specific vector, and not the eradication of transmission.[26] There are over 140 vector species widespread through the Americas, and over 100 species of animal reservoirs, which makes the eradication of the disease virtually impossible.[11,27] Control of ChD must be based on

constant surveillance, elimination of domestic vectors, screening of blood donors, treatment of the ill population and health education.

Hence, it is essential to keep continuous surveillance and control actions in order to eliminate residual foci of triatomines, preventing their spread.[27] Since 2006 residual foci of *T. infestans* remain in the States of Bahia and Rio Grande do Sul,[20] indicating the weakening of the ChDCP and posing a risk of reintroduction of this species in the country.[11,26,27] Furthermore, even though vector control program have been successful in reducing the levels of domestic infestation, they have shown to be insufficient to control triatomines in the peridomicile. Therefore, the feasibility of wide use of methods to prevent infection and control peridomestic infestations, such as insecticide treated bed-nets and dog collars, should be evaluated.[7]

3.3 Transfusion transmission

With the control of vector transmission and the growth of the AIDS epidemic[25], transfusion transmission gained attention and rose in importance, becoming the second most important form of spread of the disease in Latin America, with an estimated risk of transmission from an infected blood unit of 12-25%.[9,18]

In Brazil, the large number of rural migrants and poor screening methods made blood transfusion one of the most important pathways for ChD transmission.[20] Nevertheless, even though strategies to control transfusion-associated ChD have been available since the 1950s, it was only in the 1980s with the emergence of the AIDS epidemic that effective efforts to control transfusion transmission started.[4] In 1988 Brazilian legislation

started requiring blood donors to be registered and blood samples to be tested individually for infectious diseases with high sensitivity tests,[19,28] and in 1991 the Southern Cone Initiative (INCOSUR) was created by Brazil, Argentina, Chile, Paraguay, Uruguay and Bolivia, aiming to reduce and eliminate transfusion transmission through the strengthening of the blood banks and control of the donors (Table 1).[10,15,19]

Table 1: Objectives of the Southern Cone Initiative (INCOSUR)

I	Elimination of *T. infestans* from domestic and peridomestic areas
II	Permanent control of alternative vectors in areas previously endemic for the *T. infestans*
III	Elimination of transfusion transmission, through screening of blood donors

The efforts to control transfusion-transmitted ChD in Brazil resulted in a decrease in the prevalence among blood donors from 7.0% in the 1970s, to 4.4% in the 1980s, and to 0.6% by the end of the 1990s.[10,29] Such reduction has been corroborated by several studies: more recently, Melo et al.[10] found a 0.17% prevalence of ChD at the Blood Centre of Pernambuco. Silva and Silva[28] found a prevalence of 1.2% in the region of the Alto Paranaíba, and Lima et al.[29] demonstrated a decreasing trend in the ineligibility for blood donation due to ChD at the Uberaba Regional Blood Centre of 0.03% a year, from 1995 to 2009.

In spite of such advancements, some point out the problem of high proportions of inconclusive reactions. For example, a profile analysis of chagasic patients at the Blood Centre of Pernambuco identified that 60.3% of the reactive serologies were, in fact, inconclusive.[10] Similar results were found at the Uberaba Regional Blood Centre, with 53% of inconclusive reactions.[30]

It has been argued that the high proportion of inconclusive reactions was caused mainly by the high percentage of first-time donors, and could also be related to the frequent changes in the brands of the screening tests, a result of the tendering rules to which public blood banks are subjected.[31] Ferreira-Silva[20] analysed the differences between commercial ELISA tests from two laboratories and showed that the sensitivity and specificity levels of tests from different manufacturers differed considerably. As tests characteristics differ, each test generates false-positive results in different samples, increasing the chances of cross-reactions in healthy donors, when these tests are frequently changed,[31] leading to an unnecessary disposal of blood bags and social and psychological issues to the donors.[10,30]

As for the profile of the chagasic donor, Lima et al. 2012[29] found a predominance of ChD in people aged 30 years or above, which had 5.5 (95%CI: 4.44; 6.93) times the odds of having the disease, compared to those less than 30 years old. Similarly, Melo et al.[10] found significantly higher prevalence of ChD in donors aged above 30 years old. The lower prevalence among <30 years is considered a result of the success of the

ChDCP in the 80s and the improvement in housing conditions, which significantly reduced the incidence at younger ages.[10,29]

3.4 Oral transmission

Oral transmission has been responsible for around 100 new cases of ChD annually in Brazil.[11] It happens through the consumption of food or drinks contaminated by crushed triatomines, triatomines' faeces or infected secretions from marsupials' anal glands,[32,33] and currently represents the main transmission mechanism in regions where effective vector control has been achieved. Outbreaks of oral transmission are unpredictable and have been reported even in non-endemic rural and periurban areas,[33] probably as a result of occasional invasion of the domicile and peridomicile by wild insects.[11]

In the Amazon region[33], where hundreds of cases have been reported, oral transmission is often associated with the consumption of açaí, a local fruit,[32] and since the first cases of oral transmission were described, in 1969, several outbreaks and hundreds of new cases have been reported, leading to the classification of this region as endemic.[5] From 2000 to 2010, 138 outbreaks, with over 1000 cases of acute ChD were reported, of which 776 had been associated with oral transmission, most in the Brazilian Amazon.[33]

Three outbreaks of acute ChD associated with oral transmission have been described in the State of Amazonas in 2004, 2008 and 2010, including 17 cases of ChD associated with açaí juice. Another outbreak in Satarem, Pará, in 2006, resulted in 20 confirmed cases of ChD and one death due to delayed diagnosis.[32] Other outbreaks

have been reported in the states of Rio Grande do Sul (1968), Paraíba (1986), Catolé do Rocha municipality, and Santa Catarina (2005), besides further isolated ones with less repercussion.[5]

The concerns regarding the ChD transmission in the Amazon led to the creation, in 2004, of the *Initiative of the Amazon Countries for Surveillance and Control of Chagas Disease* (AMCHA), aiming to develop the knowledge about the disease in the region and to implement surveillance and control methods.[15,27] However, there is very little evidence that concrete action has so far been taken.[15] In 2007, the Brazilian Health Ministry provided recommendations for the control of food contamination in the region and for measures to improve diagnosis, treatment and surveillance. However, oral transmission in the region in a challenge yet to be effectively tackled, due to difficult access to rural areas, late diagnosis, the difficulty to implement good food handling practices associated with the unpredictability of outbreaks and the increasing activity of sylvatic vectors.[33]

3.5 Congenital transmission

Maternal-foetal transmission occurs in approximately 5% of the newborns from infected mothers, although, this rate varies greatly between countries, ranging from 0.5-10%.[2,34] The risk of transmission is influenced by several factors, such as maternal parasitemia levels, age, anti-*T. cruzi* immune response and parasite strain.[2,9] It presents an important transmission pathway especially in non-endemic countries, alongside with transfusion transmission, due to the number of infected immigrants.[2] In Spain, for

example, studies indicated a transmission rate of around 4%.[34] This relatively common transmission pathway for ChD does not receive adequate attention in most endemic countries.[18]

In Brazil, reported congenital transmission rate lies around 1% and seems to be higher in the State of Rio Grande do Sul, located in the borders of Paraguay and Argentina, where transmission rates are 4.3% and 6%, respectively.[34] Most cases are asymptomatic or have subtle and frequently non-specific symptoms, with a small amount presenting severe complications, such as meningoencephalitis. Furthermore, mortality among infected newborns is reported to be considerably higher than in non-infected newborns.[9] Hence, it is essential to have effective perinatal screening and monitoring programs in place. This is reinforced by the fact that the disease can be effectively treated and usually, serologically cured if treatment starts within the first year of life. If left untreated, it may evolve to symptomatic chronic disease later in life, causing disability and high medical costs.[9,11,34]

8. Discussion

The progress towards control of ChD is undeniable and supported by a vast amount of literature. The decreased political interest that resulted from such progress weakens the control and surveillance programmes, risking the re-emergence of the disease. Some of the key remaining problems, after vector and transfusion transmission control, include:

(i) Lack of political will and loss of technical capacity and human resources to maintain the ChDCP, leading to a lack of popular compliance with control strategies, failure to renew programmes and deviation of resources, especially with the emergence of other public health issues, such as dengue fever and Zika.[11,16,26,35] This is often seen as a result of an abrupt decentralisation of health services, transferring disease control and surveillance functions to peripheral governmental levels, without proper preparation for these governments to take over the surveillance responsibilities.[4,34]

Although ChD produces important social losses related to mortality, incapacity to work and medical costs, due to severe cardiac and digestive impairments that may be caused by the disease's chronic form, these costs are frequently neglected by governments. This is both because of ChD's slow chronic evolution and the little political expression of the affected populations, mostly poor and socially excluded people who are dependent on public policies.[4,11] As a result, local governments with short term policies tend to prioritise other health emergencies with more public visibility and political credit, such as dengue fever[4] and Zika.[35] This is at the expense of the ChD control program, especially where the disease has already been considered as under control and, as a consequence, losing visibility.[4,11,16]

Furthermore, it has been argued that the 2006 PAHO certification may have led to a misbelief that the disease was eradicated.[36]

(ii) The residual foci of *T. infestans*, which can proliferate in the absence of control and epidemiological surveillance, especially in pockets of poverty.[27]

(iii) The variety of triatomines that can act as vectors for the *T. cruzi*. Even though most of these “secondary” vectors have peridomestic habits, they can invade the domicile and become opportunistic dwellers, then transmitting the disease.[11,26] This was demonstrated by Villela et al.[36] who found that, after the elimination of *T. infestans*, *Panstrogylus megistus* became the most important vector in the State of Minas Gerais. It is important to highlight that despite the efforts to control transmission by the *T. infestans*, in most north-eastern states this species has never represented the most important vector, with other species such as *T. brasiliensis*, *T. pseudomaculata*, *T. sordida* and *P. megistus* having a major role in the disease transmission.[37] Furthermore, *T. sordida* is currently the most frequently captured triatomine species in Brazil and has already shown altered levels of susceptibility to insecticides.[38]

Assis et al.[39] studied the domiciliation of triatomines in the Berilo municipality, State of Minas Gerais, showing the presence of *P. megistus* and *T. pesudomaculata*, mostly in the peridomicile, but no insect was found to be infected by the *T. cruzi*. On the other hand, Barbosa-Silva et al.[40], in the State of Rio Grande do Norte, showed the existence of peridomestic infestations of *T. brasiliensis* and *T. pseudomaculata* with high levels of *T. cruzi* infection (19.2% and 27.2%, respectively).

There is evidence that *T. pseudomaculata* has become adapted to anthropic ecotopes. The species demonstrates a high capacity for domiciliary infestation and its levels of peridomiciliary colonisation have increased in many states in the past few years.[39,40] *T. brasiliensis* is considered a semi-domestic species, being capable of colonising both

domestic and peridomestic environments. These species are attracted to the intradomicile by residential lights and frequently colonise chicken coops,[39,40] but can also be found in piles of tiles, wood or corrals and associated with domestic and synanthropic animals.[40]

It is clear, therefore, that peridomestic infestation is a major factor for domestic triatomine infestation, being of major importance to work on the elimination of possible foci for triatomine infestation. Popular compliance with control strategies is essential for control and surveillance of these secondary triatomine species, through elimination of rubble and maintenance of a clean peridomicile, detecting and reporting new or residual foci of triatomines and putting insecticide-treated collars on domestic animals to avoid the association with the insect.[7,26] The use of slow-release pyrethroid insecticides might also be a useful strategy for insect control in the peridomicile, as suggested by Oliveira Filho et al.[41]

Other concerns include:

(i) Congenital transmission: while it tends to decrease as a result of the reduction of new cases of the disease, aging population, reduced number of infected women in fertile ages and decreased pregnancy rates in older women, the provision and coverage of adequate antenatal care is still essential to identify and treat the infection at an early stage.[11]

(ii) Oral transmission is an unpredictable event, which plays an important role in maintaining endemicity. A rapid detection and investigation the suspected cases is the best available approach.[7]

(iii) Clinical management of current and baseline number of cases presents a challenge, as the ageing of the infected population and consequent increased number of symptomatic individuals will pose challenges to the public health system. Since most of these individuals depend on the public healthcare system, their survival will depend on its coverage, access and quality of attention.[4]

(iv) The sylvatic foci of triatomines and development of insecticide resistance[11]. In the past years, there have been a growing number of reports of insecticide resistance in endemic countries. Reports from Bolivia and Argentina point to *T. infestans* populations with high resistance ratios (RR_{50} > 50%). In Brazil there have been reports of resistance to Deltamethrin by *T. sordida*, *T. infestans* and *P. megistus*, and to Beta-cyfluthrin by *T. infestans*. It is important to notice that resistance ratios in Brazil are still low (RR_{50} < 8.0).[42]

The natural foci of triatomines pose a special risk to the Amazon region. In the Brazilian Amazon, most cases of ChD are caused by oral transmission, and vector transmission is usually associated with extractive activities or accidental exposure, due to humans invading the forest, or animals invading human areas.[15] However, the uncontrolled deforestation in that region may lead to domiciliation of vectors. It is, therefore, important to improve surveillance and education in this area to track possible domestic

infestations, to rapidly identify and treat cases of oral transmission, and to improve food-handling practices, preventing outbreaks of oral transmission. The identification of markers for environmental changes, such as loss of biodiversity of small animals, also may work as a predictor for changes in triatomines' behaviour, signalising their dislocation to peridomestic areas and increasing the risk of transmission. In some regions, the predominance of opossums is considered a marker for such changes.[33]

An additional issue to address is the internationalisation of ChD. With the remarkable increase in population mobility, thousands of infected individuals, mostly undiagnosed, have moved to non-endemic countries. Estimates suggest that among the three million Latin American migrants living in eight European countries, 68,000 to 128,000 are infected and by 2009 only 4,300 of these had been diagnosed. These undiagnosed cases pose new challenges to non-endemic countries, with the risk of transfusion and congenital transmission and the need for medical care where little is known about the disease.[15] Still, such change in the epidemiological frame may bring a new light over this long neglected disease.

Finally, the realization of global events, such as the World Cup and the 2016 Olympics, increases the risk of introduction of new diseases in Brazil, leading to the rise of new public health emergencies, such as Zika, which shows the vulnerability of the country to many vector-borne diseases, but also the capacity to give quick responses to these emergencies[35]. However, considering the low visibility and political impact of NTDs among the general population, once again these emergencies may deviate policy

makers' attention and resources from neglected diseases, such as Leishmaniasis and Chagas' disease, which might contribute to a silent re-emergence of these diseases.

In Brazil, it is estimated that 2-3 million people are infected by the *T. cruzi*, with about 600,000 suffering from cardiac or digestive complications from the chronic symptomatic form of the disease. From 1999 to 2007, ChD was associated with over 50,000 deaths (0.6% of the country's mortality), resulting in an average of nearly 6,000 deaths a year.[43]

According to Martins-Melo et al.[43], there is a decreasing trend in the mortality of ChD, with rates reducing from 3.28 to 2.19/100.000 inhabitants, although with wide differences between the country's different regions. While the Mid-West, Southeast and South regions reflect the national decreasing trends, the Northeast region presents an increasing trend in ChD mortality. The North region presents stable mortality levels for ChD. Such regional differences in ChD mortality may reflect the unequal levels of recognition of the importance of the disease in different regions, as well as differences in quality of health care, diagnosis and control of secondary vector species, possibly leading to new cases of both vector-borne, oral and congenital disease.

9. Conclusion

A significant progress has occurred in control of Chagas' disease in Brazil, resulting in the 2006 PAHO certification. The many challenges to maintain and expand such control include: the domiciliation of new vectors; the residual and natural foci of triatomines; development of insecticide resistance; development of new drugs and new

insecticides; promotion of hygiene practices to prevent oral transmission; better peridomicile management; increase in pre-natal screening to prevent congenital transmission and the decreasing political interest in the disease.

Ethics

This review utilized previously published studies and publically available data and therefore no ethical approval was required.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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