



A Joint Statement to the Food and Drug Administration's Blood Products Advisory Committee
in support of new FDA strategies to reduce the risk of transfusion-transmitted malaria

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Presented by Ralph Vassallo MD, incoming chair, AABB Transfusion
Transmitted Diseases Committee

The Association for the Advancement of Blood and Biotherapies (AABB), America's Blood Centers and the American Red Cross appreciate the opportunity to present this statement in support of FDA's consideration of strategies to reduce the risk of transfusion-transmitted malaria (TTM). Our organizations believe an FDA-licensed nucleic acid test (NAT) for malaria holds promise to maintain or improve blood safety. The testing strategies may improve availability by removing unnecessary donor deferrals which will also support a more diversified blood supply, particularly among subsets of donors with uncommon phenotypes, such as donors from Latin American, Asian, or African countries.

We note that there are no clinical studies demonstrating the licensed assay does, in fact, reduce the risk of TTM and some members have expressed concerns that the analytic sensitivity of that test may not detect levels of parasitemia sufficient to transmit malaria to transfusion recipients—especially asymptomatic donors with semi-immunity¹. FDA should support formal modeling studies designed in consultation with malariologists, using the best available assumptions about parasite levels during asymptomatic infection before issuing final guidance. Assuming the results suggest good clinical sensitivity of the test in donor populations, a substantial likelihood that TTM will be reduced and reasonable cost effectiveness, our testing recommendations follow.

Our Recommendations and Comments

1. Our organizations strongly support FDA's consideration of multiple strategies to reduce the risk of TTM to meet the unique operational and budgetary challenges of blood collectors large and small.
2. We support flexible selective testing strategies for donors with material risk of malaria identified by revised donor screening questions, to establish donor eligibility using an FDA-licensed NAT which will protect blood safety and remove unnecessary deferrals.
3. With respect to the selective testing of donors with material risk of malaria, we urge FDA to provide flexibility specifically permitting blood establishments to continue current questions and deferrals without testing. The operational considerations will vary, and it is clear that some facilities might opt to continue use of the current Donor History

Questionnaire (DHQ), avoiding testing except in the setting of local transmission reported within the US. Please clarify the path for a deferral-only strategy as an alternative to testing in all other circumstances.

4. We support consideration of the option of universal testing with removal of all malaria risk screening questions as one of several strategies that may be available to blood establishments to address all three failure modes of current DHQ screening.
5. We support FDA’s approach to 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.”
6. We support time-limited NAT screening of all donations collected in defined ZIP Codes to address local mosquito-borne malaria transmission reported by public health authorities. This approach offers an alternative to substantial donor losses and/or complex donor qualification interventions at centers affected by locally-acquired malaria. However, since many individual cases have historically not been associated with clusters, consideration should be given to a higher trigger for testing than a single reported case. FDA should also comment on the use of alternative approaches such as enhanced post-donation surveillance as currently practiced in Florida.
7. We support resources to develop and maintain a reporting platform, similar to the [West Nile Virus Biovigilance Network](#), to provide effective malaria risk mitigation through timely notification to all centers impacted by local transmission, and FDA’s consideration of recommendations in guidance to address inevitable questions on donor travel to US geographic areas reporting local malaria transmission.
8. We support an extended implementation timeline to promote blood safety by providing adequate time to complete complex changes, including time to assess budgetary implications, planning for changes in donor screening and testing processes, blood establishment computer system modifications and validation, extensive staff training, and implementation of new screening assays.
9. We recommend FDA review our written statement with additional information on background and other details that should be considered by FDA.

Background and Specific Comments

US cases of TTM have dropped dramatically in the last 50 years.^{2,3,4} US data highlighted in the FDA’s 2022 Malaria guidance⁵ estimate the risk of TTM at less than 0.1 per million red blood cell (RBC) transfusions or approximately one case every two years. As outlined in the briefing document, “...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.” Consequently, deferral of prospective donors, never resident in endemic countries, based solely on travel to malaria-endemic areas results in the loss of a large number of otherwise eligible and healthy blood donors.

Estimated 2023 malaria deferrals from responding centers/systems representing ≥50% of US collections									
Center	Donations	Non-resident travel	Non-resident travel percent	Malaria Dx	Dx deferral percent	Resident/return to endemic	Resident/return to endemic percent	All malaria deferrals	All deferrals percent
1	4531956	11441	0.2525	79	0.0017	4327	0.0955	15847	0.35
2	1283480	2938	0.2289	29	0.0023	1158	0.0902	4125	0.32
3	1000291	1654	0.1654	24	0.0024	2306	0.2305	3984	0.40
4	421349	2960	0.7025	14	0.0033	393	0.0933	3367	0.80
5	128323	361	0.2813	NA	NA	73*	0.0569	434	0.34
6	155260	242	0.1559	2	0.0013	23	0.0148	267	0.17
7	86407	377	0.4363	3	0.0035	84	0.0972	464	0.54
8	72643	162	0.2230	4	0.0055	74	0.1019	240	0.33
Total	7679709	20135	0.2622	155	0.0020	8438	0.1099	28728	0.37

*Includes diagnosis of malaria.

We estimate roughly 45,000 donor deferrals for malaria risk annually using current criteria based on extrapolation of 28,728 deferrals from blood collection organizations responsible for almost 7.7 million donation attempts in calendar year 2023 from 8 responding blood systems or centers. This estimate uses NBCUS 2021 total donations for a denominator.

Additional Considerations: Selective Testing

Selective ID-NAT will permit qualification of a current donation (not required when the component is treated with an FDA-approved pathogen reduction device) by donors with a DHQ-determined material risk of malaria. Eligibility of donors giving affirmative responses to FDA’s proposed revised questions would be established using either an FDA-licensed NAT or an assay available for blood screening under an investigational new drug application prior to the implementation date that would be required in final Guidance.

Our members have commented on the complexity of the currently licensed malaria test which requires use of a dedicated sample tube containing a lysis/stabilizing buffer. The collection of an additional tube requires increased volume diversion to the sample pouch, which is already nearing maximum limits. Some centers may need to collect a tube for every donor or identify such a malaria “flagged” donor in real time in the donor room so that the correct tube type will be available and collected, which may impact processes during donor qualification and will require substantive blood establishment computer changes. The ability to use an equally sensitive mini-pool NAT not requiring an additional sample tube would remove barriers noted above.

Please clarify in guidance FDA’s expectation for “evaluation by a physician or healthcare provider” for donor requalification following a diagnosis of malaria, including the type of documentation that would be required.

Additional Considerations: Universal Testing

Our members have noted that the option to remove questions from the DHQ, including the most time consuming, error-prone malarial area travel question, would significantly improve donor satisfaction and streamline the eligibility process.

The major advantage of universal ID-NAT is the reduction of the current operational burden if coupled with the elimination of all travel, residence, and diagnosis questions. It is hoped that the current very low residual risk would decrease further. However, universal ID-NAT coupled with increased instrument and turnaround time (vs. mini-pool NAT, as performed for other agents), an unfavorable cost-benefit ratio, and operational burden may not be acceptable for most blood establishments and each center should formally assess all options before implementing any FDA-licensed option.

FDA should ensure that a streamlined pathway for review of additional manufacturers to enable all current testing platforms in use in the US are included to support implementation. FDA should describe the performance characteristics required for a malaria molecular assay to be used in both a mini-pool NAT format and/or as part of a multiplex test (e.g., with *Babesia*) that could facilitate broader testing and incentivize their development for commercialization.

Additional Considerations: Testing Donations in US Outbreak Areas

While some of our members may consider ceasing collections in outbreak areas, others have reported concerns that such an approach could result in blood shortages. An enhanced post-donation information process is in place in some centers. Our members have noted that the option of performing time-limited NAT screening for donations collected from donors living in outbreak areas offers an alternative to substantial donor loss and/or complex donor qualification interventions at centers affected by locally-acquired malaria. As noted above, a higher threshold for testing is desirable, and extension of rolling 3-month testing beyond mosquito season may not be necessary.

Implementation of geographic testing in outbreak areas should, however, be further characterized. A significant runway is needed for US testing laboratories to implement the FDA-licensed NAT or an alternate manufacturer's assay under an investigational new drug application prior to the implementation date of final Guidance. Blood collection organizations will also need to implement complex selective testing procedures, making testing a daunting challenge before the 2025 mosquito season begins.

Conclusion

The availability of a licensed, automated, highly sensitive NAT which detects all clinically relevant *Plasmodium* species provides a welcomed opportunity to consider alternatives to the existing burdensome approach while improving quality systems and blood safety. The need for multiple strategies, including the option to continue current questioning without testing is paramount. We look forward to future recommendations in guidance and to working with the FDA representatives on AABB's Transfusion-Transmitted Disease Committee and Donor History Task Force to reduce the risk of TTM and the burden of complex algorithms for questioning and deferral that are susceptible to error. We also would like to stress that the use of

appropriately designed interactive computer systems to elicit the donor history, linked to the blood establishment computer system to control sample acquisition, test ordering and control of products donated can reduce the error rate inherent in the complexity of the current approach.

AABB is an international, not-for-profit organization representing individuals and institutions involved in the fields of transfusion medicine and biotherapies. The Association works collaboratively to advance the field through the development and delivery of standards, accreditation, and education programs. AABB is dedicated to its mission of improving lives by making transfusion medicine and biotherapies safe, available, and effective worldwide.

Founded in 1962, America's Blood Centers is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half 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. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer this statement.

¹ Boyd MF and Kitchen SF. On attempts to hyperimmune convalescents from vivax malaria. *Am. J Trop Med.* 1942. S23(2):209-25.

² Mungai M, Tegmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med.* 2001 Jun 28;344(26):1973-8.

³ Mace KE, Lucchi NW, Tan KR. Malaria Surveillance — United States, 2018. *MMWR Surveill Summ* 2022;71(No. SS-8):1–29.

⁴ Food and Drug Administration. Briefing Document: 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. At <https://www.fda.gov/media/177309/download>. Accessed 25 March 2024.

⁵ Food and Drug Administration. Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria. Guidance for Industry. At <https://www.fda.gov/media/163737/download>. Accessed 13 March 2024.