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Research paper

Risk factors for severe malaria among hospitalized patients in the United States, 2000–2014

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KEYWORDS
Malaria;
Hospitalization;
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Abstract *Background:* Factors associated with the development of severe malaria have not been well described for cases occurring in the United States (US).
Methods: Severe malaria hospitalizations data from the 2000–2014 Nationwide Inpatient Sample were analyzed. Frequencies were reported by demographic, clinical, species, financial, geographic, and institutional characteristics, and trends and disparities were identified. Logistic regression models were used to identify potential predictors for severe disease among those with malaria.
Results: From 2000 to 2014, there were an estimated 4823 severe malaria cases, representing 21.9% of all malaria-related hospitalizations, including 182 severe malaria deaths. Severe malaria was most common among inpatients who were male, Black, aged 45–64 years, and hospitalized in the South Atlantic division of the US. Older age was associated with higher odds of severe malaria, cerebral 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. HIV infection was associated with increased odds of severe malaria, severe anemia, and renal failure.
Conclusion: Primary and secondary prevention measures, such as pre-travel consultations, chemoprophylaxis, and early diagnosis and treatment, should be emphasized and improved among high-risk prospective travelers to malaria endemic countries.
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Highlights

- There were an estimated 4823 severe malaria-related hospitalizations from 2000 to 2014 in the US.
- *Pf* accounted for most of the severe malaria-related hospitalizations, followed by *Pv, Po,* and *Pm*.
- Severe malaria was most common among inpatients who were male, Black, and aged 45—64 years.
- We found associations with severe malaria or specific complications for age, sex, and HIV.

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. The WHO estimated that 212 million cases of malaria, and 429,000 deaths due to malaria occurred in 2015 [1], though others have estimated that the number of deaths may be much higher [2]. 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 infective female *Anopheles* mosquito. These competent vectors have widespread distribution throughout the world, including the United States [3].

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, 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. Malaria can progress to severe and fatal disease, even with prompt treatment [3].

The CDC publishes an annual malaria report that discusses reported cases of malaria in the US. This 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]. Some studies have suggested the risk of uncomplicated and severe malaria is unevenly distributed across different subpopulations of travelers [5,7,8]. However, despite the large disease and economic burden [9], the factors associated with the development of severe disease due to malaria infection 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 patient characteristics and to identify potential risk factors for severe malaria, which could be used to target interventions for high-risk travelers to improve health care or the clinical outcomes of malaria in the US. This paper focused on severe malaria follows our previous paper on the overall malaria hospitalization burden [9].

Methods

Hospital discharge records from the Nationwide Inpatient Sample (NIS) were used for analysis of severe malaria-related hospitalizations in the US during 2000—2014. 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 includes data on sociodemographics, diagnosis type, disease severity, length of stay, co-diagnoses, institutional characteristics, and total charges. Details on the sampling scheme have been described elsewhere [10,11].

Cases of malaria in the NIS from 2000 to 2014 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) 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) [12].

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 [5]. Malaria complications were identified using ICD-9 codes and HCUP Clinical Classification Software (CCS) categories, which are clinically meaningful categories of ICD-9 codes [13]. 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 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 (deficiency 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. Malaria-related hospitalizations with an in-hospital death were also considered as severe malaria cases.

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