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Analysis of Trends in International Travel and the Impact on Domestic Malaria, United States, 2000-2009

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BS
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2013

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
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2015

Abstract

Analysis of Trends in International Travel and the Impact on Domestic Malaria, United States, 2000-2009
By Caroline Pilewski

Malaria has been eliminated from the United States, yet approximately 1,500 people are diagnosed with the disease in the US every year after having traveled to malaria endemic countries; particularly travel from West Africa. Worldwide travel is increasing and infectious diseases are being spread due to both the greater numbers of international travelers and the decreased time that it takes to cross borders and continents. This analysis used poisson regression to examine trends in cases of malaria imported into the United States in relation to changes in global travel. Data on imported malaria cases were taken from CDC's National Malaria Surveillance System (NMSS). The years of NMSS data that were utilized were from 2000 to 2009; after exclusion the dataset included 11,025 cases of malaria. Worldwide travel data came from the United Nations World Tourism Organization (UNWTO). The analysis did not support travel being a primary influence on the increase of imported cases that the United States has seen in recent years. Holding all other variables constant, the rate of malaria in the US would decrease by 0.1% with every increase in 100,000 travelers entering the US. However, the rate of malaria in the US attributable to travel to West Africa was 9.15 times higher than the rate of malaria in the US attributable to the referent group of Central Africa, which suggests that interventions targeted towards travelers to West Africa may still be very helpful towards the goal of lowering the number of imported cases into the United States.

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CHAPTER I

Malaria is a parasitic disease caused by the intraerythrocytic protozoa of the genus *Plasmodium* that is spread via the bite of an infected female *Anopheles* mosquito (1). Four species of *Plasmodium* cause disease in humans–*P. falciparum, P. vivax, P. malariae,* and *P. ovale*. A fifth, *P. knowlesi,* has caused infections in humans after they have had contact with macaque monkeys (2). Most of the cases imported into the United States are *P. falciparum* (1, 3). *P. falciparum* and *P. vivax* are the most common causes worldwide, with *P. falciparum* causing the most severe cases of malaria (1, 2). In 2012, 207 million cases of malaria occurred worldwide, resulting in 627,000 deaths (4, 5).

According to the World Health Organization (WHO), an estimated 3.4 billion of the world's population (nearly half of the total estimated 7.13 billion) are at risk for malaria; 1.2 billion are at high risk (4). As of 2013, malaria was found in 97 countries (4). The region where the risk for malaria is highest is in Sub-Saharan Africa–90% of all deaths in 2013 due to malaria were in the region (4). Oceania also has a high risk for malaria, but fewer people live and travel to the areas in which malaria is endemic, compared to Sub-Saharan Africa.

In order to produce eggs, the female *Anopheles* mosquito typically consumes a blood meal. The *Anopheles* mosquitoes are dusk to dawn feeders (2). Once a human has been bitten by an infected mosquito and the parasites enter the liver, the *Plasmodium* replication stage begins (6). After an incubation period of as little as 8–14 days, the host can become symptomatic once the parasites leave the liver and start lysing erythrocytes (6, 7). The parasitemia, or the level of parasites in the blood, is a measure of the severity

of the illness; a higher parasitemia corresponds to greater severity of illness. Subclinical infections can also occur (7).

P. vivax and *P. ovale* are unique in that a second liver phase can occur after the initial infection. In this stage, hypnozoites are formed and might not be released into the blood stream for months or years, often leading to a relapse (7). Infection with the other *Plasmodium* species does not lead to a relapse.

Clinically, malaria is classed as an acute febrile illness. Unlike other tropical febrile illnesses, such as typhoid, malaria is associated with high spiking fevers and chills (2, 8). The pattern of fevers and chills in the patient is usually random, although some patients present with a tertian fever (fever occurring every three days) or a quartan fever (every four days) (2). In severe cases, the most common complications are acute respiratory distress syndrome (ARDS), renal failure, jaundice, and cerebral malaria (9, 10).

Because the initial symptoms of malaria can be non-specific, laboratory tests are important to confirming diagnoses. Malaria can be diagnosed with microscopy (thin or thick blood smears), rapid diagnostic tests (RDTs), and molecular tools (nested polymerase chain reaction (PCR) and real-time PCR) (11). Most cases can be diagnosed using a thin blood smear; if the thin blood smear comes back negative, a thick blood smear can be used (2). Although the latter is more difficult to read, because the blood sample is thicker and more concentrated, thick blood smears are more sensitive in detecting parasites (10). Three negative tests are recommended before confirming that the patient does not have malaria (12).

In recent years, health workers have been able to perform RDTs in areas where there is little to no lab capacity (2), but microscopy is still considered the gold standard for diagnosis (11). In the United States, all RDT results must be confirmed by either microscopy or PCR (11). Unlike RDTs or PCR tools, microscopy enables a technician to determine parasitemia. Both microscopy and PCR provide information on *Plasmodium* species identification; with PCR able to provide information on the specific species present in the case of mixed infections (11). Because PCR is the most sensitive diagnostic tool, it is able to diagnose cases with low parasitemia, which can be difficult via microscopy (13).

Depending on how quickly a patient is diagnosed, most cases of malaria can be easily treated (12, 14). Treatment should not occur until a positive diagnosis is made, with the exception of severe cases (10). The prescribed course of treatment will vary depending on: the confirmed *Plasmodium* species; the current status of the patient; and the possible drug susceptibility of the parasites, which depends on the geographic location where the infection was acquired and whether chemoprophylaxis was used (10). If a patient took chemoprophylaxis, that particular medicine should not be included in the treatment (10). Uncomplicated cases should be treated with a course of oral antimalarials. Severe cases should be treated with intravenous therapy, including quinidine and artesunate. Intravenous artesunate is available as an investigational new drug (IND) through CDC (10, 12).

A primary public health goal for malaria is to reduce the number of cases, which requires prevention measures. There is currently no vaccine to prevent malaria, therefore successful prevention is a combination of chemoprophylaxis and bite avoidance. While

correct adherence to prophylaxis is very effective at lowering the risk of contracting malaria, no regimen is 100% effective and simply taking an antimalarial is not enough to ensure protection (9). The type of antimalarial prescribed depends on several factors: parasitic drug resistance in the geographic area of travel, contraindications in the patient, and the personal preference of the patient (14). A clinician must know where the traveler is going because some areas of the world have begun to develop drug resistance. For example, *P. falciparum* has a near-universal resistance to chloroquine. Depending on the travel destination, if a person is traveling to an area where *P. falciparum* is most prominent, their doctor should consider an antimalarial other than chloroquine (14). Travelers are advised to seek a pre-departure appointment with a physician who specializes in travel medicine and who can best advise them on prophylaxis and other prevention measures.

Treating malaria cases is a great financial burden on the healthcare payer. It is estimated that treating a single case of malaria costs $25,250, whereas it costs $161-$208 for the traveler to have a pre-travel consultation and take chemoprophylaxis (15). Although not 100% effective, correct adherence to chemoprophylaxis and proper bite prevention measures can greatly reduce the likelihood of contracting malaria (9, 15, 16).

All travelers to regions where malaria is endemic, regardless of whether or not they are taking chemoprophylaxis, should also undertake bite avoidance precautions. This might mean sleeping under an insecticide-treated bed net (ITN), spraying skin with mosquito repellent, and wearing proper clothing (7, 14). The CDC currently recommends using repellants that contain at least one of the following four ingredients: diethyltoluamide (DEET), oil of lemon eucalyptus or PMD, IR3535, and picaridin (6,

17). *Anopheles* mosquitoes are dusk to dawn feeders and being protected overnight and while sleeping is especially important.

As has been discussed, a risk factor for acquiring malaria is improper use of prophylaxis (either taking it improperly or not taking it altogether) and improper bite avoidance measures. A related risk factor is seeking pre-travel advice (18). Travelers who seek pre-travel health consultations are more likely to take prophylaxis and adhere to behavioral measures that help lower the risk of malaria.

The group of travelers that is most at-risk for contracting malaria is the group that falls under the "visiting friends and relatives" (VFR) category. VFRs are described as "immigrants, ethnically and racially distinct from the major population of their country of residence (a country where malaria is not endemic), who return to their homeland (a country where malaria is endemic) to visit friends or relatives" (19). Unlike people who travel for business or tourism, VFRs are more likely to be long-term travelers and stay in rural areas, are less likely to take prophylaxis, and are less compliant with bite avoidance precautions (14, 20). If a VFR traveler was born in the country of travel, they might assume that they still retain acquired immunity to malaria. However, for VFRs who emigrated a decade or more ago from the endemic country, their acquired immunity has waned and will no longer protect them from acquiring malaria (20). Travelers from the US are increasingly likely to fall into the VFR category; in 2012 two-thirds of the imported cases were reported as VFRs (19-21).

Travelers and tourists are not the only people who enter the United States' borders every year. There are a significant number of refugees who move to the United States from countries where malaria is endemic. Of particular concern are refugees arriving

from sub-Saharan Africa; previous studies have shown that people can arrive in the United States with sub-clinical *P. falciparum* infections (22). Current CDC recommendations are that all refugees planning to move to the United States should take pre-departure antimalarial therapy to ensure that any potential sub-clinical infections are eliminated before the refugee moves to the US (22).

Malaria has been eliminated from the United States (23), yet approximately 1,500 people are diagnosed with the disease in the US every year after having traveled to malaria endemic countries (1). In 2012, the most recent year for published figures, the CDC received 1,687 reported cases of domestic malaria, with six fatalities (19). Of these, 1,683 (99.8%) cases were classified as imported and 66% were acquired in West Africa (19). In 2011, 1,925 cases were received, which marked the largest number of cases since 1971 (1).

The *Anopheles* mosquito is still found in the United States (24), and even one case returning to the country brings a risk that the disease will return. Because worldwide travel is increasing and infectious diseases are being spread due to both the greater numbers of international travelers and the decreased time that it takes to cross borders and continents, it is likely that the number of imported cases will continue to increase (21, 25-27). In 2000, 674 million international arrivals were documented worldwide; in 2010 this number was estimated at 935 million (25, 28). Outbound travel from the United States increased 13% from 52 million in 1995 to 58.7 million in 2011 (29). Approximately 18 million US travelers visit malaria-endemic countries each year (2).

Few reports discuss malaria cases in the context of greater worldwide travel and often risks and rates cannot be calculated. Previous reports have attempted to calculate

country- and region-specific risks (14, 30) but no prior research has examined the impact of global travel on cases of malaria imported in the United States. Since there is no transmission of malaria occurring in the United States, this analysis can ensure that the cases of malaria are travel-related and not a result of local transmission.

This analysis will examine trends in imported cases of malaria imported into the United States in relation to changes in global travel. In order to ensure that the cases of malaria are travel-related and not a result of local transmission, the data source needed to examine this relationship would need to be from a country with no endemic malaria. Hence, we chose to use the National Malaria Surveillance System (NMSS) from the United States.

This report will be able to provide a greater international context to increasing imported cases of malaria. With the data provided by the National Malaria Surveillance System (NMSS), which contributes health practice and behavior data, this analysis will depict trends in domestic malaria and worldwide travel figures to better understand and predict trends in malaria in the United States (18).

CHAPTER II

Malaria is a parasitic disease caused by the intraerythrocytic protozoa of the genus *Plasmodium* that is spread via the bite of an infected female *Anopheles* mosquito (1). Four species of *Plasmodium* cause disease in humans–*P. falciparum, P. vivax, P. malariae*, and *P. ovale*. A fifth, *P. knowlesi*, has caused infections in humans after they have had contact with macaque monkeys (1, 2). Most of the cases imported into the United States are *P. falciparum* (3). *P. falciparum* and *P. vivax* are the most common causes worldwide, with *P. falciparum* causing the most severe cases of malaria (1, 2). In 2012, 207 million cases of malaria occurred worldwide, resulting in 627,000 deaths (4).

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A primary public health goal for malaria is to reduce the number of cases, which requires prevention measures. There is currently no vaccine to prevent malaria, therefore successful prevention is a combination of chemoprophylaxis and bite avoidance. While correct adherence to prophylaxis is very effective at lowering the risk of contracting malaria, no regimen is 100% effective and simply taking an antimalarial is not enough to ensure protection (9). Travelers are advised to seek a pre-departure appointment with a

physician who specializes in travel medicine and who can best advise them on prophylaxis and other prevention measures.

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The *Anopheles* mosquito is still found in the United States (31), and even one case returning to the country brings a risk that the disease will return. Because worldwide travel is increasing and infectious diseases are being spread due to both the greater numbers of international travelers and the decreased time that it takes to cross borders and continents, it is likely that the number of imported cases will continue to increase (21, 25, 26). In 2000, 674 million international arrivals were documented worldwide; in 2010 this number was estimated at 935 million (25, 28). Outbound travel from the United States increased 13% from 52 million in 1995 to 58.7 million in 2011 (29). Approximately 18 million US travelers visit malaria-endemic countries each year (2).

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METHODS

Data sources

This study used data on malaria cases in the United States from CDC's National Malaria Surveillance System (NMSS). NMSS is the oldest federal surveillance system and receives approximately 1,500 case reports annually (32). Malaria is a nationally-notifiable disease and healthcare practitioners are required to report laboratory-confirmed cases to their local or state health departments (1, 33). Cases are reported electronically through the National Notifiable Diseases Surveillance System (NNDSS), but this system does not currently have the capability to receive specific information about each case. To supplement the NNDSS information, the CDC's Malaria Branch receives malaria-specific information on cases of malaria in the US directly from states and from clinicians who call the CDC Malaria Hotline asking for medical advice on diagnosis and treatment of cases. NMSS collects information on patient demographics, laboratory data, clinical data, and travel data. The years of NMSS data that were utilized were from 2000 to 2009; this dataset includes 14,085 cases of malaria.

The variables used in the analysis from the NMSS dataset were: year of disease onset, percentage of cases reporting no prophylaxis use, and percentage of cases classified as VFRs. No prophylaxis use was self-reported and defined as having taken no prophylaxis. VFR classification was defined as the percentage of total cases that listed reason for travel as visiting friends and relatives.

Data on worldwide travel data came from the United Nations World Tourism Organization (UNWTO), which reports annual data on global travel. The UNWTO collects data from each country on the number of travelers entering that country by the traveler's country of origin or citizenship. This dataset included both inbound and outbound figures. For this study, outbound travel was defined as the number of people who entered other countries from the United States. Inbound travel was defined as someone entering the United States from another country. Within the UNWTO outbound data, there were twelve possible categories for which a country could choose to report data (see: Appendix A.1). Most countries reported data for only one of the categories, although some reported data in more than one category. No single category contained the reported data for all countries. Therefore, a schema was developed to identify the order of categories to be used (see: Appendix A.2). We assumed that those individuals traveling from the US to other countries would be returning to the United States. The travel burden was calculated as the sum of inbound and outbound travelers. This enabled the analysis to capture both foreign visitors to the United States and US citizens who were returning after travel abroad. The UNWTO data used in this analysis was for 2000 to 2009 (34-37).

In addition to travel burden, this analysis included data on malaria burden by country. The World Health Organization (WHO) publishes an annual World Malaria

Report; data from the 2013 World Malaria Report were used to define country-specific malaria burden (4). Malaria burden was defined as the annual number of presumed and confirmed cases reported by a country. This analysis used presumed and confirmed cases because it was the most sensitive disease burden measure reported by the WHO.

Both the WHO and UNWTO datasets report data for countries that were not used in this analysis. While there are countries that contribute both to the greater worldwide travel and disease burden due to malaria, if there were no imported US cases that reported travel to that country, that country and its corresponding data was not included in the analysis.

Analysis

Due to the small number of cases for individual countries, the data was collapsed into larger geographic areas, rather than analyzed at a country-level. Fourteen subregions were used to analyze the data: Caribbean, Central Africa, Central America, Central Asia, Eastern Africa, Eastern Asia, Middle East, Northern Africa, Oceania, South America, Southeast Asia, Southern Africa, Southern Asia, and Western Africa.

Cases that had unknown travel history (n=2,372) or did not specify the country of travel (n=676) were excluded from analysis due to the inability to connect those cases to a particular country and its travel and disease burden. Cases identified as having been imported from the East Asia subregion were excluded from the analysis due to low annual cases numbers (n=12). After exclusion, n=11,025 cases remained for analysis.

All data management and analysis were conducted using SAS (v 9.1.3, Cary, NC, USA). Poisson regression analysis was used to examine the relationship between cases of malaria and travel burden by subregion after accounting for other confounders. The

outcome was the number of malaria cases reported per year in the United States by subregion of acquisition. The main variable of interest was travel burden by subregion. Other potential variables of interest were: subregion of acquisition, percent of cases reporting no prophylaxis use, percent of cases reporting travel to visit friends/relatives, and disease burden for the subregion of acquisition. The expected number (λ) of cases imported from a subregion can be expressed as:

$$\lambda = E \exp(\beta_0+\beta_1X_1+ \beta_2X_2+\ldots+ \beta_pX_p)$$

where E is the main exposure of interest, travel burden, $X_1,\ldots,X_p$ are potential risk factors, and $\beta_0, \beta_1,\ldots, \beta_p$ are the regression coefficients.

Prior to regression analysis, the variables for no reported prophylaxis use and VFR status were analyzed to test for collinearity. The collinearity cutoff was a variance inflation factor (VIF) greater than 10. The VIF for both variables was 1.06 and therefore it was determined that they were not collinear.

The data used for this analysis was deidentified, but proposals were sent to both Emory University and CDC Institutional Review Boards (IRBs) for review as an exempt study.

RESULTS

A total of 14,085 cases of imported malaria were reported to the NMSS during the study period. The annual reported figures during the study period were relatively stable, with 1,398 cases in 2000 and 1,481 in 2009. The years with the most cases were 2005 and 2006, which both had 1,547 imported cases. Although the number of imported cases did increase during the study period, the global linear trend was not statistically significant (P=0.28).

West Africa was the most common subregion of acquisition with 40% (n=5,642) of cases reported in the US during the study period reporting travel to West Africa. The country from which the most cases reported having traveled from was Nigeria (n=2,531). After Nigeria, Ghana (n=1,231) and India (n=1,142) had the most cases. Cases who reported visiting Nigeria, Ghana, or India accounted for almost 35% of the total burden of imported malaria for this time period. Tables 1 and 2 present the distribution of cases by region/subregion and country of acquisition by year

The travel burden to and from countries where imported cases acquired malaria increased over the study period ($P<0.001$). In 2000, the UNWTO database reported that over 46 million travelers entering the United States had recently come from countries where an imported case would later claim recent travel. By 2005, this figure increased to nearly 55 million (Figure 1). The actual travel burden for the United States is much higher, but this analysis was only interested in the UNWTO data pertaining to countries from which the NMSS had a case.

Travelers to and from Central America contributed the largest number to the overall travel burden, with a yearly average of 34 million. Within Central American, Mexico contributed the largest number of travelers, with a yearly average of 31.5 million travelers being reported. While West Africa was the most frequently reported subregion of travel for cases, overall worldwide travel estimates indicate a low travel burden for the region. The average annual travel burden for the region was 193,000.

The disease burden reported by WHO increased, on average, 6% each year, going from 153 million estimated cases of malaria worldwide in 2000 to 254 million in 2009. Southern Asia (countries such as India and Pakistan) had the highest estimated disease

burden, with an annual average of 110 million cases during this time period, followed by Eastern Africa (n=42 million) and Western Africa (n=17 million). Overall trends indicate a marked increase in yearly overall disease burden ($P<0.001$) (Figure 1).

Overall, 33% (n=4,613) of all cases in the US reported that the reason for their travel was to visit friends/relatives. The percentage of VFRs increased from 2000 to 2005 ($P=0.02$) and decreased during the rest of the study period ($P=0.01$). In 2000, 27% all of cases were VFRs and 33% of cases were VFRs in 2009 (Figure 2). The overall trend was not statistically significant ($P=0.80$). Cases returning from West Africa were most likely to have VFR as reason for travel, with over half (52%) of the total cases being classified as VFR.

During the study period, there was an increase in NMSS cases reporting no prophylaxis use ($P<0.001$). Overall, 78% of cases did not report using any prophylaxis. The subregion for which the highest percentage of cases did not report prophylaxis use was West Africa, at 77%.

The results of the poisson regression analysis are shown in Table 3. The variables representing the percentage of VFRs and no reported prophylaxis use were not significant after backwards elimination but were kept in the final model due to their significance in prior studies (14, 20, 21). The significant factors associated with imported cases were travel burden, disease burden ($P<0.001$), and every subregion, with the exception of Southern Africa.

Holding all other variables constant, the rate of malaria in the US would decrease by 0.1% with every increase in 100,000 travelers entering the US. However, for every increase in the global disease burden of 100,000 cases, the rate of malaria imported into

the United States would increase by 0.03%. Additionally, an increase of one percent in VFRs among US cases would increase the rate of malaria by 0.9%; an increase of one percent in travelers not reporting any prophylaxis use would decrease the rate of malaria by 0.1%.

The rate of malaria in the US attributable to travel to West Africa was 9.15 times higher (95% CI: 8.92, 9.39) than the rate of malaria in the US attributable to travel in Central Africa. The rate attributable to travel in South Asia was 2.10 times higher (95% CI: 1.18, 3.73) than the rate for Central Africa. The rate of malaria attributable to travel to Southeast Asia was 0.867 times (95% CI: 0.77, 0.97) the rate for Central Africa.

DISCUSSION

Imported cases of malaria to the United States neither drastically increased during the time period from 2000 to 2009 nor decreased. While reported cases did steadily decline from 2000 to 2003 (P=0.02), cases increased in 2004 and annual figures have been around 1500 cases a year. Actual case figures are most likely higher, due to underreporting and undiagnosed cases. Guedes *et al* and Ladhani *et al* reported similar overall patterns in imported cases of malaria in Finland and in childhood cases in the United Kingdom, respectively (38, 39).

Travelers returning from West Africa represent the largest percentage of imported cases; the rate of cases in travelers returning from the subregion is significantly higher than others (RR: 9.19, 95% CI: 8.96, 9.43). Travelers to West Africa are also more likely than in other subregions to be classified as a VFR and to not report prophylaxis use. Despite the fact that an increase in travel burden was associated with a decrease in the number of cases in the United States, interventions targeted towards travelers to West

Africa to improve prophylaxis use may still be very helpful towards the goal of lowering the number of imported cases into the United States.

Although worldwide travel did increase slightly during the study period (Figure 1), the analysis does not support it being a primary influence on the increase of imported cases that the United States has seen in recent years. Countries where malaria is endemic, especially countries where disease burden is highest, do not appear to be seeing the increase in travelers that other countries are seeing which has been contributing to the overall worldwide increase. Studies conducted by Behrens *et al* in the United Kingdom and Fonseca *et al* in Portugal on incidence rates of imported malaria saw a similar relationship between overall travel and disease incidence. It was found that, while travel increased during the study period, the incidence of malaria did not (40, 41). Contrary to travel burden, disease burden due to malaria did markedly increase from 2000 to 2009 (Figure 1) and was associated with an increase in imported cases.

The model did not find statistically significant associations between VFR status and lack of prophylaxis, associations that had been found in previous studies (40, 42, 43). Given the preexisting evidence in the literature that these two factors are known risk factors for acquiring malaria in imported cases, future interventions should target increasing prophylaxis use among all travelers; especially those that are visiting friends and relatives.

The results of this study need to be interpreted in the light of several limitations. First, 3,060 cases were excluded from the final analysis due to missing information on country of travel, prophylaxis use, reason for travel. Most of these were cases were only reported to CDC through the NNDSS and only included basic demographic information

on the case. The NNDSS does not have the ability to receive malaria-specific information about each case, such as country of acquisition. CDC asks that state health departments also report malaria-specific information directly to the Malaria Branch at CDC, but not all cases are reported through this additional mechanism. The majority of the excluded cases were from later years, indicative of an increase in electronic reporting by states through the NNDSS. This increase in excluded cases resulted in an artificial trend in the data towards a decreasing case incidence over time (Figure 3). This limitation illustrates the importance of complete and detailed surveillance data. A second surveillance-related limitation is that the NMSS system only counts those travel-related cases that are diagnosed in the United States. Travelers who fall ill and are treated while abroad are not captured in the system. This contributes to an overall underestimation of the true amount of travelers from the United States that acquire malaria while in endemic areas.

The UNWTO and WHO datasets are not without their own limitations. Not all countries submit data on travel to the UNWTO, nor do all of the countries who do submit data do so using the same methodology and degree of completeness. Some countries lack the means to exhaustively document all guests crossing their borders, which could lead to an overall underestimation of the travel burden. The figures utilized in the model from the WHO dataset represent the number of presumed and confirmed cases for each country. Although this methodology was specifically chosen due to its sensitivity, this could lead to an overestimation of cases.

Nonetheless, the NMSS, UNWTO, and WHO datasets are all robust and ten years of data were utilized from each in the analysis. While not every imported case of malaria is reported to NMSS, it is estimated that the system captures the majority of imported

cases because most will seek medical attention and a diagnosis requires laboratory confirmation (32). When completed properly, NMSS case reports can provide important information about imported malaria. This is the first time that imported cases into the United States have been examined relative to global travel and disease burden. Likewise, both the UNWTO and WHO datasets are the most complete sources of data of their kind.

Notwithstanding the conclusions based off of the model, it is clear that the disease burden due to malaria is increasing in many countries. While the lack of prophylaxis and VFR status are known risk factors for imported malaria, we believe that the best allocation of resources would be towards lowering the disease burden, particularly in West African countries. However, despite the fact that decreasing disease burden will result in the greatest decrease in cases in the United States, we still need to reach out to travelers to encourage use of prophylaxis. VFRs, in particular, are a group for which prophylaxis use is low and could benefit from this outreach.

CHAPTER III

Nearly half of the estimated 7.13 billion people on the planet are said to be at risk for malaria (4, 5). Worldwide travel is increasing and infectious diseases are being spread due to both the greater numbers of international travelers and the decreased time that it takes to cross borders and continents.

While malaria has been eliminated from the United States (23), approximately 1,500 people are diagnosed with the disease in the United States every year after having traveled to malaria endemic countries (1). The *Anopheles* mosquito is still found in the United States (24), and even one case returning to the country brings a risk that the disease will return.

From 2000 to 2009, 14,085 cases of imported malaria were reported to NMSS. The actual number of imported cases is most likely higher, due to underreporting and undiagnosed cases. The majority of these cases were in travelers who had recently returned from West Africa.

After conducting our analysis, we have three primary recommendations for future directions. First, we believe that the best allocation of resources for future interventions would be towards lowering the disease burden in malaria endemic countries, particularly in West Africa. Second, although the analysis does not support worldwide travel being a primary influence on the increase of imported cases that the United States has seen in recent years, we recommend that interventions targeted towards travelers to West Africa to improve prophylaxis use may still be very helpful towards the goal of lowering the number of imported cases into the United States. Last, despite the fact that decreasing burden will result in the greatest decrease in cases in the United States, we still need to

reach out to travelers to encourage use of prophylaxis. VFRs, in particular, are a group for which prophylaxis use is low and could benefit from this outreach.

APPENDICES

Appendix A: UNWTO Data

A.1: Categories in UNWTO Outbound Dataset

Arrivals of non-resident tourists at national borders, by nationality

Arrivals of non-resident tourists at national borders, by country of residence

Arrivals of non-resident visitors at national borders, by nationality

Arrivals of non-resident visitors at national borders, by country of residence

Arrivals of non-resident tourists in hotels and similar establishments, by nationality

Arrivals of non-resident tourists in hotels and similar establishments, by country of residence

Overnight stays of non-resident tourists in hotels and similar establishments, by nationality

Overnight stays of non-resident tourists in hotels and similar establishments, by country of residence

Arrivals of non-resident tourists in all types of accommodation establishments, by nationality

Arrivals of non-resident tourists in all types of accommodation establishments, by country of residence

Overnight stays of non-resident tourists in all types of accommodation establishments, by nationality

A.2: Schema for Outbound Categories

The following list is based off of the amount of missing data in each category and the degree to which each category resembles another. If a country reports information in the

first category ("Arrivals of non-resident tourists at national borders, by country of residence"), those figures will be used in the data analysis. If a country does not report data in that first category, the second will be looked at for figures. This continues until the last category in the schema ("Overnight stays of non-resident tourists in all types of accommodation establishments, by nationality").

1. Arrivals of non-resident tourists at national borders, by country of residence
2. Arrivals of non-resident tourists at national borders, by nationality
3. Arrivals on non-resident visitors at national borders, by nationality
4. Arrivals of non-resident visitors at national borders, by country of residence
5. Arrivals of non-resident tourists in hotels and similar establishments, by country of residence
6. Arrivals of non-resident tourists in all hotels and similar establishments, by country of residence
7. Arrivals of non-resident tourists in all types of accommodation establishments, by country of residence
8. Arrivals of non-resident tourists in all types of accommodation establishments, by country of residence
9. Overnight stays of non-resident tourists in all types of accommodation establishments, by country of residence
10. Overnight stays of non-resident tourists in hotels and similar establishments, by country of residence
11. Overnight stays of non-resident tourists in hotels and similar establishments, by nationality

12. Overnight stays of non-resident tourists in all types of accommodation establishments, by nationality

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TABLES

Table 1: Number of Imported Cases, by Region and Subregion of Acquisition and Year—United States, 2000-2009

Region of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Africa	**783**	**886**	**902**	**840**	**809**	**917**	**784**	**743**	**545**	**716**
Central Africa	58	50	74	70	54	49	48	35	26	16
Eastern Africa	133	157	146	138	133	160	104	143	60	91
Northern Africa	10	9	6	7	6	7	8	10	8	12
Southern Africa	6	16	6	9	11	9	4	1	4	3
Western Africa	528	613	631	568	563	648	586	521	426	558
Africa, Unspecified	48	41	39	48	42	44	34	33	21	36
Asia	**229**	**160**	**167**	**167**	**170**	**200**	**198**	**246**	**189**	**162**
Central Asia	23	9	23	8	9	4	4	16	1	0
Eastern Asia	2	2	2	1	1	2	0	2	0	0
Southeast Asia	21	14	20	12	5	13	15	23	31	37
Southern Asia	183	135	121	146	154	181	179	205	157	122
Asia, Unspecified	0	0	1	0	1	0	0	0	0	3
Central America and the Caribbean	**231**	**194**	**106**	**117**	**139**	**177**	**91**	**112**	**43**	**81**
South America	**57**	**43**	**35**	**33**	**34**	**37**	**27**	**20**	**6**	**22**
Oceania	**22**	**19**	**37**	**37**	**36**	**30**	**22**	**27**	**10**	**7**
Middle East	**8**	**3**	**4**	**10**	**2**	**5**	**6**	**7**	**1**	**2**
Western Asia	7	3	4	10	2	5	5	7	1	1
Middle East, Unspecified	1	0	0	0	0	0	1	0	0	1
Unknown	**68**	**71**	**80**	**67**	**134**	**181**	**419**	**356**	**505**	**491**
Total	***1398***	***1376***	***1331***	***1271***	***1324***	***1547***	***1547***	***1511***	***1299***	***1481***

Table 2: Number of Imported Cases, by Country of Acquisition and Year—United States, 2000-20009

Country of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Africa	**783**	**886**	**902**	**840**	**809**	**917**	**784**	**743**	**545**	**716**
Algeria	1	0	0	0	1	0	0	0	0	0
Angola	8	4	0	3	2	2	2	1	0	2
Benin	5	3	3	2	3	0	7	5	3	6
Botswana	1	3	0	0	0	0	0	0	0	0
Burkina Faso	4	4	9	2	6	2	7	4	7	9
Burundi	1	1	1	0	3	3	0	13	0	1
Cameroon	28	25	47	41	36	27	23	23	16	0
Central African Republic	1	2	6	1	0	3	0	1	2	1
Chad	1	0	4	2	2	3	5	0	1	1
Comoros	0	0	0	1	0	0	0	0	0	0
Congo, Republic of	10	15	10	16	11	10	11	5	0	8
Côte d'Ivoire	43	29	39	18	26	24	20	24	34	32
Democratic Republic of Congo	2	0	2	1	2	0	3	0	5	2
Djibouti	0	0	0	0	4	0	0	0	0	0
Egypt	0	0	0	0	0	0	1	1	0	0
Equatorial Guinea	0	2	1	3	0	1	4	2	1	2
Eritrea	2	0	1	1	0	1	1	0	0	0
Ethiopia	9	16	16	12	15	15	9	7	11	17
Gabon	7	1	3	3	0	3	0	2	1	0
Gambia	23	9	8	20	6	8	3	6	4	2
Ghana	130	179	138	122	95	139	113	120	96	99
Guinea	16	13	10	23	15	28	30	18	21	25
Guinea-Bissau	0	0	0	0	1	0	0	0	0	0
Kenya	39	49	52	59	40	53	23	20	6	15
Liberia	34	37	39	22	27	31	28	46	0	24

Country of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Libya	1	0	0	0	0	1	0	0	0	0
Madagascar	7	7	4	1	5	4	1	1	0	0
Malawi	3	8	8	4	2	3	5	3	1	9
Mali	18	18	12	11	8	4	15	13	3	13
Mauritania	6	4	2	2	1	1	0	0	0	0
Morocco	0	0	0	1	0	0	0	0	0	0
Mozambique	7	7	2	5	6	9	6	8	7	3
Namibia	0	0	0	0	0	1	0	0	1	0
Niger	3	0	3	4	6	2	3	0	0	0
Nigeria	177	258	309	240	278	305	283	233	194	254
Rwanda	3	5	1	0	4	2	0	2	1	3
Senegal	30	11	20	34	14	26	14	14	17	10
Sierra Leone	9	17	17	42	51	47	33	24	22	50
Somalia	2	0	2	1	1	3	1	1	2	1
South Africa	5	11	6	9	10	8	4	1	3	2
Sudan	8	9	6	6	5	6	7	9	8	12
Tanzania	19	15	10	8	5	6	6	48	6	2
Togo	6	5	7	5	8	9	6	4	10	11
Uganda	26	35	30	38	37	49	46	38	21	25
Zambia	7	7	13	4	8	9	2	0	0	2
Zimbabwe	7	6	3	4	3	2	2	0	1	1
Central Africa, unspecified	1	1	1	0	1	0	0	1	0	0
East Africa, unspecified	1	1	3	0	0	1	2	2	4	12
Southern Africa, unspecified	0	2	0	0	1	0	0	0	0	1
West Africa, unspecified	24	26	15	21	18	22	24	10	15	23
Africa, unspecified	48	41	39	48	42	44	34	33	21	36
Asia	**229**	**160**	**167**	**167**	**170**	**200**	**198**	**246**	**189**	**162**

Country of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Afghanistan	2	0	2	13	13	22	42	26	21	8
Bangladesh	2	2	0	0	0	0	0	1	0	0
Bhutan	1	0	0	0	0	0	0	0	0	0
Burma	1	6	3	0	1	1	1	7	3	2
Cambodia	1	2	0	2	1	2	4	2	1	20
China	2	2	2	1	1	2	0	2	0	0
India	139	81	90	100	113	138	121	151	115	94
Indonesia	23	37	16	9	5	11	8	12	4	3
Korea, North	0	1	0	0	0	0	0	0	0	0
Korea, South	23	8	23	8	9	4	4	15	1	0
Laos	1	3	3	1	1	0	0	0	19	0
Malaysia	0	0	0	1	0	0	1	1	0	0
Nepal	0	1	0	1	1	0	0	0	0	0
Pakistan	15	14	13	23	21	10	8	15	17	17
Philippines	6	1	7	1	1	2	0	2	1	2
Sri Lanka	1	0	0	0	1	0	0	0	0	0
Taiwan	0	0	0	0	0	0	0	1	0	0
Thailand	8	2	4	4	0	5	7	10	6	12
Vietnam	0	0	1	2	1	2	1	1	0	0
Southeast Asia, unspecified	4	0	2	1	0	1	1	0	1	1
Asia, unspecified	0	0	1	0	1	0	0	0	0	3
Central America and the Caribbean	**231**	**194**	**106**	**117**	**139**	**177**	**91**	**112**	**43**	**81**
Bahamas	0	0	0	2	0	0	1	0	0	0
Belize	3	4	0	1	3	9	0	1	0	0
Costa Rica	4	2	3	3	7	4	3	0	0	0
Dominican Republic	0	0	1	1	4	8	3	11	0	4
El Salvador	35	23	7	4	8	12	1	1	0	0

Country of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Guadeloupe	1	0	0	0	0	0	0	0	0	0
Guatemala	28	38	22	16	23	12	16	12	4	3
Haiti	15	41	22	23	26	38	15	34	19	58
Honduras	95	54	29	42	45	73	36	32	16	12
Jamaica	0	0	0	0	0	0	2	0	0	0
Mexico	30	21	10	21	18	15	10	13	3	2
Nicaragua	13	5	3	2	1	3	4	4	1	1
Panama	1	1	7	1	0	0	0	4	0	0
Central America, unspecified	6	5	2	1	4	3	0	0	0	0
Caribbean, unspecified	0	0	0	0	0	0	0	0	0	1
South America	**57**	**43**	**35**	**33**	**34**	**37**	**27**	**20**	**6**	**22**
Argentina	0	1	0	0	0	0	0	0	0	0
Bolivia	1	0	0	1	0	0	2	0	0	0
Brazil	12	4	5	7	9	10	13	11	2	4
Colombia	3	0	0	1	3	6	0	0	0	3
Ecuador	30	21	16	5	4	3	5	0	0	0
French Guiana	0	0	0	0	0	1	0	1	0	1
Guyana	8	8	7	7	11	8	3	1	2	13
Peru	2	5	2	8	6	6	2	4	2	1
Suriname	1	0	0	0	0	0	1	1	0	0
Venezuela	0	1	4	1	0	2	0	0	0	0
South America, unspecified	0	3	1	3	1	1	1	2	0	0
Oceania	**22**	**19**	**37**	**37**	**36**	**30**	**22**	**27**	**10**	**7**
Marshall Islands	0	0	0	1	0	0	0	0	0	0
Papua New Guinea	19	18	33	29	30	24	17	23	9	6
Solomon Islands	3	0	2	1	2	2	0	2	1	1
Vanuatu	0	1	2	3	4	4	5	1	0	0

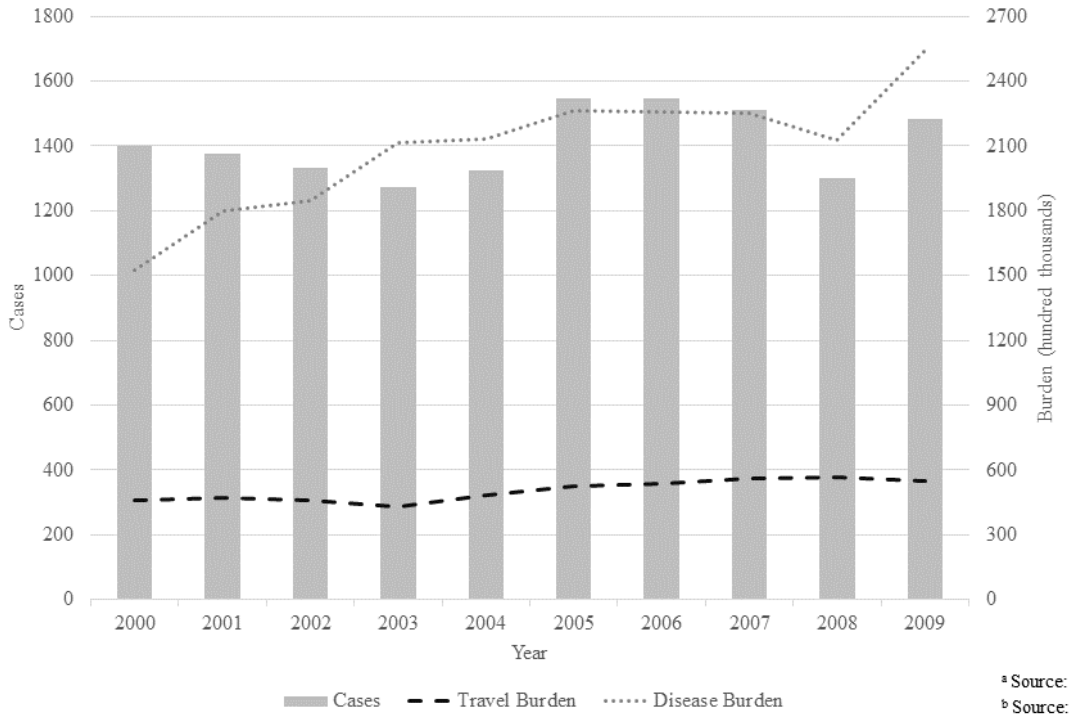
Country of Acquisition	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Oceania, unspecified	0	0	0	3	0	0	0	1	0	0
Middle East	**8**	**3**	**4**	**10**	**2**	**5**	**6**	**7**	**1**	**2**
Iran	2	0	0	0	0	0	0	0	0	0
Iraq	0	1	1	8	0	3	4	4	1	0
Saudi Arabia	1	0	0	0	1	1	1	1	0	1
Turkey	1	0	0	0	0	0	0	0	0	0
United Arab Emirates	0	0	1	0	0	0	0	0	0	0
Yemen	3	2	2	2	1	1	0	2	0	0
Middle East, unspecified	1	0	0	0	0	0	1	0	0	1
Unknown	**68**	**71**	**80**	**67**	**134**	**181**	**419**	**356**	**505**	**491**
Total	***1398***	***1376***	***1331***	***1271***	***1324***	***1547***	***1547***	***1511***	***1299***	***1481***

Table 3: Poisson regression analysis of imported malaria incidence—United States, 2000-2009

Characteristics	**Incidence Rate Ratio (IRR)**	**(95% CI)**
Intercept	—	—
Travel Burden (in hundred thousands)	0.999	0.9988, 0.9999
Disease Burden (in hundred thousands)	1.003	1.0018, 1.0033
Visiting Friends/Relatives (%)	1.009	0.9984, 1.0200
No Reported Prophylaxis (%)	0.999	0.9951, 1.0030
Region of Travel		
Africa		
Central Africa	—	—
East Africa	2.780	2.3259, 3.3226
Northern Africa	1.527	1.5274, 1.2408
Southern Africa	1.059	0.9684, 1.1585
West Africa	9.154	8.9239, 9.3910
Asia		
Central Asia	3.080	1.9462, 4.8757
Southeast Asia	0.867	0.770, 0.9667
Southern Asia	2.099	1.1800, 3.7347
Caribbean	3.288	2.8643, 3.7738
Central America	3.940	3.0846, 5.0312
South America	1.510	1.1209, 2.0329
Oceania	2.843	1.6855, 4.7938
Middle East	0.284	0.2112, 0.3807

FIGURES

Figure 1: Number of Imported Cases of Malaria to the United States [a], Travel Burden of Arrivals to the United States [b], and Disease Burden [c]—United States, 2000-2009



[a] Source: NMSS
[b] Source: UNWTO Tourism Data
[c] Source: WHO World Malaria Report

Figure 2: Trends in Imported Cases, VFRs (%), and No Reported Prophylaxis Use (%)—United States, 2000-2009

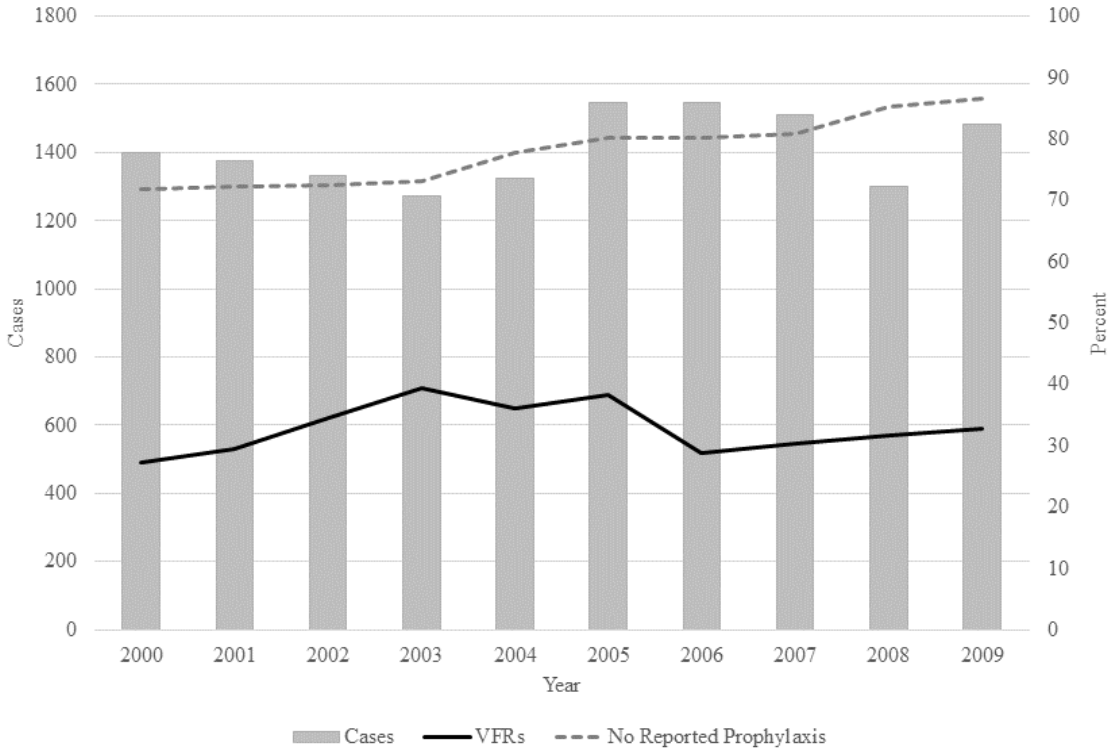


Figure 3: Trends in Imported Cases post-Exclusion—United States, 2000-2009