



April 30, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Rm 1061
Rockville, MD 20852

Submitted via <https://www.regulations.gov>

Re: Docket No. FDA-2024-N-0948, "Blood Products Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments."

Dear Dr. Califf:

America's Blood Centers (ABC) is the national organization bringing together community-based, independent blood centers. Our member organizations operate more than 600 blood collection sites providing close to 60 percent of the U.S., and a quarter of the Canadian, blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. All ABC U.S. members are licensed and regulated by the U.S. Food and Drug Administration (FDA).

ABC appreciates FDA providing an opportunity to comment 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)." The Blood Products Advisory Committee May 9, 2024 Briefing Document (Briefing Document) proposes selective testing strategies for donations from individuals with 1) a history of malaria, 2) prior residence in a malaria-endemic country, 3) travel to a malaria-endemic area by residents of nonendemic countries in the past three months, and 4) in the event of local mosquito-borne malaria transmission in a geographic area of the U.S. Additionally, FDA notes in the Briefing Document that "We also considered and rejected universal testing of all donations in lieu of such selective testing strategies."

1. ABC strongly recommends that FDA delay publication of a draft guidance until modeling studies have been completed and multiple tests for malaria are available.

ABC recognizes that malaria is a relevant transfusion-transmitted infection (RTTI) under 21 CFR 630.3 (h)(x) and that the recent approval of the Roche Cobas malaria test requires FDA to evaluate, pursuant to 21 CFR 610.40 (a)(3), whether a testing strategy utilizing this newly approved test "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." We appreciate the evidence-based decision-making FDA has engaged in to determine testing, including the decision to eliminate ZIKV testing in 2021, and applaud FDA's utilization of the BPAC to gather and review the available evidence to determine an appropriate testing strategy for malaria.

We urge the agency to ensure any additional testing burden is justified by a commensurate increase in safety. We note that the current deferral policy is extremely effective with “a total of 13 cases of TTM (average 0.59/year) [out of about 10.8 million RBC transfusions (plus 2.2 million each of plasma and platelets and 1.2 million units of cryoprecipitate) annually]¹... reported in literature between 2000 to 2021² without testing donors for malaria.

Prior to publication of a draft guidance on malaria testing, real world modeling studies should be performed to determine the sensitivity of available tests, including studies performed in malaria-endemic locations and including data on semi-immune donor populations. As the United States eradicated malaria in 1951, the acceptance of international data is essential to ensure a sufficiently powered study of a population that is relatively rare in the US. While we recognize the approval process for the Roche Cobas assay demonstrated sufficient accuracy for use as a blood screening tool, it is currently unclear in the literature whether the licensed assay can detect the potential low levels of parasitemia that may be sufficient to transmit malaria to transfusion recipients, particularly the persistent low level parasitemia that can manifest in semi-immune asymptomatic donors. However, based upon the sensitivity levels for the Roche Cobas malaria test and evidence generated from challenge tests, it does appear that it is unlikely all cases would be identified by testing.

Furthermore, there is currently only one malaria test approved for screening of the blood supply. As FDA knows, this raises concerns about the blood supply’s reliance on a single test. Without an alternative, supply chain challenges could cripple the blood supply. Therefore, ABC believes that FDA should ensure multiple tests are available prior to creating any new testing requirements.

Once modeling studies have been completed and demonstrate good clinical sensitivity, including asymptomatic donors with semi-immunity, and multiple tests are available, ABC would make the following additional recommendations.

2. ABC applauds FDA for recognizing universal testing of all donations is not a cost-effective strategy for blood safety in the United States.

ABC applauds FDA for rejecting universal testing and considering a more targeted approach. ABC further agrees with FDA that the “disadvantages [of universal testing of all donations] outweighed the advantages and would be unlikely to materially increase safety compared to a selective strategy... 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.” Additionally, a universal testing requirement would add significant financial costs for blood centers due to the costs of the tests and would also add state and county regulatory requirements to report the positive cases, including false positives.

3. ABC strongly recommends that FDA maintain the current deferrals as an option.

Malaria was eradicated in the US in 1951 and is no longer a major issue in the US, with only around 2,000 cases reported annually, the vast majority of which are linked to travel. The current deferral policies are scientifically based and have been proven to be safe and effective. However, we recognize that a move to a testing-based strategy for preventing TTM would allow for the reentry of some previously deferred donors, which for some blood centers would justify moving away from a deferral-based strategy.

¹ “[U.S. Blood Donation Statistics and Messaging Guide](#),” America’s Blood Centers and ADRP, January 2024.

² The Blood Products Advisory Committee May 9, 2024 Briefing Document.

ABC encourages FDA to ensure the move to a testing-based strategy for blood safety applies evidence-based decision making and is justified by commensurate increases in safety. While we recognize that last year saw the first cases of locally acquired malaria transmission since 2003, there is no indication that this fact suggests any change in the extremely low risk of local transmission within the US. Furthermore, there is no indication in the data that there is any change in the risk of TTM. While a change in either of these factors may result in the need for changes in the process of screening donors for malaria, we do not believe the current situation justifies a major change in donor screening that would result in a notable increase in the cost of life saving blood and blood components.

There may come a time when the need for a licensed donor screening test for Malaria may be more widespread in the United States, and we recognize that FDA must take into account the potential for the need to increase capacity to test. Offering the option to test, where some centers will test and others might not, will provide the manufacturing volume to allow manufacturers to make tests available when needed.

While we appreciate FDA not promoting a mandatory universal testing strategy, selective testing has additional challenges that must be considered by blood centers and should be part of the determination of whether the intervention is justified by the potential theoretical increase in safety. Many blood establishment computer software (BECS) systems do not currently have the capabilities for a selective testing process. Significant modifications would be required for the BECS lot release system to allow for selective, or conditional, testing, resulting in significant financial and workforce-related expense to blood centers. Some blood centers would have to create a dual process, manual and electronic, to work around any BECS challenges, which may lead to an increase in errors.

4. ABC recommends that FDA maintain the current deferral as an option, while also allowing for a selective testing strategy for individuals with a history of malaria who were not prior residents of a malaria-endemic country.

Under current FDA guidance, *Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria* (TTM guidance), individuals with a history of malaria should be deferred for three years. “After the 3-year deferral period, the donor may be eligible to donate, provided the donor has been free from malaria during this period while residing in a non-endemic country and meets all other donor eligibility criteria.”

We recognize that some donors from endemic areas with multiple malaria exposures may become semi-immune and maintain a low level of parasitemia. These donors, although infected, are asymptomatic and may unknowingly transmit malaria through blood transfusion. However, for donors from non-endemic locations or without frequent exposure to malaria, this low level parasitemia is uncommon.³

According to the Briefing Document, FDA is now proposing to test all donations from individuals with a history of malaria at each donation. FDA states, “[t]his 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 [of] all donations (<0.01% total donations).”

However, TTM cases have not resulted from donors who previously had malaria who were not prior residents of malaria-endemic countries. These donors, if they have been treated and cleared under normal

³Zhang X, Dietsch KW. The mystery of persistent, asymptomatic plasmodium falciparum infections. *Curr Opin Microbiol.*2022;70:102231.

circumstances, are unlikely to have an ongoing risk of exposure to malaria and should not be required to undergo testing at each donation.

5. ABC recommends that FDA maintain the current deferral as an option, while also allowing for a selective testing strategy for prior residents of malaria-endemic countries.

Under FDA's current TTM guidance, prior residents of a malaria-endemic country should be deferred for three years from the time they last travelled to an endemic country if they have been a resident of a non-endemic country for less than three consecutive years. Alternatively, prior residents of a malaria-endemic country should be deferred for three months from the time they return to the non-endemic country if they have resided for three or more years consecutively in non-endemic countries. According to the Briefing Document, FDA is proposing to test "all donations from prior residents of malaria-endemic countries at each donation, regardless of travel history to malaria-endemic areas."

As noted in the Briefing Document, "[m]ore recently, a total of 13 cases of TTM (average 0.59/year) were reported in literature between 2000 to 2021...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."

According to the data reported to National Blood Collection and Utilization Survey (NBCUS), in 2019, there were an estimated 169,000 blood donors deferred due to travel to or residency in a malaria endemic area/country.⁴ In a 2008 study, it was estimated that 8.6% of donors deferred for malaria risk were former residents of a malaria endemic country.⁵ Applying that percentage to the 169,000 deferred for travel to or residency in a malaria endemic area/country, it can be estimated that 14,500 donors would be deferred due to prior residency in a malaria endemic area/country.³

ABC appreciates FDA's proposed strategy could bring in additional new donors, which is especially important when we have seen decreasing rates of donation. Furthermore, this category of donors is more likely to include diverse donors that are statistically more likely to have the same red blood cell antigen profiles that are required for some frequently transfused recipients. ABC appreciates the ability of blood centers to bring in new donors and bring back previously deferred donors, and also appreciates these changes can eliminate some costs associated with recruiting additional donors to ensure the stability of the blood supply.

However, identifying all donors with prior residence in a malaria endemic country is operationally challenging at best, but likely impossible due to the fact that political boundaries change over time, country names change, and countries can become endemic and non-endemic at various times. No comprehensive data source listing malaria-endemic countries over time exists, including country name changes and clear identification of regions that have shifted between nations. It is currently challenging for blood centers to identify all donors that have lived in endemic countries within the last three years. Moving to a lifetime would require a lookback period of over 60 years, an operational challenge without a practical solution.

⁴ Kracalik I, Sapiano MRP, Wild RC, Chavez Ortiz J, Berger JJ, et al. Supplemental findings of the 2021 National Blood Collection and Utilization Survey. *Transfusion*. 2023;63(S4): S19-42.

⁵ Leiby D, Nguyen ML, Notari EP. Impact of donor deferrals for malaria on blood availability in the United States. *Transfusion*. 2008;48(10): 2222-2228.

While we recognize that at least 12 cases of transfusion transmitted malaria have been the result of transmission from former residents of malarial endemic countries, it is unclear from the currently available data that the available test would have caught all of these cases, nor that centers would have been able to identify these individuals during donor screening as prior residents of malarial endemic countries. Therefore, ABC recommends the option to test donors who have a history of prior residence in a malaria-endemic country in the past three years, and donors with 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 three consecutive years in nonendemic country(ies).

Retaining the option to continue with the current donor deferrals maintains the current high level of blood safety while recognizing that the economics of testing are not the same at every blood center. For many centers, the number of donors they are deferring for malaria risk is very low and the complexity added by introducing a new test to the workflow, as described in Section 3 of this document, would not be justified by the benefit of not needing to defer these donors. Retaining the option to defer these donors in lieu of testing continues to ensure the safety and availability of the blood supply.

6. ABC supports an option for selective testing for residents of nonendemic countries who have traveled to malaria-endemic areas in the past three months.

Under FDA's current TTM guidance, a donor who is a resident of a non-endemic country and traveled to or through a malaria-endemic area should be deferred for three months. According to the Briefing Document, FDA is proposing "testing donations from individuals who are residents of nonendemic countries (e.g., U.S.) and who travel[ed] to malaria-endemic areas in the past three months."

As noted in the Briefing Document, "[a]ccording 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." A 2009 study cited in the Briefing Document demonstrated that "[r]ecent reviews of TTM in the United States implicate only one routine US civilian traveler in 31 TTM cases occurring since 1980 where an infected donor was identified. The other 30 either grew up in malarious areas or were US-born residents with long-term tenure overseas."⁶ Furthermore, the single case of travel by a resident of a non-endemic area related TTM occurred prior to deferral changes made by FDA in 1994.⁷

ABC supports this selective testing strategy for residents of nonendemic countries who have traveled to malaria-endemic areas in the past three months, since FDA currently requires a three-month deferral, and as deferral is a more stringent option, centers could choose not to test, but instead retain their three-month deferral policy.

7. ABC supports a testing strategy for donations in regions of the U.S. with local, mosquito-borne malaria transmission, but recommends having a higher minimum threshold for triggering testing.

FDA is proposing to initiate "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...[and]

⁶ 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.

⁷ Mungai M, Tegtmeier G, Chamberland M, Parise, M. *N Engl J Med*. Transfusion-transmitted malaria in the United States from 1963 through 1999. 2001;344(26): 1973-1978.

discontinuing testing all donations for malaria in the area when no new case is identified within a rolling three-month period.”

Local transmission of malaria is rare in the US. While we saw multiple instances of local transmission in 2023, it was the first instance of local transmission in the US since 2003. While we recognize there may be factors at place, such as climate change, which could result in a change in the frequency of this type of transmission, one year does not show such a trend. If the evidence does demonstrate that the risk of local transmission has materially changed, a more aggressive mitigation strategy may be justified.

While ABC supports this testing strategy in concept, given the variability in single reported cases, there will be cases of a single, local, mosquito-borne malaria transmission. ABC recommends having a higher minimum threshold for triggering testing, given the associated logistics and expense, and the fact that many individual cases never turn into clusters. ABC further recommends FDA support modeling studies to determine the minimum threshold for triggering testing.

ABC supports defining a geographic region by zip code(s), recognizing that outbreaks across multiple zip codes might justify implementing testing at a lower number of cases. Additionally, if future outbreaks occur across larger geographic areas, the geographic region defined for testing may need to be reevaluated.

Finally, while FDA proposes “discontinuing testing all donations for malaria in the area when no new case is identified within a rolling three-month period,” the Centers for Disease Control (CDC) recommends 8 weeks of surveillance following local transmission. As noted in a 2023 CDC health update related to locally acquired malaria cases in Florida, Texas, and Maryland, “[s]urveillance for additional cases of malaria, as well as malaria-related mosquito surveillance and control, will continue in all three states for a period of 8 weeks following the most recent case in each state.”⁸ Additionally, according to the CDC, “[t]he incubation period in most cases [of malaria] varies from 7 to 30 days.”⁹ Furthermore, we question when the appropriate time frame would begin for a window where testing would be required. When a case of local transmission occurs, the mosquito bite that causes the infection likely occurred 7 to 30 days prior, plus the delay in time from onset of symptoms to definitive diagnosis, followed by additional time for reporting to the health department and CDC. As the majority of those in the US have not had an exposure to malaria, they would likely manifest recognizable illness, making detection and monitoring of potential spread easier for public health. Starting a rolling three months of testing after the diagnosis is not in line with the evidence. Additionally, ABC recommends FDA refer to “weeks,” rather than “months,” when defining the time frame, since months vary in length.

8. ABC applauds the FDA for allowing the use of an FDA-approved pathogen reduction technology device in lieu of using the screening questions for malaria risk followed by NAT for malaria.

Currently, the FDA guidance allows for blood collection establishments to use an FDA-approved pathogen reduction technology device to collect and manufacture platelet and/or plasma components from donors who are residents of a non-endemic country and who have traveled to a malaria endemic area without deferring them. In addition, this technology may also be used to collect and manufacture platelet and/or plasma from donors who were former residents of a malaria-endemic country who travel back to a malaria-endemic area after having lived in a non-endemic country for 3 or more consecutive years. The

⁸ “Important Updates on Locally Acquired malaria Cases Identified in Florida, Texas, and Maryland,” CDC Health Update, Distributed via the CDC Health Alert Network, August 28, 2023.

⁹ [CDC - Malaria - About Malaria - Disease](#), accessed April 10, 2024.

FDA-approved pathogen reduction device has been shown to be effective against *P.falciparum* when used according to the manufacturer's instructions for use. ABC encourages FDA to continue to work with manufacturers of pathogen reduction technology to facilitate the approval of this technology for red blood cells as well as for other manufacturers.

ABC appreciates the opportunity to provide comments on proposed strategies to reduce the risk of TTM. If you have any questions or require additional information, please contact Justine Coffey, Director of Regulatory Affairs and Public Policy (jcoffey@americasblood.org).

Thank you for your collaborative work to ensure a safe, adequate, and available blood supply.

Sincerely yours,

A handwritten signature in cursive script that reads "Katherine Fry". The signature is written in black ink on a white background.

Kate Fry, MBA, CAE
Chief Executive Officer