Prevalence of Malaria Parasite Infections among U.S.-Bound Congolese Refugees with and without Splenomegaly

Moses Mwesigwa,1 Jessica L. Webster,2,3 Sam Lubwama Nsobya,4 Alexander Rowan,5 Mukunda Singh Basnet,1 Christina R. Phares,2 Michelle Weinberg,2 Alexander Klosovsky,1 Marwan Naoum,1 Philip J. Rosenthal,6 and William M. Stauffer2,7*

1International Organization for Migration, Kampala, Uganda; 2Centers for Disease Control and Prevention, Atlanta, Georgia; 3Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee; 4Department of Pathology, School of Biomedical Sciences, Makerere University, Kampala, Uganda; 5Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; 6Department of Medicine, University of California, San Francisco, California; 7Departments of Medicine and Pediatrics, University of Minnesota, Minneapolis, Minnesota

Abstract. All U.S.-bound refugees from sub-Saharan Africa receive presumptive antimalarial treatment before departing for the United States. Among U.S.-bound Congolese refugees, breakthrough malaria cases and persistent splenomegaly have been reported. In response, an enhanced malaria diagnostic program was instituted. Here, we report the prevalence of plasmodial infection among 803 U.S.-bound Congolese refugees who received enhanced diagnostics. Infections by either rapid diagnostic test (RDT) or PCR were detected in 187 (23%) refugees, with 78 (10%) by RDT only, 35 (4%) by PCR only, and 74 (9%) by both. Infections identified by PCR included 103 monoinfections (87 Plasmodium falciparum, eight Plasmodium ovale, seven Plasmodium vivax, and one Plasmodium malariae) and six mixed infections. Splenomegaly was associated with malaria detectable by RDT (odds ratio: 1.8, 95% CI: 1.0–3.0), but not by PCR. Splenomegaly was not strongly associated with parasitemia, indicating that active malaria parasitemia is not necessary for splenomegaly.

During 2013–2019, more than 50,000 Congolese refugees living in east Africa resettled to the United States. During 2014–2015, 14% of Congolese refugees resettling to the United States from the Kyangwali Refugee Settlement in the Kikuube district of Uganda were noted to have splenomegaly.1 A subsequent investigation of splenomegaly in Congolese refugees resettled to the United States highlighted malaria infection as a relatively common condition, although the definitive etiology of splenomegaly in this population was not determined.2 These observations led to enhanced diagnostics for malaria infection testing for U.S.-bound Congolese refugees from Kikuube district, Uganda, to better manage malaria by detecting additional cases and by providing species-specific treatment. We determined the prevalence of plasmodial infection among 803 U.S.-bound Congolese refugees evaluated under this enhanced diagnostics program.

As part of the U.S. Refugee Resettlement Program, all U.S.-bound refugees originating in sub-Saharan Africa receive presumptive predeparture treatment with artemether/lumefantrine (AL), unless contraindicated, as recommended by the U.S. CDC to prevent symptomatic Plasmodium falciparum malaria disease during travel or following arrival. Treatment is administered in a standard 3-day course under direct observation and should be completed no sooner than 5 days before departure.

In 2015, in response to the observed high prevalence of splenomegaly in U.S.-bound Congolese refugees, the CDC added diagnosis and management recommendations, stating that all refugees with clinical splenomegaly (enlargement of the spleen) identified at their initial medical examination (occurring 3–6 months before departure to the United States) should receive a malaria rapid diagnostic test (RDT; SD Bioline Malaria Ag P.f/Pan test, Abbott Diagnostics Korea Inc., Gyeonggido, Republic of Korea) and, if positive, receive antimalarial treatment with AL. In addition, the CDC recommended that all refugees with splenomegaly receive primaquine after arrival in the United States, if glucose-6-phosphate dehydrogenase activity is normal, to presumptively eliminate Plasmodium vivax and Plasmodium ovale hypnozoites.

Despite these recommendations, many refugees had persistent splenomegaly months to years after arrival in the United States.2 In addition, there were increasing reports of breakthrough malaria, particularly Plasmodium malariae despite predeparture treatment with AL,2 which was of concern because of increasing reports of AL treatment failure for P. malariae infections.3 Because P. malariae has been well associated with splenomegaly,4–6 the reports of P. malariae in Congolese refugees raised additional concern that the documented persistent splenomegaly could be related to inadequate malaria presumptive treatment, especially if baseline prevalence of P. malariae infection was higher than expected.

In response to these concerns, and given the continuing high burden of malaria in U.S.-bound Congolese refugees from Uganda, the CDC expanded its guidance for malaria testing and treatment in 2018 to include the RDT for P. falciparum for all Congolese refugees (with or without splenomegaly) plus PCR. Refugees with a positive RDT and those diagnosed with splenomegaly (with or without a positive RDT) were treated with AL at the initial examination (approximately 6 months before departure).7 In addition, when PCR results became available (at a later date), refugees with positive results who had not previously received appropriate treatment based on species, or had a newly identified infection, were offered treatment.8 It should be noted that in addition to enhanced diagnostics and treatment at initial medical evaluation, all refugees without a contraindication (including those who received previous treatment based on a positive RDT, positive PCR, or diagnosis of splenomegaly) received AL treatment completed no sooner than 5 days before departure for the United States, consistent with previous guidance.9 An outline of this guidance is provided in Table 1.
The program was instituted to enhance the diagnosis and management of malaria in U.S.-bound Congolese refugees. The goal of this evaluation is to retrospectively report prevalence of malaria based on enhanced testing and to correlate the malaria findings with detection of splenomegaly. The proposed evaluation was reviewed by a CDC human subject advisor and determined to be a non-research evaluation of program activities.

Malaria RDT results were interpreted by International Organization for Migration laboratory personnel. DNA was extracted from blood dried on Whatman 3-MM filter paper with Chelex (Cetiva, Marlborough, MA), with nested PCR amplification of species-specific sequences of 18S subunit ribosomal RNA genes and discrimination of species by electrophoresis of amplicons, as described previously. Clinical data, including the presence of splenomegaly and RDT results, were collected retrospectively from medical records.

During February–March 2018, 803 refugees had a physical examination including an abdominal examination and tested for malaria parasites by RDT and PCR. Demographic characteristics were compared between individuals with and without detectable malaria infections using chi-squared tests. Adjusted odds ratios and 95% CIs were calculated using multivariable logistic regression models. All models were adjusted for age, gender, family size, and birth country.

This cohort consisted of an approximately equal number of women (51%) and men (49%), with age largely less than 55 (median = 14, interquartile range = 6–28) years; 41% were born in Uganda to Congolese parents, and 59% were born in the Democratic Republic of the Congo (DRC). A total of 187 (23%) refugees were positive by either RDT or PCR, 78 (10%) were positive by malaria RDT only, 35 (4%) were positive by malaria PCR only, and 74 (9%) were positive by both RDT and PCR. In the 109 infections identified by PCR, 87 (80%) had monoinfections with *P. falciparum*, eight (7.3%) with *P. ovale*, seven (6.4%) with *P. vivax*, one (0.9%) with *P. malariae*, and six (5.5%) mixed infections (Table 2).

Most (75%) malaria infections detected by PCR were among children aged 14 years and younger. The highest prevalence of infection was in those aged 6–14 years (24%) and the lowest in those aged 25–54 years (5%). In the adjusted regression analysis (Table 3), odds of malaria infection detected by PCR were more than four times higher among children aged 6–14 years than adults aged 25–54 years (OR = 4.6, 95% CI = 1.3–15.6) and almost seven times higher among adults aged 55 years or older than that in the same reference group (OR = 6.6, 95% CI = 2.1–20.5).

### Table 2

Demographic characteristics and screening results of U.S.-bound Congolese refugees screened for malaria and splenomegaly, Uganda, 2018

| Variable                  | n (%)     | (N = 803) |
|---------------------------|-----------|-----------|
| Age (years)               |           |           |
| 0–2                       | 94 (12%)  |           |
| 3–5                       | 94 (12%)  |           |
| 6–14                      | 227 (28%) |           |
| 15–24                     | 151 (19%) |           |
| 25–54                     | 201 (25%) |           |
| 55+                       | 36 (4%)   |           |
| Median (interquartile range) | 14 (6–28) |           |
| Gender                    |           |           |
| Male                      | 393 (49%) |           |
| Female                    | 410 (51%) |           |
| Family size               |           |           |
| 1–3                       | 131 (17%) |           |
| 4–7                       | 319 (40%) |           |
| 8+                        | 353 (44%) |           |
| Nationality               |           |           |
| DRC                       | 800 (99.6%) |         |
| Rwanda                    | 3 (0.4%)  |           |
| Birth country             |           |           |
| DRC                       | 328 (41%) |           |
| Rwanda                    | 2 (0.3%)  |           |
| Uganda                    | 473 (59%) |           |
| Malaria rapid diagnostic test results |       |           |
| Negative                  | 651 (81%) |           |
| Positive                  | 152 (19%) |           |
| Malaria PCR results       |           |           |
| Negative                  | 694 (86%) |           |
| Positive                  | 109 (14%) |           |
| *P. falciparum*           | 87 (80%)  |           |
| *P. malariae*             | 1 (1%)    |           |
| *P. ovale*                | 8 (7%)    |           |
| *P. vivax*                | 7 (6%)    |           |
| *P. falciparum* and *P. malariae* | 1 (1%)    |           |
| *P. falciparum* and *P. ovale* | 3 (3%)    |           |
| *P. falciparum* and *P. vivax* | 1 (1%)    |           |
| *P. falciparum*, *P. ovale*, and *P. malariae* | 1 (1%)    |           |
| Splenomegaly              |           |           |
| Negative                  | 711 (89%) |           |
| Positive                  | 92 (11%)  |           |

* CDC = Centers for Disease Control and Prevention; RDT = rapid diagnostic test; PCR = polymerase chain reaction; DRC = Democratic Republic of Congo; *P. falciparum* = *Plasmodium falciparum*; *P. malariae* = *Plasmodium malariae*; *P. ovale* = *Plasmodium ovale*; *P. vivax* = *Plasmodium vivax*. 

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**Table 1**

Overview of the CDC’s guidance for malaria and splenomegaly in U.S.-bound refugees, 2007–2018

| Year of implementation | Population | Recommendation |
|------------------------|------------|----------------|
| 2007                   | All U.S.-bound refugees originating in sub-Saharan Africa | Prededeparture treatment with artemether/ lumefantrine (AL) unless contraindicated Standard 3-day course under direct observation Completed no sooner than 5 days before departure |
| 2015                   | All refugees with splenomegaly identified at initial medical examination | Receive a malaria RDT (SD Bioline Malaria Ag P.f/Pan test) If positive, antimalarial treatment with AL Clinicians providing care for refugees with splenomegaly directed to treat with primaquine (PQ), if glucose-6-phosphate dehydrogenase (G6PD) activity is normal |
| 2018                   | All Congolese refugees (with or without splenomegaly) | Testing for malaria at initial examination expanded to include the RDT for *Plasmodium falciparum* plus PCR |
|                        | Refugees with positive RDT and all refugees with splenomegaly (with or without positive RDT) | Treatment with AL at initial examination |
|                        | Refugees with positive PCR results who were not treated previously | Treatment with AL for blood-stage infection followed by a 2-week course of PQ (if G6PD normal) for those who had *Plasmodium ovale* or *Plasmodium vivax* infections |

RDT = rapid diagnostic test.
Malaria was prevalent in U.S.-bound Congolese refugees living in Kikuube district, Uganda, in February–March 2018. Splenomegaly was prevalent in this population at rates similar to those found in 2014. Efforts to delineate the optimal treatment regimen for malaria in the population before migration to the United States would be beneficial, particularly as 18% of PCR-positive samples had P. ovale or P. vivax. Traditionally, presumptive treatment has not focused on relapsing (P. vivax and P. ovale) forms of malaria because U.S.-bound refugees have mostly not originated in areas with high prevalence of these parasites. In light of the prevalence of P. ovale and P. vivax that is higher than that expected in Congolese refugees, presumptive treatment for relapsing malaria in some refugee populations should be reconsidered. There was no clear direct association between malaria parasitemia and splenomegaly, indicating that active malaria parasitemia is not necessary for splenomegaly or that splenomegaly persists over time despite parasite clearance. Nonetheless, the background high prevalence of malaria infection suggests a likely role for malaria infection in the etiology of splenomegaly, as previously suggested. Despite anecdotal reports of high prevalence of P. malariae infection in Congolese refugees, < 1% of detected species were P. malariae in this program. The small number of P. malariae cases identified suggests this species is not a driver of splenomegaly. Etiologies other than malaria that could account for or contribute to splenomegaly should be further explored.

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Authors’ addresses: Moses Mwesigwa and Mukunda Singh Basnet, International Organization for Migration; Kampala, Uganda, E-mails: mmwesigwa@iom.int and mbasnet@iom.int. Jessica L. Webster, Centers
for Disease Control and Prevention, Oak Ridge Institute for Science and Education; Atlanta, GA, E-mail: jlw494@drexel.edu. Sam Lubwama Nsobya, Department of Pathology, School of Biomedical Sciences, Makerere University, Kampala, Uganda, E-mail: samnsobya@yahoo.co.uk. Alexander Rowan, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, E-mail: arr011@jefferson.edu. Christina R. Phares and Michelle Weinberg, Centers for Disease Control and Prevention; Atlanta, GA, E-mails: ctp7@cdc.gov and mpw5@cdc.gov. Alexander Klosovsky, International Organization for Migration, Washington, DC, E-mail: aklosovsky@iom.int. Marwan Naoum, International Organization for Migration, Nairobi, Kenya, E-mail: nnmarwan2@iom.int. Philip J. Rosenthal, Department of Medicine, University of California, San Francisco, San Francisco, CA, E-mail: philip.rosenthal@ucsf.edu. William Stauffer, Centers for Disease Control and Prevention, University of Minnesota, Departments of Medicine and Pediatrics, Minneapolis, MN, E-mail: stauf005@umn.edu.

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