

Mini Review

Chagas disease: review of needs, neglect, and obstacles to treatment access in Latin America

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Abstract

After more than one century since its discovery, Chagas disease is still extremely prevalent in 21 Latin American countries. Chagas disease is one of the most concerning public health problems in Latin America; the overall cost of CD treatment is approximately 7 billion United States dollars per year and it has a strong social impact on populations. Little progress has been made regarding the access to diagnosis and treatment at the primary health care level, calling into question the current policies to ensure the right to health and access to essential medications. In this article, diverse dimensions of access to treatment for Chagas disease are reviewed, illustrating the present state of benznidazole medication in relation to global production capacity, costs, and needs. The findings are based on an investigation requested by *Médecins Sans Frontières* Brazil through a consultancy in 2015, aiming to estimate the current costs of benznidazole production.

Keywords: Chagas Treatment. Benznidazole. Access. Latin America.

INTRODUCTION

Chagas disease (CD) has been around for more than one century¹; however, it continues to be one of the most prevalent public health problems in Latin America to date². Despite the right to health and access to essential medications, CD is a key example of the barriers to accessing primary health care (PHC) services.

Information on production costs in pharmaceutical industries is generally withheld. Decoding production costs for CD treatment may be useful for patients, managers, and governments to have adequate information for decision-making and advocacy planning to increase access to CD treatment with more precision. Given the lack of knowledge and information regarding the access to CD diagnosis and treatment, *Médecins Sans Frontières* (MSF) Brazil conducted an investigation in 2015 in collaboration with a consultant to better understand the global standards for the production of medication for the treatment of CD, specifically benznidazole (BZN).

The investigation included interviews of laboratory staff and questionnaires sent to laboratories that manufacture the raw materials for the final BZN pill. From the information collected,

an analysis model of cost appropriation was built based on the methodology proposed by Pinheiro *et al.*, in 2006³. This model has already been validated by the World Health Organization (WHO) and has been used in previous studies by the consultancy agency, particularly those investigating the cost of antiretroviral drugs. The model is based on a fluxogram where the standard cost (or unitary production cost) is pre-determined and obtained through the detailed study of the use of raw materials, labor, equipment, and the sum of all procedures that make up the global process to manufacture one unit of the physical product. Thus, direct costs (depreciation of equipment, labor, formulation, packaging, and domestic transportation), indirect costs of production (overhead, administration, research, reinvestment, and general production costs), and profit margin are analyzed in the model³. In this review, findings from the model are highlighted in order to shed light on the factors affecting access to BZN in Latin America and particularly Brazil.

OVERVIEW OF CHAGAS DISEASE IN THE AMERICAS

The WHO estimates that globally there are approximately 6 million people infected with *Trypanosoma cruzi*, the protozoan that causes CD, and furthermore, more than 70 million people are living in areas with high risk of CD transmission⁴. CD endemic areas include 21 countries in Latin America. Brazil, Mexico, Argentina, and Bolivia have the highest prevalence rates of infected people, accounting for approximately 71% (4.2 million) of the estimated cases⁵. Bolivia has the greatest

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incidence of CD; 60% of the national territory is considered an area of risk for vector transmission. In addition to being the leading killer among parasitic diseases, CD represents a significant economic burden to health care systems^{2,6}.

There has been a significant reduction in the appearance of new cases through vector transmission due to control actions promoted by intergovernmental initiatives in the Americas for the past 30 years. However, CD is still recognized as a neglected disease, which mainly affects vulnerable populations in urgent need of basic policies that promote access to health care.

Presently, the governments' absence or inefficiency in responding to CD involves various elements ranging from medical supply and training, to proper access to diagnosis and treatment. There is low investment and lack of interest from the private pharmaceutical sector on investigation towards the development of innovative tests and better medications, together with the absence of accurate epidemiological data on the disease (prevalence and incidence in endemic countries corresponds to outdated estimates). As indicated, there is an intricate net of obstacles that continue to contribute to the cycle of CD neglect.

In 2015, it was estimated that more than 80% of the people in the world affected by CD did not have access to diagnosis and specific treatment. This historical negligence is a contributing factor to the increases in the morbidity and mortality as a result of CD as well as its social costs. Although treatment is not indicated for all cases, most of those chronically infected or presenting with a chronic indeterminate form of CD [all individuals with chronic infection by *T. cruzi*—with reactive serology that do not suggest clinical symptoms of CD due to normal electrocardiogram (ECG) readings, chest radiography, esophagus's, and colons]—should receive specific treatment in accordance with the indications detailed in the 2016 Brazilian consensus on CD⁷. The findings of the BENEFIT trial have highlighted that for clinically asymptomatic patients with established Chagas' cardiomyopathy, trypanocidal therapy did not significantly reduce cardiac clinical deterioration; however, it significantly reduced serum parasite detection⁸.

The WHO has established four fundamental pillars that must be observed and implemented for CD so that access to medication is ensured in adequate quantity, quality, location, and timing. Proper access to medicines can occur when the management process ensures a rational selection (based on proper lists of essential medications and protocols); affordable prices for governments, health services providers, and consumers; and the existence of reliable health and supply systems and sustainable financing for acquisition⁹. Unfortunately, CD programs in Latin America do not satisfactorily meet any of the pillars established by the WHO. There are critical problems such as low production capacity, inaccurate data to estimate the true demand, absence of inclusive policies for patients, and outdated technical guidelines to advise and regulate the performance of health professionals based on current knowledge.

HISTORY OF CHAGAS DISEASE MEDICATION PRODUCTION

Benznidazole and nifurtimox (NFX), the first- and second-line treatment for CD, respectively, were made available in the market in the 70's, and to date, are the only two drugs available

for the treatment of CD in the world. Unfortunately, the portfolio of investigated molecules with trypanosomicide potential is limited, diminishing the possibility of innovative treatments.

Benznidazole was originally produced by Roche under the names of Rochagan® and Radanil®, and was registered in Argentina, Brazil, Bolivia, Uruguay, Peru, Nicaragua, and Japan. In April 2003, after Roche discontinued production and commercialization of BZN, fabrication technology and rights were transferred to the Brazilian government. Only in 2008, were the first batches of Brazilian BZN produced by the public Pharmaceutical Laboratory of the State of Pernambuco [*Laboratório Farmacêutico de Pernambuco* (LAFEPE)]; this BZN was still manufactured with residual raw material [Active Pharmaceutical Ingredient (API)] supplied by Roche. As it was necessary to produce API-BZN locally in order to ensure appropriate supply, the Brazilian Ministry of Health negotiated with LAFEPE to transfer production of the raw material to the local private company Nortec.

LAFEPE was the only BZN producer in the world until 2011, when the absence of the certification for Good Manufacturing Practices (GMP) for BZN production issued by the National Agency of Sanitary Vigilance [*Agência Nacional de Vigilância Sanitária* (ANVISA)] highlighted the impossibility of commercialization of the drug through the strategic Pan-American Health Organization (PAHO) fund, the main mechanism of acquisition for endemic countries. At that time, the private Argentinian laboratory Elea, also started manufacturing BZN. For its production, Elea uses the API-BZN from the private Argentinian laboratory named Maprimed. Both laboratories belong to the Chemo group. Elea then became the only producer of BZN able to commercialize use through the PAHO fund.

In line with the fundamental requirements established by the WHO, in order to ensure proper access to medication, a continuous and reliable supply system needs to be in place. Production monopolies will interfere with accessing the final product if these systems are not in place; therefore, it is crucial that there is more than one world producer to ensure that the medication gets to the patient, regardless of adverse external factors that may hinder the supply.

CURRENT BENZNIDAZOLE PRODUCERS AND THEIR CAPACITY

As outlined previously, there are two producers of API-BZN in Latin America (NORTEC and MAPRIMED) as well as two manufacturers of the final BZN product for commercial use (LAFEPE and ELEA).

NORTEC is located in Rio de Janeiro (Brazil) and is the biggest manufacturers of active pharmaceutical ingredients in Latin America. Currently registered and certified in GMP by ANVISA, it has a production capacity for API-BZN of 1,000kg per campaign that could be expanded to reach a maximum of 2,000kg.

MAPRIMED is located in Buenos Aires (Argentina) and its API-BZN production is also registered and certified in GMP, by the National Administration on Medication, Food and Medical Technology (ANMAT). The laboratory production capacity is similar to that of NORTEC, producing 1,000kg per campaign that could be expanded to a maximum of 2,000kg.

LAFEPE manufactures 100 and 12.5mg BZN pills for adult and pediatric patients, respectively. Conversely, Elea manufactures 100 and 50mg BZN pills for adults and pediatric patients, respectively.

CHAGAS DISEASE TREATMENT NEEDS

The full course of CD treatment for an adult with an average weight of 70kg requires approximately 180, 100 mg pills. In a regular treatment scheme, three pills are administered daily over a period of 60 days. Therefore, the full treatment course consists of a total of 18,000mgs of BZN (equivalent to 0.018kg of API-BZN).

If deemed clinically well, patients infected with CD will not meet eligibility criteria for treatment¹⁰. However studies have proven that widening the indications for treatment, thus expanding access to treatment, are beneficial in successfully curing CD¹¹; reducing or preventing the progression of disease¹¹⁻¹³; and breaking the chain of transmission^{14,15}, which has proven to be a safe and effective measure for primary disease prevention^{15,16}. In the past three decades, a consensus has been reached that parasite persistence is crucial for the development and progression of Chagas cardiomyopathy⁸. Thus, it is imperative that access to treatment be expanded to greater numbers of patients. The current global API-BZN production capacity (4,000 kg maximum) is not adequate to deal with the CD treatment needs. Hence, the cycle of neglect and the failure to ensure the basic pillars regarding access to treatment are perpetuated.

ESTIMATE OF BENZNIDAZOLE COSTS

The estimates of the direct costs of BZN use (Table 1) were calculated in the model using the lowest [750 United States dollars (USD) as informed by NORTEC] and the highest (2,000USD estimated from market information, since MAPRIMED did not provide the sale value) API-BZN prices per kilogram. After overviewing the direct production costs, we determined that the API-BZN price had a strong impact on the overall BZN cost. In the case of BZN, the proportional cost of the raw active compound rose from 87% to 95% when different quotations for API-BZN per kilogram were used.

Additionally, the estimates of the final costs of BZN use were calculated for public and private laboratories (Table 2). Different values for general expenses were applied when comparing the public and private laboratory as the cost appropriation model for production is based on the principle that the public laboratory does not have the adequate structure for commercialization and international marketing in line with private sector's traditional standards and costs. As expected, variations were observed between the types of laboratories; additionally, there were significant increases in total cost when the price of API-BZN varied.

COMPARISON OF MARKET PRICES AND COST ESTIMATES

MSF acquires one BZN pill manufactured by LAFEPE for 0.2129USD while the PAHO pays 0.4751USD for one pill manufactured by the ELEA private laboratory. When comparing the estimated price values for private production versus the laboratory's market prices (Table 3), with the estimated cost of API-BZN as 750USD per kilogram, we found that LAFEPE charged 66.3% more than the final estimated price. Additionally, ELEA charged 271.2% more than the final estimated price, which already included a 14% profit margin. Conversely, if we used the price estimate considering the highest API-BZN value (2,000USD per kilogram), LAFEPE's price was 32.05% less and ELEA's price was still 52.14% more than the estimated final price. The data ascertained from the model disavows the current belief that laboratories manufacturing BZN are subsidized or charge what is called a *humanitarian price*, just to cover costs. Again, we draw attention to the fact that the medication's price is linked to the variations in the API-BZN prices charged.

It is evidenced that both laboratories profit from the production and sale of BZN significantly above the 14% profit margin employed in these models. Although the expansion of access to BZN is not exclusively connected to price, it cannot be denied that costs affect people's access to treatment, especially in poor, undeveloped countries. We believe that the high prices charged by ELEA are related to the fact that for a long time the global production of BZN was monopolized by ELEA in the absence of a GMP certificate by LAFEPE, preventing its commercialization outside of Brazil. Presently, production is

TABLE 1

Estimated direct benznidazole production costs depending on final price variations in active pharmaceutical ingredient benznidazole.

Item	Lowest price API 750USD/kg			Highest price API 2,000USD/kg		
	unity	batch*	%	unity	batch*	%
Equipment	0,002854	1.427	3.0	0,002854	1.427	1.0
Labor	0,002204	1.102	3.0	0,002204	1.102	1.0
API-benznidazole	0,075	37.500	87.0	0,2	100.000	95.0
Ingredients/excipients	0,00236	1.180	3.0	0,00236	1.180	1.0
Packaging	0,00386	1930	4.0	0,00386	1930	2.0
Total direct cost	0,086278	43.139	100.0	0,211278	105.639	100.0

API: active pharmaceutical ingredient; USD: United States dollar; kg: kilograms. * Standard batch (500,000 pills) with calculated yield of 98%.

TABLE 2

Final estimated benznidazole production costs for public and private laboratories.

Item	Lowest price API 750USD/kg		Highest price API 2,000USD/kg	
	public	private	public	private
Total direct cost	0,086278	0,086278	0,211278	0,211278
General expenses (%)	11.0	25.0	11.0	25.0
Profit (%)	14.0	14.0	14.0	14.0
Price per unit*	0,1136	0,1280	0,2783	0,3134
Treatment per patient	20,45	23,04	50,09	56,41

API: active pharmaceutical ingredient; USD: United States dollar; kg: kilograms. * Standard batch (500,000 pills) with calculated yield of 98%.

TABLE 3

Benznidazole cost estimates versus market prices.

Item	Lowest price API	Highest price API	Market price LAFEPE	Market price
	750USD/kg	2,000USD/kg		Elea Laboratory
Pill price	0,1280	0,3134	0,2129	0.4751
Treatment price	23,04	56,41	38,32	85,52

API: active pharmaceutical ingredient; USD: United States dollar; kg: kilograms; LAFEPE: *Laboratório Farmacêutico de Pernambuco*.

already established and it is expected that competition will stimulate a decrease in prices stipulated by the manufacturing laboratories, especially when PAHO promotes bidding for the centralized acquisition of BZN through the strategic fund.

CONCLUSIONS

Treatment for CD is a symbol of neglect to the largest and most diverse spheres regarding access to medication established by the WHO. Even after more than a hundred years since the discovery of CD, it is still necessary to create sustainable and adequate financing and a robust agenda for investigation of new diagnostic tools and treatments.

Until the BENEFIT trial⁸, there has been very little evidence published from observational or small randomized trials to support the belief that treatment with effective trypanocidal drugs (nifurtimox or benznidazole) can positively affect the progression of CD in asymptomatic patients with *T. cruzi* infection or in patients with preexisting cardiac diseases. Because of the absence of more definitive, robust data, and with no other outcome trials planned for the near future, mainly owing to the lack of interest from pharmaceutical industries, doctors and their patients with chronic Chagas cardiomyopathy must use the best available information to guide their treatment decisions⁷.

The price of the drug influences access to medication; however, the widely inadequate response to CD cannot be solely

attributed to this factor. Nevertheless, we cannot ignore the fact that costs also deserves scrutiny and pressure in order to widen access; transparency regarding manufacturing and production is crucial in order to assure that there is no profit embedded in the production of CD treatment. Additionally, there is a need for competition in order to influence market regulation for the prices associated with BZN sales. When it comes to neglected diseases, patents of invention controlled through exploration monopolies are not the main obstacles for competition. However, in the case of CD, competition requires companies to meet production quality criteria (obtain certificates from sanitary authorities), and settings accessing BZN are vulnerable to stock ruptures that partly result from problems with the production of raw materials.

We believe that urgent changes in the response to CD globally require collaborative work among the various agents involved in combating the historical neglect that encompasses the disease and its affected people. It is unacceptable that the only medications for the treatment of CD are of high costs and thus unavailable to people infected with CD, resulting in high social costs, suffering, disabilities, and avoidable deaths.

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Conflict of interest

The authors declare that have no conflicts of interest.

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