FDA POLICY CONSIDERATIONS FOR TESTING BLOOD DONATIONS FOR MALARIA

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Objectives

- Describe FDA's regulatory framework that addresses blood safety against transfusion-transmitted malaria (TTM)
- Review FDA's current recommendations for reducing risk of TTM
- Present FDA's proposals for selectively testing blood donations for malaria
- Discuss advantages and limitations of proposed selective testing strategies
- Charge to Committee

Regulatory framework (I)

- The Code of Federal Regulations (CFR) sets forth FDA's approach to blood safety
- The CFR defines relevant transfusion-transmitted infections (RTTI) and actions that blood establishments must take to address the risk of RTTI, including donor questioning and donation testing
  - Malaria, caused by *Plasmodium* spp., is a relevant transfusion-transmitted infection (RTTI) (21 CFR 630.3 (h)(1)(x))
  - Blood establishments must conduct a medical history interview as to determine if the donor is in good health and to identify risk factors closely associated with exposure to, or clinical evidence of a RTTI…(21 CFR 630.10 (e))
    - Current approach for malaria includes questioning and deferral for malaria risk factors, such as history of malaria or recent travel

Regulatory framework (II)

- Blood establishments must test for certain RTTI, including malaria, when the following conditions are met:

  – a test is licensed, approved or cleared by FDA for use as a donor screening test and is available for such use,

  and

  – 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

(21 CFR 610.40 (a)(3))

Regulatory framework (III)

- Testing must be performed on each donation, unless:
  - Testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection
  - When evidence supports this determination, blood establishments may adopt an alternative testing procedure that has been found acceptable for this purpose by FDA
  - Supporting evidence may include seasonality or geographic risk of transmission of RTTI or effectiveness of manufacturing steps (e.g., pathogen reduction technology) that may reduce the risk of transmission of RTTI

(21 CFR 610.40 (a)(3) and (4))

Regulatory framework (IV)

- Regulatory framework allows FDA to consider selective testing strategies – not every donation must be tested

  - *T. cruzi* (Chagas disease) – One-time testing of each donor
    - Donors who test non-reactive are qualified for subsequent donation without testing
    - Blood establishments review records to determine history of testing

  - *Babesia* spp. (Babesiosis) – Regional testing of donations
    - Test each donation in certain states with highest *Babesia* risk or pathogen reduce (PR) platelets and plasma
    - In states that do not test or PR, donors are asked about a history of positive test for *Babesia* and deferred

Current recommendations (I)

- Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria; FDA Guidance for Industry, December 2022

- FDA-recognized donor history questionnaire includes two questions to assess malaria risk*

  (1) Have you ever had malaria?

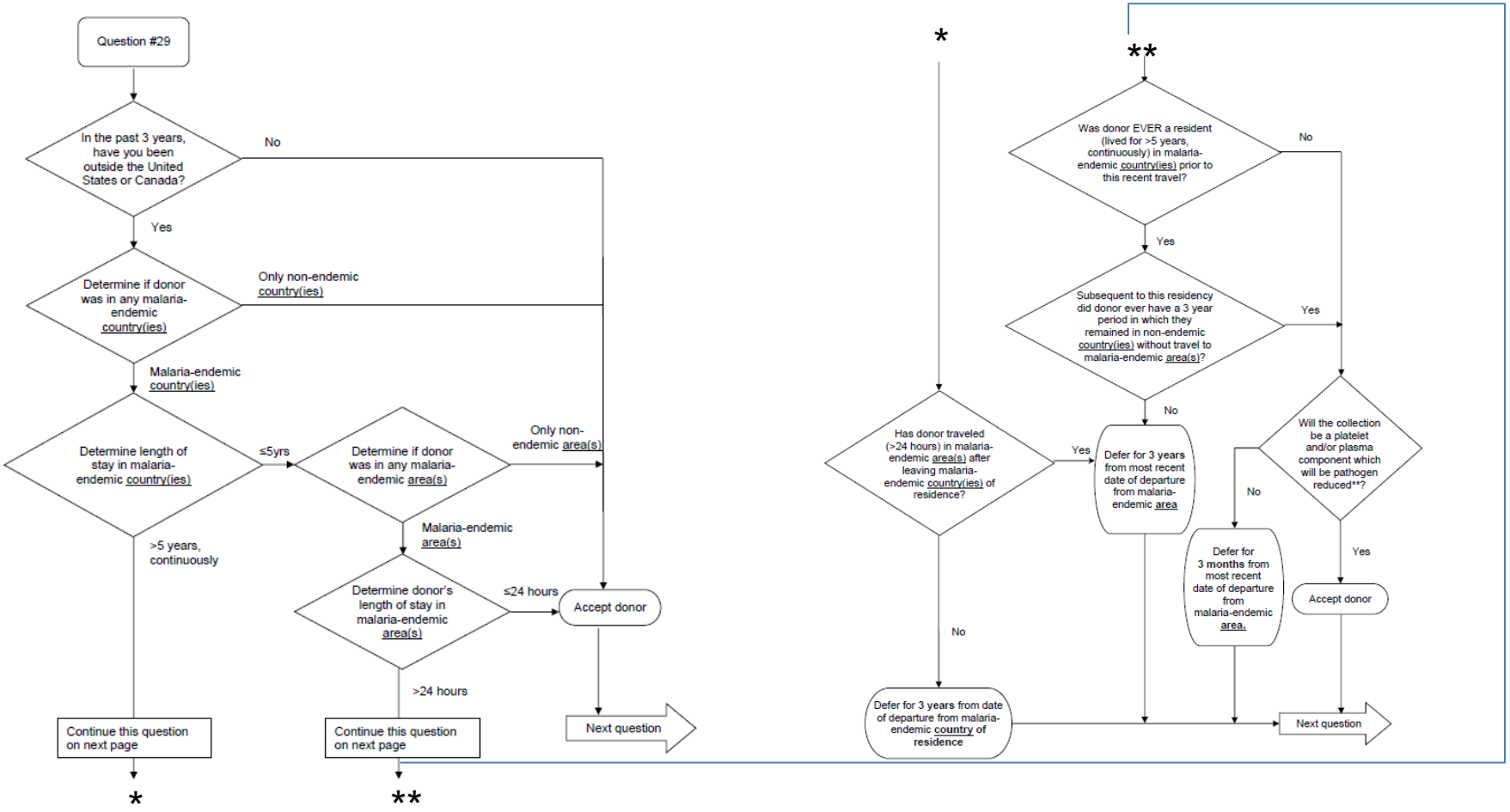
  (2) In the past 3 years, have you been outside the United States or Canada?

    - Capture question and flow chart with subsequent questions to determine eligibility

* Blood establishments are not required to assess Source Plasma donors for malaria risk (21 CFR 630.15(b)(8)).

Current DHQ

Question: 29. In the past 3 years, have you been outside the United States or Canada?



Current Recommendations (II)

Donor History Table Summary of Recommendations		Donor Deferral	Pathogen Reduction Plasma or Platelets
Travel to a malaria endemic area	Resident of a non-endemic country	3 months	Yes
	Resident of a malaria-endemic country, if spent 3 or more consecutive years in non-endemic country	3 months	Yes
	Resident of a malaria-endemic country, if spent less than 3 consecutive years in non-endemic country	3 years	No
Resident of a malaria-endemic country		3 years	No
Diagnosis of malaria		3 years	No

Limitations of current recommendations (I)

- Donor loss
  - Deferral of estimated 1% of all presenting donors for travel to malaria-endemic areas (~ 50,000-160,000 donors)
- Deferrals, particularly of prior residents, reduce diversity of blood types needed for patients
- Donor questioning is complicated
  - Potential for errors by collection staff and donors
- Deferral periods may not be sufficient to identify asymptomatic infections
  - Prior residents with partial immunity or those with a history of malaria
- FDA approved pathogen reduction devices available only for platelets and plasma components (not for WB or RBC collections)

Limitations of current recommendations (II)

- Current approach does not adequately capture malaria risk and TTM continues to occur
- 13 TTM cases reported 2000-2021
  - 7 cases: donor eligibility evaluated correctly, but donors had chronic asymptomatic infections *(criteria failed, deferral period too short)*
  - 4 cases: donors did not disclose risk or staff error *(process failed)*
  - 2 cases: unknown, not published

Proposed selective testing strategies (I)

Strategy 1A.

Selectively test blood donations from donors at risk for malaria exposure, as determined solely by donor questioning

- A history of malaria (ever)
- Travel to a malaria-endemic area (past 3 months)
- Prior residence in a malaria-endemic country (ever)

-- OR --

Strategy 1B.

Test all donors at least one time and then selectively test blood donations from donors at risk for malaria exposure, as determined by donor questioning

- A history of malaria (ever)
- Travel to a malaria-endemic area (past 3 months)

*Testing would not apply to collections of Source Plasma and pathogen-reduced platelets and plasma components

Proposed selective testing strategies (II)

Strategy 2

Test all donations in regions of the US with local mosquito-borne malaria transmission

- Triggered by public health authority reporting
- Limited to risk period

*Testing would not apply to collections of Source Plasma and pathogen-reduced platelets and plasma components

1A. Selective Testing, based on DHQ

History of malaria

Have you ever been diagnosed with malaria?

Yes

Since your last malaria diagnosis:

1. Have you been evaluated by a physician, AND
2. Have you completed any prescribed treatment, AND
3. Are you now asymptomatic and free of malaria?

Yes

Test donation with licensed NAT for *Plasmodia spp.*

No

Donor is not eligible, defer for at least 1 year

No

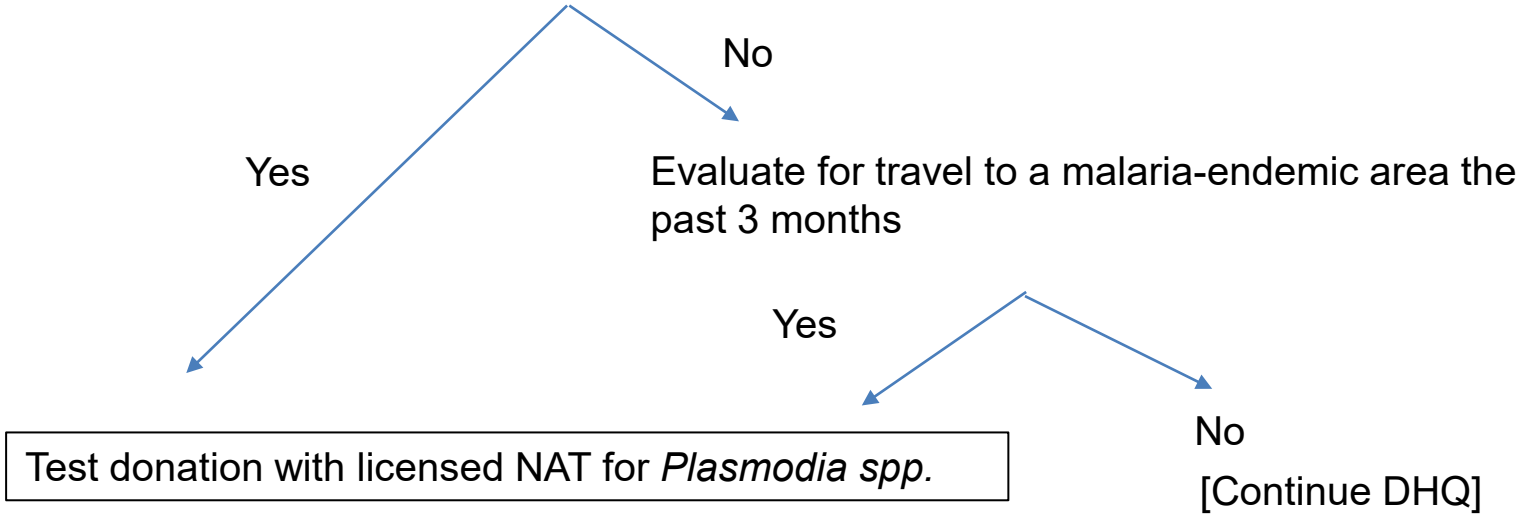
Evaluate for prior residence in malaria-endemic country and travel to malaria-endemic areas

[Continue DHQ]

1A. Selective Testing, based on DHQ

History of prior residence and travel

Determine if the donor has lived continuously for 5 years or more in a malaria endemic country



Strategy 1B: One-time and DHQ-based testing

- Propose one-time testing of all donors
  - Donors who test non-reactive would be qualified for subsequent donation without testing, subject to DHQ responses
  - Blood establishments must review records to determine history of testing

- Continue to assess donors for history of malaria and travel to a malaria-endemic area in the past 3 months
  - Donors who report a history of malaria would be asked 3 questions to assess for ongoing infection; donors would be deferred or donations tested based on response to questions
  - Propose testing all donations from individuals who report a history of travel to malaria-endemic area in past 3 months
  - No assessment for residence in a malaria-endemic country

1B. One-time and DHQ-based testing

History of malaria and travel

Have you ever been diagnosed with malaria?

Yes

Since your last malaria diagnosis:

1. Have you been evaluated by a physician, AND
2. Have you completed any prescribed treatment, AND
3. Are you now asymptomatic and free of malaria?

Yes → Test donation with licensed NAT for *Plasmodia spp.*

No → Donor is not eligible, defer for at least 1 year

No → Evaluate for travel to a malaria-endemic area in the past 3 months

[Continue DHQ]

Potential Advantages of Selective Testing (Strategies 1A and 1B)

- More robust than donor questioning alone
  - Likely identifies donors at greatest risk
- Reduces donor deferrals associated with malaria risk
  - Contributes to diverse blood supply (e.g., for patients with sickle cell disease)
  - Helps to address potential shortages, reduce urgent calls for blood donation
- Reduces overall testing burden compared to universal testing

Additional Considerations for One-time Testing (Strategy 1B)

- One-time testing of all donors would likely identify more at-risk donors with asymptomatic, ongoing malaria infection than strategy 1A and current deferrals

- Reduces some reliance on DHQ to identify risk
  - Requires testing based on donor questioning only for history of malaria and recent travel
  - Eliminates a complicated algorithm to identify prior residents of malaria-endemic countries

- Eliminates burden of repeatedly testing prior residents with no recent travel history at each donation

- Blood establishments have experience with one-time donor testing for *T. cruzi*

Limitations of selective testing strategies (I)

- Operational challenges in identifying only certain donations for testing
  - Blood establishment computer software (BECS) issues, failure to follow standard operating procedures, unique collection equipment
  - Biological product deviations reported to FDA under 21 CFR 606.171, between 2019 and 2023
    - 34 blood establishments reported distribution of over 1,000 units that were not tested for *Babesia* or *T. cruzi* under the required selective testing strategies
    - Proposed selective testing strategies for malaria based on donor questions more complicated than regional testing (*Babesia*) or one-time only testing (*T. cruzi*)

Limitations of selective testing strategies (II)

- Dependent on donor history questions to identify malaria risk and donations for testing
  - Strategies do not fully eliminate challenges with nondisclosure of information by donors and staff errors in assessing eligibility (although some questions would be simplified with both strategies)
  - One-time testing (Strategy 1B) further reduces these risks
- Potential (but negligible) risk of false positive test results and associated deferrals in a population at low risk for malaria

Strategy 2: Testing in U.S. regions with mosquito-borne malaria

- Propose testing all donations in geographic regions of the U.S. with local, mosquito borne transmission
  - When reported by public health authorities
  - Testing would be initiated when a single case is reported
  - Discontinued when no new case is reported within a 3-month rolling period
  - Region could be defined by zip code initially and expanded as appropriate

- Addresses rare, but potentially increasing, risk of local mosquito-borne transmission in U.S. (climate change, travel)
  - Establishments could continue collecting in at risk areas
  - Requires monitoring risk of local, mosquito-borne malaria transmission
  - Potential (but negligible) risk of false positive test results and required deferrals in a population at low risk for malaria

Unit and Donor Management

- Reactive donations must not be released for transfusion or further manufacturing (21 CFR 610.40 (h) and 630.30 (b))
- Donors with reactive screening test for RTTI must be deferred (21 CFR 610.41)
  - We propose deferral for at least 1 year, and until completion of medical evaluation and completion of all prescribed treatment, if applicable
  - Donors would be requalified after the deferral period and would be tested accordingly (i.e., a donor with a history of malaria would be tested at each donation)
- Currently, there is insufficient information to propose a testing algorithm for requalification before the 1-year deferral if false positive results are suspected

Charge to the Committee

1. Please comment on FDA's proposed strategies for selectively testing blood donations from donors at risk for malaria using an FDA-licensed NAT.

   Strategy 1A: Selective testing for history of malaria, history of prior residence in malaria-endemic country, history of travel to a malaria-endemic area

   Strategy 1B: One-time testing of all donors and selective testing for history of malaria and history of travel to a malaria-endemic area

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.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