

BLOOD PRODUCTS ADVISORY COMMITTEE

May 9, 2024

Topic: Proposed strategies to reduce the risk of transfusion-transmitted malaria by testing donations from donors at risk of malaria exposure for the presence of *Plasmodia* spp. nucleic acid

Issue:

We (the Food and Drug Administration (FDA)) are seeking advice from the Blood Products Advisory Committee (BPAC or Committee) on proposed strategies to reduce the risk of transfusion-transmitted malaria (TTM) by selectively testing donations from donors at risk of malaria exposure for the presence of *Plasmodia* spp. using an FDA-licensed nucleic acid test (NAT). Specifically, we request that the Committee discuss the possible advantages and disadvantages of FDA's proposed selective NAT strategies to test donations from donors at risk for malaria, owing to a history of a malaria diagnosis or prior residence in a country endemic for malaria (i.e., malaria-endemic country) or travel to a geographic area endemic for malaria (i.e., malaria-endemic area), as determined by the donor history questionnaire (DHQ). The Committee is also asked to comment on the possible advantages and disadvantages of testing donations for *Plasmodia* spp. nucleic acid in areas in the United States (U.S.) when public health authorities detect and report local mosquito-borne malaria transmission.

Background:

Malaria is primarily a mosquito-borne disease caused by infection with *Plasmodia* parasites. In 2022, malaria occurred in more than 85 countries and caused approximately 249 million cases and 608,000 deaths worldwide [1]. Young children in sub-Saharan Africa accounted for about 80% of these deaths [1]. A list of malaria-endemic countries and malaria-endemic areas is

reported and periodically updated by CDC at

<http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx>. Five recognized species of *Plasmodium* parasites are known to infect humans

and can cause illness:

P. falciparum, *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*. Clinical malaria is typically recognized as high fevers, shaking chills, and flu-like illness, although asymptomatic, chronic infection can also occur. *P. falciparum* typically causes the most severe clinical symptoms and is responsible for more than 90% of malaria-associated deaths [1]. *P. vivax*, the second most prevalent *Plasmodium* species, typically causes less severe disease and much lower mortality compared to *P. falciparum* malaria. Most individuals with malaria will clear the infection within 1-3 years. People who live in malaria-endemic countries may develop partial immunity to malaria from frequent exposure to *Plasmodia* spp. Partial immunity does not protect these individuals from *Plasmodium* spp. infection but lessens symptoms and prolongs parasitemia, such that subclinical malaria might persist for years [2].

In the U.S., malaria was eradicated in the 1950s and is no longer endemic. Almost all individuals found to have malaria in the U.S. acquired the infection during travel to malaria-endemic countries or during a period of prior residence in such countries. Each year, approximately 28 million U.S. residents travel to parts of world where malaria is endemic and about 2,000 imported cases of clinical malaria are reported annually in the U.S. Of all cases where country of origin was known, the majority (85%) of cases were imported from Africa [3].

Locally-acquired (autochthonous) mosquito-borne malaria transmission is rare in the U.S. In 2003, 8 cases of autochthonous *P. vivax* malaria were reported in Palm Beach County, Florida [4]. No autochthonous cases were reported again until in 2023, when 10 cases of locally acquired, mosquito-borne malaria occurred in four geographically-diverse U.S. states – Florida (*P. vivax*, 7

cases), Texas (*P. vivax*, 1 case), Maryland (*P. falciparum*, 1 case) and Arkansas (*P. vivax*, 1 case) [5-7]. Consequently, mosquito-borne transmission may represent a new source of risk of malaria exposure among blood donors during local outbreaks in the U.S.

Although most cases of malaria worldwide result from local mosquito-borne transmission, malaria can also be transmitted through transfusion of blood and blood components collected from asymptomatic, infected donors, or less commonly through organ transplantation or congenital transmission from a mother to fetus [8-10]. In 2001, the Centers for Disease Control and Prevention (CDC) published a comprehensive study on characteristics and number of TTM cases reported from 1963 through 1999 [8]. A total of 93 TTM cases were reported in 28 states, of which 10 TTM cases were fatal (11%).

More recently, a total of 13 cases of TTM (average 0.59/year) were reported in literature between 2000 to 2021. Nine of the 13 cases were caused by *P. falciparum* (72.7%); 2, by *P. malariae* (18.1%); and 2, by *P. ovale* (9%) [3, 11-14]. Twelve of 13 blood components implicated in causing TTM in the U.S. since 2000 were donated by prior residents of sub-Saharan Africa; the origin of country of residence of one donor could not be ascertained. Furthermore, in the past three decades, none of the TTM implicated blood components were reported to be associated with travelers from nonendemic countries.

Use of the DHQ to Reduce the Risk of TTM in the U.S.

Blood establishments currently use the DHQ to screen presenting donors and defer those individuals who may have been exposed to malaria. The donor history questionnaire presents two capture questions, followed by an assessment of affirmative responses for malaria risk:

- In the past 3 years, have you been outside the U.S. or Canada?

- Have you ever had a history of malaria?

FDA's current recommendations to reduce the risk of TTM are in the guidance document entitled, "Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria," dated December 2022 [15], and available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-reduce-risk-transfusion-transmitted-malaria>.

The guidance recommends blood establishments assess donors for the following elements to determine eligibility:

- A history of malaria in the past three years;
- A history of prior residence in a malaria-endemic country in the past 3 years;
- A history of travel to a malaria-endemic area in the past three months (for residents of nonendemic countries, and prior residents who have spent at least 3 consecutive years in a nonendemic country(ies)); and
- A history of travel to a malaria-endemic area in the past three years, if previously a resident of a malaria-endemic country who has spent less than 3 consecutive years in a nonendemic country(ies).
- As an alternative, the guidance permits blood establishments to collect platelet and/or plasma components from 1) a donor who is a resident of a non-endemic country and who has traveled to or through a malaria endemic-area or 2) a donor who is a prior resident of a malaria-endemic country who returns to a malaria-endemic area after residence for 3 or more years consecutively in non-endemic countries without a deferral period, provided the blood components are pathogen-reduced using an FDA-approved pathogen reduction device effective against *Plasmodium falciparum*, according to the manufacturer's instructions for use.

We intend to maintain the definitions of malaria, a malaria-endemic country, malaria-endemic

area, residence in a malaria-endemic country and travel to a malaria endemic area as described in the aforementioned guidance.

Note that blood establishments are not required to assess Source Plasma donors for malaria risk (21 CFR 630.15(b)(8)). Source Plasma is used for further manufacture of plasma-derived products. Pathogen inactivation and removal methods that are currently used in the manufacturing process are sufficient to reduce the risk of malaria transmission for plasma-derived products.

Although the recommended screening measures have likely reduced the risk, TTM continues to occur because of the inherent limitations of donor history screening, in particular with respect to assessing the risk of exposure for prior residents of malaria-endemic countries. This screening is complicated and likely error prone for collection staff, who may incorrectly interpret information provided at the donation, as well as for donors, who may not disclose risk. Additionally, the deferral periods (3 years or 3 months, depending on the risk exposure) might not be sufficient to identify asymptomatic infections, in particular in individuals who were prior residents of malaria-endemic countries and might have partial immunity or who have had malaria in the past. Among the 13 TTM cases reported between 2000-2021, 7 cases implicated a donor who was a prior resident of a malaria-endemic country who was appropriately evaluated by the current eligibility criteria, but had a chronic asymptomatic infection; 4 cases involved nondisclosure of risk or staff error in evaluating donor eligibility when the donor had been a prior resident of a malaria-endemic country and should have been deferred; 2 cases did not report whether the donor was found eligible in error or fell outside the current deferral criteria for prior residence in a malaria-endemic country [11, 13]. In sum, the current donor screening strategy fails to defer all donors with asymptomatic malaria.

Another disadvantage of the current donor screening strategy is the disqualification of large

numbers of healthy individuals with variable malaria risk exposures based on their travel history and prior residence in malaria-endemic countries. According to some estimates, between 1% and 3% of all presenting donors are deferred each year based on their history of travel to a malaria-endemic area [16-18]. For these reasons, a more robust strategy to identify at-risk donors is needed to adequately reduce the risk of TTM while allowing more donations by eligible, healthy donors.

Availability of a Licensed Donor Screening Test for Malaria

On March 19, 2024, FDA licensed the first test intended to screen blood donations for malaria. This test, the cobas® Malaria, is designed to detect the presence of DNA and RNA from *Plasmodium species* (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*) in whole blood from individual donors [19]. Malaria is a relevant transfusion-transmitted infection (RTTI) (21 CFR 630.3 (h)(x)). Under 21 CFR 610.40 (a)(3), blood establishments must test for certain RTTI, including malaria, when 1) a test is licensed, approved or cleared by FDA for use as a donor screening test and is available for such use; and 2) testing is necessary to reduce adequately and appropriately the risk of transmission of the RTTI by blood, or blood component, or blood derivative product manufactured from the collected blood or blood component. Therefore, the availability of an FDA-licensed NAT assay for screening blood donations for malaria has prompted the need for FDA to reevaluate our recommendations to reduce the risk of TTM. As previously noted, FDA's current recommendations for malaria risk and our proposed testing strategies do not apply to collections of Source Plasma.

Proposed selective NAT testing strategies for *Plasmodia* spp.:

We propose that a licensed NAT for *Plasmodia* spp. should be used to selectively test blood donations, based on donor risk factors for malaria, namely, a history of malaria, prior residence in a malaria-endemic country, and travel to a malaria-endemic area. In addition, because of the

recent cases of locally acquired, mosquito-borne malaria in Florida, Texas, Maryland and Arkansas, we propose NAT testing of all donations collected in geographic regions of the U.S. when public health authorities identify and report local mosquito-borne malaria transmission.

The proposed selective testing strategies account for the greater risk of TTM from blood donations from individuals who have a history of malaria or were prior residents of malaria-endemic countries compared to those individuals without such history and whose only risk of malaria exposure is travel to a malaria-endemic area. We recognize the operational challenges of identifying only certain donations for testing, compared to testing every donation. The current proposal is more complicated than other selective testing strategies, such as our current recommendations to reduce the risk of transmission of *Babesia*, which entails testing every donation collected in certain states at greatest risk for babesiosis, and for *Trypanosoma cruzi* (i.e., Chagas disease) which entails testing every donor at least once. With these selective testing strategies between fiscal years 2019 to 2023 (5 years), 34 blood establishments reported erroneously distributing over 1,000 units that were not tested for *Babesia* or *T. cruzi*. These biological product deviations were reported to FDA as required by 21 CFR 606.171. Selective testing strategies are inherently error prone compared to universal testing of each donation; however, our recommendation for selective testing for malaria is risk-based and takes into consideration the highest risk among prior residents of malaria-endemic countries. We also recognize that any selective testing strategy based on donor screening questions will not address nondisclosure of information by donors or staff errors in evaluating donors for malaria risk. However, we predict the proposed testing strategy would be more robust and less error-prone than the current approach to donor deferral based on the donor history questions alone. Further, we anticipate fewer donor deferrals, while more reliably deferring those individuals who are actually carrying *Plasmodium* infection acquired in a malaria-endemic country.

Because of the much lower risk of malaria transmission with platelet or plasma components compared to whole blood or red cell components, FDA would permit the use of an FDA-approved pathogen reduction device, effective against *Plasmodium falciparum*, according to manufacturer's instructions for use, instead of the use of the screening questions followed by NAT. An FDA-approved pathogen reduction device is currently not available for whole blood or red cell components.

Proposed strategies:

A. Selective testing strategy for individuals with a history of malaria (See Figure 1A)

We propose a selective testing strategy for donations from individuals who have ever been diagnosed with malaria as follows:

1. Ask all donors who report a history of malaria, based on the current DHQ question, the following three additional questions at each donation:
 - a. Since your last diagnosis:
 - i. Have you been evaluated by a physician or healthcare provider,
AND
 - ii. Have you completed all treatment prescribed by your physician or healthcare provide, AND
 - iii. Are you now asymptomatic and free of malaria.
2. If the response to any of the screening questions is No, defer the donor for at least 1 year.
3. If the response to all the screening questions is Yes, test all donations from such donors at each donation with a licensed NAT for *Plasmodia* spp.

This selective testing strategy uses a simplified approach to identify all prospective donors with a history of malaria at each donation. The strategy results in repetitive testing of donors with a history of malaria who return to donate again, even though the donors may not have a new

exposure to malaria since their last donation. The number of donations tested under this strategy, however, is expected to be a very small percentage all donations (<0.01% total donations) [11], and the strategy encompasses a relatively low burden of testing to identify individuals at greatest risk.

B. Selective testing strategy for prior residents of malaria-endemic countries (See Figure 1B)

We propose testing all donations from prior residents of malaria-endemic countries at each donation, regardless of travel history to malaria-endemic areas. The strategy eliminates the complexity in evaluating travel history for prior residents of malaria-endemic countries, who might be partially immune and harboring chronic malaria infection. The disadvantage of the approach is repetitive testing of prior residents who return to donate again, even if they have lived in a non-endemic country for more than 3 years and have not recently traveled to a malaria-endemic area since their last donation. We predict that the number of donations that would fall under this strategy would be relatively small and the burden of testing is relatively low.

C. Selective testing strategy for residents of nonendemic countries who travel to malaria-endemic areas in the past three months (See Figure 1B)

We propose testing donations from individuals who are residents of nonendemic countries (e.g., U.S.) and who travel to malaria-endemic areas in the past three months. These individuals would otherwise have been deferred for 3 months based on their responses to the current DHQ. This testing strategy would eliminate unnecessary deferrals of a large number of individuals with very low risk for malaria. The disadvantage might include potential false positive test results and unnecessary deferral of otherwise healthy individuals, considering the low malaria-risk in this population.

D. Testing strategy for donations in regions of the U.S. with local, mosquito-borne malaria transmission

We propose initiating testing of all donations in geographic regions of the U.S. when a single case of local, mosquito-borne malaria transmission is reported by public health authorities. The geographic region could be defined by a zip code(s) or other distribution and extended to other areas if additional cases are reported. We propose discontinuing testing all donations for malaria in the area when no new case is identified within a rolling three-month period.

In summary, we support these selective NAT testing strategies to identify individuals who are carrying *Plasmodium* parasite nucleic acid and to reduce the number of unnecessary deferrals of healthy individuals based on screening questions, alone. We considered and rejected more complicated selective testing strategies because of the operational complexity and higher likelihood of error.

We also considered and rejected universal testing of all donations in lieu of such selective testing strategies, because the disadvantages outweighed the advantages and would be unlikely to materially increase safety compared to a selective strategy. Universal testing of all donations would permit discontinuation of the malaria risk questions entirely and would address all three failure modes of current DHQ screening and deferral (staff error, nondisclosure of risk factors by the donor, and insufficient deferral periods to identify persistent, asymptomatic infection). While a universal testing strategy would simplify donor screening and donation testing algorithms and streamline operations, it would be at the expense of a greater testing burden and a larger number of donor deferrals associated with false positive test results.

Management of donors and disposition of units that test positive for *Plasmodia* spp.

For all testing strategies, we propose deferral for at least 1 year after a reactive NAT result for *Plasmodia* spp. and until completion of medical evaluation and all prescribed treatment. The reactive donation would be unsuitable and must not be released for transfusion or further manufacturing (21 CFR 630.30).

Blood establishments would be required to perform further testing using an FDA cleared diagnostic test to provide additional information concerning the donor's infection status (21 CFR 610.40 (e)).

At this time, we do not have sufficient information to propose a testing algorithm for reentering a donor before the one-year deferral period if false-positive screening test results are suspected. Therefore, all donors with reactive NAT results would become eligible again only after the one-year deferral and medical evaluation. The donation may or may not be tested again based on selective testing strategy.

Committee Discussion:

At this meeting, the following information will be presented to the Committee: 1) data on clinical malaria cases, including recent cases of locally acquired malaria and TTM risk in the U.S.; 2) performance of a licensed NAT assay intended for testing blood donations for malaria; and 3) the proposed strategies for testing blood donations for *Plasmodium* spp. by NAT.

We ask the Committee to discuss the proposed selective testing strategies for donations from individuals with a history of 1) malaria, 2) prior residence in a malaria-endemic country, and 3) travel to a malaria-endemic area by residents of nonendemic countries, and 4) in the event of local mosquito-borne malaria transmission in a geographic area of the U.S.

Points for the Committee to Consider:

1. Please comment on FDA’s proposed strategies for selectively blood donations from donors at risk for malaria using an FDA-licensed NAT.
2. Please comment on FDA’s proposal that blood establishments should implement time-limited NAT screening of all donations collected in area(s) of the U.S. when a single case of local mosquito-borne malaria is reported by public health authorities.

References:

1. World Malaria Report. 2022. <https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022>.
2. Doolan D, Dobano C, Baird J. Acquired immunity to malaria. *Clinical Microbiology Reviews* 2009. 22: 13-36.
3. Mace K, Lucchi N, Tan K. Malaria Surveillance – United States, 2018. *MMWR Surveillance Summaries*. 2022 Sep 2:71(8):1-35.
4. Local transmission of *Plasmodium vivax* malaria-Palm Beach county, Florida, 2003. *Morbidity and Mortality Weekly Report* 2003, 52(38): 908-911.
5. Blackburn D, Drennon M, Broussard K, Morrison A, Stanek D et al. Outbreak of Locally Acquired Mosquito-Transmitted (Autochthonous) Malaria - Florida and Texas, May-July 2023. *Monthly Mortality and Morbidity Weekly Report* 2023 Sep 8: 72(36): 973-978.
6. Duwell M, DeVita T, Torpey D, Chen J, Myers R, Mace K, et al. Notes from the field: Locally acquired mosquito-transmitted (autochthonous) *Plasmodium falciparum* malaria - National Capital Region, Maryland, August 2023, *Mortality and Morbidity Weekly Report*. 2023 Oct 13: 72(4): 1123-1125.

7. Locally acquired cases of malaria in Florida, Texas, Maryland, and Arkansas. Centers for Disease Control and Prevention. Oct 19, 2023.
https://www.cdc.gov/malaria/new_info/2023/malaria_US.html
8. Mungai M, Tegmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *New England Journal of Medicine* 2001, 344:1973-1978.
9. Rosso F, Rojas O, Gill C, Vargas J et al. Transmission of malaria from donors to solid organ transplant recipients: A case report and literature review. *Transplant Infectious Disease* 2021, 23(4):e13660.
10. Uneke C. Congenital *Plasmodium falciparum* malaria in sub-Saharan Africa: a rarity or frequent occurrence? *Parasitology Research* 2007, 101(4):835-842.
11. Katz L, Spencer B. Travel and Related Health History: Malaria, Prions, and Other Transfusion-Transmitted Diseases. Eder A, Goldman M Editors. Screening blood donors with the donor history questionnaire. Bethesda, MD, AABB Press: 159-193.
12. Anand A, Mace KE, Townsend RL, Madison-Antenucci S, et al. Investigation of a case of suspected transfusion-transmitted malaria. *Transfusion* 2018, 58(9):2115-2121.
13. Stubbs L, Price M, Noland D, Fuchs J et al. Transfusion-transmitted malaria: Two pediatric cases from the United States and their relevance in an increasingly globalized world. *Journal of the Pediatric Infectious Disease Society* 2021, 10(12): 1092-1095.
14. Niederhauser C and Galel S. Transfusion-transmitted malaria and mitigation strategies in nonendemic regions. *Transfusion Medicine and Hemotherapy* 2022, 49(4): 205-207
15. FDA guidance. Recommendations to reduce the risk of transfusion-transmitted malaria. December 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-reduce-risk-transfusion-transmitted-malaria>

16. Leiby D, Nguyen M, Notari E. Impact of donor deferrals for malaria on blood availability in the United States. *Transfusion* 2008, 48: 2222-2228.
17. Spencer B, Steele W, Custer B, Kleinman S et al. for the Retrovirus Epidemiology Donor Study (REDS) II Group. Risk for malaria in the United States donors deferred for travel to malaria endemic areas. *Transfusion* 2009, 49(111): 2335-2345.
18. O'Brien S, Delage G, Seed C, Pillonel J et al. The epidemiology of imported malaria and transfusion policy in nonendemic countries. *Transfusion Medicine Reviews* 2015, 29(3): 162-171.
19. FDA website. cobas Malaria. Product information and supporting documents.
March 2024. www.fda.gov/vaccines-blood-biologics/approved-blood-products/cobas-malaria

Figure 1A

A. Selective testing, based on history of malaria

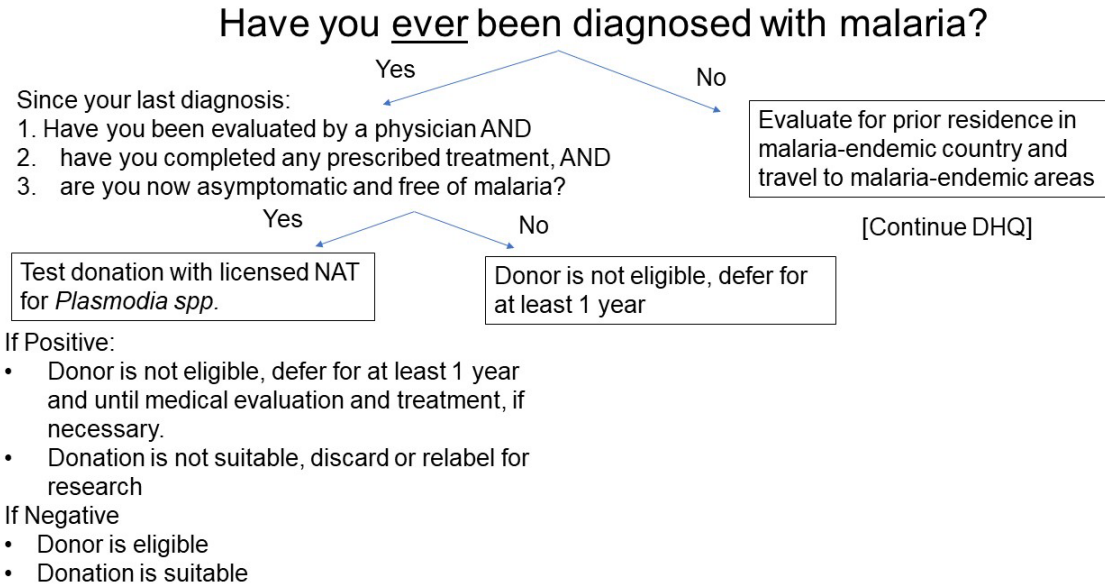


Figure 1 B

B. Selective testing of all prior residents at each donation and recent travelers from nonendemic countries

