Title
Malaria-related hospitalizations in the US: The disease and economic burden, and risk factors for severe and fatal malaria

Author
Khuu, Diana

Publication Date
2016

UNIVERSITY OF CALIFORNIA

Los Angeles

Malaria-related hospitalizations in the US:
The disease and economic burden, and
risk factors for severe and fatal malaria

A dissertation submitted in partial satisfaction

of the requirements for the degree of

Doctor of Philosophy in Epidemiology

by

Diana Khuu

2016

ABSTRACT OF THE DISSERTATION

Malaria-related hospitalizations in the US:

The disease and economic burden, and

risk factors for severe and fatal malaria

by

Diana Khuu

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2016

Frank J. Sorvillo, Chair

Although malaria has been eliminated from the US since the early 1950s, about 1,500 cases of malaria are reported in the US every year. Few studies have comprehensively quantified the disease and economic burden of malaria in the US, and the domestic impact has not been well described. Epidemiological study of malaria using hospital data has rarely been explored, and can supplement the findings from current nationwide surveillance system data to elucidate the malaria disease and economic burden. Identification of predictors of increased costs and severe malaria may be useful in developing targeted interventions.

Discharge records for malaria-related hospitalizations from the 2000-2012 Nationwide Inpatient Sample (NIS) were examined. In chapter 1, the disease burden was quantified by examining the frequencies and population rates of malaria-related hospitalization by

demographics, infecting species, clinical, financial, institutional, geographic, and seasonal characteristics. Trends over the period in the counts of malaria cases by different patient characteristics were assessed using negative binomial regression. In chapter 2, the economic burden was quantified by examining the mean and total hospital days, hospital charges, and hospital costs for malaria-related hospitalizations by demographics, species, clinical, financial, geographic, and institutional characteristics. Trends and potential predictors for hospital charges and costs were identified using linear regression. Trends and potential predictors for length of stay were identified using negative binomial regression. In chapter 3, a subset analysis on severe malaria cases was conducted, and the frequencies and population rates of severe malaria-related hospitalizations by demographics, species, clinical, financial, geographic, and institutional characteristics were examined. Trends in the rates of severe malaria hospitalizations over the study period were assessed by negative binomial regression. Multiple logistic regression models were used to identify potential predictors for severe disease (cerebral malaria, acute respiratory distress [ARDS], severe anemia, renal failure, or jaundice) and death among those with malaria-related hospitalizations.

From 2000-2012, there were an estimated 19,189 malaria-related hospitalizations (4.95 per 1 million population) in the US, including 147 in-hospital deaths and 3,888 severe malaria cases. On average, malaria patients were hospitalized for 4.39 days with charges of $25,116. From 2000-2012, malaria-related hospitalizations accounted for 84,213 hospital days, $151,825,389 in total hospital costs, and $470,102,584 in total charges. The most frequent malaria complication was renal failure (40.5%), followed by severe anemia (34.6%), ARDS (19.9%), cerebral malaria (18.7%), and jaundice (15.4%). *P. falciparum* accounted for the majority of malaria- and severe malaria-related hospitalizations. Malaria-related hospitalizations

occurred disproportionately among patients who were male, Black, or aged 25-44 years. After controlling for potential confounders, older age was associated with higher odds of severe malaria, ARDS, severe anemia, and renal failure. Males had higher odds of developing renal failure and jaundice, while females had higher odds of developing severe anemia and ARDS. HIV infection was associated with increased odds of severe malaria. Having severe malaria was associated with a longer length of stay. Older age, severe malaria, HIV infection, and longer lengths of stay were associated with higher charges and costs. Mean charges increased significantly over the study period. Patients with a malaria diagnosis were more often hospitalized in the Middle Atlantic and South Atlantic census divisions, urban teaching, private not-for-profit, and large bed size hospitals. Malaria patients who were self-payers or had Medicaid were at increased odds of having renal failure, compared to those with Medicare.

This dissertation demonstrates that malaria imposes a substantial disease and economic burden in the US, and underscores the need for improved primary and secondary prevention measures, especially among high-risk groups.

The dissertation of Diana Khuu is approved.

Lawrence R. Ash

Marjan Javanbakht

Mark L. Eberhard

Frank J. Sorvillo, Committee Chair

University of California, Los Angeles

2016

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express my immense appreciation and gratitude to my advisor and committee chair, Frank Sorvillo, who has generously guided and supported me throughout my academic career at UCLA. I feel extremely fortunate to have had the opportunity to work with and learn from him.

I would like to express my sincere gratitude to my committee members Mark Eberhard, Marjan Javanbakht, Shira Shafir, Lawrence Ash, and Benjamin Bristow for their unique contributions to my research, and for lending their brilliance, expertise, experience, and support.

I also would like to thank the UCLA Institute for Digital Research and Education (IDRE) for providing statistical consultation.

VITA

Education

2011-2013: University of California, Los Angeles

Master of Public Health (MPH) with specialization in Epidemiology

2006-2010: University of California, Irvine

Bachelor of Science (BS) in Biological Sciences

Bachelor of Arts (BA) in Public Health Policy

Work

2014-present Epidemiology Analyst

Los Angeles County Department of Public Health

Publications

Khuu D, Shafir S, Bristow B, Sorvillo F. Blastomycosis mortality in the United States, 1990-2010. Emerg Infect Dis. 2014 Nov; 20(11): 1789–1794. doi: 10.3201/eid2011.131175.

Weber J, Weller S, Sakai S, Nguyen LQ, Khuu D. Breeding system evolution in Oxalis alpina: Asymmetrical expression of tristylous incompatibility. International Journal of Plant Sciences 2013; 174(2): 179 –188.

Khuu D. Incompatibility relationships in the mid-styled morph of three *Oxalis alpina* populations. Journal of Undergraduate Research in the Biological Sciences. 2010; 40: 1-12.

Presentations

Epidemiology of prescription drug-related hospitalizations in Los Angeles County, 2005-2013. Presented at the 7th Annual Science Summit, Los Angeles County Department of Public Health in Los Angeles, CA. Mar 2016.

Blastomycosis mortality in the United States, 1990-2010. Emerg Infect Dis. 2014 Nov. Podcast.

Income inequality and health outcomes in Los Angeles County. Presented at the Annual Los Angeles County Department of Public Health Epi Scholar Presentations. Sep 2012.

Incompatibility relationships in the mid-styled morph of three *Oxalis alpina* populations. Presented at UCI Excellence in Research Symposium in Irvine, CA. Mar 2010.

Incompatibility relationships in the mid-styled morph of three *Oxalis alpina* populations. Poster presented at UCI Excellence in Research Symposium in Irvine, CA. Mar 2010.

Chapter 1: Disease Burden

Malaria-related hospitalizations in the United States, 2000-2012

Abstract

Background: Epidemiological study of malaria using hospital data has rarely been explored, and can supplement the findings from current nationwide surveillance system data to elucidate the malaria disease burden and case characteristics.

Methods: US malaria cases identified from malaria-related hospitalization discharge records in the 2000-2012 Nationwide Inpatient Sample (NIS) were examined. Frequencies and population rates were reported by demographics, infecting species, clinical, financial, institutional, geographic, and seasonal characteristics, and disparities were identified. Time trends in malaria cases by different characteristics were assessed using negative binomial regression.

Results: From 2000-2012, there were an estimated 19,189 malaria-related hospitalizations (4.95 per 1 million population) in the US, including 147 in-hospital deaths and 3,888 severe malaria cases. The rate of malaria-related hospitalizations remained stable over the study period. The largest number of malaria-related hospitalizations occurred in August. Malaria-related hospitalizations occurred disproportionately among patients who were male, Black, or aged 25-44 years. *P. falciparum* accounted for the majority of malaria-related hospitalizations. On average, malaria patients were hospitalized for 4.39 days with charges of $25,116. Patients with a malaria diagnosis were more often hospitalized in the Middle Atlantic and South Atlantic census divisions, urban teaching, private not-for-profit, and large bed size hospitals.

Conclusions: Malaria imposes a substantial disease burden in the US. Primary and secondary prevention measures, including strategies to increase the use of pre-travel consultations and prompt diagnosis and treatment, should be emphasized in high-risk groups.

Introduction

Malaria is the leading cause of death by parasitic disease in the world and remains one of the most important and intractable global public health problems. An estimated 214 million cases of malaria, and 438,000 deaths due to malaria occurred in 2015[1]. Malaria is caused by infection with the protozoan agents of the genus *Plasmodium.* Several species of *Plasmodium* (*P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*) are known to affect humans, with *P. falciparum* causing the most morbidity and the vast majority of the mortality. Transmission typically occurs through the bite from an infected female *Anopheles* mosquito, which has widespread distribution throughout the world, including the United States. Malaria transmission can also occur by blood transfusion, organ transplant, percutaneous exposure, and vertically (from mother to fetus), though these forms of transmission are uncommon[2].

If untreated, malaria can cause severe and fatal disease. Clinical manifestations can range from fever, shaking chills, muscle pains, and other non-specific symptoms in uncomplicated malaria, to jaundice, acute renal failure, severe anemia, cerebral malaria, acute respiratory distress syndrome, and other serious complications in severe malaria[2], which can be rapidly fatal. Malaria during pregnancy is associated with many adverse outcomes, including maternal mortality, maternal anemia, low birth weight, intrauterine growth retardation, and fetal loss[3].

In recent years, despite increasing anti-malarial drug and vector resistance, the scale-up of interventions in the endemic areas of the world has encouragingly reduced global malaria incidence by 37% and mortality by 60%[1,4]. However, the number of imported malaria cases has steadily increased in the US[5], where previously endemic malaria was eliminated in the 1950s. Similar to other countries[6] that eliminated malaria, this increase has mostly occurred among returned travelers, as well as among foreign visitors and immigrants from malaria-endemic countries[7]. Imported cases pose the potential threat for reintroduction of malaria into the naturally present Anopheles population in the US[8]. Many documented outbreaks of autochthonous malaria fueled by returned travelers, migrant workers, and immigrants have occurred in the US since malaria was declared eliminated[9].

Malaria is a nationally reportable disease in the US, and the CDC maintains a highly regarded surveillance system. The surveillance data is used to provide annual general malaria status updates, to detect local transmission, to monitor the patterns of resistance to antimalarial drugs, and to guide malaria prevention recommendations for international travelers[5]. However, underreporting of malaria is common in the current surveillance systems[10-11], and the complete domestic burden of malaria remains unknown.

Epidemiological study of malaria using hospital data can complement the findings from current nationwide surveillance system data to elucidate the malaria disease burden and case characteristics, and provide insight into the health care utilization and outcomes for malaria-related hospitalizations in the US. This study aims to comprehensively review and report in detail the burden of malaria-related hospitalizations in the US from 2000-2012.

Methods

Hospital discharge records from the Nationwide Inpatient Sample (NIS) were used for analysis of malaria-related hospitalizations in the US during 2000-2012. The NIS is sampled from the State Inpatient Databases (SID), and is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest publically available all-payer inpatient data source in the US, and each annual NIS dataset contains about 7-8 million hospital discharge records (about 20%) and over 100 clinical and non-clinical data elements, including sociodemographics, admission characteristics, diagnosis type, length of stay, co-diagnoses, procedures performed, institutional characteristics, and total charges[12-13]. For 2000-2011 data, the NIS was a stratified, single-stage cluster sampling of US community hospitals, in which all of the discharges from the selected hospitals were included in the NIS dataset[12]. For 2012 data, the NIS was a stratified random sample of discharges from all community hospitals participating in HCUP[13]. Details on the sampling scheme have been described elsewhere[12-13].

Cases of malaria in the NIS from 2000-2012 were identified from discharge records in the NIS by the primary and secondary diagnoses, which used the International Classification of Diseases, 9th revision (ICD-9)[14] codes of 084.0-084.9 (084.0: falciparum malaria, malignant tertian; 084.1: vivax malaria, benign tertian; 084.2: malariae, quartan; 084.3: ovale malaria; 084.4: other malaria; 084.5: mixed malaria; 084.6: malaria, unspecified; 084.7: induced malaria; 084.8: Blackwater fever; 084.9: other pernicious complications of malaria) and of 647.4 (malaria complicating pregnancy, childbirth, or puerperium).

In this study, the definition of severe malaria was modified from that used by the CDC[5]. Since no specific drugs used or laboratory results are available in the NIS, we were unable to use parasitemia ≥5% or treatment for severe malaria (i.e. artesunate or quinidine) as specified in the CDC definition[5]. Malaria complications were identified using ICD-9 codes and HCUP Clinical Classification Software (CCS)[13] categories, which are clinically meaningful categories of ICD-9 codes. Discharge records listing a malaria diagnosis along with one or more of the following criteria were considered as severe malaria cases: 1. Neurologic symptoms (cerebral malaria)– CCS codes 78, 82, 83, 85, or 95 (paralysis, epilepsy, convulsions, alteration of consciousness, coma, stupor, brain damage, other nervous system disorders); 2. Renal failure– CCS code 157; 3. Severe anemia– CCS codes 59 or 60 (deficiency anemia, acute post-hemorrhagic anemia), with procedural CCS code 222 (blood transfusion); 4. Acute respiratory distress syndrome (ARDS)– CCS code 131; 5. Jaundice– ICD-9 code 782.4; or 6. Exchange transfusion– ICD-9 code 99.01.

Data analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) with survey procedures that accounted for the complex sampling design. Variables of interest included demographics, infecting species, clinical, financial, institutional, geographic, and seasonal characteristics. National estimates of the frequency of malaria-related hospitalizations were produced using NIS discharge-level sample weights, which are provided by HCUP. Rates per US population[16] were calculated using bridged-race US census population estimates. Trends over the period in the counts of malaria cases by different patient characteristics were assessed using negative binomial regression.

Results

From 2000-2012, there were an estimated 19,189 (95% confidence interval [CI]: 18,213 – 20,165) malaria-related hospitalizations in the US, which far outnumbered that of other travel associated diseases, including filariasis, dengue, schistosomiasis, trypanosomiasis, and leishmaniasis (Table 1).

An average of 1,476 malaria-related hospitalizations occurred each year at a rate of 4.95 (95% CI: 4.70 – 5.20) per 1 million population. The rate of malaria-related hospitalizations did not change significantly over the study period. Malaria-related hospitalizations peaked in 2010, with 2,070 (95% CI: 1,533 – 2,607) cases and a rate of 6.69 (95% CI: 4.96 – 8.43) per 1 million population (Figure 1). The largest number of malaria-related hospitalizations occurred in August, followed by a small peak in January (Figure 2).

Demographic

The proportion and rate of malaria-related hospitalizations was higher for males (60.3%; 6.07 per 1 million population [95% CI: 5.72 – 6.42]) than females (39.2%; 3.81 per 1 million population [95% CI: 3.56 – 4.07]). Pregnant women accounted for 5.3% of the overall, and 13.5% of the female malaria-related hospitalizations. The most common race/ethnic group was Black, accounting for over half (51.0%) of all malaria-related hospitalizations with known race information, followed by White (24.4%), Hispanic (6.9%), Asian/Pacific Islander (5.9%), and Native American (1.0%). Blacks (16.55 per 1 million population [95% CI: 15.09 – 18.00]) also had the highest rates of malaria-related hospitalizations compared to all of the other race/ethnic groups, while Whites (1.50 per 1 million population [95% CI: 1.38 – 1.62]) had the lowest rates. Rates for Hispanics decreased slightly over the period ($p<0.01$). The mean age of patients with a malaria diagnosis was 36.8 (95% CI: 36.2 – 37.4). The number and rate of malaria-related hospitalizations increased with age, peaking at 25-44 years, then decreased (Table 2).

Species

Species information was known for about half (52.6%) of the malaria-related hospitalizations. *P. falciparum* (71.3%) accounted for the majority of malaria-related hospitalizations with known species information, followed by *P. vivax* (23.7%), *P. malariae* (3.4%), and *P. ovale* (2.9%). Few specified more than one malaria species (0.7%) or listed mixed malaria (2.0%) as a diagnosis. Unspecified malaria accounted for 34.8% of all malaria-related hospitalizations (Table 3).

Clinical

Most (84.0%) malaria-related discharge records listed malaria as the primary diagnosis. Discharge records with a malaria-related diagnosis listed a mean of 5.27 (95% CI: 5.15 – 5.39) diagnoses, with a mean of 0.99 (95% CI: 0.96 – 1.02) chronic conditions[15]. There were an estimated 3,888 (95% CI: 3,576 – 4,199) hospitalizations that were classified as having a severe malaria diagnosis, accounting for 20.3% of all malaria-related hospitalizations. Some (23.4%) patients developed multiple complications. Malaria with renal failure (8.2%; 1,573 [95% CI: 1,396 – 1,750]) was the most common complication, followed by malaria with severe anemia (7.0%; 1,346 [95% CI: 1,179 – 1,513]), malaria with acute respiratory distress syndrome (4.0%; 775 [95% CI: 658 – 892]), cerebral malaria (3.8%; 726 [95% CI: 613 – 839]), and malaria with jaundice (3.1%; 598 [95% CI: 494 – 701]) (Table 3). The proportion and rate of malaria-related hospitalizations classified as severe increased over the period ($p<0.01$).

Among discharge records with malaria listed as the primary diagnosis, the most common co-diagnoses were thrombocytopenia (30.6%), anemia (17.2%), hypertension (12.3%), and hypopotassemia (12.0%). Among discharge records with malaria listed as a secondary diagnosis, the most common primary diagnoses were unspecified septicemia (8.6%), fever (3.6%), and other specified septicemia (3.0%). The most common procedures performed for malaria patients were blood transfusion (9.8%), other therapeutic procedure (6.5%), diagnostic spinal tap (5.2%), non-heart vascular catheterization (4.8%), and respiratory intubation and mechanical ventilation (3.2%).

The majority (70.0%) of malaria patients with known source of admission were admitted from the emergency room. From 2000-2012, an estimated 147 (95% CI: 96 – 198]) in-hospital deaths occurred, accounting for 0.7% of malaria-related hospitalizations (Table 3). Malaria patients stayed an average of 4.39 (95% CI: 4.23 – 4.54) days.

Financial

The mean hospital charge for malaria-related hospitalizations was $25,116 (95% CI: 23,683 – 26,549). Over half of patients resided in a zip code with median household incomes above the national median. Private insurance (45.5%) was the largest primary payer for malaria-related hospitalizations, followed by out-of-pocket payers (22.1%), Medicaid (18.3%), and Medicare (6.8%) (Table 4).

Institutional

The Southern (37.9%) and Northeastern (32.9%) regions of the US had the highest numbers of malaria-related hospitalizations, followed by the Western (15.0%) and Midwestern (14.2%) regions. From 2000-2011 (2012 data unavailable), the Middle Atlantic (26.0%; 10.6 per 1 million population [95% CI: 9.39 – 11.92]) and South Atlantic (25.6%; 6.96 per 1 million population [95% CI: 6.12 – 7.80]) census divisions accounted for over half of all malaria-related hospitalizations over the study period. The East South Central census division had the lowest rate of malaria-related hospitalizations (1.9%; 1.75 per 1 million population [95% CI: 1.21 – 2.29]) (Figure 3).

Patients with a malaria diagnosis were more often hospitalized at urban, teaching hospitals (65.4%), than urban non-teaching (30.4%) or rural (3.9%) hospitals; at private, non-profit hospitals (72.5%), than government, nonfederal (19.1%) and private, investor-owned (7.9%) hospitals; and at hospitals with large bed size (61.6%) than medium (27.7%) or small (10.5%) bed size.

Discussion

Malaria hospitalizations routinely occur in the US, and the associated morbidity, mortality, and cost burden is substantial. From 2000-2012, hospitalizations for malaria far outnumbered that of other travel associated diseases. While we are unable to ascertain travel status, it is extremely likely that most malaria hospitalizations represent travel-related cases, which are largely preventable.

The estimated frequencies of malaria-related hospitalizations can be compared to surveillance data to quantify the discrepancy and level of underreporting in the national malaria surveillance system. In some years (2000, 2001, and 2010) during the study period, the number of malaria-related hospitalizations exceeded the total number of malaria cases reported by the malaria surveillance system[5], which includes both inpatient and outpatient cases. If it is assumed that hospital cases represented about 69% of all malaria cases, as was consistently reported in recent malaria surveillance reports[5,17-18], and the actual number of hospitalizations are as reported in this study, then the estimated total number of malaria cases occurring in the US is on average about 2,139 each year.

Malaria-related deaths may also be underreported. From 2000-2012, the total number of malaria-related in-hospital deaths in the NIS was similar to the total number of malaria-related deaths in the national Multiple Cause of Death (MCOD) data from US death certificates (n=151)[19], which was nearly double the number reported in the national malaria surveillance reports (n=76)[5,17-18,20-30]. Further, only about 63% of death certificates listing malaria as a cause of death reported an inpatient medical facility as the place of death on the death certificate[19], indicating possible underestimates of malaria-related deaths in the MCOD data as well.

Malaria surveillance system data shows a strong overall increasing trend in the number of reported malaria cases since the early 1970s[5]. This pattern has been similarly reported in other countries[6] that eliminated malaria, which is likely due to the increase in international travel to malaria-endemic regions[31]. Although we did not find a statistically significant trend in malaria-related hospitalizations from 2000-2012, the overall numbers generally reflected the patterns reported in the surveillance reports[11].

The overrepresentation of malaria among men has been well documented. Compared to women, men may be less likely to seek pre-travel advice, less likely to adhere to appropriate personal vector avoidance and chemoprophylaxis, suffer more mosquito bites, and exhibit other high-risk behaviors[32-33]. The large proportion of pregnant women among female malaria-related hospitalizations, which was greater than that reported in the malaria surveillance system, is concerning as malaria during pregnancy can be especially dangerous for the mother and fetus[3]. The age distribution of malaria patients, which may reflect the age distribution of international travelers, is also consistent with previous reports[5]. The race/ethnicity distribution of malaria in the US has been infrequently reported. The overrepresentation of malaria among Blacks may reflect the distribution of international travel among visitors, immigrants, or expatriates from endemic areas, including countries in the Caribbean and Africa[5]. Some immigrants may be more likely to return to their countries of origin with endemic malaria to visit friends or relatives, and tend to have longer stays or stay at familial communities with higher risk lodging that increases their exposure to vectors[6,34]. Importantly, these individuals may perceive themselves to be immune or at low risk, and may forego malaria prevention measures[34].

The predominant infecting species for malaria-related hospitalizations with known species information was *P. falciparum*, consistent with its well-documented relative virulence and global distribution[5]. *P. falciparum* can cause higher parasitemia and more serious complications than the other *Plasmodium* species because it lacks preference for particular red blood cell age classes[35], and is associated with sequestration and cytoadherence[36]. Although *P. falciparum* is recognized for its ability to cause serious morbidity and mortality and is confirmed as the primary threat in this study, the disease burden caused by *P. vivax* should not be discounted[37-38]. The reasons for not ascertaining the infecting species for nearly half of malaria-related hospitalizations are not known, as species information is important in determining the appropriate treatment regimen[39]. Improved reporting or additional laboratory training on malaria microscopy may be needed to improve the rates or capacity of species identification in the US.

The proportion of hospitalizations classified as having severe malaria was slightly higher than that reported from the surveillance system in recent years[11], which is expected since hospitalized cases are selected for severity and exclude milder outpatient cases. The relative proportions of specific complications that defined severe malaria were consistent with surveillance data. The number of in-hospital deaths observed underscore the importance of prevention and early diagnosis. Available treatment regimens for malaria are highly effective when properly and promptly administered, and symptoms can resolve within days[39].

Large geographical disparities consistent with surveillance data were found along the east coast, which may be due to the popularity of the northeastern region states as destinations for immigrants from malaria-endemic countries, and thus an increased popularity of malaria endemic countries as travel destinations for those visiting friends and relatives among residents of the northeastern region[40-41]. Additional provider training for malaria awareness, diagnosis, and management may be warranted in these areas. Improved public health messages and adequate access to quality pre-travel clinical care are needed to increase the use of pre-travel consultations, chemoprophylaxis, and vector avoidance[32,42-44], particularly among those returning to countries of origin to visit friends or relatives[6,36]. Improvements in secondary prevention by recognition, diagnosis, and treatment in primary care are also needed to avert the development of more severe conditions requiring hospitalization. Prompt diagnosis and treatment is crucial for good prognosis. Febrile illness with a history of international travel must always include malaria as a diagnostic consideration. Physician index of suspicion should be especially heightened during the summer and winter holiday seasons, which are popular travel times of the year to Africa[45].

Some limitations of this study should be considered. The national estimates from the NIS are based on weighted frequencies subject to sampling error, and the actual number of malaria-related hospitalizations may be greater or less than reported here. Error in the estimation of the malaria-related hospitalization frequency and rate is possible due to misdiagnoses, since malaria is a relatively rare disease with some non-specific clinical manifestations. Moreover, malaria can be difficult to diagnose, requiring a skilled microscopist[46]. Underreporting of potentially relevant diagnoses and the high proportion of clinically imprecise ICD diagnosis codes, such as those corresponding to “general”, “other”, “unspecified", or “mixed” conditions, or those corresponding to conditions that can have a wide clinical spectrum (e.g., renal failure), precludes accurate identification of all malaria-related hospitalizations, of relevant clinical manifestations for classifying severe malaria cases, and of the infecting species. Since this administrative data is discharge record based and not patient based, recrudescent malaria cases that result in re-hospitalizations may lead to multiple counting. Although the random and intentional (state-level suppression) missing data on race may not affect relative proportions, race-specific frequency and rate estimates are underestimated since only cases with known race were included in the calculations. Factors of interest not available in the NIS included lab results, specific diagnostic and treatment method, and other factors. Travel history, immigration and immunity status, destination and purpose of international travel, and chemoprophylaxis use were also not available in NIS data to determine relative risk and to confirm the findings from the malaria surveillance system.

Conclusion

This study brings to light the importance of imported malaria in the US. Despite the reduction of malaria incidence in developing countries, malaria continues to be an important public health problem in the US despite its elimination in the early 1950s, and the disease burden remains substantial. Malaria hospitalizations and deaths are largely preventable through use of personal protective measures, adherence to correct prophylactic regimens, and ensuring rapid and correct diagnosis and treatment. CDC provides free guidance on malaria risk and prophylaxis by region, and staff is available for guidance on therapy.

References

1. World Malaria Report 2015. World Health Organization. Geneva, Switzerland: World Health Organization; 2016. http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf

2. Centers for Disease Control. Malaria [Accessed 15 Apr 2015]. Available at: http://www.cdc.gov/malaria/

3. Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. Clinical microbiology reviews. 2004;17(4): 760-769.

4. Steketee RW, Campbell CC. Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. Malar J. 2010; 9: 299.

5. Cullen KA, Mace KE, Arguin PM. Malaria surveillance--United States, 2013. MMWR Surveill Summ. 2016 Mar 4; 65(2):1-22.

6. Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, Whitty CJM. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. Bmj. 2012;344.

7. Hagmann SHF, Van PV, Stauffer WM, Miller AO, Connor BA, Hale DC, Coyle CM, et al. Travel-associated disease among US residents visiting US GeoSentinel clinics after return from international travel. Family Practice, 2014, Vol. 31, No. 6, 678–687 doi:10.1093/fampra/cmu063

8. Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y, Chareonviriyaphap T, Coetzee M, Mbogo CM, et al. A global map of dominant malaria vectors. Parasit Vectors. 2012; 5(1): 69.

9. Zucker JR. Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks. Emerg Infect Dis. 1996;2(1): 37-43.

10. Abanyie FA, Arguin PM, Gutman J. State of malaria diagnostic testing at clinical laboratories in the United States, 2010: a nationwide survey. Malar J. 2011;10: 340.

11. Doyle TJ, Glynn MK, Groseclose SL. Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. American Journal of Epidemiology. 2002;155(9): 866-874.

12. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide

Inpatient Sample (NIS) 2011. Agency for Healthcare Research and Quality, Rockville, MD. June 2013. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2011.jsp

13. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2012. Agency for Healthcare Research and Quality, Rockville, MD. June 2014. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2012.jsp

14. Centers for Disease Control and Prevention. Classification of Diseases, Functioning, and Disability. Conversion table. [Accessed 12 Sep 2014]. Available at: http://www.cdc.gov/nchs/icd/icd9cm.htm

15. Healthcare Cost and Utilization Project (HCUP). Clinical Classifications Software (CCS) for ICD-9-CM and Chronic Condition Indicator. HCUP Tools & Software. Agency for Healthcare Research and Quality, Rockville, MD. 2015. [Accessed 26 Jun 2016]. Available at https://www.hcup-us.ahrq.gov/tools_software.jsp

16. United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Bridged-Race Population Estimates, United States July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin. Compiled from 1990-1999 bridged-race intercensal population estimates (released by NCHS on 7/26/2004); revised bridged-race 2000-2009 intercensal population estimates (released by NCHS on 10/26/2012); and bridged-race Vintage 2014 (2010-2014) postcensal population estimates (released by NCHS on 6/30/2015). Available on CDC WONDER Online Database. Accessed at http://wonder.cdc.gov/bridged-race-v2014.html on Apr 15, 2016 1:00:23 PM

17. Cullen KA, Arguin PM. Malaria Surveillance—United States, 2011. MMWR Surveill Summ. 2013; 62: 1-17.

18. Cullen KA, Arguin PM; Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2012. MMWR Surveill Summ. 2014 Dec 5; 63(12):1-22.

19. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2014 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2014, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on Jun 11, 2016 5:44:01 PM

20. Causer LM, Newman RD, Barber AM, Roberts JM, Stennies G, Bloland PB, Parise ME, Steketee RW. Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2000. MMWR Surveill Summ. 2002 Jul 12; 51(SS05);9-21.

21. Filler S, Causer LM, Newman RD, Barber AM, Roberts JM, MacArthur J, Parise ME, Steketee RW. Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2001. MMWR Surveill Summ. 2003 Jul 18; 52(SS05);1-14.

22. Shah S, Filler S, Causer LM, Rowe AK, Bloland PB, Barber AM, Roberts JM, Desai MR, Parise ME, Steketee RW. Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2002. MMWR Surveill Summ. 2004 Apr 30; 53(SS01);21-34.

23. Eliades MJ, Shah S, Ngyuen-Dinh P, Newman RD, Barber AM, Roberts JM, Mail S, Parise ME, Steketee RW. Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2003. MMWR Surveill Summ. 2005 Jun 3; 54(SS02);25-39.

24. Skarbinski J, James EM, Causer LM, Barber AM, Mali S, Nguyen-Dinh P, Roberts JM, Parise ME, Slutsker L, Newman RD. Centers for Disease Control and Prevention (CDC). Malaria surveillance—United States, 2004. MMWR Surveill Summ. 2006 May 26;55(SS04):23-37.

25. Thwing J, Skarbinski J, Newman RD, Barber AM, Mali S, Roberts JM, Slutsker L, Arguin PM. Centers for Disease Control and Prevention (CDC). Malaria surveillance—United States, 2005. MMWR Surveill Summ. 2007 Jun 8;56(SS06):23-38.

26. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2006. MMWR Surveill Summ. 2008 Jun 20;57(5):24-39.

27. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2007. MMWR Surveill Summ. 2009 Apr 17; 58(SS02);1-16

28. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance-United States, 2008. MMWR Surveill Summ. 2010 Jun 25;59(7):1-15.

29. Mail S, Tan KR, Arguin PM. Malaria surveillance-United States, 2009. MMWR Surveill Summ. 2011 Apr 22;60(3):1-15.

30. Mali S, Kachur SP, Arguin PM. Malaria surveillance-United States, 2009. MMWR Surveill Summ. 2012 Mar 2; 61(SS02);1-17.

31. World Tourism Organization. UNWTO tourism highlights: 2014 edition. Madrid, Spain: World Tourism Organization; 2014. [Accessed 25 Mar 2015]. Available at: http://mkt.unwto.org/publication/unwto-tourism-highlights-2014-edition

32. Schlagenhauf P, Weld L, Goorhuis A, et al. Travel-associated infection presenting in Europe (2008-2012): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. Lancet 2015; 15:55-64.

33. Schlagenhauf P, Chen LH, Wilson ME, Freedman DO, Tcheng D, Schwartz E, et al. Sex and gender differences in travel-associated disease. Clin Infect Dis. 2010; 50:826–32. http://dx.doi. org/10.1086/650575

34. Leder K, Torresi J, Libman MD, Cramer JP, Castelli F, Schlagenhauf P, Wilder-Smith A, et al. GeoSentinel surveillance of illness in returned travelers, 2007–2011. Annals of internal medicine. 2013;158(6): 456-468.

35. Kerlin DH, Gatton ML. Preferential Invasion by Plasmodium Merozoites and the Self-Regulation of Parasite Burden. PLoS ONE. 2013; 8(2): e57434.

36. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014; 383: 723–35. http://dx.doi.org/10.1016/S0140-6736(13)60024-0

37. Hwang J, Cullen KA, Kachur SP, Arguin PM, Baird JK. Severe morbidity and mortality risk from malaria in the United States, 1985-2011. Open Forum Infect Dis. 2014 Jun 30;1(1):ofu034. doi: 10.1093/ofid/ofu034.

38. Mendis K, Sina BJ, Marchesini P, Carter R. The neglected burden of Plasmodium vivax malaria. The American journal of tropical medicine and hygiene. 2001;64(1)suppl: 97-106.

39. Centers for Disease Control and Prevention. Treatment of Malaria. 2013. [Accessed 26 Mar 2016]. Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf

40. International Trade Administration. National Travel and Tourism Office. US Department of Commerce. US Travel and Tourism Statistics (Inbound). Region of origin profiles: Africa. Page 6. [Accessed 28 Jun 2016]. Available at: http://tinet.ita.doc.gov/outreachpages/download_data_table/2012_Africa_Market_Profile.pdf

41. International Trade Administration. National Travel and Tourism Office. US Department of Commerce. US Travel and Tourism Statistics (US Resident Outbound). US to overseas for leisure/visit friends & relatives (VFR). Page 7. [Accessed 28 Jun 2016]. Available at: http://tinet.ita.doc.gov/outreachpages/download_data_table/2012-US-Leisure-VFR.pdf

42. Hamer DH, Connor BA. Travel health knowledge, attitudes and practices among United States travelers. Journal of travel medicine. 2004;11(1): 23-26.

43. LaRocque RC, Rao SR, Tsibris A, Lawton T, Barry MA, Marano N, Brunette G, Yanni E, Ryan ET. Pre-travel health advice-seeking behavior among US international travelers departing from Boston Logan International Airport. Journal of travel medicine. 2010;17(6): 387-391.

44. Centers for Disease Control and Prevention. Malaria. Yellow Book 2015. [Accessed 15 Apr 2016]. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria

45. International Trade Administration. National Travel and Tourism Office. US Department of Commerce. Monthly arrivals to the United States, 1996-2015. [Accessed 28 Jun 2016]. Available at: http://travel.trade.gov/research/monthly/arrivals/

46. Ash LR, Orihel TC. Atlas of Human Parasitology 5th ed. Chicago: ASCP Press; 2007.

Table 1. Number of hospitalizations for selected travel-associated infectious diseases in the US, NIS 2000-2012

Disease	Malaria	Strongyloidiasis	Filariasis	Dengue	Schistosomiasis	Trypanosomiasis	Leishmaniasis
ICD-9-CM	084,647.4	127.2	125	061	120	086	085
2000	1,757	262	535	72	127	114	61
2001	1,822	325	285	119	157	107	103
2002	1,278	320	211	134	149	64	70
2003	1,226	342	304	101	77	158	78
2004	1,206	309	226	106	187	105	90
2005	1,488	329	270	236	177	122	76
2006	1,420	344	252	141	166	135	86
2007	1,347	404	291	294	222	192	151
2008	1,093	412	325	344	164	278	81
2009	1,464	408	321	193	134	241	107
2010	2,070	481	282	565	236	156	182
2011	1,626	442	337	242	257	172	108
2012	1,395	530	390	430	240	185	75
Annual Average	1,476	378	310	229	176	156	98

Note: All numbers are national estimates based on weighted frequencies.

Table 2. Number and rate of malaria-related hospitalizations in the US, by demographic, NIS, 2000-2012

	Unweighted Frequency	*Percent of malaria-related hospitalizations*	*Weighted Frequency*	*Lower 95% CL Wgt. Freq*	*Upper 95% CL Wgt. Freq*	*Rate per 1M pop*	*Lower 95% CL Rate*	*Upper 95% CL Rate*
Sex								
Male	2,413	60.3%	11,569	10,910	12,228	6.07	5.72	6.42
Female	1,571	39.2%	7,524	7,028	8,021	3.81	3.56	4.07
Pregnant	211	5.3%	1,015	817	1,213	0.26	0.03	0.20
Missing	20	0.5%	96	-	-	-	-	-
Race								
White	811	20.2%	3,883	3,572	4,194	1.50	1.38	1.62
Black	1,689	42.3%	8,125	7,412	8,837	16.55	15.09	18.00
Hispanic	232	5.7%	1,099	920	1,278	1.90	1.59	2.20
Asian/Pacific Islander	199	4.9%	943	798	1,089	5.05	4.27	5.83
Native American	33	0.9%	164	106	222	5.10	3.29	6.90
Other	357	8.9%	1,703	1,495	1,910	-	-	-
Missing	683	17.1%	3,273	-	-	-	-	-
Age (years)								
Under 5	159	4.0%	763	617	909	2.96	2.39	3.52
5-14	306	7.7%	1,485	1,253	1,717	2.79	2.36	3.23
15-24	659	16.5%	3,160	2,881	3,439	5.74	5.23	6.24
25-44	1,488	37.3%	7,148	6,690	7,606	6.62	6.19	7.04
45-64	1,049	26.1%	5,009	4,621	5,397	5.19	4.79	5.59
65-84	306	7.5%	1,448	1,280	1,616	3.38	2.99	3.77
Over 85	29	0.7%	136	91	181	2.12	1.42	2.82
Missing	8	0.2%	35	-	-	-	-	-
Mean (range)	36.8	(0	96)	36.2	37.4	-	-	-
Total	4,004	100.0%	19,189	18,213	20,165	4.95	4.70	5.20

Note: Unweighted frequencies are the raw frequencies in the NIS, and weighted raw frequencies represent national estimates.

Table 3. Clinical characteristics of malaria-related hospitalizations in the US, NIS, 2000-2012

	Unweighted Frequency	*Percent of malaria-related hospitalizations*	*Weighted Frequency*	*Lower 95% CL Wgt Freq*	*Upper 95% CL Wgt Freq*
Malaria diagnosis					
Primary	3,364	84.0%	16,127	15,248	17,007
Secondary	640	16.0%	3,062	2,779	3,345
Clinical classification					
Uncomplicated malaria	3,189	79.7%	15,302	14,458	16,145
Severe malaria	815	20.3%	3,888	3,576	4,199
Cerebral malaria	151	3.8%	726	613	839
Malaria with anemia	282	7.0%	1,346	1,179	1,513
Malaria with renal failure	329	8.2%	1,573	1,396	1,750
Malaria with ARDS	161	4.0%	775	658	892
Malaria with jaundice	125	3.1%	598	494	701
Infecting species					
Species identified	2,106	52.6%	10,091	9,461	10,720
Falciparum	1,502	37.5%	7,200	6,677	7,723
Vivax	499	12.4%	2,387	2,150	2,623
Malariae	71	1.7%	333	255	411
Ovale	62	1.6%	306	228	384
Species not identified	1,898	47.4%	9,099	8,624	9,573
Mixed malaria	82	2.0%	390	291	489
Other malaria	282	7.1%	1,360	1,182	1,539
Unspecified malaria	1,395	34.8%	6,684	6,237	7,131
Blackwater fever	15	0.4%	74	36	111
Complicated malaria	105	2.6%	499	399	599
Number of diagnoses					
1	448	11.2%	2,165	1,924	2,407
2-3	1,151	28.7%	5,534	5,114	5,955
4-6	1,241	31.0%	5,925	5,529	6,321
7-10	820	20.5%	3,918	3,600	4,235
11 or more	344	8.6%	1,647	1,467	1,827
Missing	0	0.0%	0	-	-
Number of chronic conditions*					
0	318	20.2%	1,548	1,338	1,757
1-3	961	60.9%	4,651	4,224	5,078
4 or more	299	18.9%	1,449	1,277	1,620
Missing	0	0.0%	0	-	-
Number of procedures performed					
0	2,702	67.5%	12,931	12,217	13,645
1	688	17.2%	3,309	3,001	3,618
2 or more	614	15.3%	2,948	2,659	3,238
Missing	0	0.0%	0	-	-

*Admission Source**					
Admitted from ER	1,893	50.8%	9,036	8,379	9,694
Admitted from another hospital	107	2.9%	512	404	621
Admitted from another facility	20	0.5%	97	54	140
Admitted from routine/birth/other	700	18.8%	3,304	2,927	3,680
Missing	1,005	27.0%	4,845	-	-
In-hospital death					
Did not die during hospital stay	3,971	99.2%	19,028	18,059	19,998
In-hospital death	30	0.7%	147	96	198
Missing	3	0.1%	14	-	-
Length of Stay (days)					
0-1	597	14.9%	2,870	2,602	3,138
2-3	1,695	42.3%	8,125	7,600	8,649
4-6	1,173	29.3%	5,619	3,595	4,207
7+	539	13.5%	2,575	2,344	2,806
Missing	0	0	0	-	-
Mean (range)	4.39	(0	135)	4.23	4.55
Total	4,004	100.0%	19,189	18,213	20,165

**Admission source: 2000-2011 data only. Number of chronic conditions 2008-2012 data only*

Note: Unweighted frequencies are the raw frequencies in the NIS, and weighted raw frequencies represent national estimates.

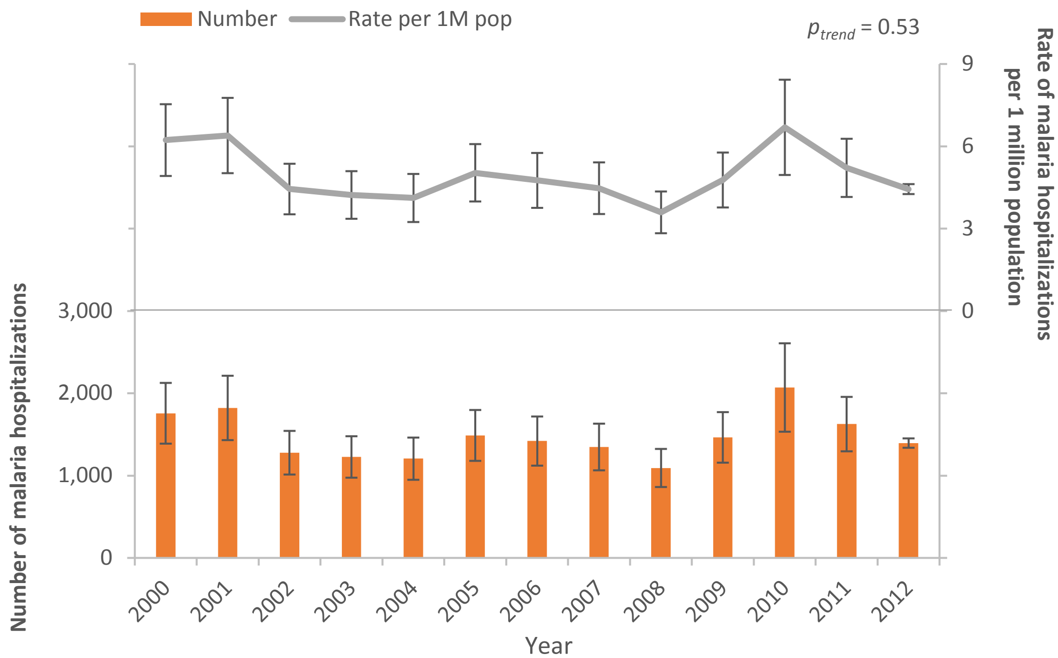
Table 4. Financial characteristics of malaria-related hospitalizations in the US, NIS, 2000-2012

	Unweighted Frequency	*Percent of malaria-related hospitalizations*	*Weighted Frequency*	*Lower 95% CL Wgt Freq*	*Upper 95% CL Wgt Freq*
Hospital charges*					
Mean (range)	25,116	(194	1,021,738)	23,683	26,549
Missing	100	2.5%	472	-	-
*Income**					
High	2,219	55.4%	10,588	9,942	11,233
Low	1,576	39.4%	7,589	6,994	8,185
Missing	209	5.2%	1,012	-	-
Primary payer					
Medicare	274	6.8%	1,301	1,143	1,459
Medicaid	734	18.3%	3,575	3,169	3,980
Private insurance	1,822	45.5%	8,686	8,179	9,194
Self-pay	884	22.1%	4,237	3,818	4,655
No charge	84	2.1%	406	279	532
Other	194	4.8%	928	782	1,075
Missing	12	0.3%	57	-	-
Total	4,004	100.0%	19,189	18,213	20,165

*Adjusted for inflation to 2015 US dollars. Income category is based on median household income by national quartiles for patient zip code.

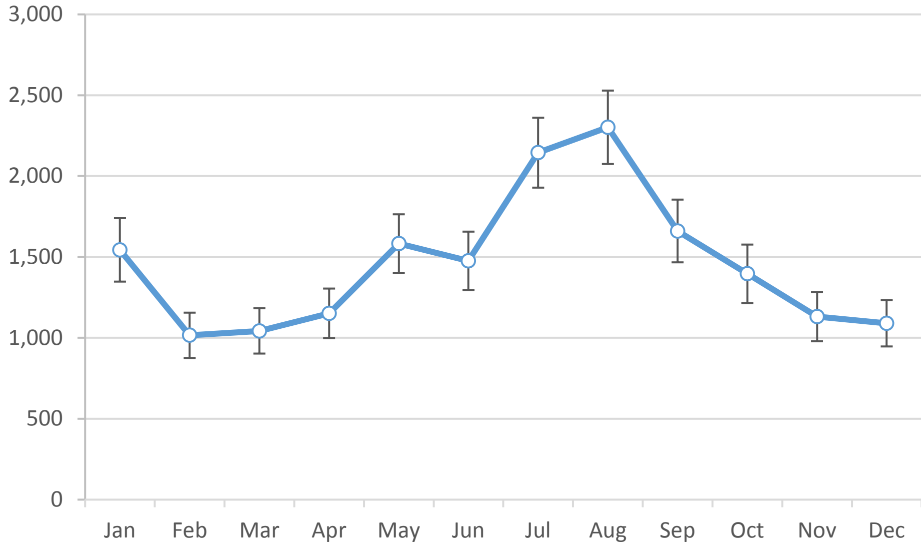
Note: Unweighted frequencies are the raw frequencies in the NIS, and weighted raw frequencies represent national estimates.

Figure 1. Number and rate of malaria hospitalizations in the US, NIS, 2000-2012



Note: All numbers are national estimates based on weighted frequencies.

Figure 2. Number of malaria-related hospitalizations in the US, by month, NIS, 2000-2012



Note: All numbers are national estimates based on weighted frequencies and nonmissing data.

Figure 3. Rate of malaria-related hospitalizations in the US, by division, NIS, 2000-2011

Note: All numbers are national estimates based on weighted frequencies.

Chapter 2: Economic burden

Economic impact of malaria-related hospitalizations in the United States, 2000-2012

Abstract

Background: Despite its elimination in the early 1950s, about 1,500 cases of malaria are reported in the US every year. Few studies have quantified the direct and indirect costs of imported malaria in the US, and the domestic economic impact is largely unknown.

Methods: Disparities in the mean and total hospital days, hospital charges, and hospital costs for malaria-related hospitalizations in the US by demographic, clinical, species, financial, geographic, and institutional characteristics were examined using discharge records from the 2000-2012 Nationwide Inpatient Sample (NIS), which is the largest publicly available all-payer inpatient health care database in the US. Trends and potential predictors for hospital charges and costs were identified using linear regression. Trends and potential predictors for length of stay were identified using negative binomial regression.

Results: From 2000-2012, 19,189 malaria cases resulted in 84,213 hospital days for malaria-related hospitalizations, $151,825,389 in total hospital costs, and $470,102,584 in total charges. Mean charges increased significantly over the study period. Males, Blacks, and patients aged 25-44 years represented the demographic groups with the highest direct and indirect costs. Having severe malaria was associated with a longer length of stay. Older age, severe malaria, HIV infection, and longer lengths of stay were associated with higher charges and costs.

Conclusions: Malaria results in substantial direct and indirect costs in the US. Primary and secondary prevention measures should be prioritized among high-risk groups to reduce the economic burden.

Introduction

Malaria is the leading cause of death by parasitic disease in the world and remains one of the most important and intractable global public health problems. An estimated 214 million cases of malaria, and 438,000 deaths due to malaria occurred in 2015[1]. Malaria is caused by infection with the protozoan agents of the genus *Plasmodium.* Several species of *Plasmodium* (*P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*) are known to affect humans, with *P. falciparum* causing the most morbidity and the vast majority of the mortality[2].

The scale-up of interventions in the malaria endemic areas of the world has dramatically reduced global malaria incidence and mortality over recent years[1]. In contrast, the number of malaria cases has steadily increased in the US[3] with increases in international travel[4-5]. An estimated 14% of international travelers develop a febrile illness, with malaria being the most common cause of febrile illness (19%) among international travelers[6-8]. About 1,500 cases of malaria, including about 5 deaths, are reported each year[3] in the US, mostly among returned travelers, and to a lesser extent among foreign visitors or immigrants from countries with endemic malaria[3]. Despite the abundance of available prevention[2] tools and its elimination since the early 1950s[9], malaria continues to impose a substantial disease burden in the US. Few studies have quantified the costs of imported malaria in the US[10-11], and the domestic economic impact is largely unknown.

Study of the economic burden of malaria using hospital data in the US has rarely been explored, and can provide insight to the direct and indirect costs of imported malaria. This study aims to examine the malaria-associated direct costs by assessing hospital charges and costs, which represent health care resource utilization, and the indirect costs by assessing lengths of hospital stay, which represent lost productivity associated with malaria. A better understanding of these distributions and trends can help to inform improved targeted malaria prevention strategies in the US, especially for subgroups that incur high costs.

Methods

Hospital discharge records from the Nationwide Inpatient Sample (NIS) were used for analysis of malaria-related hospitalizations in the US during 2000-2012. The NIS is sampled from the State Inpatient Databases (SID), and is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). For 2000-2011 data, the NIS was a stratified, single-stage cluster sampling of US community hospitals, in which all of the discharges from the selected hospitals were included in the NIS dataset[12]. For 2012 data, the NIS was a stratified random sample of discharges from all community hospitals participating in HCUP[13]. Details on the sampling scheme have been described elsewhere[12-13]. The NIS is the largest publically available all-payer inpatient data source in the US, and each annual NIS dataset contains 7-8 million hospital discharge records (about 20%) and over 100 clinical and non-clinical data elements, including sociodemographics, admission characteristics, diagnosis type, disease severity, length of stay, co-diagnoses, procedures performed, institutional characteristics, and total charges[12-13].

Cases of malaria in the NIS from 2000-2012 were identified from discharge records in the NIS by the primary and secondary diagnoses, which used the International Classification of Diseases, 9th revision (ICD-9)[14] codes of 084.0-084.9 (084.0: falciparum malaria, malignant tertian; 084.1: vivax malaria, benign tertian; 084.2: malariae, quartan; 084.3: ovale malaria; 084.4: other malaria; 084.5: mixed malaria; 084.6: malaria, unspecified; 084.7: induced malaria; 084.8: Blackwater fever; 084.9: other pernicious complications of malaria) and of 647.4 (malaria complicating pregnancy, childbirth, or puerperium).

In this study, the definition of severe malaria was based on that used by the CDC[3] with some modification due to data availability. Since no specific drugs used or laboratory results are available in the NIS, we were unable to use parasitemia ≥5% or treatment for severe malaria (i.e. artesunate or quinidine) as specified in the CDC definition[3]. Malaria complications were identified using ICD-9 codes and HCUP Clinical Classification Software (CCS)[15] categories, which are clinically meaningful categories of ICD-9 codes. Discharge records listing a malaria diagnosis along with one or more of the following criteria were considered as severe malaria cases: 1. Neurologic symptoms (cerebral malaria)– CCS codes 78, 82, 83, 85, or 95 (paralysis, epilepsy, convulsions, alteration of consciousness, coma, stupor, brain damage, other nervous system disorders); 2. Renal failure– CCS code 157; 3. Severe anemia– CCS codes 59 or 60 (deficiency anemia, acute post-hemorrhagic anemia), with procedural CCS code 222 (blood transfusion); 4. Acute respiratory distress syndrome (ARDS)– CCS code 131; 5. Jaundice– ICD-9 code 782.4; or 6. Exchange transfusion– ICD-9 code 99.01.

Hospital charges represent the amount that hospitals bill for services, and are generally more than the total costs and more than the amount paid by the payers[16]. Hospital costs, which reflect the amount hospital services actually cost according to the required detailed reports by hospitals to the Centers for Medicare and Medicaid Services, were calculated by multiplying the charges by the hospital-level charge-to-cost ratios provided by HCUP available for 2001 and after. All charge and cost data were adjusted for inflation to 2015 US dollars using the general Consumer Price Index[17].

Data analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) with survey procedures that accounted for the complex sampling design. National estimates of the mean and sum of length of stay (LOS), hospital charges, and hospital costs for malaria-related hospitalizations by different characteristics were produced using NIS discharge-level sample weights, which were provided by HCUP. Direct costs (assessed using hospital charges and costs) and indirect costs (assessed using LOS) for malaria-related hospitalizations were compared to that for other select travel-associated diseases.

For total charges, trends were assessed using simple linear regression, and potential predictors were assessed using multiple linear regression. For LOS, trends were assessed using simple negative binomial regression, and potential predictors were assessed using multiple negative binomial regression. Potential predictors simultaneously tested included demographic, clinical, financial, and institutional variables. Directed acyclic graphs were used to examine the possible relationships between variables involved with LOS or total hospital charges[18-19] (Figure A1). Imputation of missing variables was not feasible due to the large size of the NIS and limited computing power.

Results

From 2000-2012, malaria-related hospitalizations accounted for 84,213 (95% confidence interval [CI]: 79,536 – 88,891) hospital days, and $470,102,584 (95% CI: in $437,342,864 – $502,862,303) in total charges. From 2001-2012, malaria-related hospitalizations accounted for $151,825,389 (95% CI: $140,471,910 – $163,178,869) in total hospital costs. The economic burden of malaria-related hospitalizations far exceeded those of other travel-associated diseases, including filariasis, dengue, schistosomiasis, trypanosomiasis, leishmaniasis, and typhoid fever (Table 1). The mean LOS and cost for malaria-related hospitalizations remained relatively constant (Figure 1, 2), while the mean charges increased significantly ($p_{trend} < 0.01$) from 2000-2012 (Figure 2).

Demographic

In this study, patients of working age (25-64 years) comprised the majority of malaria hospitalizations and hospital days. Mean hospital days, charges, and costs increased with age for those older than 45 years (Table 2, 3). Controlling for all other covariates, older age was associated with higher costs (Table A1). Controlling for all other covariates, Blacks had shorter LOS compared to Whites (Table A1). Blacks also had lower charges compared to Whites (Table A2).

Species

P. falciparum accounted for the majority of hospital days, hospital charges, and hospital costs among malaria-related hospitalizations with known species information (52.6%), followed by *P. vivax*, *P. ovale*, and *P. malariae* (Table 2, 3, 4).

Clinical

The majority (69.6%) of cases with known admission source were admitted from the emergency room, and accounted for 71.9% of the total charges and 69.7% of the total costs (Table 3, 4). Discharge records listing malaria as a secondary diagnosis had longer mean LOS and greater mean charges and costs than those with a primary malaria diagnosis. Severe malaria cases comprised 20.3% of all malaria-related hospitalizations, but accounted for 37.7% of the total hospital days, 49.1% of the total charges, and 48.1% of the total costs (Table 2, 3, 4). A diagnosis of ARDS was the strongest predictor of increased mean LOS, charge, and cost of malaria-related hospitalization, followed by severe anemia, cerebral malaria, and renal failure (Table A1, A2). Malaria cases with ARDS (4.0%) had especially prolonged mean LOS (16.3 days), high mean charges ($159,498), and high mean costs ($51,083), which disproportionately accounted for 15.0% of total hospital days, 26.0% of total charges, and 24.6% of total costs (Table 2, 3, 4). Having jaundice did not affect the LOS, charges, or costs (Table A1, A2). Co-occurring HIV infection and type II diabetes mellitus were associated with higher mean charges and costs (Table A2). Having medical procedures performed during hospitalization was associated with increased LOS, charges, and costs (Table 2, 3, 4). LOS was the most important predictor of mean charges and costs (Table A1, A2).

Financial

The most common primary payer for patients with a malaria-related hospitalization was private insurance, accounting for 45.1% of hospital days, 42.3% of hospital charges, and 40.7% of hospital costs. Controlling for all other covariates, patients with Medicare as their primary payer for hospitalizations had longer mean LOS compared to those with other payers (Table 2, A1). Patients with Medicare also had greater mean charges and costs compared to those with other primary payers (Table 3, 4), but primary payer was no longer associated with mean charges or costs after controlling for other covariates (Table A2). Median income for zip code was not associated with LOS, charges, or costs (Table 2, 3, A1, A2).

Institutional

Mean LOS for malaria-related hospitalizations did not vary by region (Table 2, A1). However, the mean charges and costs were higher in the Western region compared to all other regions (Table 3, 4), even after controlling for all other covariates (Table A2). Malaria patients who stayed at rural hospitals had lower mean LOS and charges mean compared to those at urban hospitals (Table 2, 3), even after controlling for other covariates (Table A1, A2). Mean LOS did not vary by hospital control/ownership (Table 2, A1). However, the mean charge was much higher and the mean cost was much lower for patients who stayed at private, investor-owned hospitals compared to government, non-federal hospitals (Table 3,4), while the mean cost was lower for even after controlling for other covariates (Table A2). Compared to patients who stayed at hospitals with large bed size, those who were hospitalized in hospitals with small bed size had higher mean costs (Table A2).

Discussion

Malaria imposes a great disease and economic burden with substantial direct and indirect costs in the US. Malaria-related hospitalizations resulted in a total of nearly half a billion dollars in hospital charges and over 150 million in hospital costs for 84,000 hospital days in the US from 2000-2012. Although the mean LOS, charge, and cost per hospitalization for malaria were lower than that for other travel-associated diseases, including filariasis, dengue, schistosomiasis, trypanosomiasis, leishmaniasis, and typhoid fever, malaria accounted for a much larger total bill and hospital days due to the excess number of cases. Furthermore, malaria-related hospital charges demonstrated an increasing trend over the study period, suggesting a growing economic burden due to malaria in the US.

The heavy economic burden of malaria, much of which is attributable to the use of high-cost services as indicated by the large proportion of cases admitted from the emergency room and the large proportion of cases with severe malaria complications underscores the need for education and prevention efforts. Pre-travel consultations give health care providers an important opportunity to explain the destination-specific malaria risk, counsel on mosquito avoidance techniques, prescribe and encourage compliance with chemoprophylaxis, and educate on malaria and its warning signs. Pre-travel consultations are recommended by the CDC[20] for international travelers for its effectiveness in reducing the risk of insect bites, malaria acquisition[21], and delayed presentation to medical attention when symptoms occur. However, few prospective travelers visit health care providers for pre-travel health consultations due to barriers such as cost[22-24] and other factors, despite studies showing that pre-travel consultation with adherence to chemoprophylaxis results in net savings for both the traveler and the payer, especially as travel duration and malaria risk increases[25].

Improvements in disseminating targeted messages to prospective travelers, especially during peak travel seasons, are needed to increase the use of malaria prevention measures and decrease the economic burden. Several populations known to be at particularly high risk include prospective travelers with travel destinations in Sub-Saharan Africa and parts of the Caribbean, where the relatively more virulent malaria infecting species, *P. falciparum*, is endemic and where the majority of the global malaria burden occurrs[1,3,26]. Among imported cases in the US, *P. falciparum* is similarly the predominant infecting species, as this study showed that *P. falciparum* disproportionately accounted for over three quarters of all hospital days, charges, and costs among malaria-related hospitalizations with known species information.

Those who return to their countries of origin to visit friends and relatives (VFR)[20,27], and Blacks are two, possibly partially overlapping populations at high risk of contracting malaria. VFR travelers to malaria-endemic countries tend to have increased exposure to malaria vectors and lower malaria risk perception (e.g. belief in immunity)[20]. In this study, Blacks were by far the largest race group among malaria-related hospitalizations accounting for about half of all hospital days, charges, and costs, and were associated with having a shorter LOS compared to Whites, which is consistent with patterns of immigration, and travel for VFR in malaria-endemic countries. Some VFR travelers may also have protective factors of malaria and severe malaria, such as malaria protective genetic variations (e.g. sickle cell trait)[28] and acquired partial immunity[29], which may partially explain the association between Black race and shorter LOS in this study. This advantage of acquired immunity to malaria, however, wanes without sustained exposure[29], and all prospective travelers who are VFR should be encouraged to take full preventive precautions, including vector avoidance and chemoprophylaxis, similarly to malaria-naive patients. Another possible explanation for the observed association between shorter LOS and Blacks compared to Whites may be institutionalized racism[30].

Those who are immunocompromised (e.g. older age, HIV[31-32], type II diabetes[33], pregnant[34], taking immunosuppressant medication[20]) may be more susceptible to malaria and severe manifestations. This study supports that older age, comorbid HIV infection, and type II diabetes are associated with increased hospital charges and costs among malaria patients. However, in this study we did not observe pregnancy to be associated with increased direct or indirect costs. It is possible that pregnant women are more cautious and more likely to present to medical attention earlier during the course of disease, and thus have less severe disease. It is important that health care providers have a high index of suspicion for malaria in patients presenting with unexplained febrile illness and elicit appropriate travel history[35] to enable prompt appropriate diagnosis[36] and treatment[37].

In addition to host and environmental factors, we also found associations between institutional factors and direct and indirect costs for malaria-related hospitalizations, which were largely consistent with the overall patterns observed for all discharges in the NIS[38]. Confounding of the association between payer and LOS is also possible, in which patients with private insurance or no insurance may have been wealthier or had better baseline health before malaria, and thus were able to recover from malaria faster and with fewer complications. Malaria patients hospitalized in the western region had much higher charges and costs compared to all other regions, consistent with the higher charges and costs for all discharges in the NIS in the western region. LOS and hospital charges for patients hospitalized in rural locations were lower, which may be because more complicated, resource demanding cases are referred to hospitals in more urban locations, which tend to offer higher level services. The higher hospital charges and lower hospital costs for patients hospitalized at private, investor-owned hospitals compared to public, government, nonfederal hospitals, may be due to differences in the business missions and in the number of patients served that require financial assistance and cost-shifting. The higher hospital costs for malaria patients hospitalized in hospitals with small bed size compared to large bed size is not consistent with that of overall discharges in the NIS, and may possibly be related to the relatively smaller bargaining power for acquiring malaria-related supplies compared to larger hospitals.

The NIS provides valuable information on direct and indirect costs, but some limitations should be considered. The economic burden of malaria cannot be fully captured by malaria-related hospitalizations alone. The number of days spent in the hospital has implications for, but does not quantify the costs of foregone income, opportunity costs of lost productivity in wage and household work, or the overall duration of impaired quality of life, which all extend to further costs during time spent as an outpatient in recovery[25]. Although hospital charges overestimate the direct costs of malaria-related hospitalizations since a markup is included, it does not account for professional fees, certain serology diagnostics, certain procedures used for diagnosis and treatment, the costs of treatment or management before and after hospitalization, the costs of outpatient services, and the cost of some emergency department services. The direct and indirect costs for fatal cases are also not included. Furthermore, the public expenditures on prevention, surveillance, and treatment (e.g. vector control, health facilities, education, research), and the cost of transportation to medical facilities and necessary support[39] are not accounted for in the total charges or costs, and the true total direct costs are likely to be more than what we report from this study. Error in the identification of the malaria-related hospitalizations, and its corresponding direct and indirect costs, is possible due to misdiagnoses, since malaria is a relatively rare disease with some non-specific clinical manifestations that can be difficult to diagnose[36]. The random and intentional (state-level suppression) missing values, especially for race, result in underestimation of the total and subgroup estimates since cases with missing values are excluded from the calculations of mean and sums. The final hospital bill for patients and other payers, and the accuracy of the patient discharge records cannot be verified by follow-up since identifying information have been stripped to preserve confidentiality. Other potential factors of interest, including wealth, baseline health, laboratory results, pre-travel consultation, travel history, destination and purpose of travel, immigration and immunity status, and vector avoidance and chemoprophylaxis use were not available in NIS data to determine their distribution and association with direct and indirect costs of malaria.

Conclusion

This study demonstrates the magnitude of the economic impact of malaria in the US, which remains substantial despite its elimination in the early 1950s. Primary and secondary prevention measures should be emphasized in high-risk groups to reduce the economic burden. Health care providers and prospective travelers are encouraged to be familiar with malaria risk and prevention recommendations by country[20], which is publicly available from the CDC.

References

1. World Malaria Report 2015. World Health Organization. Geneva, Switzerland: World Health Organization; 2016. http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf

2. Centers for Disease Control. Malaria [Accessed 15 Apr 2015]. Available at: http://www.cdc.gov/malaria/

3. Cullen KA, Mace KE, Arguin PM. Malaria surveillance--United States, 2013. MMWR Surveill Summ. 2016 Mar 4; 65(2):1-22.

4. International Trade Administration. National Travel and Tourism Office. US Department of Commerce. US Travel and Tourism Statistics (Inbound). Region of origin profiles: Africa. Page 6. [Accessed 28 Jun 2016]. Available at: http://tinet.ita.doc.gov/outreachpages/download_data_table/2012_Africa_Market_Profile.pdf

5. International Trade Administration. National Travel and Tourism Office. US Department of Commerce. US Travel and Tourism Statistics (US Resident Outbound). US to overseas for leisure/visit friends & relatives (VFR). Page 7. [Accessed 28 Jun 2016]. Available at: http://tinet.ita.doc.gov/outreachpages/download_data_table/2012-US-Leisure-VFR.pdf

6. Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, Sotir MJ. Surveillance for travel-related disease—GeoSentinel surveillance system, United States, 1997–2011. MMWR Surveill Summ. 2013;62(3): 1-23.

7. Odolini S, Parola P, Gkrania-Klotsas E, Caumes E, Schlagenhauf P, López-Vélez, et al. Travel-related imported infections in Europe, EuroTravNet 2009. Clin Microbiol Infect 2012;18:468-74.

8. Jensenius M, Han PV, Schlagenhauf P, Schwartz E, Parola P, Castelli F, von Sonnenburg F, Loutan L, Leder K, Freedman DO; GeoSentinel Surveillance Network. Acute and potentially life-threatening tropical diseases in western travelers--a GeoSentinel multicenter study, 1996-2011. Am J Trop Med Hyg. 2013 Feb;88(2):397-404. doi: 10.4269/ajtmh.12-0551.

9. Centers for Disease Control and Prevention. The History of Malaria, an Ancient Disease [Accessed 26 Mar 2016]. Available at: http://www.cdc.gov/malaria/about/history/index.html

10. Hickey PW, Cape KE, Masuoka P, Campos JM, Pastor W, Wong EC, Singh N. A local, regional, and national assessment of pediatric malaria in the United States. Journal of travel medicine. 2011;18(3): 153-160.

11. Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among US travelers, 1963–2001. Annals of internal medicine. 2004;141(7): 547-555.

12. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2011. Agency for Healthcare Research and Quality, Rockville, MD. June 2013. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2011.jsp

13. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2012. Agency for Healthcare Research and Quality, Rockville, MD. June 2014. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2012.jsp

14. Centers for Disease Control and Prevention. Classification of Diseases, Functioning, and Disability. Conversion table. [Accessed 12 Sep 2014]. Available at: http://www.cdc.gov/nchs/icd/icd9cm.htm

15. Healthcare Cost and Utilization Project (HCUP). Clinical Classifications Software (CCS) for ICD-9-CM and Chronic Condition Indicator. HCUP Tools & Software. Agency for Healthcare Research and Quality, Rockville, MD. 2015. [Accessed 26 Jun 2016]. Available at https://www.hcup-us.ahrq.gov/tools_software.jsp

16. Healthcare Cost and Utilization Project (HCUP). Cost-to-Charge Ratio Files. HCUP Tools & Software. Agency for Healthcare Research and Quality, Rockville, MD. 2015. [Accessed 26 Jun 2016]. Available at https://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp

17. US Department of Labor, Bureau of Labor Statistics. Consumer price index. [Accessed 26 Mar 2016]. Available at: http://www.bls.gov/cpi/

18. Hernán MA, Robins JM. Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming; 2016.

19. Rothman KJ, Last TL, Greenland S. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer Health, 2012.

20. Centers for Disease Control and Prevention. Malaria. Yellow Book 2015. [Accessed 15 Apr 2016]. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria

21. Schlagenhauf P, Weld L, Goorhuis A, Gautret P, Weber R, von Sonnenburg F, Lopez-Vélez R, Jensenius M, Cramer JP, Field VK, Odolini S. Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance

data, and evaluation of the effect of the pre-travel consultation. The Lancet Infectious Diseases. 2015 Jan 31;15(1):55-64. doi:10.1016/S1473-3099(14)71000-X

22. Heywood AE, Watkins RE, Iamsirithaworn S, Nilvarangkul K, MacIntyre CR. A cross-sectional study of pre-travel health-seeking practices among travelers departing Sydney and Bangkok airports. BMC public health . 2012;12(1): 321.

23. Hamer DH, Connor BA. Travel health knowledge, attitudes and practices among United States travelers. Journal of travel medicine. 2004;11(1): 23-26.

24. LaRocque RC, Rao SR, Tsibris A, Lawton T, Barry MA, Marano N, Brunette G, Yanni E, Ryan ET. Pre-travel health advice-seeking behavior among US international travelers departing from Boston Logan International Airport. Journal of travel medicine. 2010;17(6): 387-391.

25. Adachi K, Coleman MS, Khan N, Jentes ES, Arguin P, Rao SR, LaRocque RC, et al. Economics of Malaria Prevention in US Travelers to West Africa. Clinical infectious diseases. 2013; 58(1):11-21. doi: 10.1093/cid/cit570

26. Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, Whitty CJM. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. Bmj. 2012;344.

27. Hagmann SHF, Van PV, Stauffer WM, Miller AO, Connor BA, Hale DC, Coyle CM, et al. Travel-associated disease among US residents visiting US GeoSentinel clinics after return from international travel. Family Practice, 2014, Vol. 31, No. 6, 678–687 doi:10.1093/fampra/cmu063

28. Taylor SM, Cerami C, Fairhurst RM. Hemoglobinopathies: Slicing the Gordian Knot of Plasmodium falciparum Malaria Pathogenesis. PLoS. 2013. Pathog 9(5): e1003327. doi:10.1371/journal.ppat.1003327.

29. Crompton PD, Moebius J, Portugal S, Waisberg M, Hart G, Garver LS, Miller LH, Barillas C, Pierce SK. Malaria Immunity in Man and Mosquito: Insights into Unsolved Mysteries of a Deadly Infectious Disease. Annual review of immunology. 2014;32: 157-187.

30. Jha AK, Fisher ES, Li Z, Orav EJ, Epstein AM. Racial trends in the use of major procedures among the elderly. New England Journal of Medicine. 2005 Aug 18;353(7):683-91.

31. Chalwe V, Jean-Pierre Van geertruyden, Mukwamataba D, et al. Increased Risk for Severe Malaria in HIV-1–infected Adults, Zambia. Emerging Infectious Diseases. 2009;15(5):749-755. doi:10.3201/eid1505.081009.

32. Cohen C, Karstaedt A, Frean J, Thomas J, Govender N, Prentice E, Dini L, Galpin J, Crewe-Brown H. Increased prevalence of severe malaria in HIV-infected adults in South Africa. Clin Infect Dis. 2005 Dec 1;41(11):1631-7. Epub 2005 Oct 26.

33. Danquah I, Bedu-Addo G, Mockenhaupt FP. Type 2 diabetes mellitus and increased risk for malaria infection. Emerg Infect Dis. 2010 Oct;16(10):1601-4. doi:10.3201/eid1610.100399.

34. Schantz-Dunn J, Nour NM. Malaria and Pregnancy: A Global Health Perspective. Rev Obstet Gynecol. 2009 Summer; 2(3): 186–192. PMCID: PMC2760896

35. Vicas AE, Albrecht H, Lennox JL, del Rio C. Imported malaria at an inner-city hospital in the United States. Am J Med Sci. 2005 Jan;329(1):6-12.

36. Ash LR, Orihel TC. Atlas of Human Parasitology 5th ed. Chicago: ASCP Press; 2007.

37. Centers for Disease Control and Prevention. Treatment of Malaria. 2013. [Accessed 26 Apr 2016]. Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf

38. Healthcare Cost and Utilization Project (HCUP). HCUPnet. Agency for Healthcare Research and Quality, Rockville, MD. 2016. [Accessed 26 Jun 2016]. Available at http://hcupnet.ahrq.gov/HCUPnet.jsp

39. World Health Organization. WHO Guide to identifying the economic consequences of disease and injury. Geneva, Switzerland: WHO Press; 2009. [Accessed 26 Mar 2015]. Available at: http://www.who.int/choice/publications/d_economic_impact_guide.pdf

Table 1. Economic burden of malaria compared to other travel-associated diseases in the US, NIS 2000-2012

Disease	**Discharges** Total (95% CI)	**Hospital days** Total (95% CI)	**Charges** Total (95% CI)	**Costs** Total (95% CI)
Malaria	19,189 (18,213 - 21,165)	84,213 (77,146 - 91,281)	470,102,584 (437,342,864 - 502,862,303)	151,825,389 (140,471,910 - 163,178,869)
Filariasis	4,018 (3,154 - 4,882)	28,994 (21,652 - 36,336)	175,955,414 (142,329,400 - 209,581,428)	50,985,532 (42,604,329 - 59,366,735)
Dengue	2,978 (2,650 - 3,305)	13,263 (11,932 - 14,593)	96,471,677 (80,586,765 - 112,356,588)	27,213,099 (23,050,696 - 31,375,502)
Schistosomiasis	2,271 (1,973 - 2,570)	17,497 (14,961 - 20,033)	120,871,302 (99,904,331 - 141,838,274)	38,295,037 (31,587,143 - 45,002,931)
Trypanosomiasis	1,994 (1,594 - 2,394)	15,421 (11,868 - 18,975)	131,498,304 (102,041,929 - 160,954,678)	39,852,177 (31,157,556 - 48,546,798)
Leishmaniasis	1,264 (1,061 - 1,468)	10,084 (8,354 - 11,814)	64,408,278 (50,281,308 - 78,535,248)	19,836,231 (15,596,123 - 24,076,340)
Typhoid fever	5,553 (5,163 – 5,943)	32,342 (29,884 - 34,799)	159,887,764 (146,101,316 – 173,674,212)	51,376,236 (45,954,328 – 56,798,145)

Note: All numbers are national estimates based on weighted frequencies.
All charges and costs adjusted for inflation to 2015 US dollars. Costs for 2001-2012 only.

Table 2. Hospital days for malaria in the US, by characteristic, NIS 2000-2012

Characteristics	Total discharges N	(%)	Mean length of stay Mean	(95% CI)	Total hospital days Total	(95% CI)	Percent
Sex							
Male	11,569	(60.3)	4.14	(3.95 - 4.33)	47,922	(44,798 - 51,047)	56.9%
Female	7,524	(39.2)	4.78	(4.51 - 5.06)	35,993	(33,103 - 38,884)	42.7%
Pregnant	1,015	(5.3)	4.12	(3.64 - 4.60)	4,182	(3,407 - 4,957)	5.0%
Race							
White	3,883	(20.2)	4.88	(4.53 - 5.23)	18,950	(17,122 - 20,777)	22.5%
Black	8,125	(42.3)	4.32	(4.07 - 4.58)	35,136	(31,900 - 38,371)	41.7%
Hispanic	1,099	(5.7)	4.76	(3.77 - 5.75)	5,227	(3,982 - 6,472)	6.2%
Asian/Pacific Islander	943	(4.9)	4.67	(3.99 - 5.35)	4,408	(3,555 - 5,262)	5.2%
Native American	164	(0.9)	5.37	(2.48 - 8.25)	881	(343 - 1,420)	1.0%
Other	1,703	(8.9)	3.87	(3.55 - 4.19)	6,592	(5,743 - 7,441)	7.8%
Age (years)							
Under 5	763	(4.0)	3.88	(3.43 - 4.33)	3,113	(2,482 - 3,744)	3.6%
5-14	1,485	(7.7)	3.63	(3.32 - 3.93)	5,387	(4,503 - 6,271)	6.4%
15-24	3,160	(16.5)	3.88	(3.46 - 4.30)	12,258	(10,665 - 13,850)	14.6%
25-44	7,148	(37.3)	3.78	(3.59 - 3.98)	27,030	(24,958 - 29,102)	32.1%
45-64	5,009	(26.1)	5.05	(4.67 - 5.44)	25,304	(22,790 - 27,817)	30.0%
65-84	1,448	(7.5)	6.75	(6.08 - 7.41)	9,772	(8,379 - 11,165)	11.6%
Over 85	136	(0.7)	9.89	(7.48 - 12.31)	1,349	(817 - 1,882)	1.6%
Malaria diagnosis							
Primary	16,127	(84.0)	3.88	(3.75 - 4.02)	62,650	(58,989 - 66,311)	74.4%
Secondary	3,062	(16.0)	7.04	(6.38 - 7.70)	21,563	(19,000 - 24,126)	25.6%
Infecting Species							
Falciparum	7,200	(37.5)	4.68	(4.41 - 4.94)	33,666	(30,967 - 36,365)	40.0%
Vivax	2,387	(12.4)	3.50	(3.27 - 3.73)	8,349	(7,465 - 9,233)	9.9%
Ovale	333	(1.7)	3.91	(3.43 - 4.40)	1,198	(902 - 1,494)	1.4%
Malariae	306	(1.6)	3.41	(2.98 - 3.84)	1,136	(872 - 1,400)	1.3%
Clinical classification							
Uncomplicated malaria	15,302	(79.7)	3.43	(3.33 - 3.53)	52,493	(49,689 - 55,297)	62.3%
Severe malaria	3,888	(20.3)	8.16	(7.52 - 8.80)	31,721	(28,535 - 34,906)	37.7%
Cerebral malaria	726	(3.8)	10.27	(8.38 - 12.15)	7,455	(5,763 - 9,146)	8.9%
Severe anemia	1,346	(7.0)	8.31	(7.22 - 9.40)	11,182	(9,291 - 13,073)	13.3%
Renal failure	1,573	(8.2)	8.63	(7.68 - 9.58)	13,576	(11,579 - 15,572)	16.1%
ARDS	775	(4.0)	16.31	(14.14 - 18.48)	12,642	(10,296 - 14,989)	15.0%

Jaundice	598	(3.1)	4.64	(3.93 - 5.34)	2,770	(2,169 - 3,371)	3.3%
Pre-existing conditions							
HIV infection	274	(1.4)	6.72	(4.75 - 8.68)	1,839	(1,180 - 2,497)	2.2%
Diabetes mellitus (type II)	1,394	(7.3)	5.53	(4.89 - 6.17)	7,713	(6,488 - 8,938)	9.2%
Essential hypertension	2,659	(13.9)	5.13	(4.73 - 5.54)	13,649	(12,100 - 15,198)	16.2%
Procedures performed							
0	12,931	(67.5)	3.11	(3.03 - 3.18)	40,159	(38,128 - 42,189)	47.7%
1	3,309	(17.2)	4.35	(4.16 - 4.55)	14,404	(13,143 - 15,665)	17.1%
2 or more	2,948	(15.3)	10.06	(9.15 - 10.96)	29,651	(26,277 - 33,025)	35.2%
Admission Source*							
Emergency department	9,036	(50.8)	4.38	(4.14 - 4.62)	39,539	(36,277 - 42,801)	47.0%
Another hospital	512	(2.9)	6.12	(5.19 - 7.04)	3,134	(2,424 - 3,843)	3.7%
Another facility	97	(0.5)	7.35	(4.68 - 10.02)	715	(346 - 1,084)	0.8%
Routine/birth/other	3,304	(18.8)	4.29	(3.86 - 4.71)	14,163	(12,272 - 16,055)	16.8%
In-hospital death							
Did not die	19,028	(99.2)	4.32	(4.17 - 4.47)	82,178	(77,680 - 86,675)	97.6%
Died	147	(0.7)	12.86	(8.33 - 17.40)	1,893	(1,015 - 2,771)	2.2%
Median income for zip code							
High	10,588	(55.4)	4.18	(3.97 - 4.38)	29,501	(27,291 - 31,711)	53.0%
Low	7,589	(39.4)	4.53	(4.25 - 4.81)	29,038	(26,328 - 31,748)	41.3%
Primary payer							
Medicare	1,301	(6.8)	7.81	(6.92 - 8.69)	10,155	(8,534 - 11,775)	12.1%
Medicaid	3,575	(18.3)	4.87	(4.34 - 5.40)	17,409	(15,025 - 19,793)	20.7%
Private insurance	8,686	(45.5)	4.02	(3.82 - 4.22)	34,926	(32,441 - 37,412)	41.5%
Self-pay	4,237	(22.1)	3.65	(3.47 - 3.83)	15,455	(13,986 - 16,925)	18.4%
No charge	406	(2.1)	4.48	(3.68 - 5.28)	1,817	(1,274 - 2,360)	2.2%
Other	928	(4.8)	4.43	(3.92 - 4.94)	4,110	(3,390 - 4,831)	4.9%
Hospital Region							
Northeast	6,488	(33.8)	4.34	(4.06 - 4.62)	28,180	(25,475 - 30,885)	33.5%
Midwest	2,771	(14.4)	3.94	(3.60 - 4.29)	10,926	(9,502 - 12,349)	13.0%
South	7,089	(36.9)	4.66	(4.39 - 4.93)	33,006	(29,751 - 36,261)	39.2%
West	2,841	(14.8)	4.26	(3.87 - 4.65)	12,102	(10,707 - 13,497)	14.4%
Hospital Location							
Rural	761	(3.9)	3.23	(2.91 - 3.55)	2,455	(2,029 - 2,882)	2.9%
Urban	18,390	(95.9)	4.44	(4.27 - 4.60)	81,621	(76,962 - 86,280)	96.9%
Hospital Ownership*							
Gov., nonfederal, public	1,477	(19.1)	4.43	(3.78 - 5.07)	6,540	(4,716 - 8,364)	19.6%
Private, non-profit, voluntary	5,520	(72.5)	4.28	(4.04 - 4.53)	23,643	(21,345 - 25,940)	70.8%

Private, investor owned	613	(7.9)	5.22	(4.41 - 6.03)	3,195	(2,454 - 3,937)	9.6%
Hospital bed size							
Small	1,911	(10.5)	4.18	(3.80 - 4.57)	7,997	(6,871 - 9,123)	9.5%
Medium	5,353	(27.7)	4.50	(4.14 - 4.85)	24,077	(21,262 - 26,892)	28.6%
Large	11,887	(61.6)	4.37	(4.19 - 4.56)	52,002	(48,439 - 55,565)	61.8%
Total	19,189	(100.0)	4.39	(4.23 - 4.55)	84,213	(79,536 - 88,891)	100.0%

Note: All numbers are national estimates based on weighted frequencies and nonmissing data.

Numbers and proportions may not sum to total or 100% due to missing values.

Length of stay in days.

*Admission source for 2000-2011. Hospital ownership for 2008-2012.

Table 3. Hospital charges for malaria-related hospitalizations in the US, by characteristic, NIS 2000-2012

Characteristics	Total discharges N	(%)	Mean charges Mean	95% CI	Total Charges Total	95% CI	Percent
Sex							
Male	11,569	(60.3)	23,711	(21,917 - 25,505)	268,150,669	(244,610,795 - 291,690,543)	57.0%
Female	7,524	(39.2)	27,315	(24,983 - 29,647)	200,372,829	(180,027,218 - 220,718,439)	42.6%
Pregnant	1,015	(5.3)	19,071	(15,673 - 22,469)	18,638,054	(14,607,071 - 22,669,038)	4.0%
Race							
White	3,883	(20.2)	29,800	(26,316 - 33,284)	113,195,314	(98,142,428 - 128,248,199)	24.1%
Black	8,125	(42.3)	24,349	(22,047 - 26,650)	193,621,606	(171,172,565 - 216,070,647)	41.2%
Hispanic	1,099	(5.7)	23,931	(19,095 - 28,767)	25,393,644	(19,575,841 - 31,211,447)	5.4%
Asian/Pacific Islander	943	(4.9)	35,571	(27,722 - 43,420)	30,952,988	(23,088,088 - 38,817,888)	6.6%
Native American	164	(0.9)	27,326	(14,843 - 39,808)	4,486,362	(2,058,654 - 6,914,069)	1.0%
Other	1,703	(8.9)	21,440	(18,831 - 24,048)	35,199,817	(29,701,966 - 40,697,668)	7.5%
Age (years)							
Under 5	763	(4.0)	19,733	(16,041 - 23,426)	15,659,308	(11,756,788 - 19,561,829)	3.2%
5-14	1,485	(7.7)	20,168	(15,369 - 24,967)	29,163,425	(20,045,649 - 38,281,201)	6.2%
15-24	3,160	(16.5)	19,876	(16,904 - 22,848)	61,338,575	(51,255,569 - 71,421,580)	13.0%
25-44	7,148	(37.3)	20,750	(18,909 - 22,590)	144,342,878	(129,513,244 - 159,172,512)	30.7%
45-64	5,009	(26.1)	31,111	(27,714 - 34,507)	151,757,775	(132,880,961 - 170,634,589)	32.3%
65-84	1,448	(7.5)	42,450	(36,918 - 47,982)	60,513,575	(50,376,368 - 70,650,782)	12.9%
Over 85	136	(0.7)	55,607	(39,053 - 72,160)	7,327,048	(4,169,625 - 10,484,471)	1.6%
Malaria diagnosis							
Primary	16,127	(84.0)	21,822	(20,455 - 23,189)	343,445,573	(316,656,293 - 370,234,853)	73.1%
Secondary	3,062	(16.0)	42,519	(37,424 - 47,614)	126,657,011	(109,455,047 - 143,858,974)	26.9%
Infecting Species							
Falciparum	7,200	(37.5)	27,997	(25,204 - 30,790)	197,432,091	(175,121,245 - 219,742,937)	42.0%
Vivax	2,387	(12.4)	17,438	(15,546 - 19,331)	39,660,088	(34,272,951 - 45,047,225)	8.4%
Ovale	333	(1.7)	21,572	(14,841 - 28,303)	6,236,290	(3,842,607 - 8,629,972)	1.3%
Malariae	306	(1.6)	18,276	(12,322 - 24,229)	5,897,425	(3,666,069 - 8,128,782)	1.3%
Clinical classification							
Uncomplicated malaria	15,302	(79.7)	16,026	(15,319 - 16,733)	239,088,209	(224,407,987 - 253,768,431)	50.9%
Severe malaria	3,888	(20.3)	60,816	(54,790 - 66,843)	231,014,375	(204,207,048 - 257,821,701)	49.1%
Cerebral malaria	726	(3.8)	78,640	(64,139 - 93,141)	56,081,123	(43,157,257 - 69,004,990)	11.9%
Severe anemia	1,346	(7.0)	58,362	(50,053 - 66,672)	75,439,017	(62,056,463 - 88,821,571)	16.0%
Renal failure	1,573	(8.2)	69,540	(59,476 - 79,605)	108,166,783	(89,391,349 - 126,942,217)	23.0%
ARDS	775	(4.0)	159,498	(135,642 - 183,353)	122,384,394	(98,312,853 - 146,455,936)	26.0%

Jaundice	598	(3.1)	30,363	(23,272 - 37,454)	17,821,196	(12,879,374 - 22,763,018)	3.8%
Pre-existing conditions							
HIV infection	274	(1.4)	50,363	(29,925 - 70,801)	13,558,324	(7,436,678 - 19,679,969)	2.9%
Diabetes mellitus (type II)	1,394	(7.3)	38,090	(31,132 - 45,049)	51,697,259	(40,754,406 - 62,640,113)	11.0%
Essential hypertension	2,659	(13.9)	31,424	(27,306 - 35,543)	81,145,760	(68,207,081 - 94,084,439)	17.3%
Procedures performed							
0	12,931	(67.5)	14,101	(13,559 - 14,642)	178,472,726	(168,151,053 - 188,794,399)	38.0%
1	3,309	(17.2)	23,286	(21,821 - 24,750)	74,058,443	(67,168,553 - 80,948,333)	15.8%
2 or more	2,948	(15.3)	75,550	(67,218 - 83,882)	217,571,415	(190,212,569 - 244,930,261)	46.3%
Admission Source*							
Emergency department	9,036	(50.8)	24,167	(22,096 - 26,239)	210,415,486	(188,252,853 - 232,578,119)	44.8%
Another hospital	512	(2.9)	37,291	(22,569 - 52,012)	18,744,077	(10,749,269 - 26,738,884)	4.0%
Another facility	97	(0.5)	23,565	(14,388 - 32,743)	2,291,932	(1,060,463 - 3,523,401)	0.5%
Routine/birth/other	3,304	(18.8)	19,260	(15,653 - 22,867)	61,265,553	(48,981,736 - 73,549,370)	13.0%
In-hospital death							
Did not die	19,028	(99.2)	24,332	(22,957 - 25,707)	451,635,717	(420,599,745 - 482,671,689)	96.1%
Died	147	(0.7)	123,868	(88,190 - 159,546)	17,616,115	(10,238,149 - 24,994,080)	3.7%
Length of stay (days)							
0-1	2,870	(14.9)	6,291	(5,919 - 6,663)	17,527,961	(15,767,147 - 19,288,774)	3.7%
2-3	8,125	(42.3)	11,967	(11,486 - 12,449)	94,277,201	(88,124,754 - 100,429,649)	20.1%
4-6	5,619	(29.3)	24,019	(23,008 - 25,031)	132,801,420	(123,709,297 - 141,893,543)	28.2%
7+	2,575	(13.5)	89,327	(80,828 - 97,826)	225,496,002	(197,981,108 - 253,010,897)	48.0%
Median income for zip code							
High	10,588	(55.4)	27,499	(25,046 - 29,953)	187,843,331	(168,586,530 - 207,100,133)	52.8%
Low	7,589	(39.4)	27,062	(24,609 - 29,514)	171,762,630	(152,306,752 - 191,218,507)	41.8%
Primary payer							
Medicare	1,301	(6.8)	47,338	(39,531 - 55,145)	60,059,142	(47,959,685 - 72,158,599)	12.8%
Medicaid	3,575	(18.3)	25,534	(22,479 - 28,589)	90,793,234	(78,013,673 - 103,572,795)	19.3%
Private insurance	8,686	(45.5)	23,836	(21,587 - 26,086)	198,918,428	(177,721,139 - 220,115,717)	42.3%
Self-pay	4,237	(22.1)	21,067	(18,904 - 23,230)	87,871,806	(77,164,901 - 98,578,712)	18.7%
No charge	406	(2.1)	20,402	(15,762 - 25,042)	8,179,382	(5,370,380 - 10,988,383)	1.7%
Other	928	(4.8)	24,707	(20,622 - 28,792)	22,707,508	(17,984,136 - 27,430,880)	4.8%
Hospital Region							
Northeast	6,488	(33.8)	24,270	(22,288 - 26,253)	157,472,245	(141,510,669 - 173,433,820)	33.5%
Midwest	2,771	(14.4)	20,400	(17,136 - 23,663)	56,319,625	(45,861,893 - 66,777,356)	12.0%
South	7,089	(36.9)	23,459	(21,124 - 25,794)	163,797,262	(142,331,012 - 185,263,511)	34.8%
West	2,841	(14.8)	37,215	(31,505 - 42,925)	92,513,453	(76,757,079 - 108,269,826)	19.7%
Hospital Location							

Rural	761	(3.9)	11,114	(9,655 - 12,573)	8,407,121	(6,787,432 - 10,026,810)	1.8%
Urban	18,390	(95.9)	25,716	(24,221 - 27,210)	460,907,749	(428,185,320 - 493,630,178)	98.0%
Hospital Ownership*							
Gov., nonfederal, public	1,477	(19.1)	27,655	(21,013 - 34,297)	40,847,510	(27,268,377 - 54,426,642)	18.7%
Private, non-profit, voluntary	5,520	(72.5)	27,273	(25,097 - 29,448)	147,457,787	(132,308,318 - 162,607,256)	67.7%
Private, investor owned	613	(7.9)	48,253	(39,450 - 57,056)	29,555,906	(21,989,436 - 37,122,376)	13.6%
Hospital bed size							
Small	1,911	(10.5)	22,943	(19,958 - 25,927)	41,916,608	(34,927,454 - 48,905,761)	8.9%
Medium	5,353	(27.7)	25,097	(22,143 - 28,051)	130,945,330	(111,687,804 - 150,202,856)	27.9%
Large	11,887	(61.6)	25,480	(23,650 - 27,309)	296,452,933	(270,885,763 - 322,020,103)	63.1%
Total	19,189	(100.0)	25,116	(23,683 - 26,549)	470,102,584	(437,342,864 - 502,862,303)	100.0%

Note: All numbers are national estimates based on weighted frequencies and nonmissing data.

Numbers and proportions may not sum to total or 100% due to missing values.

Charges adjusted for inflation to 2015 US dollars.

* Admission source data for 2000-2011. Hospital ownership data for 2008-2012.

Table 4. Hospital costs for malaria-related hospitalizations in the US, by characteristic, NIS 2001-2012

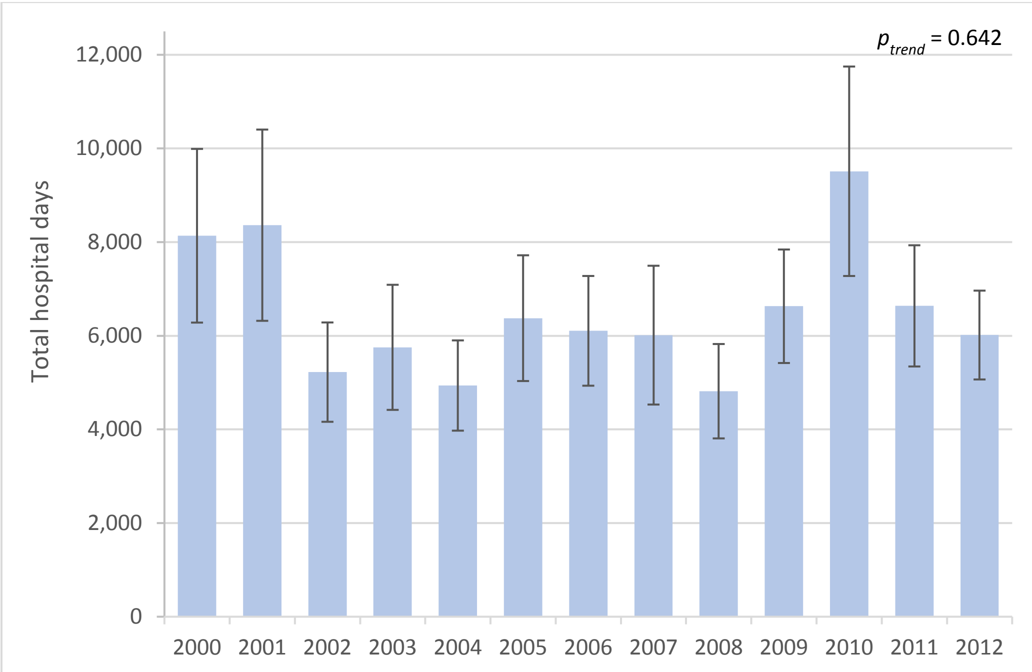
Characteristics	Total discharges N	(%)	Mean	Mean 95% CI	Costs Total	Costs 95% CI	Percent
Sex							
Male	10,494	(60.2)	8,546	(7,864 - 9,228)	86,912,010	(78,432,437 - 95,391,583)	57.2%
Female	6,842	(39.3)	9,581	(8,817 - 10,345)	64,472,843	(58,168,547 - 70,777,140)	42.5%
Pregnant	882	(5.1)	8,007	(6,097 - 9,916)	6,887,150	(4,993,014 - 8,781,286)	4.5%
Race							
White	3,453	(19.8)	10,127	(8,975 - 11,280)	34,061,811	(29,520,668 - 38,602,954)	22.4%
Black	7,542	(43.3)	8,764	(8,021 - 9,508)	63,686,381	(56,321,077 - 71,051,686)	41.9%
Hispanic	915	(5.3)	9,972	(6,450 - 13,493)	8,458,904	(5,271,953 - 11,645,854)	5.6%
Asian/Pacific Islander	878	(5.0)	10,703	(8,360 - 13,046)	8,640,446	(6,416,235 - 10,864,658)	5.7%
Native American	159	(0.9)	10,521	(2,309 - 18,734)	1,618,924	(252,088 - 2,985,761)	1.1%
Other	1,568	(9.0)	7,560	(6,592 - 8,528)	10,987,297	(9,162,915 - 12,811,680)	7.2%
Age (years)							
Under 5	724	(4.2)	7,416	(6,030 - 8,802)	5,165,645	(3,874,897 - 6,456,393)	3.3%
5-14	1,376	(7.9)	7,017	(6,058 - 7,976)	8,920,148	(7,183,395 - 10,656,901)	5.9%
15-24	2,831	(16.3)	7,411	(6,360 - 8,463)	20,249,387	(16,929,788 - 23,568,987)	13.3%
25-44	6,429	(36.9)	7,420	(6,672 - 8,168)	46,940,253	(41,417,735 - 52,462,771)	30.9%
45-64	4,601	(26.4)	11,243	(10,008 - 12,478)	50,727,406	(44,036,385 - 57,418,427)	33.4%
65-84	1,310	(7.5)	13,593	(11,912 - 15,274)	17,790,206	(14,777,818 - 20,802,594)	11.7%
Over 85	121	(0.7)	16,618	(12,225 - 21,011)	2,032,344	(1,179,265 - 2,885,423)	1.3%
Malaria diagnosis							
Primary	14,635	(84.0)	7,853	(7,347 - 8,358)	111,943,801	(102,527,692 - 121,359,910)	73.7%
Secondary	2,798	(16.1)	14,696	(12,995 - 16,398)	39,881,589	(34,515,652 - 45,247,525)	26.3%
Infecting Species							
Falciparum	6,564	(37.7)	10,031	(9,066 - 10,996)	64,725,182	(57,311,198 - 72,139,166)	42.6%
Vivax	2,124	(12.2)	6,464	(5,740 - 7,188)	13,068,602	(11,176,795 - 14,960,409)	8.6%
Ovale	365	(1.5)	8,967	(5,713 - 12,220)	2,493,587	(1,407,487 - 3,579,687)	1.6%
Malariae	282	(1.6)	6,243	(4,486 - 8,001)	1,572,720	(1,008,113 - 2,137,327)	1.0%
Clinical classification							
Uncomplicated malaria	13,737	(78.8)	5,893	(5,637 - 6,148)	78,854,805	(73,360,054 - 84,349,556)	51.9%
Severe malaria	3,695	(21.2)	20,343	(18,267 - 22,419)	72,970,585	(64,041,943 - 81,899,226)	48.1%
Cerebral malaria	693	(4.0)	26,915	(21,078 - 32,753)	18,830,357	(13,933,518 - 23,727,196)	12.4%
Severe anemia	1,273	(7.3)	21,161	(18,302 - 24,019)	25,321,430	(20,827,385 - 29,815,476)	16.7%
Renal failure	1,535	(8.8)	22,042	(18,549 - 25,535)	32,281,000	(26,135,795 - 38,426,205)	21.3%
ARDS	737	(4.2)	51,083	(43,098 - 59,068)	37,740,961	(29,855,027 - 45,626,895)	24.9%

Jaundice	569	(3.3)	10,681	(8,030 - 13,332)	6,087,948	(4,287,134 - 7,888,761)	4.0%
Pre-existing conditions							
HIV infection	250	(1.4)	16,566	(9,809 - 23,323)	4,082,002	(2,184,179 - 5,979,825)	2.7%
Diabetes mellitus (type II)	1,320	(7.6)	12,206	(10,188 - 14,225)	15,646,479	(12,435,740 - 18,857,217)	10.3%
Essential hypertension	2,481	(14.2)	10,844	(9,470 - 12,217)	25,810,844	(21,624,055 - 29,997,634)	17.0%
Procedures performed							
0	11,620	(66.7)	4,993	(4,826 - 5,159)	56,550,570	(53,098,131 - 60,003,010)	37.2%
1	3,045	(17.5)	8,452	(7,979 - 8,925)	24,870,646	(22,269,376 - 27,471,915)	16.4%
2 or more	2,767	(15.9)	26,074	(23,176 - 28,972)	70,404,173	(61,146,072 - 79,662,275)	46.4%
Admission Source*							
Emergency department	7,848	(45.0)	9,149	(8,382 - 9,917)	69,812,527	(62,066,494 - 77,558,560)	46.0%
Another hospital	458	(2.6)	14,852	(10,161 - 19,542)	6,559,307	(4,120,187 - 8,998,427)	4.3%
Another facility	77	(0.4)	10,943	(6,824 - 15,062)	883,803	(384,219 - 1,383,388)	0.6%
Routine/birth/other	2,853	(16.4)	8,473	(6,760 - 10,186)	22,896,259	(17,728,000 - 28,064,518)	15.1%
In-hospital death							
Did not die	17,282	(99.1)	8,709	(8,217 - 9,201)	146,600,303	(135,786,393 - 157,414,213)	96.6%
Died	137	(0.8)	40,836	(28,824 - 52,848)	5,153,429	(2,835,000 - 7,471,858)	3.4%
Length of stay (days)							
0-1	2,598	(14.9)	2,441	(2,308 - 2,574)	6,135,092	(5,488,800 - 6,781,385)	4.0%
2-3	7,355	(42.2)	4,408	(4,243 - 4,574)	31,329,844	(29,052,202 - 33,607,487)	20.6%
4-6	5,134	(29.5)	8,667	(8,308 - 9,027)	43,879,895	(40,582,192 - 47,177,597)	28.9%
7+	2,345	(13.5)	30,826	(27,852 - 33,800)	70,480,558	(61,311,703 - 79,649,414)	46.4%
Median income for zip code							
High	7,062	(40.5)	8,626	(8,006 - 9,245)	59,011,872	(53,635,386 - 64,388,358)	52.0%
Low	6,415	(36.8)	8,986	(8,238 - 9,735)	55,934,352	(49,448,556 - 62,420,147)	41.6%
Primary payer							
Medicare	1,169	(6.7)	15,506	(12,951 - 18,061)	17,899,881	(14,213,176 - 21,586,586)	11.8%
Medicaid	3,333	(19.1)	9,869	(8,533 - 11,206)	31,707,449	(26,520,233 - 36,894,664)	20.9%
Private insurance	7,842	(45.0)	8,236	(7,435 - 9,037)	61,737,680	(54,885,788 - 68,589,573)	40.7%
Self-pay	3,824	(21.9)	7,767	(7,070 - 8,464)	29,549,492	(25,704,001 - 33,394,983)	19.5%
No charge	392	(2.3)	7,015	(5,659 - 8,371)	2,846,798	(1,871,514 - 3,822,082)	1.9%
Other	822	(4.7)	8,859	(7,354 - 10,364)	7,523,879	(5,864,574 - 9,183,185)	5.0%
Hospital Region							
Northeast	5,990	(34.4)	8,855	(8,146 - 9,565)	52,156,526	(46,109,691 - 58,203,361)	34.4%
Midwest	2,472	(14.2)	8,230	(6,789 - 9,671)	22,069,474	(17,464,036 - 26,674,913)	14.5%
South	6,442	(37.0)	8,333	(7,472 - 9,194)	50,288,847	(43,190,472 - 57,387,222)	33.1%
West	2,529	(14.5)	11,559	(9,878 - 13,239)	27,310,542	(22,756,391 - 31,864,694)	18.0%
Hospital Location							

Rural	659	(3.8)	5,862	(5,054 - 6,670)	3,939,033	(3,122,022 - 4,756,043)	2.6%
Urban	16,736	(96.0)	9,081	(8,550 - 9,612)	147,638,744	(136,314,008 - 158,963,479)	97.2%
Hospital Ownership*							
Gov., nonfederal, public	1,477	(8.5)	9,579	(7,465 - 11,693)	14,700,973	(9,891,455 - 19,510,491)	22.1%
Private, non-profit, voluntary	5,520	(31.7)	8,578	(7,966 - 9,190)	45,921,481	(40,909,677 - 50,933,284)	69.1%
Private, investor owned	613	(3.5)	9,659	(7,633 - 11,684)	5,811,813	(4,222,756 - 7,400,869)	8.7%
Hospital bed size							
Small	1,750	(10.0)	8,228	(7,398 - 9,058)	13,448,298	(11,351,436 - 15,545,160)	8.9%
Medium	4,818	(27.6)	9,368	(8,315 - 10,421)	43,219,543	(36,867,386 - 49,571,700)	28.5%
Large	10,827	(62.1)	8,885	(8,228 - 9,542)	94,909,935	(85,735,492 - 104,084,378)	62.5%
Total	17,433	(100.0)	8,947	(8,437 - 9,457)	151,825,389	(140,471,910 - 163,178,869)	100%

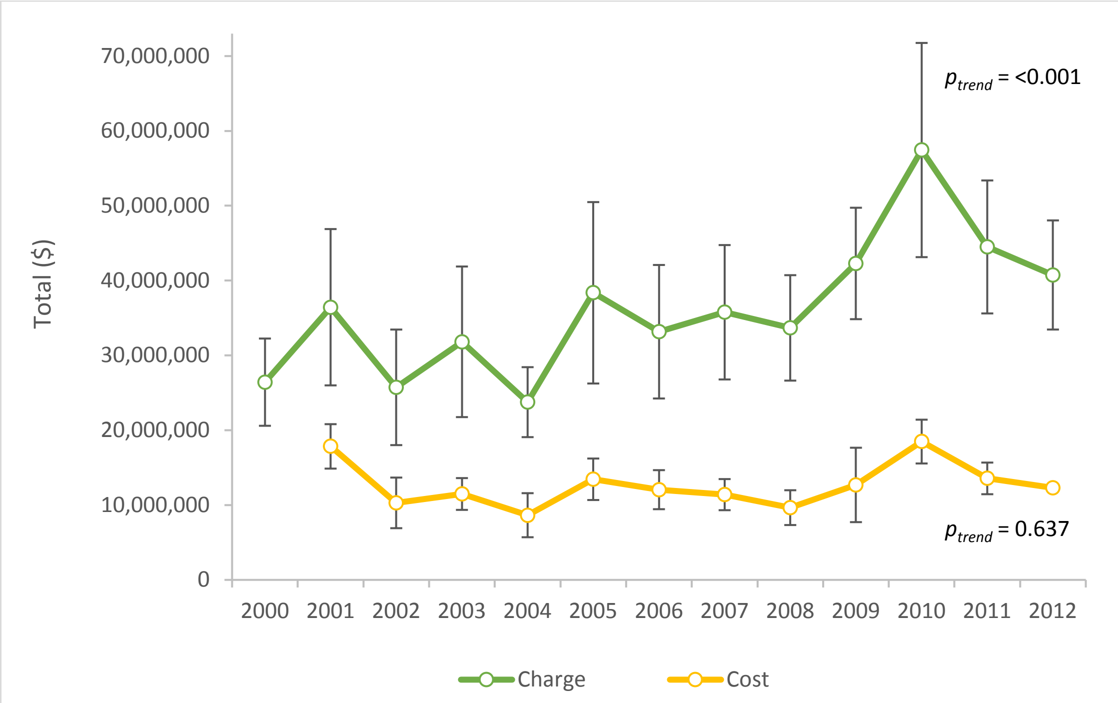
Note: All numbers are national estimates based on weighted frequencies and nonmissing data. Numbers and proportions may not sum to total or 100% due to missing values. All costs adjusted for inflation to 2015 US dollars.
*Admission source data for 2001-2011. Hospital ownership data for 2008-2012.

Figure 1. Total hospital days for malaria-related hospitalizations in the US, NIS 2000-2012



Note: All numbers are national estimates based on weighted frequencies and nonmissing data.

Figure 2. Total charges and costs for malaria-related hospitalizations in the US, by year, NIS 2000-2012



Note: All numbers are national estimates based on weighted frequencies and nonmissing data.
All values adjusted for inflation to 2015 US dollars.
Cost data available only for 2001-2012.

Table A1. Negative binomial regression of length of stay, US, NIS 2008-2012

Characteristics	Estimate	(95% CL)
Age (continuous)	0.00	(0.00, 0.01)
Sex (referent: male)		
Female	0.00	(-0.09, 0.09)
Race/ethnicity (referent: White)		
Black	-0.17	(-0.31, -0.04)*
Hispanic	-0.16	(-0.43, 0.11)
API	-0.14	(-0.29, 0.02)
Other race	-0.17	(-0.33, -0.01)*
Severe malaria complications (referent: no)		
Cerebral malaria	0.41	(0.19, 0.63)*
Malaria with severe anemia	0.47	(0.28, 0.66)*
Malaria with renal failure	0.22	(0.07, 0.37)*
Malaria with ARDS	0.86	(0.69, 1.03)*
Malaria with jaundice	0.01	(-0.16, 0.18)
Pre-existing conditions (referent: no)		
HIV infection	0.19	(-0.06, 0.43)
Diabetes mellitus (type II)	0.16	(-0.03, 0.35)
Essential hypertension	-0.04	(-0.10, 0.19)
Income by zip code (referent: high)		
Low	-0.01	(-0.11, 0.09)
Primary payer (referent: Medicare)		
Medicaid	-0.21	(-0.53, 0.11)
Private insurance	-0.39	(-0.63, -0.16)*
Self-pay	-0.46	(-0.70, -0.23)*
No charge	-0.33	(-0.62, -0.04)*
Other payer	-0.29	(-0.64, 0.05)
Hospital region (referent: West)		
Northeast	-0.06	(-0.35, 0.22)
Midwest	-0.14	(-0.43, 0.16)
South	-0.04	(-0.16, 0.25)
Hospital Location (referent: urban)		
Rural	-0.40	(-0.64, -0.16)*
Hospital Control (referent: gov., public)		
Private, non-profit	-0.11	(-0.25, 0.02)
Private, investor owned	0.00	(-0.20, 0.19)
Hospital bed size (referent: large)		
Small	0.05	(-0.21, 0.03)
Medium	0.01	(-0.64, -0.16)

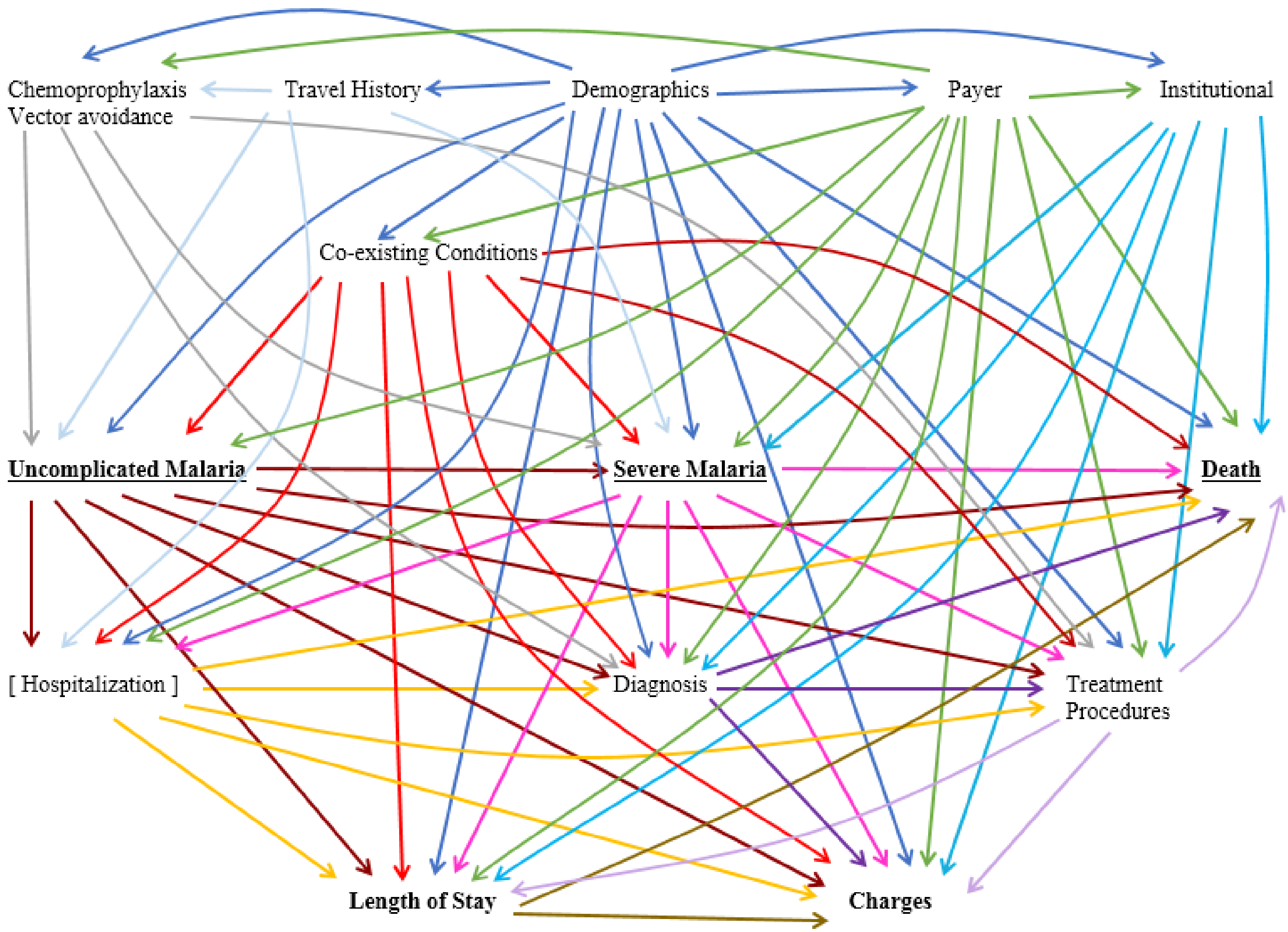
*p < 0.05

Table A2. Multiple linear regression of log(charges) and log(costs), US, NIS 2008-2012

	Outcome			
	log(charges)		log(costs)	
Characteristics	**Estimate**	**(95% CL)**	**Estimate**	**(95% CL)**
Age (continuous)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)*
Sex (referent: male)				
Female	-0.05	(-0.12, 0.02)	-0.04	(-0.09, 0.01)
Race/ethnicity (referent: White)				
Black	-0.10	(-0.19, 0.00)*	-0.03	(-0.11, 0.06)
Hispanic	0.06	(-0.12, 0.25)	0.06	(-0.1, 0.22)
API	0.07	(-0.07, 0.22)	0.02	(-0.09, 0.14)
Other race	-0.03	(-0.13, 0.08)	0.01	(-0.09, 0.11)
Severe malaria complications (referent: no)				
Cerebral malaria	0.14	(-0.04, 0.31)*	0.20	(0.06, 0.34)*
Malaria with severe anemia	0.33	(0.20, 0.46)*	0.34	(0.24, 0.43)*
Malaria with renal failure	0.25	(0.15, 0.35)*	0.18	(0.10, 0.26)*
Malaria with ARDS	0.60	(0.42, 0.78)*	0.63	(0.47, 0.79)*
Malaria with jaundice	-0.12	(-0.27, 0.04)	-0.02	(-0.14, 0.09)
Pre-existing conditions (referent: no)				
HIV infection	0.31	(0.10, 0.51)*	0.26	(0.10, 0.42)*
Diabetes mellitus (type II)	0.19	(0.08, 0.30)*	0.11	(0.01, 0.21)*
Essential hypertension	-0.02	(-0.12, 0.09)	-0.02	(-0.11, 0.06)
Length of stay (referent: 0-1 days)				
2-3 days	0.60	(0.50, 0.70)*	0.56	(0.47, 0.65)*
4-6 days	1.17	(1.06, 1.28)*	1.13	(1.03, 1.22)*
7+ days	1.86	(1.70, 2.02)*	1.82	(1.69, 1.95)*
Income by zip code (referent: high)				
Low	-0.01	(-0.09, 0.08)	-0.04	(-0.10, 0.02)
Primary payer (referent: Medicare)				
Medicaid	-0.08	(-0.25, 0.1)	0.00	(-0.15, 0.15)
Private insurance	-0.08	(-0.24, 0.08)	-0.09	(-0.24, 0.05)
Self-pay	-0.08	(-0.25, 0.09)	-0.10	(-0.26, 0.05)
No charge	0.03	(-0.23, 0.28)	0.01	(-0.21, 0.22)
Other payer	-0.06	(-0.27, 0.15)	0.00	(-0.19, 0.19)
Hospital region (referent: West)				
Northeast	-0.24	(-0.37, -0.10)*	-0.22	(-0.33, -0.12)*
Midwest	-0.42	(-0.57, -0.28)*	-0.24	(-0.39, -0.09)*
South	-0.55	(-0.67, -0.43)*	-0.37	(-0.48, -0.27)*
Hospital Location (referent: urban)				
Rural	-0.34	(-0.57, -0.10)*	0.04	(-0.16, 0.24)
Hospital Control (referent: gov., public)				
Private, non-profit	0.01	(-0.13, 0.15)	-0.07	(-0.19, 0.05)
Private, investor owned	0.48	(0.30, 0.66)*	-0.18	(-0.33, -0.03)*
Hospital bed size (referent: large)				
Small	0.07	(-0.08, 0.22)	0.14	(0.04, 0.23)*
Medium	-0.12	(-0.23, 0.00)*	0.03	(-0.04, 0.1)

*$p < 0.05$

Figure A1. Directed acyclic graphs of relationships involved in length of stay and charges for malaria-related hospitalizations in the US



Chapter 3: Severe malaria

Risk factors for severe malaria and death among hospitalized patients in the United States, 2000-2012

Abstract

Background: The factors associated with the development of severe malaria have not been well described for cases occurring in the US.

Methods: Hospital discharge records from the Nationwide Inpatient Sample (NIS), which is the largest publicly available all-payer inpatient health care database in the US, were used for analysis of malaria-related hospitalizations in the US during 2000-2012. National estimates of the frequency and population rates were reported by different demographic, clinical, species, financial, geographic, and institutional characteristics, and disparities were identified. Time trends in severe malaria cases over the study period were assessed by negative binomial regression. Multiple logistic regression models were used to identify potential predictors for severe disease among those with malaria (cerebral malaria, acute respiratory distress syndrome [ARDS], severe anemia, renal failure, or jaundice).

Results: From 2000-2012, there were an estimated 3,888 severe malaria cases, representing 20.3% of all malaria-related hospitalizations. Severe malaria occurred at a rate of 1.00 per 1 million population in the US, and the rate increased over the study period. The most frequent malaria complication was renal failure (40.5%), followed by severe anemia (34.6%), ARDS (19.9%), cerebral malaria (18.7%), and jaundice (15.4%). *P. falciparum* accounted for 82.4% of severe malaria-related hospitalizations with known species information. Rates of severe malaria were highest among patients who were male, Black, age 25-44 years, and hospitalized in the northeast region. After controlling for potential confounders, older age was associated with higher odds of severe malaria, ARDS, severe anemia, and renal failure. Males had higher odds of developing renal failure and jaundice, while females had higher odds of developing severe anemia and ARDS. HIV infection was associated with increased odds of severe malaria. Malaria patients who were self-payers or had Medicaid were at increased odds of having renal failure, compared to those with Medicare.

Conclusions: Severe and fatal malaria exacts a considerable, and increasing, burden in the US. Primary and secondary prevention measures, including strategies to increase the use of pre-travel consultations and prompt diagnosis and treatment, should be emphasized in high-risk groups.

Introduction

Malaria is the leading cause of death by parasitic disease in the world and remains one of the most important and intractable global public health problems. An estimated 214 million cases of malaria, and 438,000 deaths due to malaria occurred in 2015[1]. Malaria is caused by infection with the protozoan agents of the genus *Plasmodium.* Several species of *Plasmodium* (*P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*) are known to affect humans, with *P. falciparum* causing the most morbidity and the vast majority of the mortality. Transmission typically occurs through the bite from an infected female *Anopheles* mosquito, which has widespread distribution throughout the world, including the United States. Malaria transmission can also occur by blood transfusion, organ transplant, percutaneous exposure, and vertically (from mother to fetus), though these forms of transmission are relatively uncommon[2].

If untreated, malaria can cause severe and fatal disease. Clinical manifestations can range from fever, shaking chills, muscle pains, and other non-specific symptoms in uncomplicated malaria, to jaundice, acute renal failure, severe anemia, cerebral malaria, acute respiratory distress syndrome, and other serious complications in severe malaria[2], which can be rapidly fatal. Malaria during pregnancy is associated with many adverse outcomes, including maternal mortality, maternal anemia, low birth weight, intrauterine growth retardation, and fetal loss[3].

Surveillance data indicates that the number of imported uncomplicated malaria and severe malaria cases has steadily increased over the last few decades in the US[4] and in other countries[5] where previously endemic malaria has been eliminated. These cases mostly occur among returned travelers, and to a lesser extent, among foreign visitors or immigrants, from malaria-endemic countries[6].

European studies have suggested the risk of uncomplicated and severe malaria is unevenly distributed across different subpopulations of travelers[5,7-8]. However, despite the growing disease and economic burden, the factors associated with the development of severe malaria have not been well described for cases occurring in the US. A stratified analysis of the specific malaria complications has rarely been conducted, and is of interest since each complication may have different risk factors, require different types and levels of resources and expertise, and result in different outcomes. In the current study, we analyzed US hospital data to examine the demographic characteristics, and identify potential risk factors for severe malaria and death.

Methods

Hospital discharge records from the Nationwide Inpatient Sample (NIS) were used for analysis of severe malaria-related hospitalizations in the US during 2000-2012. The NIS is sampled from the State Inpatient Databases (SID), and is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality

(AHRQ). The NIS is the largest publically available all-payer inpatient data source in the US, and each annual NIS dataset contains 7-8 million hospital discharge records (about 20%) and over 100 clinical and non-clinical data elements, including sociodemographics, admission characteristics, diagnosis type, disease severity, length of stay, co-diagnoses, procedures performed, institutional characteristics, and total charges. For 2000-2011 data, the NIS was a stratified, single-stage cluster sampling of US community hospitals, in which all of the discharges from the selected hospitals were included in the NIS dataset[9]. For 2012 data, the NIS was a stratified random sample of discharges from all community hospitals participating in HCUP[10]. Details on the sampling scheme have been described elsewhere[9-10].

Cases of malaria in the NIS from 2000-2012 were identified from discharge records in the NIS by the primary and secondary diagnoses, which used the International Classification of Diseases, 9th revision (ICD-9)[11] codes of 084.0-084.9 (084.0: falciparum malaria, malignant tertian; 084.1: vivax malaria, benign tertian; 084.2: malariae, quartan; 084.3: ovale malaria; 084.4: other malaria; 084.5: mixed malaria; 084.6: malaria, unspecified; 084.7: induced malaria; 084.8: Blackwater fever; 084.9: other pernicious complications of malaria) and of 647.4 (malaria complicating pregnancy, childbirth, or puerperium).

In this study, the definition of severe malaria was modified from that used by the CDC[4]. Since no specific drugs used or laboratory results are available in the NIS, we were unable to use parasitemia $\geq$5% or treatment for severe malaria (i.e. artesunate or quinidine) as specified in the CDC definition[4]. Malaria complications were identified using ICD-9 codes and HCUP Clinical Classification Software (CCS)[12] categories, which are clinically meaningful categories of ICD-9 codes. Discharge records listing a malaria diagnosis along with one or more of the following criteria were considered as severe malaria cases: 1. Neurologic symptoms (cerebral malaria)–

CCS codes 78, 82, 83, 85, or 95 (paralysis, epilepsy, convulsions, alteration of consciousness, coma, stupor, brain damage, other nervous system disorders); 2. Renal failure– CCS code 157; 3. Severe anemia– CCS codes 59 or 60 (deficiency anemia, acute post-hemorrhagic anemia), with procedural CCS code 222 (blood transfusion); 4. Acute respiratory distress syndrome (ARDS)– CCS code 131; 5. Jaundice– ICD-9 code 782.4; or 6. Exchange transfusion– ICD-9 code 99.01.

All-Patient Refined Diagnosis Related Groups (APR-DRG) severity and risk of mortality variables[13], which measure the extent of physiologic decompensation or organ system loss of function, and the likelihood of death (based on the combinations of principal diagnoses, secondary diagnoses, non-operating room procedures, operating room procedures, and age), were additionally used to describe the uncomplicated malaria and severe malaria cases.

Data analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) with survey procedures that accounted for the complex sampling design. National estimates of the frequency were produced using NIS discharge-level sample weights, which are provided by HCUP. Rates per 1 million US population[14] were calculated using bridged-race US census population estimates. Trends in the rates of severe malaria hospitalizations over the study period were assessed by negative binomial regression.

Separate multiple logistic regression models were used to identify potential predictors for severe malaria, and for each severe malaria defining complication among hospitalizations in the US from 2000-2012. Variables and covariates were selected based on associations documented in the literature, which included sociodemographic, financial, and institutional characteristics, and some pre-existing conditions, such as HIV[15-16], type II diabetes mellitus[17], and essential hypertension[18]. Directed acyclic graphs were used to examine the possible relationships between variables involved with severe malaria[19-20] (Figure A1).

Results

From 2000-2012, there were an estimated 3,888 (95% confidence interval [CI]: 3,481 – 4,294) severe malaria hospitalizations (Table 1) that occurred at a rate of 1.00 (95% CI: 0.90 – 1.11) per 1 million population (Figure 1, Table 2). Severe malaria accounted for 20.3% of all (n=19,189) malaria-related hospitalizations in the US. Some (23.2%) patients developed multiple complications. The most frequent malaria complication was renal failure with 1,573 hospitalizations accounting for 40.5% of severe malaria hospitalizations, followed by severe anemia (n=1,346 [34.6%]), ARDS (n=775 [19.9%]), cerebral malaria (n=726 [18.7%]), and jaundice (n=598 [15.4%]) (Table 1). The rates of severe malaria overall and for each specific malaria complication increased ($p_{trend} \leq 0.01$) over the study period (Figure 1, A2). The percent of all malaria-related hospitalizations that were severe cases also increased from 10.9% to 26.1% ($p_{trend} \leq 0.01$).

Over the study period, an estimated 122 (3.1%) severe malaria-related hospitalizations ended in death. Those with ARDS had the highest risk of death (13.0%), accounting for 84.4% of all severe malaria-related hospitalizations ending in death. About 5.2% of those with renal failure, 5.2% of those with cerebral malaria, and 2.1% of those with severe anemia had an in-hospital death (Table 1). Controlling for demographic covariates, having ARDS, renal failure, or cerebral malaria was associated with increased odds of death (Table 3).

Species

Infecting *Plasmodium* species information was known for 56.7% of severe malaria-related hospitalizations. While *P. falciparum* accounted for 68.3% of uncomplicated malaria-related hospitalizations, it accounted for 82.4% of severe malaria-related hospitalizations with known species information; these were followed by *P. vivax* (14.7%), *P. malariae* (1.5%), and *P. ovale* (2.8%). A similar pattern held for all of the severe malaria complications (Figure 2). Increases in the rates of severe malaria for infections with *P. falciparum* ($p_{trend} \leq 0.01$) were observed.

Age

The number and rate of severe malaria-related hospitalizations increased with age, peaking at 45-64 years (Table 1, 2). Rates for the specific complications generally followed this pattern, except ARDS, which had rates that consistently increased with age, and jaundice, which had rates peaking earlier at age 25-44 years (Table 2). Increases ($p_{trend} \leq 0.01$) in the rates of severe malaria for age groups 25-44 and older were observed. Older age was associated with severe malaria, malaria with renal failure, ARDS, severe anemia, and fatal malaria (Table 3, 4).

Sex

Severe malaria-related hospitalization generally occurred more often and at a higher rate among males, and this disparity was greatest for those with jaundice and renal failure. Malaria with severe anemia was an exception, and was more common among females (Tables 1, 2). Of the 102 (2.6%) severe malaria hospitalizations among pregnant women, 88 (72.1%) had severe anemia, and 10 (8.2%) had ARDS (Table 1).

Sex was not associated with the overall odds of severe malaria, but the odds varied by malaria complication. Males had higher odds of developing renal failure and jaundice, while females had higher odds of developing severe anemia and ARDS (Table 4).

Race/ethnicity

Blacks had by far the highest rates of overall severe malaria, and of all severe malaria defining complications. Temporal increases in the rates of severe malaria for Whites and Blacks ($p_{trend} \leq 0.01$) were observed. Blacks accounted for over half (52.2%) of severe malaria-related hospitalizations with known race information, higher than that of Whites, and much higher than that of Hispanics, Asian/Pacific Islanders, and other race/ethnicity groups. Blacks were also the largest race/ethnicity group for all severe malaria defining complications, except for ARDS, which had a larger proportion among Whites (Table 1). Asian/Pacific Islanders had higher rates of overall severe malaria, severe anemia, and renal failure compared to Whites (Table 2). Controlling for all other covariates, Hispanics had lower odds of developing severe malaria compared to Whites (Table 4).

Clinical

Malaria was the primary diagnosis (75.5%) for the majority of severe malaria-related hospitalizations, though the proportion varied widely by complication. Those with jaundice (92.0%) were most likely, while those with cerebral malaria (57.6%) were least likely to have a primary malaria diagnosis (Table 1). The most common primary diagnoses among severe malaria cases with a secondary malaria diagnosis were unspecified septicemia (14.2%), other specified septicemia (5.5%), and acute respiratory failure (4.0%) (Table A2). Malaria was a secondary diagnosis for all severe malaria-related hospitalizations that ended in death.

Over half (51.9%) of discharge records for severe malaria-related hospitalizations of all complications listed 8 or more diagnoses. Thrombocytopenia, hyposmolality and/or hyponatremia, hypopotassemia, dehydration, acidosis, septicemia, and essential hypertension were frequently listed co-diagnoses of severe malaria hospitalizations (Table A1).

HIV infection was reported in 2.9%, type II diabetes in 9.2%, and essential hypertension in 19.2% of severe malaria hospitalizations. Those with renal failure had the highest proportion of all 3 pre-existing conditions (Table 1). Controlling for all other covariates, HIV infection increased the odds of severe malaria. Small numbers limited the ability to detect the association by severe complication in this study. Type II diabetes and essential hypertension were not associated with severe malaria or any severe malaria complication (Table 4).

The most common procedure performed for severe malaria-related hospitalizations was blood transfusion (40.7%), followed by vascular catheterization (17.3%), and respiratory intubation and mechanical ventilation (15.6%) (Table A3).

Most (77.9%) patients with severe malaria had major or extreme physiologic decompensation or organ system loss of function, and about half (48.8%) had a major or extreme risk of dying. Nearly all patients with ARDS had major or extreme loss of organ system function (98.6%) and major or extreme risk of dying (95.0%) (Table 1).

The mean length of stay for severe malaria-related hospitalizations was 8.2 days. Those with ARDS had the longest hospital stays (16.3 days), while those with jaundice had the shortest hospital stays (4.6 days) (Table 1).

Financial

The mean hospital charge for severe malaria-related hospitalizations was $60,816. The mean charge varied greatly among complications, ranging from $30,363 for malaria with jaundice, to $159,498 for malaria with ARDS (Table 1). Malaria patients who were self-payers or had Medicaid were at increased odds of having renal failure, compared to those with Medicare (Table 4).

Institutional

The Southern region of the US had the highest numbers of severe malaria-related hospitalizations, followed by the Northeastern, Western, and Midwestern regions (Table 1). The Northeastern region had the highest rates of all severe malaria complications, except for ARDS, which had similar rates in the Northeastern and Southern regions. The Western region had the lowest rates of severe malaria and all of the severe malaria defining complications, except for cerebral malaria, which had similar rates in the Western and Midwestern regions (Table 2). Controlling for all other covariates, those in the Northeastern and Midwestern region were associated with lower odds of severe malaria compared to the patients treated in the Western region of the US. Those in the Northeastern region had lower odds of cerebral malaria, severe anemia, and ARDS. The odds of cerebral malaria were also lower in the Midwestern regions compared to the Western region (Table 4).

Patients with a severe malaria diagnosis were more often hospitalized in urban areas (96.4%) (Table 1). Rural hospital location was associated with lower odds of severe malaria, particularly for renal failure (Table 4).

Discussion

Severe and fatal malaria exacts a considerable, and increasing, burden in the US. This burden may be heavier than previously recognized, as the number and proportion of severe malaria cases (and deaths) identified from the NIS was much higher than that reported from the malaria surveillance system[4]. For example, in 2012, there were an estimated 365 (20.3%) severe malaria-related hospitalizations, compared to 231 (13.7%) reported severe cases. This increased sensitivity is unsurprising, given underreporting[21-22] in passive surveillance systems. In addition, as previously noted elsewhere[23], the number of complications and co-diagnoses of severe malaria cases has gradually increased in recent years. The observed increases may also be due to the general increase in more complete reporting of co-diagnoses in recent years, though all estimates and associations presented here took the differences across multiple years of NIS data into account with adjustment for year of hospitalization.

In this study, stratified analyses of malaria complications, in addition to overall analyses of severe malaria, showed differences in demographic, clinical, financial, and institutional distributions and their roles as possible risk factors. In terms of case burden, renal failure was the most common severe malaria complication followed closely by severe anemia, which is consistent with previous reports[4]. ARDS was among the most serious complications for severe malaria-related hospitalizations in the US with its high case fatality rate, number of comorbidities including bacterial co-infection[24], number of procedures performed, number of hospital days, and mean hospital charges. Jaundice was the least frequent severe complication of malaria in the US, which is consistent with previous reports[4], and the high proportion of jaundice cases with a primary malaria diagnosis and with no procedures performed, and low case fatality rate indicates that they were more likely to represent milder cases than those that had other malaria complications.

Cerebral malaria is a severe clinical manifestation of malaria typically associated almost exclusively[25] with *P. falciparum*. Interestingly, 17.6% of cerebral malaria hospitalizations were attributed to *P. vivax* mono-infection in this study, which adds to the growing body of evidence[26-27] that *P. vivax* may cause serious disease including cerebral malaria. This may be especially relevant for diagnosis of returning travelers from *P. vivax*-endemic Latin America or Asia presenting with fever and neurological symptoms. We also found that those aged 45-64 years, but not those 65 and older, had a statistically significant increase in the odds of cerebral malaria compared to those aged 0-14. This finding is not consistent with several studies that indicate that the risk of cerebral malaria increases with older age among those living in non-endemic areas[29-30]. It is possible that the relationship does not follow a strictly linear pattern in travelers hospitalized with cerebral malaria in the US, although the reasons are unclear.

Associations between severe malaria and several factors were identified in this study. Based on cases with known species information, the predominant infecting species for severe malaria-related hospitalizations was *P. falciparum*, which is consistent with its well-documented relative virulence[31]. Although *P. falciparum* is often the correctly assumed species involved in severe malaria of all complications, the other species also produced serious disease classifiable as severe malaria, and should not be discounted[32-33]. Additional laboratory training on species identification through malaria microscopy may be needed, as only about half of severe malaria hospitalizations had species information.

Older age was found to increase the risk of ARDS, cerebral malaria, severe anemia, and renal failure; male sex was found to increase the risk of renal failure[34] and jaundice[35]; and female sex was found to increase the risk of ARDS[36] and severe anemia[37] among patients with malaria in this study, which is consistent with previous reports. Although we observed an association between race and severe malaria, race may serve as a proxy for other possibly more relevant risk factors that may better explain the variation in *Plasmodium* infection and the subsequent development of severe malaria. Such factors may include genetic profiles, patient travel history, chemoprophylaxis use, purpose of travel, underlying medical conditions and perceived immune status, which unfortunately were not available in administrative hospital discharge data. Hispanics may have lower odds of severe malaria because they may more frequently travel to destinations in Central and South America, where there are relatively lower levels of malaria transmission, and where the predominant infecting species present is *P. vivax.* Nonetheless, travelers of all demographics going to destinations with malaria transmission are still vulnerable to malaria and severe malaria, and are encouraged to take full preventive precautions[5,38-39].

The proportion of severe malaria patients with HIV infection (2.9%) was much higher than that of the general population (0.3%)[40]. Having HIV infection as a diagnosis was associated with increased odds of severe malaria in this study, which is consistent with many studies[15-16] in support of HIV infection as a risk factor for severe malaria. HIV infection may compromise the immune response to *Plasmodium*, resulting in higher parasitemia and more severe disease. The proportion of severe malaria patients with diabetes (9.2%) was similar to that of the general population (9.3%)[41], while the proportion of severe malaria patients with essential hypertension (19.2%) was much lower than the general population (29.1%)[42]. Some studies have suggested that diabetes may be a risk factor[17], and that hypertension may be a protective factor[18] for severe malaria. However, we did not find diabetes or essential hypertension to be associated with severe malaria or any specific complication of malaria.

Severe malaria cases may be referred from smaller, rural hospitals to larger urban, teaching hospitals, which tend to offer a higher level of care. This may explain the observed lower odds of renal failure at rural hospitals. The more eastern regions of the US had higher incidence but lower odds of severe malaria. Differences in medical practice patterns or unmeasured patient characteristics by region may have led to better recognition and management of malaria, especially with cerebral malaria.

Delays in seeking care and delayed or misdiagnoses may be common due to nonspecific clinical manifestations, disease rarity, and low patient, clinician, and laboratory personnel experience with malaria in the US. Clinicians assessing the etiology of unexplained fever or severe infection should always include malaria in the differential diagnosis and elicit travel history at initial presentation with rapid diagnosis and prompt initiation of appropriate treatment to reduce the risk of progression of severe and fatal malaria cases[4,24,43].

The use of NIS in this study has many strengths, including its large and representative sample size to study rare diseases. However, some limitations of this study should be considered. Without information on specific medications used or laboratory results, some severe malaria cases may have been classified as uncomplicated, as indicated by the sizeable number of uncomplicated hospitalizations with major or extreme loss of function, major or extreme risk of dying, or an in-hospital death. On the other hand, the number of severe malaria cases may have been overestimated by using ICD codes reported in discharge records, which may have more available documentation of all conditions and procedures performed as compared to the CDC surveillance system. The high proportion of clinically imprecise ICD diagnosis codes, such as those corresponding to conditions that can have a wide clinical spectrum (e.g., non-traumatic acute kidney injury), and changes in the criteria for certain conditions over time, may also preclude consistent and accurate identification of relevant clinical manifestations for classifying cases and co-morbidities. Since the NIS is discharge record and not patient based, recrudescent malaria cases that result in re-hospitalizations may lead to multiple counting. Imputation of missing variables was not feasible due to the large size of the NIS and limited computing power. Random and intentional (state-level suppression) missing data on race and sensitive conditions (e.g. HIV)[9-10] may have resulted in some error in the race-specific number and rate estimates, and in the assessment of HIV as a risk factor. Selection bias[19-20] is possible in the assessment of associations with severe malaria in this study since both severe malaria and the potential predictors of interest may affect the hospitalization rate (Figure A1). In addition, other potential risk factors of interest, including laboratory results[44-45], pre-travel consultation, travel history, destination and purpose of travel, immigration and immunity status, and vector avoidance and chemoprophylaxis use[39,46-47] were not available in NIS data to determine their associations with severe malaria.

Conclusion

This study provides insight to the burden of severe malaria and the specific malaria complications in the US, and is generalizable to US travelers, foreign visitors, and immigrants. In light of the increases in international travel, primary and secondary prevention measures should be emphasized in high-risk groups. Clinicians in the US must maintain a high index of suspicion for malaria for patients with a history of international travel. The CDC provides information on malaria risk and prevention recommendations by region[39], and has staff that provides free guidance on diagnosis[48] and treatment[49].

References

1. World Malaria Report 2015. World Health Organization. Geneva, Switzerland: World Health Organization; 2016. http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf

2. Centers for Disease Control. Malaria [Accessed 15 Apr 2015]. Available at: http://www.cdc.gov/malaria/

3. Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. Clinical microbiology reviews. 2004;17(4): 760-769.

4. Cullen KA, Mace KE, Arguin PM. Malaria surveillance--United States, 2013. MMWR Surveill Summ. 2016 Mar 4; 65(2):1-22.

5. Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, Whitty CJM. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. Bmj. 2012;344.

6. Hagmann SHF, Van PV, Stauffer WM, Miller AO, Connor BA, Hale DC, Coyle CM, et al. Travel-associated disease among US residents visiting US GeoSentinel clinics after return from international travel. Family Practice, 2014, Vol. 31, No. 6, 678–687 doi:10.1093/fampra/cmu063

7. Odolini S, Gautret P, Parola P. Epidemiology of Imported Malaria in the Mediterranean Region. Mediterr J Hematol Infect Dis. 2012; 4(1): e2012031. doi: 10.4084/MJHID.2012.031

8. Seringe E, Thellier M, Fontanet A, et al. Severe Imported Plasmodium falciparum Malaria, France, 1996–2003. Emerging Infectious Diseases. 2011;17(5):807-813. doi:10.3201/eid1705.101527.

9. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2011. Agency for Healthcare Research and Quality, Rockville, MD. June 2013. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2011.jsp

10. Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2012. Agency for Healthcare Research and Quality, Rockville, MD. June 2014. [Accessed 26 Mar 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2012.jsp

11. Centers for Disease Control and Prevention. Classification of Diseases, Functioning, and

Disability. Conversion table. [Accessed 12 Sep 2014]. Available at: http://www.cdc.gov/nchs/icd/icd9cm.htm

12. HCUP Clinical Classifications Software. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. April 2016. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.

13. 3M APR DRG Classification System. Methodology Overview. 3M Health Information Systems. 2013. [Accessed 29 June 2016]. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/grp031_aprdrg_meth_ovrview.pdf

14. United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Bridged-Race Population Estimates, United States July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin. Compiled from 1990-1999 bridged-race intercensal population estimates (released by NCHS on 7/26/2004); revised bridged-race 2000-2009 intercensal population estimates (released by NCHS on 10/26/2012); and bridged-race Vintage 2014 (2010-2014) postcensal population estimates (released by NCHS on 6/30/2015). Available on CDC WONDER Online Database. Accessed at http://wonder.cdc.gov/bridged-race-v2014.html on Apr 15, 2016 1:00:23 PM

15. Chalwe V, Jean-Pierre Van geertruyden, Mukwamataba D, et al. Increased Risk for Severe Malaria in HIV-1–infected Adults, Zambia. Emerging Infectious Diseases. 2009;15(5):749-755. doi:10.3201/eid1505.081009.

16. Cohen C, Karstaedt A, Frean J, Thomas J, Govender N, Prentice E, Dini L, Galpin J, Crewe-Brown H. Increased prevalence of severe malaria in HIV-infected adults in South Africa. Clin Infect Dis. 2005 Dec 1;41(11):1631-7. Epub 2005 Oct 26.

17. Danquah I, Bedu-Addo G, Mockenhaupt FP. Type 2 diabetes mellitus and increased risk for malaria infection. Emerg Infect Dis. 2010 Oct;16(10):1601-4. doi: 10.3201/eid1610.100399.

18. Gallego-Delgado J, Rodriguez A. Malaria and hypertension. Another co-evolutionary adaptation? Front Cell Infect Microbiol. 2014 Sep 3;4:121. doi:10.3389/fcimb.2014.00121. eCollection 2014.

19. Hernán MA, Robins JM. Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming; 2016.

20. Rothman KJ, Last TL, Greenland S. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer Health, 2012.

21. Abanyie FA, Arguin PM, Gutman J. State of malaria diagnostic testing at clinical laboratories in the United States, 2010: a nationwide survey. Malar J. 2011;10: 340.

22. Doyle TJ, Glynn MK, Groseclose SL. Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. American Journal of Epidemiology. 2002;155(9): 866-874.

23. Das BS. Renal failure in malaria. J Vector Borne Dis. 2008 Jun;45(2):83-97.

24. Vicas AE, Albrecht H, Lennox JL, del Rio C. Imported malaria at an inner-city hospital in the United States. Am J Med Sci. 2005 Jan;329(1):6-12.

25. Trampuz A, Jereb M, Muzlovic I, Prabhu RM. Clincal review: Severe malaria. Critical Care. 2003; 7:315-323. doi: 10.1186/cc2183.

26. Neki NS. Cerebral malaria caused by Plasmodium vivax. JIACM 2013; 14(1): 69-70.

27. Tanwar GS, Khatri PC, Sengar GS, Kochar A, Kochar SK, Middha S, Tanwar G, Khatri N, Pakalapati D, Garg S, Das A, Kochar DK. Clinical profiles of 13 children with Plasmodium vivax cerebral malaria. Ann Trop Paediatr. 2011;31(4):351-6. doi: 10.1179/1465328111Y.0000000040.

28. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A. Plasmodium vivax Malaria. Emerging Infectious Diseases. 2005;11(1):132-134. doi:10.3201/eid1101.040519.

29. Mühlberger N, Jelinek T, Behrens RH, Gjørup I, Coulaud JP, Clerinx J, Puente S, Burchard G, Gascon J, Grobusch MP, Weitzel T, Zoller T, Kollaritsch H, Beran J, Iversen J, Hatz C, Schmid ML, Björkman A, Fleischer K, Bisoffi Z, Guggemos W, Knobloch J, Matteelli A, Schulze MH, Laferl H, Kapaun A, McWhinney P, Lopez-Velez R, Fätkenheuer G, Kern P, Zieger BW, Kotlowski A, Fry G, Cuadros J, Myrvang B; TropNetEurop; Surveillance importierter Infektionen in Deutschland Surveillance Networks. Age as a risk factor for severe manifestations and fatal outcome of falciparum malaria in European patients: observations from TropNetEurop and SIMPID Surveillance Data. Clin Infect Dis. 2003 Apr 15;36(8):990-5. Epub 2003 Apr 2.

30. Leder K, Black J, O'Brien D, Greenwood Z, Kain KC, Schwartz E, Brown G, Torresi J. Malaria in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis. 2004 Oct 15;39(8):1104-12. Epub 2004 Sep 27.

31. Walker DM, Oghumu S, Gupta G, McGwire BS, Drew ME, Satoskar AR. Mechanisms of cellular invasion by intracellular parasites. Cell Mol Life Sci. 2014 Apr;71(7):1245-63. doi: 10.1007/s00018-013-1491-1. Epub 2013 Nov 13.

32. Hwang J, Cullen KA, Kachur SP, Arguin PM, Baird JK. Severe morbidity and mortality risk from malaria in the United States, 1985-2011. Open Forum Infect Dis. 2014 Jun 30;1(1):ofu034. doi: 10.1093/ofid/ofu034.

33. Mendis K, Sina BJ, Marchesini P, Carter R. The neglected burden of Plasmodium vivax malaria. The American journal of tropical medicine and hygiene. 2001;64(1)suppl: 97-106.

34. Coggins CH, Breyer Lewis J, Caggiula AW, Castaldo LS, Klahr S, Wang SR. Differences between women and men with chronic renal disease. Nephrol Dial Transplant. 1998 Jun;13(6):1430-7.

35. Yu Z, Zhan J, Li C, Zhou H. Age and gender analysis of jaundice patients. The Journal of Bioscience and Medicine. 2012; 2(2): 1-3.

36. Taylor WJ, Hanson J, Turner GH, White NJ, Dondorp AM. Respiratory Manifestations of Malaria. Chest. 2012;142(2):492-505. doi:10.1378/chest.11-2655.

37. Käser AK, Arguin PM, Chiodini PL, Smith V, Delmont J, Jiménez BC, Färnert A, Kimura M, Ramharter M, Grobusch MP, Schlagenhauf P. Imported malaria in pregnant women: A retrospective pooled analysis. Travel Med Infect Dis. 2015 Jul-Aug;13(4):300-10. doi: 10.1016/j.tmaid.2015.06.011. Epub 2015 Jul 9.

38. Leder K, Torresi J, Libman MD, Cramer JP, Castelli F, Schlagenhauf P, Wilder-Smith A, et al. GeoSentinel surveillance of illness in returned travelers, 2007–2011. Annals of internal medicine. 2013;158(6): 456-468.

39. Centers for Disease Control and Prevention. Malaria. Yellow Book 2015. [Accessed 15 Apr 2016]. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria

40. Hall HI, An Q, Tang T, Song R, Chen M, Green T, Kang J. Prevalence of diagnosed and undiagnosed HIV infection – United States, 2008-2012. MMWR Morb Mortal Wkly Rep. 2015;64(24):657-680.

41. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014. [Accessed 15 Jun 2016]. Available at: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

42. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012. NCHS data brief, no

133. Hyattsville, MD: National Center for Health Statistics. 2013. [Accessed 15 Jun 2016]. Available at: http://www.cdc.gov/nchs/data/databriefs/db133.pdf

43. Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among U.S. travelers, 1963-2001. Ann Intern Med. 2004 Oct 5;141(7):547-55.

44. van Wolfswinkel ME, Hesselink DA, Zietse R, Hoorn EJ, van Genderen PJ. Hyponatraemia in imported malaria is common and associated with disease severity. Malar J. 2010 May 25;9:140. doi: 10.1186/1475-2875-9-140.

45. Patel U, Gandhi G, Friedman S, Niranjan S. Thrombocytopenia in malaria. J Natl Med Assoc. 2004 Sep;96(9):1212-4.

46. Hamer DH, Connor BA. Travel health knowledge, attitudes and practices among United States travelers. Journal of travel medicine. 2004;11(1): 23-26.

47. LaRocque RC, Rao SR, Tsibris A, Lawton T, Barry MA, Marano N, Brunette G, Yanni E, Ryan ET. Pre-travel health advice-seeking behavior among US international travelers departing from Boston Logan International Airport. Journal of travel medicine. 2010;17(6): 387-391.

48. Ash LR, Orihel TC. Atlas of Human Parasitology 5th ed. Chicago: ASCP Press; 2007.

49. Centers for Disease Control and Prevention. Treatment of Malaria. 2013. [Accessed 26 Apr 2016]. Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf

Table 1. Characteristics of severe malaria hospitalizations in the US, by complication, NIS, 2000-2012

Characteristic	Uncomplicated malaria N	%	Severe malaria N	%	Malaria with ARDS N	%	Cerebral malaria N	%	Malaria with severe anemia N	%	Malaria with renal failure N	%	Malaria with jaundice N	%
Demographic														
Sex														
Male	9,169	(59.9)	2,400	(61.7)	420	(54.0)	440	(59.5)	640	(47.5)	1,167	(74.5)	458	(76.8)
Female	6,046	(39.5)	1,478	(38.0)	355	(46.0)	281	(38.6)	702	(52.1)	407	(25.5)	139	(23.2)
Pregnant	912	(6.0)	102	(2.6)	10	(1.2)	*		88	(6.4)	*		*	
Race														
White	2,935	(19.2)	948	(24.4)	285	(36.0)	256	(34.6)	251	(18.4)	350	(22.2)	124	(20.0)
Black	6,386	(41.7)	1,738	(44.7)	234	(30.4)	306	(41.2)	594	(44.3)	802	(51.1)	266	(44.8)
Hispanic	918	(6.0)	181	(4.7)	28	(3.7)	36	(5.2)	98	(7.4)	49	(3.0)	33	(5.6)
Asian/Pacific Islander	783	(5.1)	160	(4.1)	40	(5.6)	24	(3.3)	74	(5.7)	74	(4.9)	*	
Other	1,566	(10.2)	301	(7.7)	62	(8.1)	38	(5.2)	155	(11.3)	92	(5.8)	49	(8.0)
Age (years)														
Under 15	1,934	(12.6)	314	(8.1)	36	(4.3)	49	(6.5)	166	(12.4)	44	(2.7)	44	(8.0)
15-24	2,810	(18.4)	350	(9.0)	64	(8.1)	51	(7.2)	145	(10.6)	100	(6.4)	73	(12.0)
25-44	5,928	(38.7)	1,220	(31.4)	207	(27.3)	148	(20.3)	437	(32.6)	448	(28.6)	248	(41.6)
45-64	3,605	(23.6)	1,404	(36.1)	279	(36.0)	321	(43.1)	423	(31.2)	711	(45.0)	203	(33.6)
65 or older	995	(6.5)	590	(15.2)	189	(24.2)	153	(20.9)	169	(12.8)	271	(17.3)	30	(4.8)
Mean	35.0		43.7		48.7		48.4		40.4		48.7		38.6	
Clinical														
Malaria diagnosis														
Primary	13,192	(86.2)	2,936	(75.5)	510	(65.8)	422	(57.6)	1,054	(78.0)	1,231	(78.1)	549	(92.0)
Secondary	2,110	(13.8)	952	(24.5)	265	(34.2)	304	(42.4)	291	(22.0)	342	(21.9)	49	(8.0)
Pre-existing conditions														
HIV	160	(1.0)	113	(2.9)	18	(2.3)	21	(2.9)	37	(2.7)	64	(4.1)	*	
Diabetes (type II)	1,038	(6.8)	356	(9.2)	95	(12.3)	57	(7.9)	131	(9.7)	211	(13.4)	28	(4.7)
Essential hypertension	1,913	(12.5)	746	(19.2)	165	(21.3)	156	(21.5)	205	(15.2)	387	(24.6)	68	(11.4)
Procedures performed														
0	11,627	(76.0)	1,304	(33.5)	110	(14.3)	255	(35.1)	*		674	(42.9)	377	(64.0)
1	2,243	(14.7)	1,066	(27.4)	60	(7.5)	135	(19.2)	641	(47.9)	315	(20.1)	103	(16.8)
2 or more	1,431	(9.4)	1,517	(39.0)	605	(78.3)	336	(45.7)	704	(52.1)	585	(37.1)	117	(19.2)
Severity of illness†														
No/minor loss of function	3,887	(25.4)	94	(2.4)	*		29	(4.5)	61	(5.0)	*		*	
Moderate loss of function	6,112	(39.9)	676	(17.4)	*		159	(24.4)	308	(25.4)	30	(2.0)	185	(35.3)
Major loss of function	2,285	(14.9)	1,669	(42.9)	135	(20.0)	216	(33.2)	534	(44.0)	775	(52.7)	275	(52.4)
Extreme loss of function	119	(0.8)	1,049	(27.0)	533	(78.6)	243	(37.3)	312	(25.7)	660	(44.9)	64	(12.3)
Risk of mortality†														
No/minor risk of dying	9,396	(61.4)	807	(20.8)	*		160	(24.7)	337	(27.8)	10	(0.7)	280	(53.3)
Moderate risk of dying	2,065	(13.5)	980	(25.2)	24	(3.5)	160	(24.6)	377	(31.0)	434	(30.0)	137	(26.1)

Major risk of dying	524 (3.4)	941 (24.2)	195 (28.8)	126 (19.4)	283 (23.3)	546 (37.2)	59 (11.2)
Extreme risk of dying	67 (0.4)	761 (19.6)	449 (66.2)	199 (30.6)	218 (18.0)	474 (32.3)	49 (9.4)
Mean length of stay (days)	3.4	8.2	16.3	10.3	8.3	8.6	4.6
In-hospital death	25 (0.2)	122 (3.1)	103 (13.0)	40 (5.2)	31 (2.1)	81 (5.2)	*
Financial							
Mean charge‡	16,026	60,816	159,498	78,640	58,362	69,540	30,363
Income§							
High	8,486 (55.5)	2,102 (54.1)	416 (54.0)	352 (48.4)	735 (55.3)	817 (52.3)	288 (48.8)
Low	6,045 (39.5)	1,545 (39.7)	237 (29.8)	254 (34.0)	532 (39.0)	641 (40.4)	213 (35.2)
Primary payer							
Medicare	858 (5.6)	443 (11.4)	149 (19.3)	146 (20.3)	108 (8.2)	182 (11.6)	25 (4.0)
Medicaid	2,924 (19.1)	650 (16.7)	99 (12.4)	98 (13.1)	293 (21.3)	218 (13.7)	96 (16.8)
Private insurance	7,141 (46.7)	1,545 (39.7)	326 (42.2)	273 (37.3)	545 (40.4)	632 (40.4)	245 (40.8)
Self-pay	3,375 (22.1)	864 (22.2)	125 (16.1)	134 (18.3)	298 (22.7)	394 (25.2)	163 (27.2)
No charge	318 (2.1)	88 (2.3)	*	21 (2.6)	19 (1.4)	43 (2.7)	14 (2.4)
Other	648 (4.2)	281 (7.2)	67 (8.7)	49 (6.5)	76 (5.7)	100 (6.1)	54 (8.8)
Institutional							
Region							
Northeast	5,407 (35.3)	1,082 (27.8)	160 (19.9)	186 (25.2)	376 (27.0)	470 (29.2)	153 (24.8)
Midwest	2,286 (14.9)	485 (12.5)	114 (14.3)	56 (7.9)	141 (10.3)	208 (13.1)	84 (13.6)
South	5,405 (35.3)	1,684 (43.3)	331 (44.1)	295 (41.1)	593 (45.0)	683 (44.4)	270 (46.4)
West	2,204 (14.4)	637 (16.4)	170 (21.7)	189 (25.8)	236 (17.7)	213 (13.4)	91 (15.2)
Hospital Location							
Rural	637 (4.2)	124 (3.2)	29 (3.7)	27 (4.0)	45 (3.2)	15 (0.9)	18 (3.2)
Urban	14,642 (95.7)	3,749 (96.4)	741 (95.6)	693 (95.3)	1,300 (96.8)	1,549 (98.4)	575 (96.0)
Total (% of severe malaria)	15,302 (79.7)¶	3,888 (20.3)¶	775 (18.5)	726 (17.4)	1,346 (32.2)	1,573 (37.6)	598 (14.3)

Note: All numbers are national estimates based on weighted frequencies. Numbers and proportions may not sum to total or 100% due to missing values.
*Small cells were suppressed to preserve confidentiality
†All patient refined diagnosis related group (APRDRG) severity of illness and risk of mortality based on 2002-2012 data only.
‡Adjusted for inflation to 2015 US dollars.
§Income category is based on median household income by national quartiles for patient zip code.
¶Percent of all malaria hospitalizations

Table 2. Rates* of severe malaria in the US, by demographic and geography, NIS, 2000-2012

Characteristic	Uncomplicated malaria Rate	(95% CI)	Severe malaria Rate	(95% CI)	Malaria with ARDS Rate	(95% CI)	Cerebral malaria Rate	(95% CI)	Malaria with severe anemia Rate	(95% CI)	Malaria with renal failure Rate	(95% CI)	Malaria with jaundice Rate	(95% CI)
Sex														
Male	4.81	(4.51, 5.11)	1.26	(1.13, 1.39)	0.22	(0.17, 0.27)	0.23	(0.18, 0.28)	0.34	(0.28, 0.39)	0.61	(0.53, 0.69)	0.24	(0.19, 0.29)
Female	3.06	(2.84, 3.29)	0.75	(0.66, 0.84)	0.18	(0.14, 0.22)	0.14	(0.11, 0.18)	0.36	(0.30, 0.41)	0.21	(0.16, 0.25)	0.07	(0.05, 0.10)
Race														
White	1.13	(1.03, 1.24)	0.37	(0.31, 0.42)	0.11	(0.08, 0.14)	0.10	(0.07, 0.12)	0.10	(0.07, 0.12)	0.14	(0.11, 0.17)	0.05	(0.03, 0.06)
Black	13.00	(11.79, 14.22)	3.54	(3.09, 3.99)	0.48	(0.35, 0.60)	0.62	(0.47, 0.78)	1.21	(0.98, 1.44)	1.63	(1.37, 1.90)	0.54	(0.40, 0.69)
Hispanic	1.58	(1.31, 1.86)	0.31	(0.21, 0.41)	0.05	(0.01, 0.08)	0.06	(0.02, 0.10)	0.17	(0.10, 0.24)	0.08	(0.04, 0.12)	0.06	(0.02, 0.10)
API	4.19	(3.48, 4.90)	0.86	(0.56, 1.15)	0.22	(0.08, 0.35)	0.13	(0.02, 0.24)	0.40	(0.19, 0.60)	0.39	(0.22, 0.57)	0.04	(0.00, 0.09)
Age (years)														
Under 14	2.45	(2.08, 2.82)	0.40	(0.29, 0.50)	0.05	(0.01, 0.08)	0.06	(0.03, 0.10)	0.21	(0.14, 0.29)	0.06	(0.02, 0.09)	0.06	(0.03, 0.09)
15-24	5.10	(4.62, 5.58)	0.64	(0.49, 0.78)	0.12	(0.06, 0.17)	0.09	(0.04, 0.14)	0.26	(0.17, 0.36)	0.18	(0.10, 0.26)	0.13	(0.07, 0.20)
25-44	5.49	(5.10, 5.87)	1.13	(0.98, 1.28)	0.19	(0.14, 0.25)	0.14	(0.09, 0.18)	0.41	(0.32, 0.49)	0.41	(0.33, 0.50)	0.23	(0.17, 0.29)
45-64	3.73	(3.40, 4.07)	1.45	(1.27, 1.64)	0.29	(0.22, 0.36)	0.33	(0.25, 0.41)	0.44	(0.34, 0.53)	0.74	(0.62, 0.85)	0.21	(0.15, 0.27)
65 or older	2.02	(1.73, 2.30)	1.20	(0.98, 1.42)	0.38	(0.27, 0.50)	0.31	(0.21, 0.42)	0.34	(0.23, 0.46)	0.55	(0.41, 0.69)	0.06	(0.01, 0.11)
Region														
Northeast	7.60	(6.85, 8.36)	1.52	(1.28, 1.76)	0.22	(0.15, 0.3)	0.26	(0.17, 0.35)	0.53	(0.41, 0.65)	0.66	(0.52, 0.8)	0.22	(0.15, 0.28)
Midwest	2.66	(2.32, 3.01)	0.57	(0.44, 0.69)	0.16	(0.1, 0.22)	0.08	(0.04, 0.12)	0.20	(0.13, 0.27)	0.29	(0.2, 0.38)	0.12	(0.06, 0.18)
South	3.81	(3.44, 4.19)	1.19	(1.04, 1.33)	0.23	(0.18, 0.29)	0.21	(0.16, 0.26)	0.42	(0.34, 0.5)	0.48	(0.4, 0.56)	0.19	(0.14, 0.24)
West	2.47	(2.21, 2.72)	0.71	(0.58, 0.85)	0.12	(0.08, 0.16)	0.13	(0.09, 0.17)	0.17	(0.12, 0.21)	0.15	(0.11, 0.19)	0.06	(0.04, 0.09)
Total	3.95	(3.73, 4.16)	1.00	(0.90, 1.11)	0.20	(0.17, 0.23)	0.19	(0.01, 0.16)	0.35	(0.30, 0.39)	0.41	(0.36, 0.45)	0.15	(0.13, 0.18)

Note: All numbers are national estimates based on weighted frequencies. Numbers and proportions may not sum to total or 100% due to missing values.
API: Asian and Pacific Islander
*Rates per 1 million US population

Table 3. Multiple logistic regression† analysis of fatal malaria, US, NIS, 2000-2012

Covariate	OR	(95% CI)
Complication		
Malaria with ARDS	40.85	(15.37, 108.61)*
Cerebral malaria	7.01	(2.55, 19.28)*
Malaria with severe anemia	2.71	(0.97, 7.56)
Malaria with renal failure	9.33	(3.80, 22.9)*
Malaria with jaundice		-

* $p \leq 0.05$

†Separate model for each complication. All models included age (continuous), sex, race (Black vs. not Black). Age was statistically significant in all models with OR ranging from 1.05 to 1.07.

Table 4. Multiple logistic regression analysis of severe malaria, by complication, US, NIS, 2000-2012

	Outcome											
	Severe malaria		Malaria with ARDS		Cerebral malaria		Malaria with severe anemia		Malaria with renal failure		Malaria with jaundice	
Covariate	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age (ref: age 0-14)												
Age 15-24	0.72	(0.49, 1.07)	1.24	(0.45, 3.44)	0.64	(0.25, 1.62)	0.60	(0.34, 1.06)	2.29	(0.88, 5.96)	0.96	(0.39, 2.39)
Age 25-44	1.20	(0.85, 1.68)	1.87	(0.72, 4.83)	0.84	(0.38, 1.86)	0.95	(0.60, 1.49)	3.76	(1.60, 8.81)*	1.61	(0.78, 3.33)
Age 45-64	2.44	(1.70, 3.50)*	3.85	(1.50, 9.84)*	2.79	(1.28, 6.08)*	1.52	(0.92, 2.53)	9.71	(4.04, 23.33)*	2.33	(1.12, 4.85)*
Age 65+	4.44	(2.64, 7.47)*	7.36	(2.32, 23.32)*	2.26	(0.60, 8.50)	2.27	(1.04, 4.95)*	20.56	(7.45, 56.79)*	1.03	(0.39, 2.70)
Sex (ref: male)												
Female	0.97	(0.80, 1.17)	1.58	(1.10, 2.26)*	1.07	(0.76, 1.51)	1.80	(1.39, 2.34)*	0.49	(0.36, 0.66)*	0.38	(0.22, 0.66)*
Race (ref: white)												
Black	0.90	(0.72, 1.14)	0.52	(0.33, 0.83)*	0.70	(0.43, 1.14)	1.15	(0.80, 1.66)	1.14	(0.80, 1.63)	1.07	(0.62, 1.86)
Hispanic	0.55	(0.37, 0.82)*	0.32	(0.14, 0.75)*	0.57	(0.26, 1.26)	1.32	(0.76, 2.28)	0.38	(0.17, 0.85)*	0.52	(0.17, 1.55)
Other race	0.66	(0.48, 0.89)*	0.59	(0.33, 1.05)	0.40	(0.21, 0.76)*	1.30	(0.85, 1.99)	0.65	(0.41, 1.04)	0.70	(0.34, 1.44)
Comorbidity (ref: no)												
HIV	2.85	(1.48, 5.50)*		-		-		-		-		-
Diabetes	0.81	(0.58, 1.13)	1.14	(0.61, 2.14)	0.59	(0.29, 1.19)	1.14	(0.72, 1.80)	1.20	(0.78, 1.83)	0.48	(0.16, 1.40)
Hypertension	0.98	(0.75, 1.27)	0.96	(0.60, 1.53)	1.06	(0.66, 1.72)	0.75	(0.49, 1.14)	1.05	(0.74, 1.49)	0.71	(0.35, 1.43)
Income (ref: high)												
Low	1.10	(0.92, 1.33)	0.88	(0.61, 1.26)	1.09	(0.74, 1.59)	1.06	(0.81, 1.41)	1.20	(0.91, 1.60)	0.98	(0.61, 1.56)
Payer (ref: Medicare)												
Medicaid	1.26	(0.75, 2.14)	1.05	(0.39, 2.82)	0.58	(0.17, 1.96)	1.74	(0.76, 4.00)	1.96	(1.01, 3.81)*	1.16	(0.47, 2.87)
Private insurance	1.07	(0.66, 1.75)	0.87	(0.37, 2.05)	0.44	(0.15, 1.34)	1.40	(0.62, 3.16)	1.53	(0.83, 2.80)	0.96	(0.45, 2.07)
Self-pay	1.32	(0.80, 2.18)	0.96	(0.39, 2.35)	0.49	(0.15, 1.61)	1.62	(0.70, 3.76)	2.37	(1.26, 4.46)*	1.09	(0.48, 2.50)
No charge	1.09	(0.51, 2.30)	0.35	(0.04, 3.22)	0.64	(0.14, 3.00)	0.95	(0.24, 3.69)	2.00	(0.72, 5.56)	0.93	(0.19, 4.51)
Other payer	2.10	(1.13, 3.91)*	1.94	(0.70, 5.35)	0.76	(0.21, 2.80)	1.85	(0.70, 4.91)	2.44	(1.06, 5.63)*	1.43	(0.53, 3.86)
Region (ref: west)												
Northeast	0.57	(0.43, 0.76)*	0.43	(0.24, 0.76)*	0.43	(0.24, 0.76)*	0.60	(0.39, 0.93)*	0.70	(0.46, 1.07)	0.69	(0.36, 1.33)
Midwest	0.64	(0.43, 0.95)*	0.56	(0.28, 1.12)	0.35	(0.14, 0.87)*	0.59	(0.33, 1.06)	1.15	(0.63, 2.10)	0.56	(0.21, 1.52)
South	1.03	(0.78, 1.34)	0.84	(0.53, 1.33)	0.62	(0.39, 1.00)	1.03	(0.70, 1.53)	1.09	(0.74, 1.62)	1.16	(0.64, 2.07)
Location (ref: urban)												
Rural	0.58	(0.44, 0.78)*	0.66	(0.36, 1.23)	0.79	(0.45, 1.37)	0.69	(0.45, 1.07)	0.16	(0.12, 0.21)*	0.57	(0.13, 2.52)

* $p \le 0.05$

Figure 1. Number and rate of severe malaria hospitalizations in the US, NIS, 2000-2012

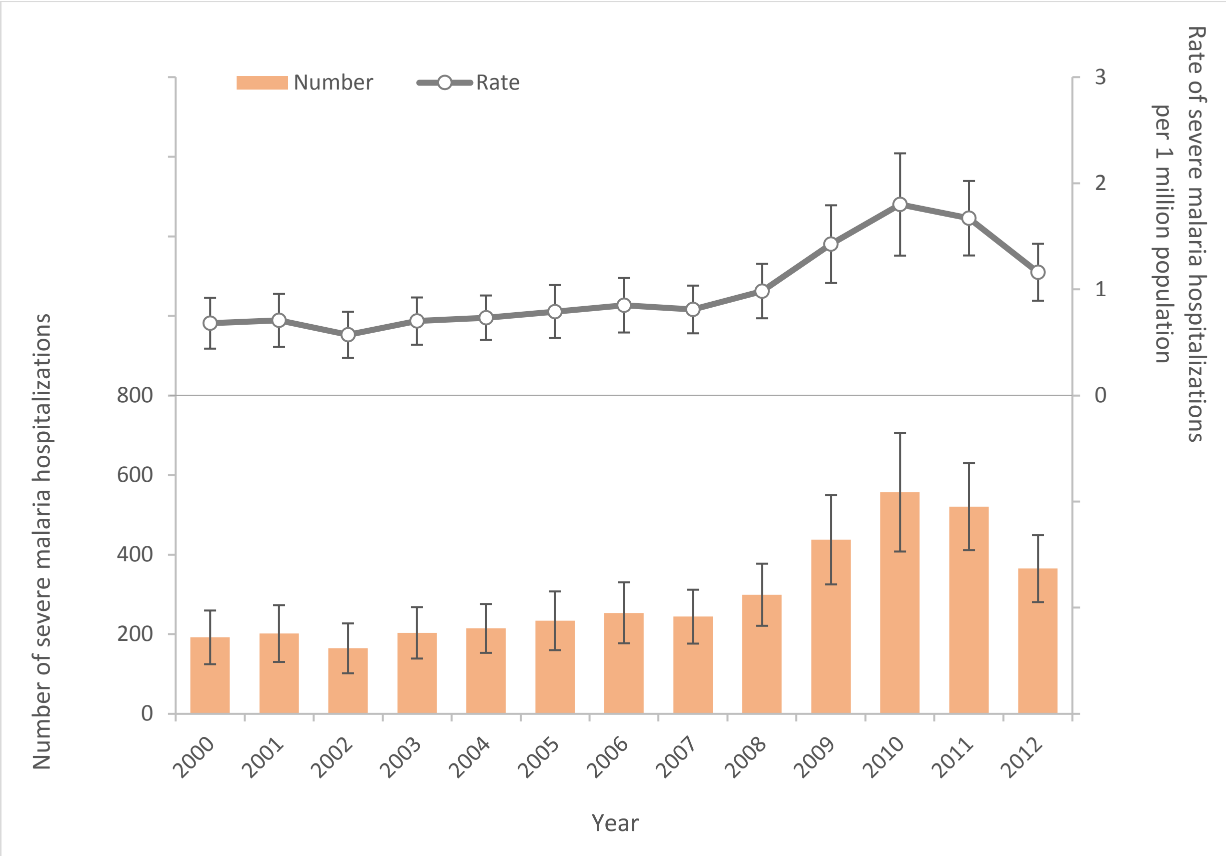
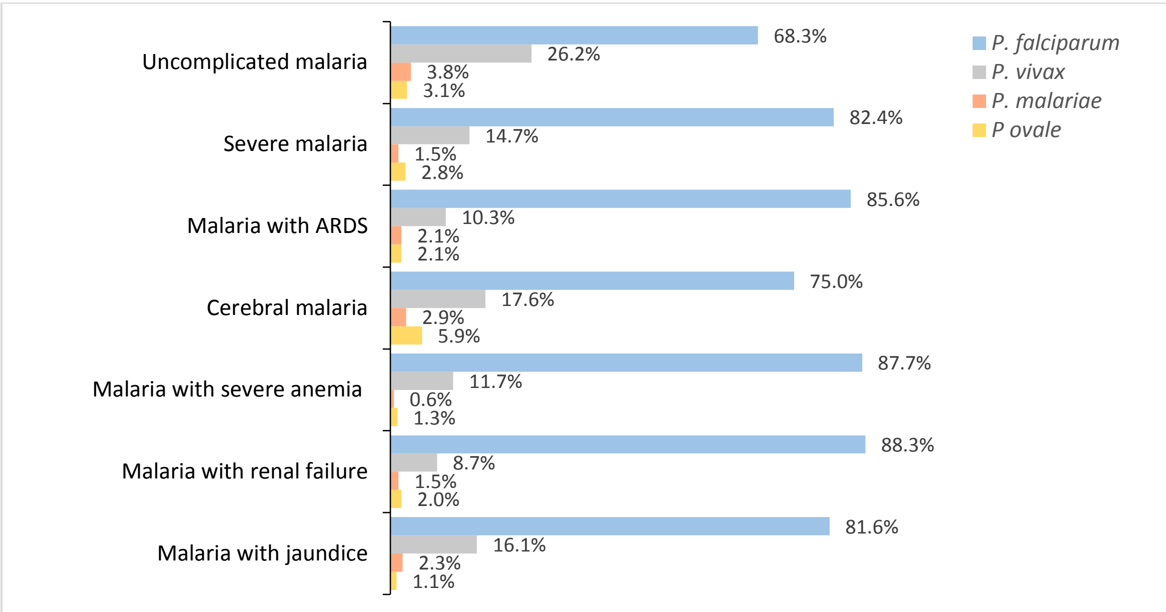


Figure 2. Uncomplicated and severe malaria hospitalizations in the US, by infecting species, NIS, 2000-2012



Note: Percents based on malaria-related hospitalizations with known infecting species. Totals may exceed 100% due to mixed infections.

Figure A1. Directed acyclic graph of relationships between variable involved with severe malaria-hospitalizations in the US

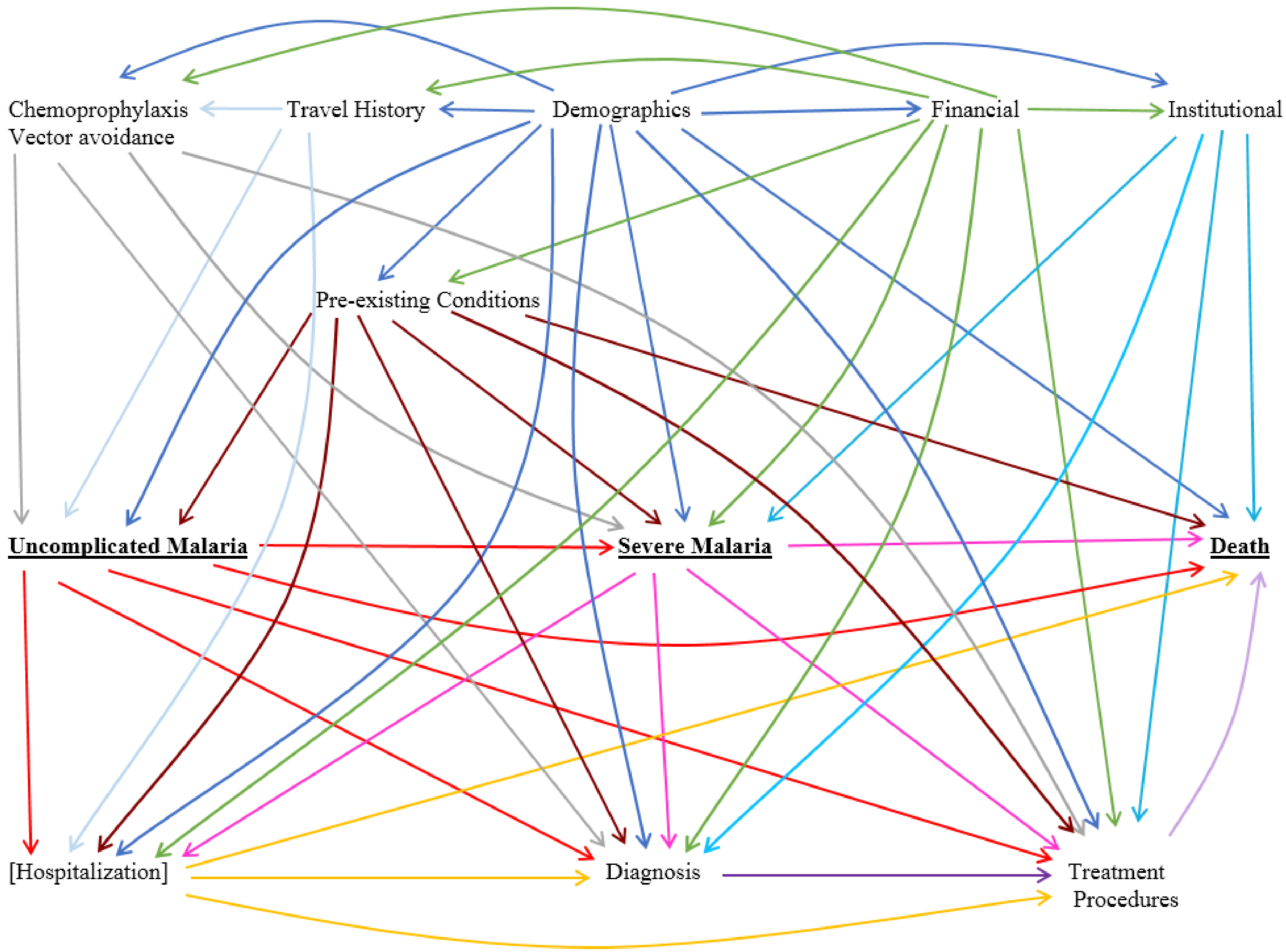
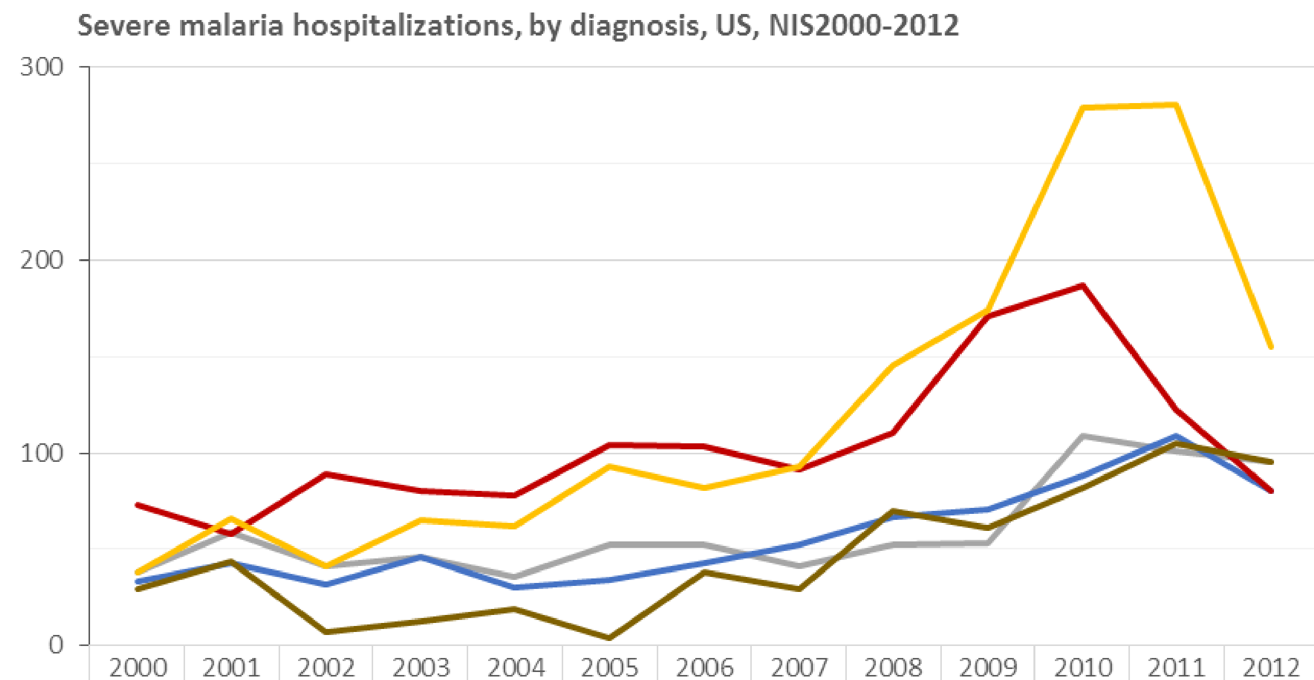


Figure A2. Severe malaria hospitalizations, by complication, US, 2000-2012



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Malaria with ARDS	38	59	41	46	36	52	52	41	52	53	109	101	95
Cerebral malaria	33	43	32	46	30	34	43	52	67	71	88	109	80
Malaria with severe anemia	73	58	89	80	78	104	103	91	110	171	187	122	80
Malaria with renal failure	38	66	41	65	62	93	82	93	145	174	279	280	155
Malaria with jaundice	29	44	*	13	19	*	38	29	70	61	82	105	95

* Small cells (<10) were suppressed to preserve confidentiality.

Table A1. Top 10 co-diagnoses of severe malaria hospitalizations in the US, by complication, NIS, 2000-2012

	Co-diagnosis	ICD-9 code	N	(%)
Malaria with ARDS	THROMBOCYTOPENIA UNSPECIFIED	287.5	272	(34.8)
	ACUTE KIDNEY FAILURE, UNSPECIFIED	584.9	200	(25.5)
	HYPOSMOLALITY AND/OR HYPONATREMIA	276.1	196	(25.5)
	PNEUMONIA ORGANISM UNSPECIFIED	486	200	(25.5)
	ANEMIA UNSPECIFIED	285.9	198	(24.8)
	SEVERE SEPSIS	995.92	178	(23.0)
	UNSPECIFIED ESSENTIAL HYPERTENSION	401.9	155	(19.9)
	SEPTICEMIA, UNSPECIFIED	038.9	149	(19.3)
	HYPOPOTASSEMIA	276.8	144	(18.6)
	ACIDOSIS	276.2	133	(17.4)
Cerebral malaria	THROMBOCYTOPENIA UNSPECIFIED	287.5	189	(25.2)
	ACUTE KIDNEY FAILURE, UNSPECIFIED	584.9	162	(21.9)
	UNSPECIFIED ESSENTIAL HYPERTENSION	401.9	156	(21.2)
	ANEMIA UNSPECIFIED	285.9	143	(19.2)
	SEPTICEMIA, UNSPECIFIED	038.9	106	(14.6)
	ACUTE RESPIRATORY FAILURE	518.81	106	(14.6)
	HYPOPOTASSEMIA	276.8	96	(13.2)
	HYPOSMOLALITY AND/OR HYPONATREMIA	276.1	97	(13.2)
	ACIDOSIS	276.2	96	(13.2)
	POSTTRANSFUSION PURPURA / OTHER SECONDARY THROMBOCYTOPENIA	287.4	80	(11.3)
Malaria with severe	THROMBOCYTOPENIA UNSPECIFIED	287.5	489	(36.2)
	ACUTE KIDNEY FAILURE, UNSPECIFIED	584.9	230	(17.0)
	HYPOSMOLALITY AND/OR HYPONATREMIA	276.1	219	(16.3)
	HYPOPOTASSEMIA	276.8	211	(15.6)
	UNSPECIFIED ESSENTIAL HYPERTENSION	401.9	205	(15.2)
	DEHYDRATION	276.51	163	(12.1)
	OTHER PANCYTOPENIA	284.1	134	(9.9)

	ACIDOSIS	276.2	125	(9.2)
	ACUTE RESPIRATORY FAILURE	518.81	124	(9.2)
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, TYPE II OR UNSPECIFIED	250.00	111	(8.2)
Malaria with renal failure	THROMBOCYTOPENIA UNSPECIFIED	287.5	655	(41.3)
	ANEMIA UNSPECIFIED	285.9	404	(25.5)
	UNSPECIFIED ESSENTIAL HYPERTENSION	401.9	387	(24.3)
	DEHYDRATION	276.51	345	(21.9)
	HYPOSMOLALITY AND/OR HYPONATREMIA	276.1	337	(21.6)
	HYPOPOTASSEMIA	276.8	252	(15.8)
	ACIDOSIS	276.2	236	(15.2)
	ACUTE RESPIRATORY FAILURE	518.81	210	(13.4)
	SEVERE SEPSIS	995.92	208	(13.4)
	SEPTICEMIA, UNSPECIFIED	038.9	196	(12.5)
Malaria with jaundice	THROMBOCYTOPENIA UNSPECIFIED	287.5	324	(53.6)
	ANEMIA UNSPECIFIED	285.9	204	(34.4)
	DEHYDRATION	276.51	113	(19.2)
	HYPOSMOLALITY AND/OR HYPONATREMIA	276.1	114	(19.2)
	ACUTE KIDNEY FAILURE, UNSPECIFIED	584.9	86	(14.4)
	HYPOPOTASSEMIA	276.8	75	(12.8)
	UNSPECIFIED ESSENTIAL HYPERTENSION	401.9	68	(11.2)
	POSTTRANSFUSION PURPURA / OTHER SECONDARY THROMBOCYTOPENIA	287.4	59	(10.4)
	HEADACHE	784.0	59	(9.6)
	DIARRHEA	787.91	51	(8.8)

Note: All numbers are national estimates based on weighted frequencies.

*Percent of malaria complication-specific hospitalizations.

Table A2. Top 10 primary diagnoses among severe malaria hospitalizations with a secondary malaria diagnosis in the US, NIS, 2000-2012

Primary diagnosis	ICD-9	N	%
SEPTICEMIA, UNSPECIFIED	038.9	135	(14.2)
OTHER SPECIFIED SEPTICEMIAS	038.8	52	(5.5)
ACUTE RESPIRATORY FAILURE	518.81	38	(4.0)
ACUTE KIDNEY FAILURE, UNSPECIFIED	584.9	34	(3.3)
OTHER SPECIFIED REHABILITATION PROCEDURE	V57.89	32	(3.3)
HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE	042	28	(3.0)
PNEUMONIA ORGANISM UNSPECIFIED	486	24	(2.5)
OBSTRUCTIVE CHRONIC BRONCHITIS WITH ACUTE EXACERBATION	491.21	19	(1.6)
FEVER, OTHER DISTURBANCE OF TEMPERATURE REGULATION	780.6	15	(1.6)
ACQUIRED HEMOLYTIC ANEMIA UNSPECIFIED	283.9	14	(1.5)

Table A3. Top 10 procedures performed for severe malaria hospitalizations in the US, NIS, 2000-2012

Procedure	CCS	N	%
Blood transfusion	222	1,581	(40.7)
Other vascular catheterization, not heart	54	674	(17.3)
Respiratory intubation and mechanical ventilation	216	608	(15.6)
Other therapeutic	231	317	(8.2)
Diagnostic spinal tap	4	292	(7.5)
Hemodialysis	58	252	(6.5)
Other non-OR therapeutic cardiovascular procedures	63	228	(5.9)
Enteral and parental nutrition	223	158	(4.1)
Diagnostic bronchoscopy and biopsy of bronchus	37	154	(4.0)
Diagnostic ultrasound of heart (echocardiogram)	193	142	(3.7)