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Temporal trends of gestational malaria in the United States

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ABSTRACT

Background: Although regarded as rare in the United States (US), increased global traffic and importation of malaria from endemic countries may lead to a rise in gestational malaria in the US.

Methods: This multi-year retrospective study analyzed trends in diagnosed cases of gestational malaria from 2002 to 2017 using joinpoint regression models. We also assessed the association between gestational malaria and selected maternal-fetal adverse outcomes.

Results: Mothers diagnosed with gestational malaria tended to be older, and the majority of diagnosed cases (52.9%) were among Non-Hispanic (NH) Blacks. Diagnosed cases of gestational malaria are on the rise in the US. Mothers diagnosed with gestational malaria were 5 times as likely (OR = 5.05, 95% CI: 4.05–6.29) to be anemic as compared to those without malaria. Compared to NH-Whites, NH-Black mothers were twice as likely to experience stillbirth, had nearly 50% greater adjusted odds of severe preeclampsia, and had about 30% elevated likelihood for preterm labor.

Conclusions: There is a need to dedicate appropriate resources to identify women that are at risk for gestational malaria in order to prevent related pregnancy complications.

1. Introduction

Malaria is a parasitic infection that accounts for a considerable level of morbidity and mortality worldwide (Tsuji and Kain, 2009). Human transmission of malaria occurs through the bloodstream by the protozoan parasite, *Plasmodium*. Of the five *Plasmodium* species that infect humans, *P. falciparum* is associated with poorer clinical outcomes *and P. vivax* comprises the majority of case (Geleta and Ketema, 2016; Howes et al., 2016). Major complications of malaria include severe anemia, respiratory distress, renal failure, and death (White, 2018). Approximately 3.2 billion people live in endemic regions such as sub-Saharan Africa, which accounts for over 90% of malaria-related cases and deaths (Odhiambo and Sartorius, 2018; World Health Organization, 2020). Health initiatives such as antimalarial therapies, insecticide-treated nets, and indoor residual spraying have greatly reduced the global burden of malaria (Kenangalem et al., 2019; Centers for Disease Control and Prevention, 2019a; Choi et al., 2019). Yet, in 2018 alone, there were approximately 228 million cases of malaria and 405,000 malaria-related deaths globally (World Health Organization, 2020).

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Pregnancy-associated immune-related changes in pregnancy places expectant mothers at an increased risk of contracting malaria (World Health Organization, 2003). Compared to non-pregnant women, those that are pregnant have triple the likelihood of developing severe malaria. Malaria during pregnancy poses significant risks to the mother and fetus (Newal, 2009). Malaria-related complications in pregnant women include miscarriage, intrauterine growth disturbances, premature delivery, low birth weight, hemorrhage, and neonatal transmission of malaria (Newal, 2009; Dombrowski et al., 2018; Ouédraogo et al., 2012). Pregnant women are more likely to be asymptomatic than their non-pregnant counterparts, increasing the potential for the progression of severe pregnancy outcomes in incognizant hosts (Khan et al., 2014). Malaria has been linked to more than 10,000 maternal and 200,000 neonatal fatalities annually. An estimated 25 million pregnant women are at risk for contracting malaria worldwide (Newal, 2009).

Malaria remains a poverty-driven disease that is endemic in low and middle-income countries (LMIC) (Ren, 2019). While LMIC carry the greatest burden of malaria, the disease was eradicated in the US in the 1940s following the implementation of public health interventions such as dichlorodiphenyl-trichloroethane (DDT) spraying campaigns (Newal, 2009). In spite of these efforts, 2000 new cases of malaria occur in the US annually as a result of increased global traffic from travel and immigration (Centers for Disease Control and Prevention, 2020). Considering that women of childbearing age make up a considerable proportion of people that travel to endemic regions, those that are pregnant are specifically advised against travelling to countries that pose risks of malaria infection (Arguin et al., 2015; Pillay and Macdonald, 2012). In 2012, pregnant women made up 6% of travel-related cases of malaria among women in the US (Arguin et al., 2015).

Several studies have examined gestational malaria, but few are specific to the US (Pillay and Macdonald, 2012; Perez et al., 2016; Khuu et al., 2017). The reports that included data about pregnant women with malaria focused primarily on disease transmission and health complications (Khuu et al., 2017; Centers for Disease Control and Prevention, 2018). The most recent study in the US to investigate trends in malaria-related maternal hospitalizations included data up until 2014 and disproportionately represented men (Khuu et al., 2017). Given that malaria also affects pregnant women and poses severe health outcomes, updated information is required specific to this population (Newal, 2009; Dombrowski et al., 2018; Ouédraogo et al., 2012; Khan et al., 2014). To the authors' knowledge, this is the first national analysis of temporal trends of gestational malaria in the US.

2. Methods

We conducted a retrospective, cross-sectional analysis using the Nationwide Inpatient Sample (NIS) dataset covering the period from January 1, 2002 to December 31, 2017. This data was assembled from hospitals across the United States and managed by the Agency for Healthcare Research and Quality (AHRQ). The NIS database utilized for this study is a robust sample of all payer, publicly available database of inpatient hospitalizations in the country. The database contains an array of clinical and non-clinical information including: urban/rural setting, hospital teaching status, race/ethnicity, and US Census Bureau geographic region etc. We utilized International Classification of Disease, Ninth revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes prior to October 1, 2015, and ICD 10-CM/PCS after that. Because the study was performed on de-identified, publicly available data, the Institutional Review Board (IRB) of Baylor College of Medicine deemed it as exempt.

We restricted the study sample to inpatient hospitalizations of pregnant adolescent and adult women, 15–49 years, who were diagnosed with malaria. Malaria was coded using ICD-9-CM diagnoses codes beginning with '647.4' and '084' and ICD-10-CM diagnosis codes 'B50', 'B51', 'B52', 'B53'and 'B54'. As a secondary aim, we also examined five selected maternal-fetal outcomes: maternal anemia, poor fetal growth, stillbirth, severe preeclampsia and preterm labor. Anemia was coded using ICD-9 codes beginning with '280', '281', '282', '283' '284', '285', '648.2' and ICD-10 codes beginning with 'D5', 'D60', 'D61', 'D62', 'D63', 'D64', 'O99.0'. Poor fetal growth was coded in ICD-9 format as '656.5' and in ICD-10 format as 'O36.59'. Stillbirth was coded using ICD-9 diagnosis codes beginning with '656.4', 'V27.1', 'V27.3', 'V27.4', 'V27.6', 'V27.7' and ICD-10 diagnosis codes beginning with 'O36.4', 'Z37.1', 'Z37.3', 'Z37.4', 'Z37.6' and 'Z37.7'; severe preeclampsia was coded using ICD-9 diagnosis codes beginning with '642.5' and ICD-10 codes beginning with 'O14.1'; whereas preterm labor was identified using ICD-9-CM diagnosis codes beginning with '644' and ICD-10-CM codes beginning with 'O60'. We conducted bivariate analyses to study the relationships between various patient socio-demographic and hospital characteristics versus prevalence of malaria.

Next, we created joinpoint regression models to estimate and describe the trends in the rates of gestational malaria over the study period. Joinpoint regression is a modeling technique which is used to analyze the varying trends of an outcome over time (National Cancer Institute, 2019). 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 simulation technique 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.

Lastly, we restricted the data to pregnancy hospitalizations with a diagnosis of malaria. After removing missing information from the covariates, survey logistic regression models were run to compute adjusted odds ratios for the association between our selected socio-demographic features, hospital characteristics, and the selected outcomes for the study, namely, maternal anemia, poor fetal growth, stillbirth, severe preeclampsia and preterm labor. 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).

3. Results

We analyzed a total of 76,023,717 pregnancy hospitalizations from 2002 to 2017, of which 1761 had a diagnosis of malaria corresponding to a rate of 2.3 per 100,000 pregnancy-related hospitalizations.

3.1. Socio-demographic factors

Table 1 shows the relationship between socio-demographic factors, hospital features, and comorbid characteristics among hospitalized pregnant women with or without malaria. There was a positive relationship between prevalence of malaria and maternal age, with the highest prevalence observed among women aged 35–49 years. The prevalence of malaria was greatest among NH-Blacks, while NH-White and Hispanic mothers experienced the lowest prevalence of the disease. Among pregnant women for whom discharge status was known, those that were discharged against medical advice (DAMA) had the highest prevalence of gestational malaria (6.54 per 100,000) followed by mothers that were transferred to other facilities (4.76 per 100,000).

Excluding hospitalized pregnant women with missing information on zip code income, mothers in the lowest income quartile (0th to 25th percentile) accounted for the highest proportion of malaria. However, pregnant women in the highest income quartile (76th to 100th percentile) had the greatest prevalence of malaria (2.97 per 100,000). Among in-hospital pregnant women for whom insurance status was known, those covered by Medicaid, and those that self-paid for medical services exhibited the highest prevalence of gestational malaria. Pregnant women on private insurance experienced the lowest prevalence of diagnosed cases of gestational malaria (0.98 per 100,000 pregnancy-related hospitalizations).

We found that hospitalized pregnant women in the Southern part of the US accounted for the largest proportion of malaria cases, while those in the Midwest had the highest prevalence of the infection. Notably, there were no hospitalized pregnant women in the West with malaria. Although the largest proportion of gestational malaria cases was diagnosed in urban teaching hospitals (approximately 40% of the cases), the highest prevalence of gestational malaria was observed in rural hospital settings. The prevalence of gestational malaria was very high (9.51 per 100,000 pregnancy hospitalization) among those with anemia whereas the prevalence was similar among pregnancies complicated by stillbirth, severe preeclampsia, or preterm labor.

3.2. Temporal trends

Fig. 1 depicts the trends in malaria rates among hospitalized pregnant women over the study period using observed data and joinpoint regression estimate overlays. The joinpoint regression estimator indicates that the average annual percent change (AAPC) of malaria among pregnant women increased significantly over the period by 5.7% (95% CI [0.7, 10.9]). From a baseline of 2.15 per 100,000 in 2002, the rate of malaria infection among pregnant women climbed variably and peaked in 2016 at 5.01 per 100,000 hospitalizations.

3.3. Health complications associated with gestational malaria

Table 2 illustrates the association between various patient and hospital characteristics versus selected maternal-fetal outcomes (anemia, poor fetal growth, stillbirth, severe preeclampsia, and preterm labor) among pregnancy-related hospitalizations. Mothers diagnosed with gestational malaria were 5 times as likely (OR = 5.05, 95% CI: 4.05–6.29) to be anemic as compared to those without malaria. The adjusted odds of other adverse events during pregnancy were similar for women with gestational malaria and those without the diagnosis. Whereas advancing maternal age showed a positive association with stillbirth, maternal age was negatively associated with preterm labor. Compared to NH-Whites, NH-Black mothers were almost twice as likely to experience anemia and stillbirth; had about 50% greater adjusted odds of severe preeclampsia, and about 30% elevated likelihood for preterm labor. Although Hispanic mothers had slight to moderate risks for stillbirth and severe preeclampsia respectively, they appeared to enjoy mild protection from preterm labor.

Maternal death was the strongest discharge status associated with stillbirth, (OR = 2.23; 95% CI [1.88, 2.64]) while transfer to another facility showed the greatest association with severe preeclampsia (OR = 2.34; 95% CI [2.22,2.46]) and preterm labor (OR = 2.90; 95% CI [2.78,3.03]). Higher zip code income was protective of anemia, poor fetal growth, stillbirth, preeclampsia, and preterm labor. Compared to pregnant women under Medicare, those in other healthcare coverage categories exhibited higher adjusted odds for poor fetal growth, adverse maternal-fetal outcomes. Regional differences were associated with anemia, stillbirth, severe preeclampsia, and preterm labor. Compared to pregnant women in the Northeast, those in other regions experienced slight to moderate higher odds of stillbirth and severe preeclampsia. We noted an inverse relationship between hospital size and adverse pregnancy outcomes with large hospital sizes exhibiting greater adjusted odds for the diagnoses of stillbirth, severe preeclampsia, and preterm labor. Compared to rural facilities, diagnoses of severe preeclampsia and preterm labor were highest in urban hospitals. Hospitalizations associated with stillbirth were more likely in rural and urban teaching hospitals than in urban non-teaching facilities.

4. Discussion

This population-based, nationally representative study investigated socio-demographic factors, temporal trends, and adverse maternal-fetal outcomes among pregnant women with malaria in the US from 2002 to 2017. The most recent study to measure

Table 1
Socio-demographic factors, hospital features, and comorbid characteristics among hospitalized pregnant women with or without malaria.

	Malaria				Prevalence of malaria per 100,000 pregnancy hospitalizations
	No		Yes		
Patient characteristics					
Age	n	%	n	%	
15–24 years	23,789,034	31.3%	421	23.9%	1.77
25–34 years	38,016,592	50.0%	784	44.5%	2.06
35–49 years	14,216,330	18.7%	556	31.6%	3.91
Race					
NH-White[a]	33,710,143	44.3%	299	17.0%	0.89
NH-Black[a]	9,983,809	13.1%	931	52.9%	9.32
Hispanic	14,088,849	18.5%	111	6.3%	0.79
Other	6,624,668	8.7%	235	13.3%	3.55
Missing	11,614,487	15.3%	184	10.4%	1.58
Discharge status					
Routine	72,897,529	95.9%	1681	95.5%	2.31
Transfer	819,260	1.1%	39	2.2%	4.76
Died	57,278	0.1%	0	0.0%	0.00
DAMA[b]	381,951	0.5%	25	1.4%	6.54
Other	1,844,844	2.4%	15	0.9%	0.81
Missing	21,093	0.0%	0	0.0%	0.00
Zip income quartile					
Lowest quartile	16,532,293	21.7%	379	21.5%	2.29
2nd quartile	14,421,506	19.0%	333	18.9%	2.31
3rd quartile	13,781,102	18.1%	312	17.7%	2.26
Highest quartile	12,211,700	16.1%	363	20.6%	2.97
Missing	19,075,354	25.1%	373	21.2%	1.96
Primary payer					
Medicare	3,550,930	4.7%	232	13.2%	6.53
Medicaid	25,614,441	33.7%	485	27.5%	1.89
Private insurance	30,450,644	40.1%	299	17.0%	0.98
Self-pay	3,807,596	5.0%	246	14.0%	6.46
Other/Missing	12,598,345	16.6%	499	28.3%	3.96
Hospital characteristics					
Hospital region					
Northeast	9,889,580	13.0%	253	14.4%	2.56
Midwest	20,895,553	27.5%	550	31.2%	2.63
South	44,992,786	59.2%	958	54.4%	2.13
West	244,036	0.3%	0	0.0%	0.00
Hospital bed size					
Small	8,059,262	10.6%	30	1.7%	0.37
Medium	27,503,543	36.2%	376	21.4%	1.37
Large	40,215,115	52.9%	1354	76.9%	3.37
Missing	244,036	0.3%	0	0.0%	0.00
Hospital location and teaching status					
Rural	12,613,168	16.6%	527	29.9%	4.18
Urban non-teaching	16,173,251	21.3%	264	15.0%	1.63
Urban teaching	29,145,471	38.3%	699	39.7%	2.40
Missing	18,090,065	23.8%	270	15.3%	1.49
Comorbidities					
Anemia					
No	66,797,567	87.9%	883	50.1%	1.32
Yes	9,224,388	12.1%	877	49.8%	9.51
Poor fetal growth					
No	74,523,365	98.0%	1746	99.1%	2.34
Yes	1,498,591	2.0%	14	0.8%	0.93
Stillbirth					
No	75,571,405	99.4%	1749	99.3%	2.31
Yes	450,551	0.6%	11	0.6%	2.44
Severe preeclampsia					
No	75,070,697	98.7%	1736	98.6%	2.31
Yes	951,258	1.3%	24	1.4%	2.52
Preterm labor					
No	70,371,196	92.6%	1629	92.5%	2.31
Yes	5,650,760	7.4%	131	7.4%	2.32

[a] NH stands for Non-Hispanic.
[b] DAMA stands for Discharged Against Medical Advice.

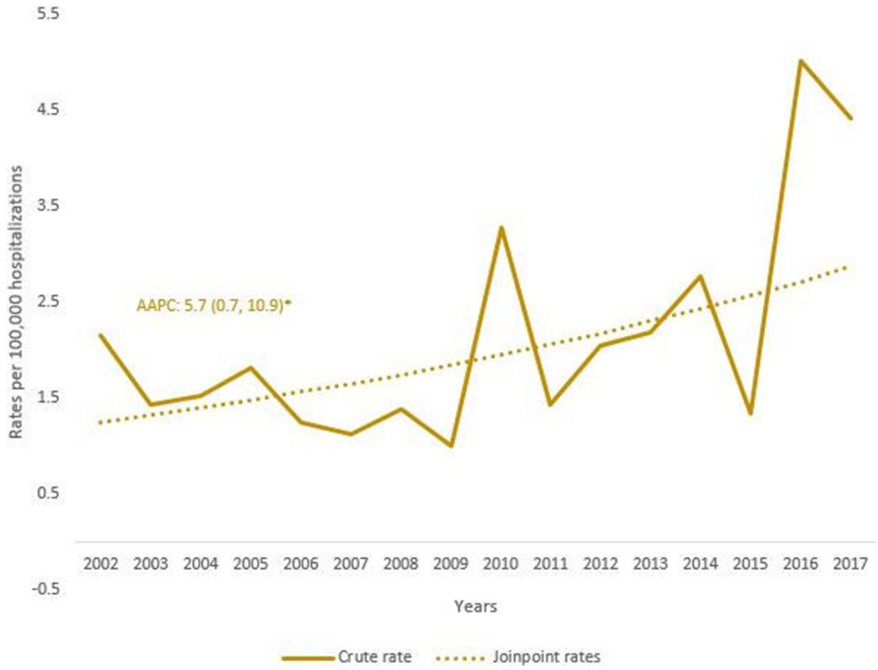

Fig. 1. Trends in rates of malaria per 100,000 maternal hospitalizations from 2002 to 2017.

trends in malaria hospitalizations nationwide analyzed data up until 2014 and largely overrepresented men (Khuu et al., 2017). Our findings show that hospitalizations among pregnant women with malaria peaked in 2016 at 5.01 per 100,000, underscoring the necessity for updated data. To the authors' knowledge, this is the first national analysis of temporal trends among pregnant women living with malaria in the US. During the 15-year period of the study, AAPC significantly increased by 5.7% among hospitalized pregnant women with malaria. These results are consistent with a previous study that found a positive trend in hospitalizations among patients with malaria in the US (Khuu et al., 2017). This increasing trend may be the result of greater global traffic (Spencer et al., 2010).

Although the prevalence of malaria in the US is low as compared to endemic countries, maternal hospitalizations for malaria are not atypical in the US (Centers for Disease Control and Prevention, 2019b). Contrary to our expectation, we found that there was no association between malaria and stillbirth, severe preeclampsia and preterm labor. The eradication of malaria from the US in the 1940s could explain this finding because low and high transmission settings present with unique clinical outcomes (Howes et al., 2016; Centers for Disease Control and Prevention, 2015). Moreover, there may be an association between gestational malaria and other adverse pregnancy outcomes not included in the scope of this study but have been found to be significantly associated with gestational malaria in other reports (Newal, 2009; Dombrowski et al., 2018; Ouédraogo et al., 2012; Khan et al., 2014). Further research is needed to consider the effect of gestational malaria on additional pregnancy complications in the US.

Although the adjusted odds of adverse events were similar among women with and without gestational malaria, these outcomes were uniquely associated with various sociodemographic factors and hospital characteristics. Among in-hospital pregnant women, Black women aged 35–49 years experienced greater prevalence rates of malaria. These results somewhat agree with the literature which found that hospitalized, Black patients aged 45–64 years had the greatest prevalence of malaria (Khuu et al., 2017). We also found that pregnant women designated as “DAMA” were nearly three times as likely to have malaria, and had over twice the adjusted odds of stillbirth compared to those that were routinely discharged. The significant burden of a lack of stable social support systems, substance abuse co-morbidity and low-income status frequently experienced by patients that leave AMA may explain the elevated risk for gestational malaria as well as malaria-associated pregnancy complications (Paul et al., 2019; Glasgow et al., 2010). DAMA has also been linked to deleterious feto-neonatal outcomes such as respiratory distress, low birth weight and fetal death.

Compared to pregnant women with malaria under Medicare, those who self-paid for healthcare coverage were more likely to experience stillbirth, severe preeclampsia and preterm labor. Patients that self-pay for medical services are more likely to be low-income (Becker and Newsom, 2003). We also observed an inverse relationship between income level and the likelihood for the five adverse outcomes. Pregnant women in the highest income quartile experienced the fewest complications. The information available in the data was at hospital discharge level and not patient level. Furthermore, it was not possible to track a patient over time due to the cross-sectional nature of the dataset. Therefore, we were not able to identify the point in pregnancy at which the malaria diagnosis was made. Additionally, information on travel history of mothers diagnosed with gestational malaria, management of the disease or follow-up tests to verify effectiveness/response to the treatment was not available in the dataset. Additional information that was absent from the data we analyzed but would have likely impacted our analysis included types of

Table 2
Adjusted survey binomial logistic regression model to assess the association between various malaria and maternal-fetal outcomes among pregnant women.

	Anemia	Poor fetal growth	Stillbirth	Severe Preeclampsia	Preterm Labor
	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)
Malaria					
No	reference				
Yes	5.05(4.05–6.29)	0.37(0.12–1.14)	0.80(0.20–3.18)	0.91(0.38–2.18)	0.96(0.65–1.42)
Patient characteristics					
Age					
15–24 years	reference				
25–34 years	0.87(0.86–0.88)	0.76(0.76–0.77)	1.03(1.01–1.04)	0.89(0.88–0.91)	0.88(0.87–0.88)
35–49 years	1.03(1.01–1.04)	0.62(0.61–0.64)	1.21(1.18–1.23)	0.89(0.87–0.91)	0.82(0.81–0.84)
Race					
NH-White	reference				
NH-Black	2.09(2.04–2.14)	1.22(1.19–1.25)	1.82(1.78–1.87)	1.47(1.43–1.52)	1.27(1.24–1.30)
Hispanic	1.23(1.17–1.3)	0.69(0.66–0.72)	1.05(1.02–1.08)	1.18(1.10–1.26)	0.94(0.91–0.97)
Other	1.29(1.24–1.34)	1.18(1.14–1.21)	1.09(1.06–1.13)	1.01(0.97–1.04)	0.96(0.94–0.99)
Discharge status					
Routine	reference				
Transfer	1.37(1.34–1.4)	0.67(0.64–0.71)	0.64(0.59–0.7)	2.34(2.22–2.46)	2.9(2.78–3.03)
Died	2.06(1.96–2.16)	0.12(0.08–0.18)	2.23(1.88–2.64)	1.00(0.84–1.18)	0.35(0.3–0.41)
DAMA	1.11(1.08–1.14)	0.73(0.67–0.78)	1.19(1.09–1.30)	1.03(0.96–1.11)	1.83(1.76–1.91)
Other	1.57(1.50–1.65)	0.91(0.85–0.97)	0.37(0.34–0.42)	1.34(1.23–1.46)	0.70(0.66–0.73)
Missing					
Zip income quartile					
Lowest quartile	reference				
2nd quartile	0.95(0.93–0.97)	1.00(0.98–1.02)	0.95(0.93–0.97)	0.98(0.96–1.00)	0.95(0.94–0.97)
3rd quartile	0.93(0.90–0.95)	0.98(0.95–1.00)	0.91(0.89–0.93)	0.96(0.93–0.98)	0.91(0.89–0.93)
Highest quartile	0.83(0.79–0.86)	0.98(0.95–1.02)	0.79(0.77–0.81)	0.88(0.84–0.91)	0.89(0.86–0.91)
Primary payer					
Medicare	reference				
Medicaid	0.73(0.70–0.76)	1.60(1.54–1.66)	1.37(1.31–1.42)	1.59(1.51–1.68)	2.19(2.12–2.25)
Private Insurance	0.56(0.54–0.58)	1.48(1.43–1.53)	1.22(1.17–1.27)	1.66(1.60–1.73)	1.96(1.90–2.01)
Self Pay	0.66(0.62–0.7)	1.28(1.21–1.35)	1.72(1.64–1.81)	1.53(1.44–1.63)	2.09(2.00–2.18)
Hospital characteristics					
Hospital region					
Northeast	reference				
Midwest	1.16(1.09–1.23)	1.01(0.95–1.06)	1.06(1.01–1.10)	1.10(1.03–1.16)	0.99(0.94–1.05)
South	1.19(1.11–1.27)	1.11(1.05–1.18)	1.16(1.12–1.20)	1.28(1.20–1.37)	1.12(1.06–1.18)
West	1.14(1.06–1.22)	0.98(0.92–1.04)	1.08(1.04–1.13)	1.13(1.06–1.19)	1.09(1.03–1.16)
Hospital bed size					
Small	reference				
Medium	0.92(0.87–0.97)	1.06(1.01–1.12)	1.08(1.05–1.12)	1.22(1.16–1.29)	1.21(1.13–1.28)
Large	0.93(0.88–0.98)	1.2(1.14–1.26)	1.17(1.14–1.21)	1.49(1.41–1.57)	1.43(1.35–1.51)
Hospital location and teaching status					
Rural	reference				
Urban non-teaching	0.88(0.83–0.94)	1.08(1.02–1.13)	0.93(0.90–0.96)	1.20(1.14–1.26)	1.15(1.1–1.21)
Urban teaching	1.16(1.08–1.23)	1.35(1.28–1.42)	1.10(1.07–1.14)	2.13(2.00–2.26)	1.59(1.51–1.68)

treatment received and the species of the infecting agent. Future studies with more in-depth clinical information should also include considerations of patient-level data such as travel history and immigration status that are otherwise not available in the NIS database (Khuu et al., 2017).

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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