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Trends and associated characteristics for Chagas disease among women of reproductive age in the United States, 2002 to 2017

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ABSTRACT

Background: American trypanosomiasis, commonly referred to as Chagas disease, is caused by a single cell protozoan known as *Trypanosoma cruzi* (*T. cruzi*). Although those affected are mainly in Latin America, Chagas has been detected in the United States (US), Canada and in many European countries due to migration. Few studies have explored the epidemiology of Chagas within the US or changes in disease burden over the past decade. The objective of this study was to explore the trends and associated characteristics for Chagas disease among hospitalized women of reproductive age in the US.

Methods: We analyzed admissions data including socio-demographic and hospital characteristics for inpatient hospitalization for women of reproductive age (15–49 years) in the US from 2002 through 2017. We employed Joinpoint regression analysis to determine trends in the prevalence of Chagas disease over this period.

Results: A total of 487 hospitalizations of Chagas disease were identified, corresponding to 3.7 per million hospitalizations over the study period. The rate statistically increased from 1.6 per million in 2002 to 7.6 per million hospitalizations in 2017. Chagas was most prevalent among older women, Hispanics and those in the highest zip income bracket. The in-hospital mortality rate was about 10 times greater among women with Chagas compared to those without the condition (3.1% versus 0.3%), and the condition tended to be clustered in women treated at large, urban teaching hospitals in the Northeastern region of the US.

Conclusion: Chagas disease diagnosis appears to be increasing among hospitalized women of reproductive age in the US with a 10-fold elevated risk of mortality.

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1. Introduction

American trypanosomiasis, commonly referred to as Chagas disease, is a tropical infection caused by the protozoan, *Trypanosoma cruzi* (*T. cruzi*) (CDC - Chagas Disease - Epidemiology and Risk Factors, 2020). Its primary vectors are insects belonging to the *Reduviidae* family, or "kissing" bugs, and the disease is typically spread via insect bites. While Chagas disease is found almost exclusively in the Western Hemisphere within rural areas of South America, Central America, and Mexico, more than 8 million people are presumed to be affected worldwide resulting in more than 10,000 deaths annually (CDC - Chagas Disease - Epidemiology and Risk Factors, 2020; WHO, 2020a). Because of this, Chagas has been designated a neglected disease by the World Health Organization, and as a major public health concern (WHO, 2020b).

Within the United States, more than 230,000 individuals are diagnosed with Chagas disease (Manne-Goehler et al., 2016). This figure, however, is just an approximation and likely underestimates the true burden of the condition. Because American trypanosomiasis is not endemic within humans in the US, its incidence is most commonly linked to global migration and travel. This could lead to underestimation of the true disease prevalence as a result of the incomplete ascertainment of cases within the undocumented immigrant populations, many of whom arrive from areas where American trypanosomiasis is endemic. Additionally, due to low clinical suspicion of the disease by healthcare providers in the US, under-diagnosis in clinical settings could contribute to the overall prevalence estimates.

Among those infected in the US, approximately 10% are women of reproductive age (CDC - Chagas Disease - Congenital Chagas Disease, 2020). While Chagas disease is primarily a vector-borne illness and transmitted via insect bites, vertical transmission is possible and can result in congenital infection in newborns. This occurs in up to 5% of infants born to mothers with American trypanosomiasis, and the infection commonly persists with severe clinical symptoms presenting later in life (CDC - Chagas Disease - Congenital Chagas Disease, 2020). Focusing preventive measures on women of reproductive age presents an opportunity to reduce the prevalence of Chagas disease in the newborn.

Data on the prevalence and risk factors of Chagas disease among women of reproductive age in the United States are scanty. Literature shows that those from poorer regions of Latin America are most commonly affected (Moncayo and Silveira, 2017), but similar factors have been sparsely studied within North America. Further, there is limited epidemiologic data regarding the incidence and prevalence of American trypanosomiasis in general over time. The objective of this study is to fill these gaps and explore trends and associated characteristics of Chagas disease among women of reproductive age in the United States.

2. Methods

Our analysis covered the period from January 1, 2002 through December 31, 2017 using cross-sectional data from the Nationwide Inpatient Sample (NIS). The NIS, made available by the Healthcare Cost and Utilization Project (HCUP), currently constitutes the largest all-payer, publicly available inpatient database in the US (HCUP-US NIS Overview, 2020). Each year, to create the sample of inpatient hospitalizations, HCUP employs a two-stage cluster sampling design that first stratifies all nonfederal community hospitals from participating states by five major hospital characteristics: rural/urban location, number of beds, geographic region, teaching status, and ownership. Then, from each unique stratum, 20% of hospitals are selected using a systematic random sampling technique. NIS employed International Classification of Disease, Ninth revision, Clinical Modification (ICD-9-CM) till third quarter of 2015 and ICD 10-CM from October 1st 2015 till date to code the diagnoses and procedures associated with each hospitalization.

We restricted the analysis to women of reproductive age (i.e.15–49 years) and identified whether or not they had Chagas disease using ICD-9-CM codes '086.0', '086.1' and '086.2'; and ICD-10 codes beginning with 'B57'. Covariates included in the study were age, which was sub-grouped as follows: 15–24 years, 25–34 years, and 35–49 years. Race/ethnicity was available in the dataset as Non-Hispanic White (NH-White), Non-Hispanic Black (NH-Black), Hispanic and NH-Others. Discharge status was re-categorized as routine, transfer, died, discharged against medical advice (DAMA) and others. Socio-economic level based on zip codes was categorized into quartiles. Primary Payer was designated as Medicare, Medicaid, private insurance, self-pay and others. Hospital regions included Northeast, Midwest, South, and West. Hospital location and type were available as rural, urban-teaching, urban non-teaching; while bed size was defined as small, medium, and large. HCUP publishing guidelines recommends suppressing the report of sample sizes less than or equal to 10, for privacy protections. Also, missing information was not reported to prevent inference based on small sample sizes.

We calculated the proportion and prevalence of Chagas across socio-demographic and hospitalization characteristics. Next, we used Joinpoint regression (Joinpoint Regression Program, 2019) to estimate and describe temporal changes in the rates of Chagas during the 16-year study period. Joinpoint regression is valuable in identifying key periods in time marking changes in the rate of events over time. The iterative model-building process was initiated by fitting the annual rate data to a straight line with no joinpoints, which assumed a single trend best described the data. Then a joinpoint – reflecting a change in the trend – was added to the model and a Monte Carlo permutation test assessed the improvement in model fit. The process continued until a final model with an optimal (best-fitting) number of joinpoints was selected, with each joinpoint indicating a change in the trend, and an average annual percent change (AAPC) was then estimated to describe how the rate changed over the entire study period. After removing the missing information from the covariates, survey logistic regression models were run to compute unadjusted and adjusted odds ratios for the association between our selected socio-demographic features, hospital characteristics, and Chagas. All tests of hypotheses were two-tailed with a type 1 error rate set at 5%. Data analyses were performed using R

(version 3·6·1) and RStudio (Version 1·1·423). The Institutional Review Board of Baylor College of Medicine designated our study as exempt since we utilized publicly available, de-identified data for the study.

3. Results

Our analysis included a total of 131,529,240 hospitalizations for women of reproductive age in the US from 2002 to 2017. Among these, a total of 487 admissions had an associated diagnosis of Chagas disease, yielding a prevalence of 3.7 cases per million hospitalizations over the study duration. Socio-demographic characteristics for women both with and without Chagas disease are shown in Table 1. The proportion of Chagas disease among hospitalized women increased with age as only 6.8% of cases were in women aged 15–24 years while 76.6% of women with Chagas disease were aged 35–49 years. The prevalence of Chagas also followed a dose-response curve with age and was more than 7 times greater among the oldest reproductive aged women (7.58 cases/million) than in the youngest (1.03 cases/million). Hispanic women comprised the greatest proportion of Chagas disease patients accounting for 75.8% of cases, while NH-White and NH-Black women accounted for 10.5% or less. About 84.2% of those with Chagas disease were discharged routinely. However, the prevalence of Chagas disease was highest among those who died during hospital admission (35.36 cases/million). We also noted a greater frequency of Chagas disease among women

Table 1
Socio-demographic characteristics of Chagas hospitalizations among women of reproductive age.

	Chagas				
	No		Yes		Prevalence per million hospitalizations
	n	%	*n*	%	
Age					
15–24 years	32,061,482	24.4%	33	6.8%	1.03
25–34 years	50,228,984	38.2%	81	16.6%	1.61
35–49 years	49,238,287	37.4%	373	76.6%	7.58
Race					
NH-White	61,281,660	46.6%	51	10.5%	0.83
NH-Black	19,307,968	14.7%	Suppressed[a]		
Hispanic	19,935,421	15.2%	369	75.8%	18.51
Other	9,314,024	7.1%	49	10.1%	5.26
Missing	21,689,679	16.5%	Suppressed[a]		
Discharge status					
Routine	120,703,761	91.8%	410	84.2%	3.40
Transfer	4,147,370	3.2%	Suppressed[a]		
Died	424,171	0.3%	15	3.1%	35.36
DAMA	1,431,117	1.1%	Suppressed[a]		
Other	4,765,738	3.6%	53	10.9%	11.12
Missing	56,595	0.0%	Suppressed[a]		
Zip income quartile					
Lowest quartile	28,415,683	21.6%	91	18.7%	3.20
2nd quartile	24,053,270	18.3%	79	16.2%	3.28
3rd quartile	22,443,358	17.1%	45	9.2%	2.01
Highest quartile	19,406,677	14.8%	154	31.6%	7.94
Missing	37,209,764	28.3%	119	24.4%	3.20
Primary payer					
Medicare	9,526,407	7.2%	35	7.2%	3.67
Medicaid	40,069,811	30.5%	173	35.5%	4.32
Private insurance	56,526,990	43.0%	85	17.5%	1.50
Self-pay	11,987,233	9.1%	110	22.6%	9.18
Other/missing	13,418,311	10.2%	85	17.5%	6.33
Hospital region					
Northeast	23,431,507	17.8%	213	43.7%	9.09
Midwest	28,847,366	21.9%	30	6.2%	1.04
South	51,189,969	38.9%	152	31.2%	2.97
West	28,059,910	21.3%	93	19.1%	3.31
Hospital bed size					
Small	16,793,825	12.8%	59	12.1%	3.51
Medium	35,024,526	26.6%	92	18.9%	2.63
Large	79,252,558	60.3%	337	69.2%	4.25
Missing	457,843	0.3%	Suppressed[a]		
Hospital location and teaching status					
Rural	14,315,388	10.9%	Suppressed[a]		
Urban non-teaching	48,350,394	36.8%	46	9.4%	0.95
Urban teaching	68,405,126	52.0%	436	89.5%	6.37
Missing	457,843	0.3%	Suppressed[a]		

[a] Per HCUP publishing guidelines for privacy protections, we have suppressed cells containing values less than or equal to 10 and omitted missing data to prevent inference of these values.

who self-paid for their medical care (9.18 per million), than among those utilizing private insurance (1.50/million), Medicare (3.67/million), or Medicaid (4.32/million). With respect to zip income quartiles, the greatest proportion and prevalence of Chagas was observed in women within the highest income quartile and accounted for almost one-third of all cases of Chagas disease. The majority of women with Chagas disease were treated in large, urban teaching hospitals. Hospitals in the Northeast had the fewest admissions overall, but had the greatest number of Chagas disease cases ($n = 213$) and highest prevalence (9.09/million).

Fig. 1 depicts an increasing trend in the rates of Chagas disease among hospitalized women of reproductive age in the US. The rate of diagnosis of Chagas increased from 1.60 per million hospitalizations in 2002 to 7.59 per million hospitalizations in 2017, yielding a positive average annual percent change (AAPC) of 6.8% [95% CI 1.9–12.0] over the study period, which was statistically significant.

Adjusted survey logistic regression revealed a significant association between age and diagnosis of Chagas disease in both unadjusted and adjusted models as seen in Table 2. Women aged 35–49 years had the greatest adjusted odds for Chagas disease (aOR 9.39 [4.18–21.07], $p < .0001$). Compared to NH-Whites, the likelihood of Chagas disease was more than 25-fold among Hispanic women (aOR 25.85 [5.64–118.5), $p < .0001$]. In-hospital death was strongly associated with Chagas disease as women who died in hospital were approximately seven times as likely to have been diagnosed with Chagas disease compared to women who were routinely discharged. Women in the lowest, second, and third zip income quartiles were protected and had lower adjusted odds for Chagas disease diagnosis compared to those in the highest zip income quartile. Region of residence was predictive of Chagas disease diagnosis, and women from the South and West regions experienced about 50% and 65% lower adjusted odds for Chagas disease diagnosis, respectively, than those in the Northeast. By contrast, there was no significant association between Chagas disease and primary payer for hospital visit, hospital size, location or teaching status in our adjusted models.

4. Discussion

Significant findings of our analysis include evidence of a dose-response relationship between age and prevalence of Chagas disease among hospitalized women of reproductive age. Hispanic women comprised the greatest proportion of hospitalized women with American trypanosomiasis and had exceedingly high odds of being diagnosed with the infection compared to their NH-White and NH- Black counterparts. Women of higher socioeconomic status were also more likely to have the disease despite making up the smallest proportion of the study group. While hospital location was associated with diagnosis of Chagas disease, hospital size did not exhibit significant correlation. We also ascertained that there had been an increasing prevalence of Chagas disease over the past two decades which is likely to continue with increasing globalization.

The association between Hispanic ethnicity and diagnosis of American trypanosomiasis is unsurprising as migration from Latin America, where Chagas disease is endemic, has been considered the fundamental cause for the presence of the disease in the US.

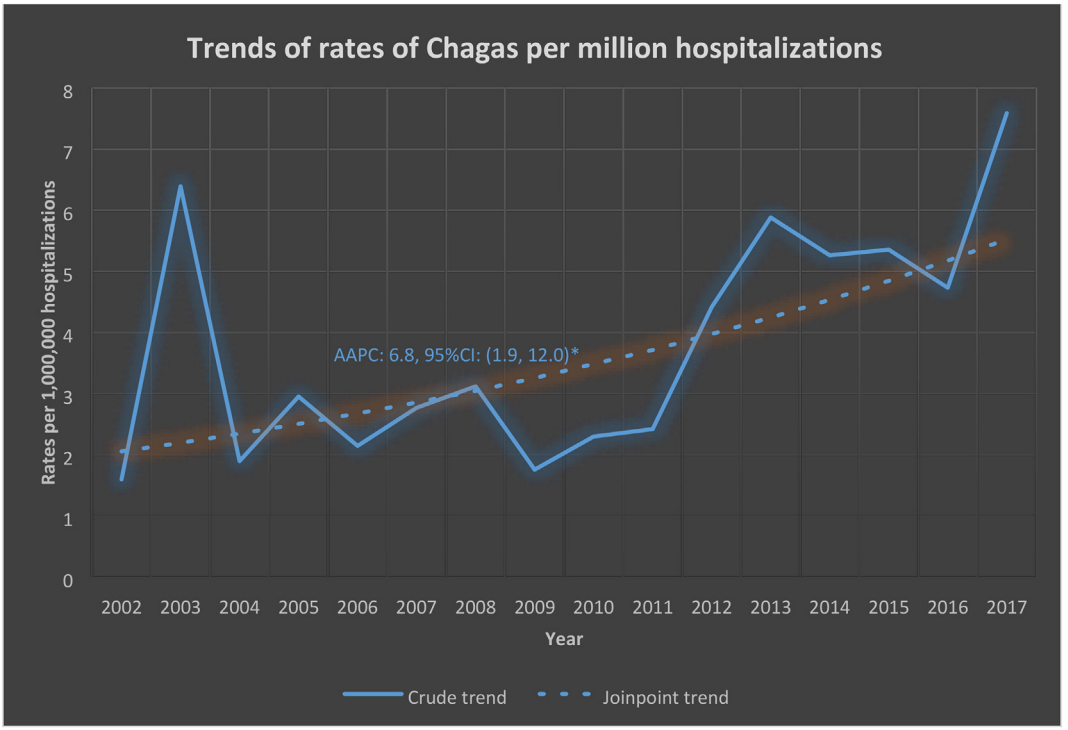

Fig. 1. Joinpoint trends of rates of Chagas hospitalizations 2002–2017.

Table 2
Unadjusted and adjusted association between various socio-demographic and hospital characteristics and Chagas disease.

	Chagas			
	Unadjusted		Adjusted	
	OR(95%)[a]	*p*-Value	OR(95%)[a]	*p*-Value
Age				
15–24 years	Reference		Reference	
25–34 years	1.56(0.63–3.83)	0.34	1.76(0.7–4.38)	0.23
35–49 years	6.29(3.25–9.34)	<0.0001	9.39(4.18–21.07)	<0.0001
Race				
NH-White	Reference		Reference	
NH-Black	0.54(0.08–3.65)	0.53	0.45(0.06–3.43)	0.44
Hispanic	49.05(15.75–138.65)	<0.0001	25.85(5.64–118.5)	<0.0001
Other	6.21(1.43–10.02)	0.01	5.16(1.07–24.94)	0.04
Discharge status				
Routine	Reference		Reference	
Transfer	0.71(0.17–2.89)	0.63	0.74(0.17–3.17)	<0.0001
Died	10.42(3.27–33.15)	<0.0001	6.68(2.03–22.01)	<0.0001
Other	3.27(1.60–6.66)	<0.0001	2.61(1.32–5.17)	0.01
Zip income quartile				
Highest quartile	Reference		Reference	
Lowest quartile	0.41(0.20–0.84)	0.01	0.25(0.12–0.52)	<0.0001
2nd quartile	0.41(0.19–0.89)	0.02	0.37(0.18–0.78)	0.01
3rd quartile	0.25(0.11–0.57)	<0.0001	0.24(0.11–0.52)	<0.0001
Primary payer				
Medicare	Reference		Reference	
Medicaid	1.17(0.48–2.88)	0.73	1.2(0.47–3.11)	0.7
Private Insurance	0.41(0.16–1.03)	0.06	0.5(0.19–1.33)	0.17
Self-Pay	2.48(0.93–6.66)	0.07	2.36(0.86–6.49)	0.1
Other	1.72(0.70–4.21)	0.23	1.49(0.59–3.76)	0.39
Hospital region				
Northeast	Reference		Reference	
Midwest	0.11(0.04–0.29)	<0.0001	0.41(0.16–1.10)	0.08
South	0.33(0.16–0.66)	<0.0001	0.49(0.24–0.98)	0.04
West	0.36(0.18–0.75)	0.01	0.34(0.17–0.68)	<0.0001
Hospital bed size				
Small	Reference		Reference	
Medium	0.75(0.29–1.94)	0.55	0.73(0.28–1.94)	0.53
Large	1.21(0.49–3.02)	0.68	1.32(0.52–3.37)	0.56
Hospital location and teaching status				
Rural	Reference		Reference	
Urban non-teaching	2.74(0.35–8.45)	0.34	1.16(0.15–9.25)	0.89
Urban teaching	8.26(2.51–13.29)	<0.0001	5.76(0.76–43.54)	0.09

[a] OR: Odds Ratio, CI: Confidence Interval.

Goehler et al also reinforce this linkage, and did demonstrate that states with the greatest distribution of Latin American immigrants have higher rates of Chagas disease (Manne-Goehler et al., 2016; Bern and Montgomery, 2009). Chagas disease is a chronic illness and many who travel to the United States are long term carriers. The early exposure to the bite of a kissing bug compounded with migration from an endemic region may contribute to the association between age and race/ethnicity with Chagas disease observed in our study.

While our findings indicate that there has been an increase in Chagas disease within the US, others showed evidence of decreasing trypanosomiasis cases within Latin America. *Perez-Molina* et al reported that the prevalence of Chagas disease had decreased by more than 60% in endemic Latin American countries since 1980 (Pérez-Molina and Molina, 2018). Improvement in reducing the prevalence of Chagas was achieved through public awareness and health measures to try and minimize vector transmission, measures not yet established in the US (Coura et al., 2014; Coura, 2013). Instead, there have been few initiatives to assess for Chagas disease, and even then, the focus has been on transmission via blood donation (Bennett et al., 2018). Meta-analyses and prior studies also note that living in a rural area is a risk factor for Chagas disease, (Roca et al., 2011; Conners et al., 2016; Custer et al., 2012) whereas rural hospitals in our study population had the lowest prevalence of trypanosomiasis. These differences may be ascribed to mode of transmission in the US being through migration, especially to urban areas. Furthermore, the kissing bug thrives in palm thatched roofs and rural, adobe housing buildings that are common in endemic regions, but not in the US (Rozendaal and World Health Organization, 1997).

Strengths of our study include a large sample size and nationwide data both of which limit the amount of geographic or regional selection bias in our analysis. However, our study populations were derived from inpatient data and are thus inherently more sick or likely to have additional comorbidities compared to the general population. Additionally, we did take into account in our analysis the contribution of immigration status, duration of residence in the US, or recent travel to endemic regions since this information was not available in the NIS.

Our study revealed that Chagas disease is an important chronic condition among women of reproductive age in the United States. The prevalence reported in the study might represent an underestimate because the condition is not routinely investigated in clinical settings among at-risk populations. The persistently increasing prevalence of Chagas disease among women of reproductive age calls for additional preventive measures and clinical initiatives in order to reduce the burden of this neglected tropical disease in the US.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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