

# Multiple causes of death related to Chagas' disease in Brazil, 1999 to 2007

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## ABSTRACT

**Introduction:** Chagas' disease is a major public health problem in Brazil and needs extensive and reliable information to support consistent prevention and control actions. This study describes the most common causes of death associated with deaths related to Chagas' disease (underlying or associated cause of death). **Methods:** Mortality data were obtained from the Mortality Information System of the Ministry of Health (approximately 9 million deaths). We analyzed all deaths that occurred in Brazil between 1999 and 2007, where Chagas' disease was mentioned on the death certificate as underlying or associated cause (multiple causes of death). **Results:** There was a total of 53,930 deaths related to Chagas' disease, 44,543 (82.6%) as underlying cause and 9,387 (17.4%) as associated cause. The main diseases and conditions associated with death by Chagas' disease as underlying cause included direct complications of cardiac involvement, such as conduction disorders/arrhythmias (41.4%) and heart failure (37.7%). Cerebrovascular disease (13.2%), ischemic heart disease (13.2%) and hypertensive diseases (9.3%) were the main underlying causes of deaths in which Chagas' disease was identified as an associated cause. **Conclusions:** Cardiovascular diseases were often associated with deaths related to Chagas' disease. Information from multiple causes of death recorded on death certificates allows reconstruction of the natural history of Chagas' disease and suggests preventive and therapeutic potential measures more adequate and specific.

**Keywords:** Chagas' disease. Mortality. Underlying cause of death. Multiple causes of death. Epidemiology. Brazil.

## INTRODUCTION

The World Health Organization (WHO) recommends mortality statistics to be presented by the underlying cause of death. This is defined as the disease or injury, which initiated the cascade of events leading directly to death, or the circumstances of accident or violence that produced fatal injury<sup>1</sup>. However, especially for infectious and parasitic diseases, there is a need for more comprehensive information on fatal events. Additionally, there is a clear relevance to consider all causes of death recorded on death certificates. These include in addition to the underlying causes of death the associated causes that increase the risk of complications, and other contributing causes not directly related to the process that led to death. These three groups together are called multiple causes of death<sup>2,3</sup>.

In Brazil, with significant reduction of vector and blood-borne transmission, the number of cases of acute form of Chagas' disease has been drastically reduced in most endemic areas<sup>4</sup>. In addition, both increased knowledge about the natural history of disease and better effectiveness of clinical and surgical interventions, led to the reduction of specific mortality and increased survival of infected individuals<sup>5</sup>. Recent estimates amount to 2 to 3 million individuals infected with the causing agent *Trypanosoma cruzi* in Brazil<sup>6-8</sup>. A large proportion of these cases occurred in old persons, which increases particularly the risk of

association non-infectious chronic diseases such as cardiovascular diseases and neoplasms<sup>9</sup>.

Given this new scenario of morbidity and mortality caused by Chagas' disease and the association with other chronic diseases, it is reasonable to expect that a higher number of causes of death directly or indirectly related to this disease will be observed in the next decades<sup>10</sup>.

The present nationwide study aimed to describe contributing causes of death associated with death due to Chagas' disease.

## METHODS

### Study design and population

We performed a nationwide population-based study using secondary mortality data. We included all deaths in Brazil during the period 1999 to 2007, where Chagas' disease was recorded in any part of the medical certificate of cause of death (underlying or associated cause of death). The underlying cause of death is defined the disease or injury that initiated the train of morbid events and that led directly to death<sup>1</sup>, and multiple causes as the set of all causes listed on death certificates without distinct classification (basic, consequential or contributing)<sup>11</sup>.

Chagas' disease as a cause of death was defined in the presence of any clinical forms included in the category B57 (Chagas' disease) of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)<sup>1</sup>.

### Data Source

We obtained data from the Mortality Information System (*Sistema de Informações sobre Mortalidade - SIM*) of the Brazilian

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Ministry of Health. *Sistema de Informações sobre Mortalidade* data are public domain and can be obtained from the website of the Statistical Department of the Unified Health System (*Departamento de Informática do Sistema Único de Saúde - DATASUS*)<sup>12</sup>. *Sistema de Informações sobre Mortalidade* data sets are based on the death certificates (*Declaração de óbito*), which consist of standardized forms to be filled out by the physicians in charge<sup>13</sup>. The death certificates contain demographic and clinical information regarding the underlying and multiple causes of death.

We included only deaths from 1999 and later, as a new version of SIM was launched that year, based on a new death certificate form<sup>13</sup>. In this new form, a line was added in part I (line d) upon the recommendation of the World Health Organization, to enable the declaration of a larger number of diagnoses and of associated causes of death<sup>14</sup>.

### Data processing and analysis

Data processing has been described in detail previously<sup>10</sup>. Briefly, we downloaded and processed all 243 mortality data sets from the study period, with about 9 million entries. Field codes from different data sets were standardized. We then selected all death certificates with Chagas' disease in any line of the certificate as cause of death (both underlying and associated causes). As in many death certificates more than one cause was noted per line, we created new variables for different causes of death.

Duplication of death events was eliminated by identifying and counting causes in the database. Only one cause was included (category or grouping of ICD-10) if two (or more) causes belonging to this class were recorded in the same death certificate<sup>2</sup>.

In order to reconstruct the disease process that possibly led to death related to Chagas' disease, all causes reported on the death certificate were analyzed, even ill-defined and those characterized by WHO as *modes of death*, such as *cardiorespiratory arrest* and *multiple organ failure*<sup>1,3</sup>.

Data were stored and analyzed using STATA version 11 (Stata Corporation, College Station, USA).

### Ethical considerations

The information on deaths related to Chagas' disease were obtained from computerized databases of the SIM as provided on the website of the DATASUS. This information is public domain and has no variables related to the identification of individuals. Thus, it was not necessary to submit the project to an institutional Ethics Review Board.

## RESULTS

In Brazil, from 1999 to 2007, there were 53,930 deaths in which Chagas' disease was mentioned as a cause of death, 44,543 (82.6%) as the underlying cause and 9,387 (17.4%) as an associated cause of death. During the observation period, the mean mortality rate increased by 21.4% (2.8 vs. 3.4 deaths per 100,000 inhabitants), while the increase of mean proportional mortality was 20% (0.5% vs. 0.6%). Chagas' disease, as the underlying cause, was the fourth leading cause of death (10.8%) of all infectious and parasitic diseases in the period.

Among the underlying causes of death due to Chagas' disease, 37,800 (84.9%) were due to chronic cardiac forms, and 4,208 (9.4%)

due to chronic digestive forms. In 1,097 (2.5%) cases, acute cardiac involvement was mentioned, in 1,157 (2.6%) chronic involvement of other organs, and in 281 (0.6%) other clinical forms of the disease (involvement of the nervous system and acute form without cardiac involvement).

The associated causes of death in those with Chagas' disease as the underlying cause are presented in **Table 1**. There was a clear predominance of conditions occurring during the natural history of Chagas' disease, specifically diseases of the circulatory, respiratory and digestive systems. Direct complications of cardiac involvement, especially conduction disorders/arrhythmias and heart failure, were mentioned in more than 35% of deaths, followed by shock (15%) (**Table 1**). The mean number of mentions of heart conditions or causes in deaths due to Chagas' disease as the underlying cause was 1.00 (44,643/44,543) per death certificate, while the mean mentions for circulatory diseases (Chapter IX - ICD-10) was 1.17 (52,212/44,543).

Interestingly, there was a considerable number of deaths due to complications related to medical treatment and surgical procedures (T80-T88 and Y83-Y84), affecting 4% of total deaths due to Chagas' disease (**Table 1**).

Regarding contributory causes, there was a predominance of causes of death related to chronic diseases of the circulatory system, namely hypertensive diseases, ischemic heart and cerebrovascular disease (**Table 1**).

**Table 2** details underlying causes of death for deaths in which Chagas' disease was mentioned as an associated cause. Here the pattern is slightly different. The most common underlying causes were diseases of the circulatory and respiratory systems which reached 59% of deaths in which Chagas' disease was associated cause, followed by neoplasms and digestive diseases, with 11.6% and 10.6% of deaths, respectively (**Table 2**). Cerebrovascular diseases, ischemic heart disease and hypertensive diseases were the main underlying causes of death, when Chagas' disease was identified as an associated cause. Chronic pulmonary diseases, particularly chronic obstructive pulmonary disease were also an important cause of death (**Table 2**). Despite the predominance of causes related to the chronic cardiovascular and pulmonary complex, acute infectious diseases such as septicemia and pneumonia also played an important role as the underlying cause, accounting for 10.1% deaths (**Table 2**).

## DISCUSSION

The present study shows that information from multiple causes of death recorded on death certificates allowed partial reconstruction of the natural history and the reconstitution of the morbid process of determining death by Chagas' disease<sup>3</sup>. Given the fact that multiple causes and conditions often lead to death of an individual, the use of merely the underlying cause of disease is not sufficient to describe the real epidemiological situation of a chronic condition such as Chagas' disease. In addition, the use of multiple causes of death allows identification of conditions that may be synergistic to death and opens new perspectives for the prevention and treatment of these comorbidities<sup>2</sup>.

We observed that the main conditions associated with death by Chagas' disease have been inserted into the group of diseases of the

**TABLE 1 - Associated causes of death in those patients with Chagas disease as underlying cause, 1999-2007 (multiple mentions possible, Chagas' disease as associated cause excluded).**

Associated causes of death (ICD-10)	Number	Percentage
Disorders of conduction/Arrhythmias (I44-I49)	18,440	41.4
Heart failure (I50)	16,816	37.7
Shock (R57)	6,933	15.6
Cardiomyopathy (I40-I43)	4,902	11.0
Symptoms and signs involving the circulatory and respiratory systems (R00-R09)	4,101	9.2
Other diseases of the respiratory system (J95-J99)	3,756	8.4
Hypertensive diseases (I10-I15)	3,047	6.8
Ischaemic heart diseases (I20-I25)	2,767	6.2
Cerebrovascular diseases (I60-I69)	2,742	6.1
Other diseases of intestines (K55-K63)	2,645	5.9
Other respiratory diseases principally affecting the interstitium (J80-J84)	2,488	5.6
Pneumonia (J12-J18)	2,099	4.7
Sepsis (A41)	1,949	4.4
Ill-defined and unknown causes of mortality (R95-R99)	1,943	4.4
Multiple organ failure (R68)	1,936	4.3
Renal failure (N17-N19)	1,905	4.3
<i>Diabetes mellitus</i> (E10-E14)	1,542	3.5
Complications and ill-defined descriptions of heart disease (I51)	1,346	3.0
Chronic lower respiratory diseases (J40-J47)	1,180	2.6
Surgical and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure (Y83-Y84)	1,108	2.5
Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)	945	2.1
Malnutrition (E40-E46)	873	2.0
Metabolic and electrolyte disorders (E86-E90)	854	1.9
Senility (R54)	796	1.8
Complications of surgical and medical care, not elsewhere classified (T80-T88)	651	1.5
Diseases of arteries, arterioles and capillaries (I70-I79)	591	1.3
Diseases of liver (K70-K77)	591	1.3
Diseases of oesophagus, stomach and duodenum (K20-K31)	500	1.1
Symptoms and signs involving the digestive system and abdomen (R10-R19)	476	1.1
Mental and behavioural disorders due to psychoactive substance use (F10-F19)	434	1.0
Cachexia (R64)	418	0.9
Other diseases of the digestive system (K90-K93)	385	0.9
Diseases of peritoneum (K65-K67)	350	0.8
Lung diseases due to external agents (J60-J70)	298	0.7
Other disorders of the nervous system (G90-G99)	272	0.6
Other and unspecified disorders of the circulatory system (I95-I99)	183	0.4
Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	181	0.4
Intestinal infectious diseases (A00-A09)	115	0.2
Other associated causes of death	3,699	8.3
<b>Total</b>	<b>96,257</b>	<b>NC</b>

NC: not calculated.

**TABLE 2 - Underlying causes of death on death certificates with Chagas disease as an associated cause, Brazil, from 1999 to 2007.**

<b>Underlying causes of death (ICD-10)</b>	<b>Number</b>	<b>Percentage</b>
Cerebrovascular diseases (I60-I69)	1,243	13.2
Ischaemic heart diseases (I20-I25)	1,236	13.2
Hypertensive diseases (I10-I15)	868	9.3
Chronic lower respiratory diseases (J40-J47)	563	6.0
Pneumonia (J12-J18)	532	5.7
Sepsis (A40-A41)	414	4.4
Other diseases of intestines (K55-K63)	398	4.2
<i>Diabetes mellitus</i> (E10-E14)	365	3.9
Diseases of arteries, arterioles and capillaries (I70-I79)	171	1.8
Malignant neoplasm of esophagus (C15)	165	1.8
Diseases of liver (K70-K77)	157	1.7
Disorders of gallbladder, biliary tract and pancreas (K80-K87)	146	1.6
Other diseases of the respiratory system (J95-J99)	144	1.5
Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)	127	1.3
Cardiomyopathy (I42-I43)	115	1.2
Diseases of esophagus, stomach and duodenum (K20-K31)	113	1.2
Malignant neoplasm of stomach (C16)	102	1.1
Malignant neoplasm of bronchus and lung (C34)	102	1.1
Malignant neoplasms of ill-defined, secondary and unspecified sites (C76-C80)	98	1.0
Malnutrition (E40-E46)	92	1.0
Malignant neoplasm of prostate (C61)	88	0.9
Renal failure (N17-N19)	81	0.9
Other diseases of urinary system (N30-N39)	69	0.7
Lung diseases due to external agents (J60-J70)	66	0.7
Diseases of peritoneum (K65-K67)	63	0.7
Intestinal infectious diseases (A00-A09)	62	0.7
Malignant neoplasm of colon (C18)	59	0.6
Tuberculosis/sequelae of tuberculosis (A15-A19, B90)	58	0.6
Human immunodeficiency virus (HIV) disease (B20-B24)	57	0.6
Other diseases of the digestive system (K90-K93)	55	0.6
Sequelae of other and unspecified infectious and parasitic diseases (B94)	55	0.6
Complications and ill-defined descriptions of heart disease (I51)	51	0.5
Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	51	0.5
Falls (W00-W19)	44	0.5
Complications of medical and surgical care (Y40-Y84)	44	0.5
Other underlying causes of death	1,333	14.2
<b>Total</b>	<b>9,387</b>	<b>100.0</b>

circulatory system, corroborating previous studies<sup>3,15</sup>. Consistent with the clinical descriptions and the predominance of chronic chagasic cardiopathy (CCC) as the main cause of death, cardiac complications were the main associated diseases, particularly arrhythmias/conduction disorders, heart failure and cardiomyopathies. The frequent presence of other associated causes considered terminal, such as shock, pneumonia and sepsis reflects the severity of the process related to Chagas' disease<sup>3</sup>. The importance of hypertensive disease and ischemic heart disease as contributing causes was also evident, similarly to cerebrovascular diseases. This association with Chagas' disease has concerned some investigators previously<sup>16-20</sup>.

The identification of underlying causes responsible for the deaths in which Chagas' disease is presented as associated cause increases knowledge also on the association of causes related to mortality due

to Chagas' disease. Due to the increased survival among patients with Chagas' disease in recent decades<sup>5</sup>, there was a greater likelihood of accumulation of chronic diseases such as diabetes, atherosclerosis, obesity, cancer and hypertensive diseases<sup>3</sup> causing deaths related to ischemic heart diseases and cerebrovascular diseases as major underlying causes of death, when Chagas' disease is presented as an associated cause.

Our data also call attention to cerebrovascular disease, especially ischemic stroke, which is an event often overlooked and not recognized as a complication of Chagas' disease<sup>3,18</sup>. Studies have shown that the diagnosis of Chagas' disease often occurred only after the occurrence of stroke<sup>19</sup> and some considered Chagas' disease as a possible independent risk factor for mortality from ischemic stroke, possibly by cardioembolic mechanism<sup>17,20,21</sup>. Several risk factors, such as heart

failure, mural thrombi, ventricular apical aneurysm, hypertension and cardiac arrhythmias have been shown to be associated with stroke in patients with Chagas' disease<sup>19,21</sup>. In a study based on autopsies performed in a reference hospital in the State of Bahia between 1956 and 2001, cerebral infarction was reported in 17.5% of autopsies of chagasic patients with heart failure, and complications were associated with death in 52% of cases<sup>16</sup>.

Rassi Jr et al.<sup>22</sup> reviewed studies on the causes of deaths and the frequency of sudden death in different population groups and found that sudden death, cardiac insufficiency and cerebral thromboembolism were the principal causes of death in Chagas' disease. The highest and lowest frequency of a particular case depended on the characteristics of the study population, with predominance of sudden death in those studies that included outpatients, and heart failure in studies with patients hospitalized for cardiac decompensation.

In a study from the State of São Paulo, sudden death (including in arrhythmic disorders /conduction disorder) was rarely mentioned on death certificates, in only 12.8% of deaths<sup>3</sup>. The high frequency of heart failure in deaths related to Chagas' disease suggests poor prognosis for patients with this condition, which seems to be associated with increased risk of death, as compared to patients with heart failure due to other etiologies<sup>23</sup>.

The association between arterial hypertension and Chagas' disease in the development of severe cardiac involvement is still a matter of debate in the literature<sup>24,25</sup>. In this study, the increase of hypertensive diseases associated with diabetes mellitus can be attributed to increasing mortality at more advanced ages<sup>3</sup>. In fact, the prevalence of cardiovascular causes observed in the study is partially related to the coexistence of chronic Chagas' disease with the aging process of the population<sup>9</sup>, since cardiovascular diseases are the leading causes of morbidity and mortality among the elderly<sup>26</sup>. In this study, most deaths from Chagas' disease concerned the elderly and patients with chronic cardiac form of the disease. In addition to the functional changes associated with aging of the cardiovascular system, elderly patients were also subject to damage associated with Chagas' heart disease and other cardiovascular diseases such as arterial hypertension and ischemic heart disease. Consequently, they were more vulnerable to clinical decompensation or development of lesions in organs such as brain, kidneys or the heart itself, which culminated in death<sup>9</sup>.

In fact, the predominance of cardiovascular causes observed in the study is linked to coexistence of chronic Chagas' disease<sup>9</sup> with the aging process of the population, since cardiovascular diseases are the leading causes of morbidity and mortality among the elderly<sup>26</sup>. In addition, the frequent association of chronic disease causes significant demand for health services and medications that predispose to numerous risks, whereas the association between Chagas' disease and other chronic diseases may increase mortality and worsen the quality of life of those who find themselves in this unfavorable condition<sup>26</sup>.

A current challenge is to provide assistance, taking into account the harmful effects of a combination of Chagas' disease and other chronic degenerative diseases<sup>9,26</sup>. The elderly chagasic patients should receive priority attention of health services and social assistance, deserving attention of public managers and health professionals, in order to minimize morbidity and mortality by Chagas' disease.

In addition to cardiovascular disease, there are relevant associations with respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) and pulmonary embolism, digestive diseases and neoplasms. Infectious diseases, particularly sepsis and pneumonia (although this is classified in the diseases of the respiratory system) also play a role. Intestinal infectious diseases, tuberculosis, mainly by co-infection with human immunodeficiency virus (HIV), responsible for high mortality among untreated patients may aggravate these conditions<sup>27</sup>. Knowledge on the associations of causes of death as described in our study may assist in the prevention of joint action of these diseases, in the determination of the deaths for Chagas' disease.

Interpretation of results should consider limitations of the study, such as problems arising from disease notification and data entry<sup>28</sup>. Secondary data often show inconsistencies in the quantity and quality of their information<sup>3</sup>. Deaths may be under-reported, despite the progress made during the observation period in terms of SIM coverage and quality of information on causes of deaths. The coverage (ratio of deaths reported/estimated) also presents variations between regions in the country, mainly in the North and Northeast regions<sup>3</sup>.

Similar to underreporting of deaths, the occurrence of deaths from ill-defined causes is also uneven between regions, with worse indicators outside the state capitals, among children <1 years of age, in the poorest population strata, and in rural areas. Deaths due to ill-defined causes, rather than identifying the quality of information in the death certificate, probably point to deficiencies in access to health services and quality of attention.

The results of this study show internal consistency and coherence with existing knowledge about Chagas' disease, as well as being highly representative, since it included all death certificates during the period 1999 to 2007 in Brazil, a country of continental dimensions.

We conclude that cardiovascular diseases, particularly heart diseases and cerebrovascular diseases, were the most important associated causes of death in those with Chagas' disease as cause of death. The information from all causes of death recorded on death certificates allows partial reconstruction of the natural history of Chagas' disease and some suggests preventive measures and adequate and specific therapeutic. Knowledge of the full range of causes of deaths related to the disease opens new perspectives for the prevention of deaths and help to guide appropriate care and specific measures.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABSTRACT IN PORTUGUESE

### Causas múltiplas de morte relacionadas à doença de Chagas no Brasil, 1999 a 2007

**Introdução:** A doença de Chagas é um importante problema de saúde pública no Brasil e necessita de informações amplas e confiáveis que subsidiem suas ações de prevenção e controle. Este estudo descreve as causas de morte que mais frequentemente se associaram aos óbitos relacionados à doença de Chagas como causa básica e associada de morte. **Métodos:** Dados de mortalidade foram obtidos do Sistema de Informação sobre Mortalidade do Ministério da Saúde

(aproximadamente 9 milhões de óbitos). Foram analisados todos os óbitos ocorridos no Brasil entre 1999 e 2007, nos quais a doença de Chagas foi mencionada na declaração de óbito como causa básica ou associada (causas múltiplas de morte). **Resultados:** Ocorreram 53.930 óbitos relacionados à doença de Chagas, 44.543 (82,6%) como causa básica e 9.387 (17,4%) como causa associada. As principais doenças e condições associadas ao óbito por doença de Chagas como causa básica foram as complicações diretas do envolvimento cardíaco, como os transtornos de condução/arritmias (41,4%) e a insuficiência cardíaca (37,7%). As doenças cerebrovasculares (13,2%), doenças isquêmicas do coração (13,2%) e as doenças hipertensivas (9,3%) foram as principais causas básicas nos óbitos em que a doença de Chagas foi identificada como causa associada. **Conclusões:** As doenças cardiovasculares foram as que mais frequentemente se associaram aos óbitos relacionados à doença de Chagas. As informações relativas às causas múltiplas de morte registradas na declaração de óbito permitem recompor a história natural da doença de Chagas e indicam medidas preventivas e terapêuticas mais adequadas e específicas.

**Palavras-chaves:** Doença de Chagas. Mortalidade. Causa básica de morte. Causas múltiplas de morte. Epidemiologia. Brasil.

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