Mortality from neglected tropical diseases in Brazil, 2000–2011
Francisco Rogeriândio Martins-Melo,a Alberto Novaes Ramos Jr.,a Carlos Henrique Alencarb & Jorg Heukelbacha

Objective To describe mortality from neglected tropical diseases (NTDs) in Brazil, 2000–2011.
Methods We extracted information on cause of death, age, sex, ethnicity and place of residence from the nationwide mortality information system at the Brazilian Ministry of Health. We selected deaths in which the underlying cause of death was a neglected tropical disease (NTD), as defined by the World Health Organization (WHO) and based on its International statistical classification of diseases and related health problems, 10th revision (ICD-10) codes. For specific NTDs, we estimated crude and age-adjusted mortality rates and 95% confidence intervals (CI). We calculated crude and age-adjusted mortality rates and mortality rate ratios by age, sex, ethnicity and geographic area.
Findings Over the 12-year study period, 12,491,280 deaths were recorded; 76,847 deaths (0.62%) were caused by NTDs. Chagas disease was the most common cause of death (58,928 deaths; 76.7%), followed by schistosomiasis (63,198 deaths; 8.2%) and leishmaniasis (3466 deaths; 4.5%). The average annual age-adjusted mortality from all NTDs combined was 4.30 deaths per 100,000 population (95% CI: 4.21–4.40). Rates were higher in males: 4.98 deaths per 100,000; people older than 69 years: 33.12 deaths per 100,000; Afro-Brazilians: 5.25 deaths per 100,000; and residents in the central-west region: 14.71 deaths per 100,000.
Conclusion NTDs are important causes of death and are a significant public health problem in Brazil. There is a need for intensive integrated control measures in areas of high morbidity and mortality.

Introduction
Neglected tropical diseases (NTDs) can result in disabilities, disfigurement, impaired childhood growth and cognitive development, death and increasing poverty in affected communities.1 Worldwide, about 2 billion people are at risk of one or more NTDs and more than 1 billion people are affected by these diseases.1–3 Up to half a million deaths and up to 57 million disability-adjusted life years lost have been attributed annually to NTDs.1,2,4,5

Brazil accounts for a large proportion of NTDs occurring in Latin America, including leprosy (86%), dengue fever (40%), schistosomiasis (96%), Chagas disease (25%), cutaneous leishmaniasis (39%) and visceral leishmaniasis (93%).4–8 Most NTDs occur in populations with low-socioeconomic status, mainly in the north and north-east of the country.6

Knowledge of the magnitude of NTD-related deaths in endemic countries is essential for monitoring and evaluation of the impact of interventions and the effectiveness of specific control measures.9–11 However, there are only a few systematic and large-scale studies investigating NTD-related mortality.9,10,12–16 Here, we describe the epidemiological characteristics of deaths due to NTDs in Brazil over a period of 12 years.

Methods
We obtained mortality data from the nationwide mortality information system of the Brazilian Ministry of Health, which is publicly accessible.7 Death certificates, which are completed by physicians, include the following variables: multiple causes of death, age, sex, education, ethnicity, marital status, date of death, place of residence and place of death. We downloaded and processed a total of 324 mortality data sets (one for each of the 27 states per year). We included all deaths in Brazil from 2000 to 2011, in which any NTD was recorded on death certificates as the underlying cause of death. We selected all NTDs as defined by the World Health Organization (WHO) based on its International statistical classification of diseases and related health problems, 10th revision (ICD-10) codes,16 whether or not the disease is known to be endemic in Brazil (Table 1).14 Population data were based on the national population censuses (2000 and 2010) with interpolation for other years (2001–2009 and 2011).19

Analysis
For specific NTDs, we estimated average annual crude and age-adjusted mortality rates and 95% confidence intervals (CI). For all NTDs combined, we calculated crude, age-specific and age-adjusted mortality rates by sex, ethnicity and geographic area. Age-adjusted rates were calculated by the direct method based on the 2010 census. Age-specific rates were computed for the following age groups: 0–4, 5–9, 10–14, 15–19, 20–39, 40–59, 60–69 and older than 69 years. We included all data sets, even if information about some variables were not available in all cases. Details of missing data are presented in the tables.

We estimated (i) mortality rate ratios for all NTDs combined, by age, sex and ethnicity, based on the crude mortality rates; (ii) the proportion of all deaths attributed to NTDs; and (iii) the proportion of deaths from infectious and parasitic causes, (ICD-10 codes A00–B99), attributed to NTDs. For comparison, we also calculated deaths attributed to human immunodeficiency virus (HIV), tuberculosis and malaria.20

We used Stata version 11.2 (StataCorp LP, College Station, United States of America) for all analyses. The map of NTD mortality rates Fig. 1 was created using ArcGIS version 9.3 (ESRI, Redlands, United States of America). We used publicly available secondary data, which are anonymized to prevent identification of individuals. This study was approved by the Ethical Review Board of the Federal University of Ceará, Fortaleza, Brazil, registration number 751 109/2014.

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Correspondence to Jorg Heukelbach (email: heukelbach@web.de).
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The median age at death from all NTDs combined was 63.8 years, (range: 0–108.5). Deaths from NTDs were most common in males (44 237/76 840; 57.6%); people older than 69 years (27 168/76 662; 35.4%); Caucasians (32 907/68 956; 47.7%); and residents in the south-east region (35 933/76 847; 46.8%). These deaths most commonly occurred in hospitals (55 791/76 629; 72.8%), followed by deaths at home (15 680/76 629; 20.5%). The median age of death was highest for chronic diseases such as Chagas disease, schistosomiasis and leprosy and lowest for soil-transmitted helminth infections, rhabdiasis, dengue fever and leishmaniasis (Table 2). The sex distribution also differed according to the disease; more than 70% (2117/2935) of leprosy deaths and 62.8% of leishmaniasis deaths (2177/3466) occurred in males (Table 2).

The average annual crude mortality rate was 3.45 deaths per 100 000 inhabitants (95% CI: 3.37–3.54), with an age-adjusted rate of 4.30 deaths per 100 000 inhabitants (95% CI: 4.21–4.40; Table 2 and Table 3). Average annual age-adjusted rates were significantly higher in males than females (Table 3). Age-specific rates increased with age, with 33.12 deaths per 100 000 inhabitants in people older than 69 years. Rates were 1.8 times higher in Afro-Brazilians compared to Caucasians (Table 3).

Of the five regions, the central-west region had the highest age-adjusted rate (14.71 deaths per 100 000 inhabitants) and the southern region the lowest (1.52 deaths per 100 000 inhabitants; Fig. 1). The proportion of all deaths caused by NTDs was 0.62% (Table 2).

## Discussion

We have described mortality from NTDs in Brazil during a 12 year period. In general, NTDs with a predominantly chronic pathology showed the highest mortality. Chagas disease caused the highest number of deaths, followed by schistosomiasis and leishmaniasis, while leprosy also caused a considerable burden.

The high mortality from Chagas disease is a particular feature of Latin American countries, especially Brazil.21 During recent decades, there have been major efforts to reduce the burden of Chagas disease on the continent and transmission rates have been reduced considerably.21 22 However, because of the chronic nature of the disease, mortality rates will fall slowly.23 24

Brazil harbours most of the schistosomiasis burden in Latin America;24 the main endemic areas are in the north-east region of the country.24 Control programme measures implemented in recent decades were based mainly on periodical stool surveys in endemic areas, followed by treatment of positive cases. Consequently, morbidity and mortality from schistosomiasis have been reduced, but the disease has not been eliminated.25 26 Schistosomiasis control continues to be a challenge, with persistence and expansion of disease foci, even after years of integrated control measures.25 26 Internal migration of people,
combined with the wide geographical distribution of intermediate snail hosts and poor sanitary conditions favour the permanence and establishment of new foci in Brazil. 25

A considerable number of deaths were attributed to leishmaniasis, dengue fever and leprosy. Three forms of leishmaniasis – visceral, cutaneous, and mucocutaneous – differ in incidence, severity and geographic distribution in Brazil. 6,7,8 Cutaneous leishmaniasis occurs in all 27 states, with most cases reported in the north region, 27 whereas locally-transmitted cases of visceral leishmaniasis, the most serious form of the disease, are reported from 21 states, with the greatest burden in the north-east region. 9,12,29 Visceral leishmaniasis is potentially fatal if not diagnosed and treated promptly 9,10 and is responsible for most leishmaniasis deaths. 7 There has been an increase in mortality from visceral leishmaniasis in Brazil in recent years. This is mainly due to the introduction of the disease into new geographic areas and host factors increasing case fatality rate, such as malnutrition, increasing age and immunosuppression, the latter being mainly due to HIV.9,28

Dengue fever has a wide geographic distribution and is also a national public health concern in Brazil. 31 Despite intensified control measures in the country, in recent years there has been a steady increase in the number of dengue-related hospitalizations, severe cases and deaths.12,32 Increased geographical spread of the vector mosquitoes and the simultaneous presence of multiple dengue serotypes may partly explain the increases in severe dengue. 11,32

The considerable number of leprosy deaths is surprising, since leprosy is usually seen as a disease with low case fatality. 14,33,34 However, leprosy – even with continuously reduced new cases during the past decades – is an under-recognized cause of death. 35 Based on the chronic nature of the disease and the transmission dynamics, deaths from leprosy will continue to occur for decades.

In general, age-adjusted NTD mortality rates were higher among males. This indicates gender-specific patterns of infectious disease exposure, as the relationship between gender and risk of infection is conditioned by different socioeconomic, environmental and behavioural factors. 16,11,37 Males are less likely to seek early treatment, leading to increased morbidity and severity, which is particularly evident in the case of leprosy. 14,35

For all NTDs combined, mortality rates increased with age and were highest among older age groups. This can be explained by the chronic nature of major NTDs with high mortality impact in Brazil, especially Chagas disease, schistosomiasis and leprosy. 36,31,32,33 Interaction with chronic comorbidities which are common in these age groups, such as cardiovascular diseases, diabetes mellitus, hypertension and cancer, multiply the risk of severe disease and death. 36 In people diagnosed with an NTD, possible co-infection with other NTDs and the presence of other chronic conditions should be assessed. 9,32,36

Afro-Brazilians had higher NTD mortality rates compared with the Caucasian population. Similar to many other infectious diseases worldwide, this may be attributed to socioeconomic factors, poor housing, water and sanitation and reduced access to health care, which makes people vulnerable to neglected and poverty-related diseases in endemic areas. 11,35 This pattern is also observed in other countries in Latin America and elsewhere. 37,38

Our use of secondary mortality data leads to several limitations. 11,12,14,35 Deaths may be underreported, despite recent progress in terms of the completeness and quality of mortality records. 9,30 The proportion of deaths from ill-defined causes is distributed unequally between regions, urban and rural areas, age groups, and socioeconomic strata. 33 In the year 2000, the proportion of deaths that were reported varied considerably, from 55.2% in Maranhão state in the north-east region to 100.0% in some states of the south and south-east regions. The coverage has improved steadily: in 2011, the regional differences were reduced, with the lowest coverage of 79.1%, also in Maranhão state.

Mortality from NTDs might be underestimated if underlying causes of death were coded as a pathology resulting from some NTDs, without mention of the infection that caused the pathology. For example, gastrointestinal bleeding, portal hypertension and oesophageal varices may be caused by schistosomiasis and Chagas disease.
### Table 2. Mortality from neglected tropical diseases, by cause, Brazil, 2000–2011

| Disease (ICD-10 code) | No. (% of total NTDs) | Median age (years) | Males (%) | Average annual no. of deaths | Notified deaths ( %) | Deaths from infectious and parasitic diseases ( %) | Crude mortality rates per 100 000 population per year (95% CI) | Age-adjusted mortality rates per 100 000 population per year (95% CI) |
|------------------------|-----------------------|-------------------|-----------|------------------------------|---------------------|-----------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|
| Chagas disease (B57)   | 58 928 (76.7)         | 65.6              | 57.3      | 4 910.7                      | 0.47                | 10.55                                         | 2.65 (2.57–2.72)                                               | 3.37 (3.29–3.46)                                                   |
| Schistosomiasis (B65)  | 6 319 (8.2)           | 62.8              | 54.3      | 526.6                        | 0.05                | 1.13                                          | 0.28 (0.26–0.31)                                               | 0.35 (0.33–0.38)                                                   |
| Leishmaniasis (B55)    | 3 466 (4.5)           | 30.7              | 62.8      | 288.8                        | 0.03                | 0.62                                          | 0.16 (0.14–0.17)                                               | 0.16 (0.14–0.18)                                                   |
| Dengue (A90–A91)       | 3 156 (4.1)           | 41.4              | 51.5      | 263.0                        | 0.03                | 0.56                                          | 0.14 (0.13–0.16)                                               | 0.16 (0.14–0.17)                                                   |
| Leprosy (A30–B92)      | 2 936 (3.8)           | 64.2              | 72.1      | 244.7                        | 0.02                | 0.53                                          | 0.13 (0.12–0.15)                                               | 0.16 (0.15–0.18)                                                   |
| Taeniasis/ cysticercosis (B68, B69) | 1 231 (1.6) | 46.8 | 56.3 | 102.6 | 0.01 | 0.22 | 0.06 (0.05–0.07) | 0.06 (0.05–0.08) |
| Soil-transmitted helminthias (B76, B77, B79) | 518 (0.7) | 27 | 46.5 | 43.2 | NC | 0.09 | 0.02 (0.02–0.03) | 0.02 (0.01–0.03) |
| Rabies (A82)           | 113 (0.1)             | 147               | 65.5      | 9.4                          | NC                  | 0.02                                          | 0.01 (0.00–0.01)                                               | 0.01 (0.00–0.01)                                                   |
| Echinococcosis (B67)   | 82 (0.1)              | 556               | 62.2      | 6.8                          | NC                  | 0.01                                          | NC                                                            | NC                                                                  |
| Filariasis (B74)       | 66 (0.1)              | 596               | 40.9      | 5.5                          | NC                  | 0.01                                          | NC                                                            | NC                                                                  |
| Human African trypanosomiasis (sleeping sickness) (B58) | 9 (< 0.1) | 647 | 36.4 | 0.8 | NC | NC | NC | NC |
| Endemic treponematoses (A65, A66, A67) | 8 (< 0.1) | 563 | 50.0 | 0.7 | NC | NC | NC | NC |
| Onchocerciasis (river blindness) (B73) | 5 (< 0.1) | 2.2 | 60.0 | 0.4 | NC | NC | NC | NC |
| Buruli ulcer (A31.1)   | 3 (< 0.1)             | 76.1              | 33.3      | 0.3                          | NC                  | 0.13                                          | NC                                                            | NC                                                                  |
| Dracunculiasis (guinea-worm disease; B72) | 3 (< 0.1) | 623 | 33.3 | 0.3 | NC | NC | NC | NC |
| Trachoma (A71)         | 2 (< 0.1)             | 319               | 100.0     | 0.2                          | NC                  | 0.06                                          | NC                                                            | NC                                                                  |
| Foodborne trematodiases (B66.0, B66.1, B66.3, B66.4) | 2 (< 0.1) | 561 | 50.0 | 0.2 | NC | NC | NC | NC |
| Total deaths from NTDs | 76 847 (100.0)        | 63.8              | 57.6      | 6 403.9                      | 0.62                | 13.75                                         | 3.45 (3.37–3.54)                                               | 4.30 (4.21–4.40)                                                   |

CI: confidence interval; HIV: human immunodeficiency virus; ICD-10: International statistical classification of diseases and related health problems, 10th revision; NA: not applicable; NC: not calculated; NTDs: neglected tropical diseases.

1. Mortality by cause divided by the total number of deaths in the period (12 491 280 deaths).
2. Mortality by cause divided by deaths from infectious and parasitic diseases – ICD-10 codes A00-B99 (558 706 deaths).
3. Average crude mortality rates.
4. Mortality rates standardized to the 2010 Brazilian population.
5. Visceral leishmaniasis – B55.0: 2727; Cutaneous leishmaniasis – B55.1: 174; Mucocutaneous leishmaniasis – B55.2: 67; Leishmaniasis, unspecified – B55.9: 498.
6. Cysticercosis – B69 2007 deaths; Taeniasis – B68 13 deaths.
7. Ascariasis – B77: 827 deaths; Hookworm – B76: 25 deaths; Trichuriasis – B79: 1 death.
8. Yaws – A66.23 deaths; Pinta – A67.4 deaths; Bejel (endemic syphilis) – A65.4 deaths.
9. Fascioliasis – B66.3.4 deaths; Opisthorchiasis – B66.0.1 death; Paragonimiasis – B66.4.1 death; Clonorchiasis – B66.3.0 deaths.
can cause heart failure.\textsuperscript{23,35,36} We could have included certificates where NTDs were recorded as cause of death in any part of the death certificate rather than only as the underlying cause. However, we opted to present an analysis based on the underlying causes of deaths as this is the usual standard applied in mortality data analysis.\textsuperscript{24,25} Analysis by ethnicity is limited by missing data.

We conclude that NTDs continue to be an important public health problem in Brazil. There is a need to improve integrated control measures in the areas with the highest morbidity and mortality burden. Specific disease control programs for diseases which are usually considered of chronic nature and not a cause of death, should also take case-fatality rates into account.

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Competing interests: None declared.
The results of a study of deaths in Brazil during the period 2000–2011 revealed 12,491 deaths attributed to neglected tropical diseases (NTDs), representing 0.62% of all deaths. The mortality rate for NTDs was 4.21–4.40 per 100,000 population; the highest rate was in the age group 69 years and older. The most common cause of death due to NTDs was Chagas disease (58,928 deaths; 76.7% of all deaths). Other NTDs included schistosomiasis (6,319 deaths; 8.2%) and leishmaniasis (3,466 deaths; 4.5%). The annual mortality rate was calculated by age and area of residence, and the results were used to develop integrated and targeted interventions to control the most common NTDs in Brazil.

The findings of this study highlight the importance of addressing NTDs, which are still largely neglected despite their significant public health impact in Brazil. The results emphasize the need for integrated and intensive measures to control these diseases, particularly in high-risk areas, to prevent further deaths and reduce the burden on public health systems.

**Résumé**

**Objectif** Décrire la mortalité due aux maladies tropicales négligées au Brésil sur la période 2000–2011.

**Méthodes** Nous avons prélevé des informations sur la cause des décès, l'âge, le sexe, l'origine ethnique et le lieu de résidence dans le système d'information national sur la mortalité du ministère de la Santé brésilien. Nous avons sélectionné les décès pour lesquels la cause sous-jacente était une maladie tropicale négligée, au sens de la définition de l'Organisation mondiale de la Santé (OMS) et selon les codes de sa Classification statistique internationale des maladies et des problèmes de santé connexes, 10e révision (CIM-10). Nous avons estimé le taux de mortalité brut et ajusté en fonction de l'âge ainsi que l'intervalle de confiance (IC) de 95% relatifs à des maladies tropicales négligées spécifiques. Nous avons calculé le taux de mortalité brut et ajusté en fonction de l'âge ainsi que les ratios de taux de mortalité par âge, sexe, origine ethnique et situation géographique.

**Résultats** Sur la période de 12 années étudiée, 12,491 décès ont été enregistrés; 76,847 de ces décès (0,62%) étaient dus à des maladies tropicales négligées. La maladie de Chagas était la cause de décès la plus courante (58,928 décès; 76,7%), suivie de la schistosomiasis (6,319 décès; 8,2%) et de la leishmaniasis (3,466 décès; 4,5%). La mortalité annuelle moyenne ajustée en fonction de l'âge due à l'ensemble des maladies tropicales négligées était de 4,30 décès pour 100 000 personnes (IC 95%: 4,21-4,40). Le taux était plus élevé chez les hommes: 4,98 décès pour 100 000 personnes; les personnes de plus de 69 ans: 33,12 décès pour 100 000 personnes; les Afro-Bresiliens: 5,25 décès pour 100 000 personnes; et les habitants de la région Centre-Ouest: 14,71 décès pour 100 000 personnes.

**Conclusion** Les maladies tropicales négligées représentent des causes de décès importantes et un grave problème de santé publique au Brésil. Des mesures de lutte intégrées et intensives sont nécessaires dans les régions qui présentent une morbidité et une mortalité élevées.
Resumen

La mortalidad de las enfermedades tropicales desatendidas en Brasil, 2000–2011

Objetivo Describir la mortalidad de las enfermedades tropicales desatendidas en Brasil, 2000–2011.

Métodos Se extrajo información referente a la causa del fallecimiento, edad, sexo, etnia y lugar de residencia del sistema de información de la mortalidad nacional del Ministerio de Salud de Brasil. Se seleccionaron fallecimientos en los que la causa subyacente de la muerte fue una enfermedad tropical desatendida, según la definición de la Organización Mundial de la Salud (OMS) y en base a los códigos de la Décima Revisión de la Clasificación Estadística Internacional de Enfermedades y Problemas Relacionados con la Salud (CIE-10). En el caso de enfermedades tropicales desatendidas concretas, se estimaron las tasas de mortalidad brutas y ajustadas por edades y los intervalos de confianza (IC) del 95%. Se calcularon las tasas de mortalidad brutas y ajustadas por edades y las razones de tasas de mortalidad ajustadas por edad, sexo, etnia y zona geográfica.

Resultados Durante el periodo de estudio de 12 años, se registraron 12 491 280 fallecimientos; 76 847 fallecimientos (0,62%) fueron causados por enfermedades tropicales desatendidas. La causa de fallecimiento más común fue la enfermedad de Chagas (58 928 fallecimientos; 76,7%), seguida de la esquistosomiasis (6319 fallecimientos; 8,2%) y la leishmaniasis (3466 fallecimientos; 4,5%). La media de mortalidad anual ajustada por edades de todas las enfermedades tropicales desatendidas combinadas fue de 4,30 fallecimientos por cada 100 000 habitantes (IC del 95%: 4,21–4,40). Las tasas fueron más altas en los hombres: 4,98 fallecimientos por cada 100 000 habitantes; personas mayores de 69 años: 33,12 fallecimientos por cada 100 000 habitantes; afrobrasileños: 5,25 fallecimientos por cada 100 000 habitantes; y residentes en la región centro-oeste: 14,71 fallecimientos por cada 100 000 habitantes.

Conclusión Las enfermedades tropicales desatendidas son importantes causas de fallecimiento y son un problema de salud pública significativo en Brasil. Existe la necesidad de tomar medidas de control intensivas integradas en zonas de morbidad y mortalidad altas.

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