

# **Transfusion-Transmitted Malaria in the United States**

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# Overview



- Scientific rationale behind the FDA's current measures to mitigate transfusion-transmitted malaria (TTM) risk in the United States
- Parasite and host factors that contribute to TTM
- Donor characteristics and clinical presentation of TTM
- Effect of malaria risk deferrals on donor availability
- Nucleic acid-based test (NAT) as a tool to screen blood donors for malaria risk
- Conclusions

# Discussion Issues



- In the U.S., the safety of blood supply against the risk of TTM is currently maintained by deferral of individuals who have had a history of malaria or have had traveled or lived in endemic countries
- While effective, the current strategy fails to capture all asymptotically infected donors resulting in infrequent but continued cases of TTM and loss of otherwise healthy donors who are not actually infected with the *Plasmodium* parasite
- A more robust strategy based on testing of at-risk donors would adequately reduce the risk of TTM while allowing more donations by eligible, healthy donors

# FDA Measures to Mitigate the Risk of TTM in the U.S.



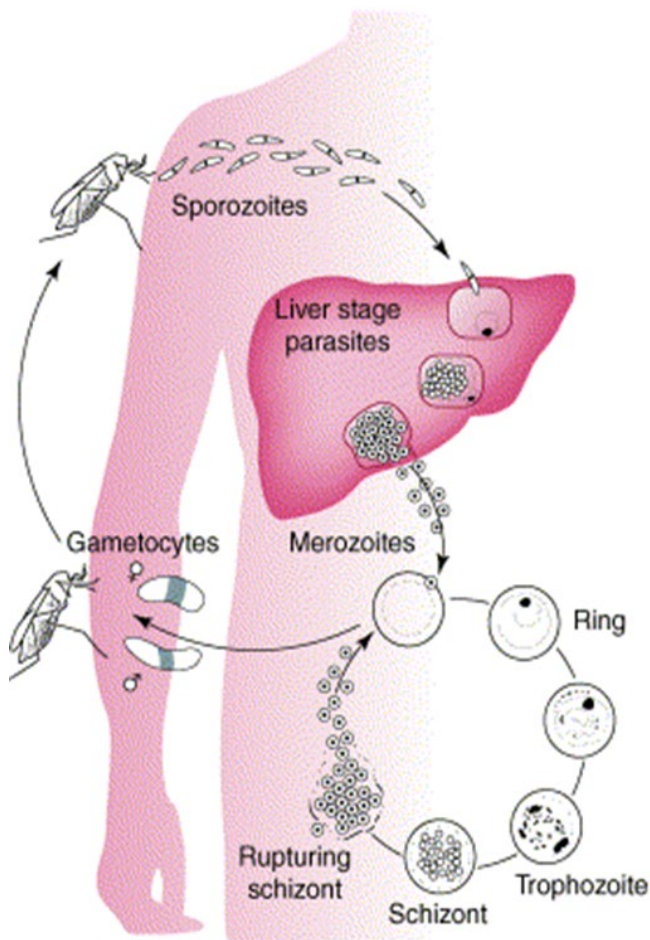
- 2013 FDA Guidance: Recommendations for Questioning, Deferral, Reentry and Product Management to Reduce the Risk of TTM
- 2020 FDA Guidance: Revised Recommendations to Reduce the Risk of TTM
  - Changed the deferral for travel to a malaria-endemic area from 12 months to 3 months after departure from that area
  - Allowed the use of pathogen reduction devices that demonstrate effective reduction of *Plasmodium falciparum* in lieu of certain questions
    - Only available for plasma and platelet components
    - No FDA-approved PRT system for whole blood or RBCs
- March 2024: FDA licensed the first test to screen blood donors for *Plasmodium* infection

# ***Plasmodium* Life Cycle, Biology and Host Pathogenesis: Implications for TTM**



- TTM in the U.S. is the consequence of asymptomatic chronic infections in blood donors acquired during travel or prior residence in endemic countries
- *Plasmodium* life cycle, parasite biology and partial immunity in host resulting from multiple exposures are major determinants of chronic malaria infections
- Parasite virulence, course and duration of infection, and host immunity and pathogenesis varies by species

# Asymptomatic Phases of *Plasmodium* Infection: Implications for TTM



- Prerythrocytic liver stage cycle. Depending on *Plasmodium* species, 7-30 days post-infectious mosquito bite, liver form merozoites are released in blood circulation
  - *P. vivax* and *P. ovale* malarias have dormant liver form stages (hypnozoites) causing relapse infections which may last from months to several years
- Asymptomatic chronic blood stage infection. The majority of chronic blood stage infections are cleared in about 12 months
  - In rare instances, chronic blood stage infections may persist for years or even life-long due to partial host immunity or inherent biology of infecting *Plasmodium* species
- The interval between departure from an endemic country and eligibility to donate blood is a major consideration in mitigating TTM risk

# Current DHQ Deferrals or PRT

Donor History		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 – 3 or more consecutive years in non-endemic country	3 months	Yes
	Resident of a malaria-endemic country – 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

# Duration of Onset of Clinical Illness after Leaving an Endemic Area, 2018



Interval between date of arrival in U.S. and onset of illness	Total No. imported malaria cases (%)
Onset before arrival	173 (14.0)
0-29	890 (71.9)
30-89	83 (6.7)
90-179	33 (2.7)
180-364	45 (3.6)
≥365	14 (1.1)

- Travelers from nonendemic countries: 3-month deferral
  - >92% of clinical cases reported within the 3 months of departure from an endemic area
- History of malaria and prior residents of endemic countries: 3-year deferral
  - Approximately 99% of reported clinical malaria cases occurred within first year of arrival from endemic areas/countries



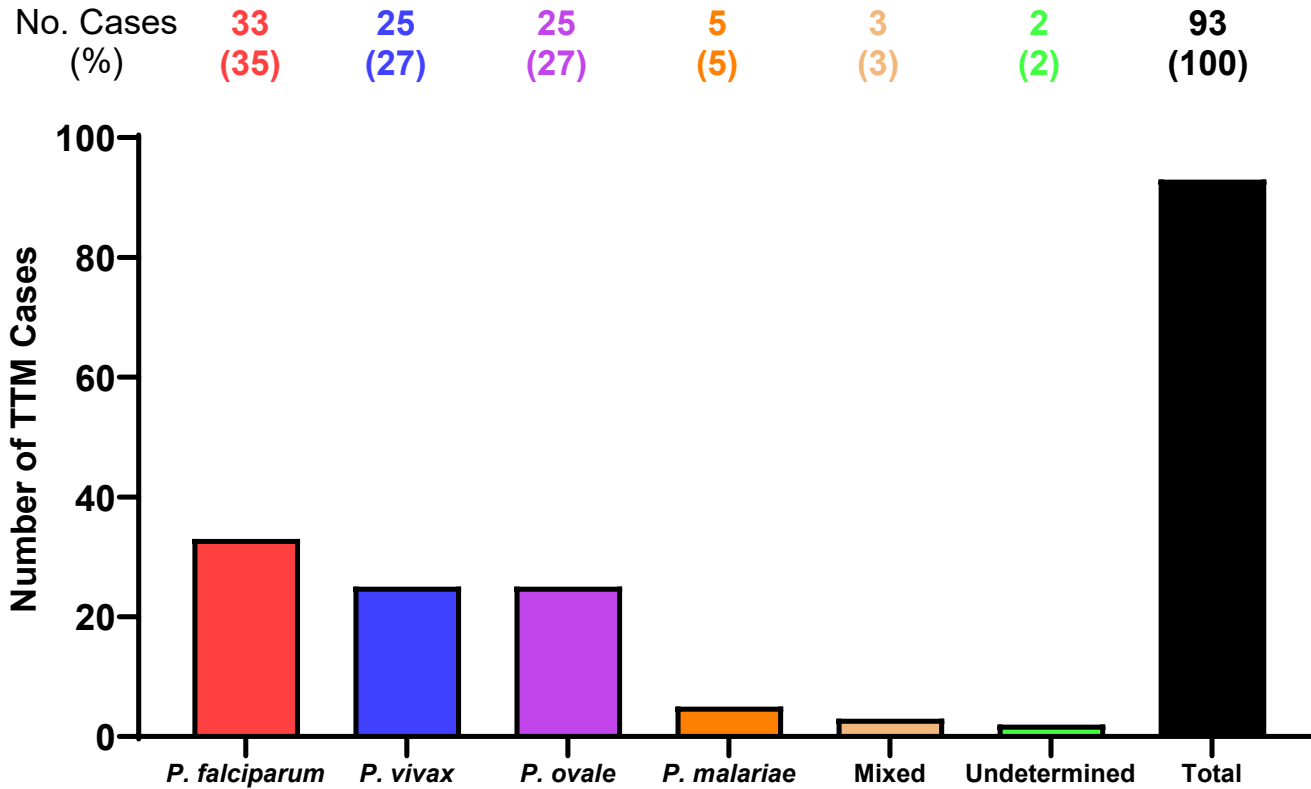
# Historical Characteristics of Donors Implicated in TTM in the U.S., 1963-1999



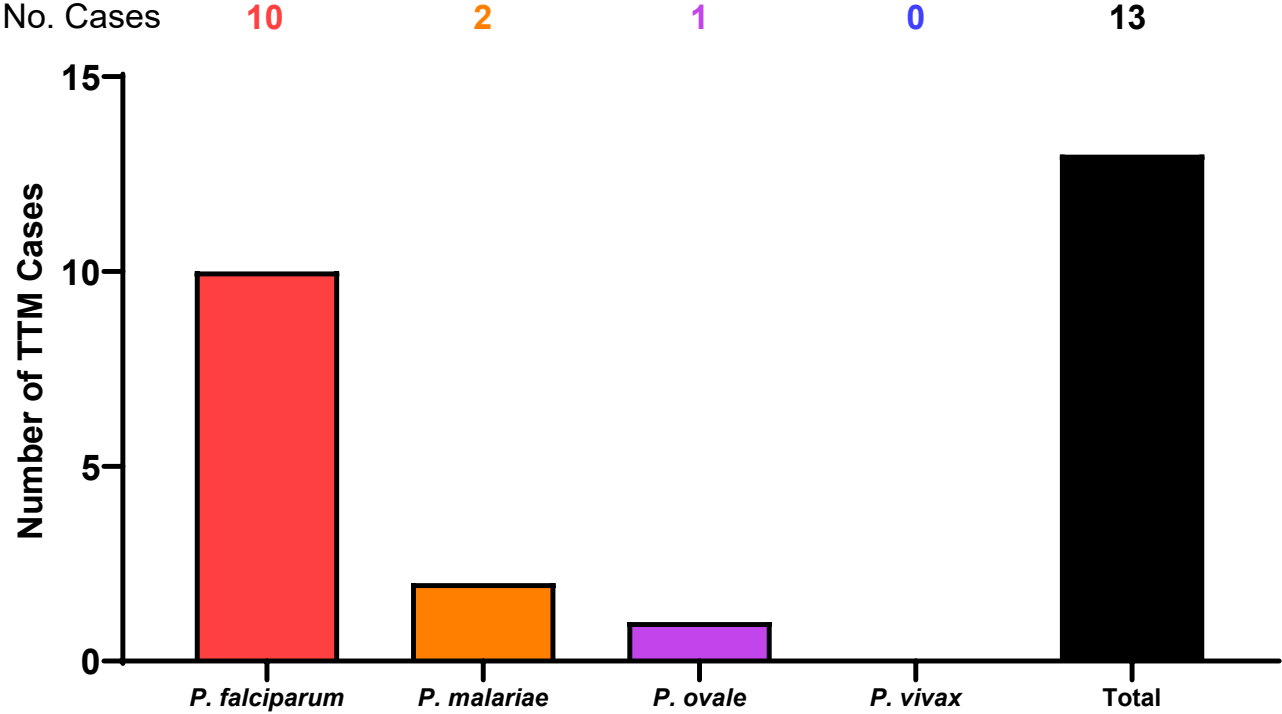
Donor Characteristic	1963-1969 N=11	1970-1979 N=24	1980-1989 N=17	1990-1999 N=12
Prior residents of endemic countries	4 (36)	5 (21)	15 (88)	10 (83)
U.S. civilian traveler	0	2 (8)	0	1 (8)
Visitor to Country of Origin	1 (9)	4 (17)	2 (12)	1 (8)
U.S. Military Personnel	6 (55)	13 (54)	0	0

Figures in parentheses denote percentage of all TTM cases for whom country of origin was known

# TTM in the U.S. between 1963-1999



# TTM in the U.S. between 2000-2021





# Limitations of the Current FDA Recommendations in Capturing Asymptomatic Malaria in Donors (2000-2021)

- Current approach does not adequately capture malaria risk
- 13 TTM cases reported 2000-2021, all implicated prior resident of a malaria endemic country
  - 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)

# Clinical Presentations of TTM



- Signs and symptoms resemble mosquito-borne malaria infections – fever, chills and malaise which may progress to severe disease including severe malarial anemia and other clinical complications
- Clinical features and disease severity in TTM depends on the causative *Plasmodium* species
- Incubation period of TTM may vary between 1 to 12 weeks post-transfusion
- Fatality rate of TTM is approximately 11%
- There is often delayed diagnosis of TTM in U.S. (1 to 180 days) resulting in delayed treatment and adverse outcomes

# Blood Components that Cause TTM



- TTM is transmitted by infected red blood cells (iRBC) present in whole blood or blood components
  - In a few instances, whole blood derived platelets containing residual infected RBCs, and in rare cases fresh plasma and organ transplantation have been implicated in causing TTM
- *Plasmodium* parasites can survive at 4° C for more than 14 days in banked RBCs
  - Cryopreserved RBCs can also cause TTM
- Leukocyte reduction and irradiation do not remove and do not inactivate infected red cells and do not prevent TTM

# Effect of Malaria Risk Deferrals on Donor Availability



- Approximately 50,000-160,000 blood donors are deferred annually for malaria risk in the U.S.
- Individuals deferred for malaria-risk are ethnically and racially diverse and often have rare blood group types
- Such donors fill a critical need in transfusion medicine, particularly among the U.S. minority populations and transfusion-dependent patients with sickle cell disease or thalassemia
- Individuals might self-defer and not present to donate
- Deferred donors are less likely to return to donate blood

# Nucleic Acid Test (NAT)-Based Testing for Malaria



- Microscopy and antigen detection test (routine malaria diagnosis methods) are  $\geq 1,000$ -fold less sensitive than NAT-based assays
- Microscopy and antigen detection methods are not amenable for high throughput adaptation to serve as donor screening assay
- The licensed *Plasmodium* NAT
  - Sensitivity and specificity were demonstrated in preclinical and clinical studies for five *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*)
- Specificity of the licensed *Plasmodium* NAT
  - False positives are negligible
- The licensed *Plasmodium* NAT is available in high throughput format



# NAT in Detecting Asymptomatic Phases of *P. falciparum* Malaria

- In Controlled Human Malaria Infection (CHMI) studies, post-*P. falciparum* sporozoite challenge by mosquito-bites in malaria naïve volunteers, average time for the release of liver form merozoites is 5 - 7 days
- NAT could detect *P. falciparum* parasites in blood samples in the majority of volunteers by day 7 post-sporozoite challenge. Compared to microscopy, NAT reduced the window period of detection by an average 3.7 days
  - Predicts a short window period before NAT detection among travelers
- NAT detects low-level parasitemias in asymptomatic carriers in endemic settings
  - Predicts the ability to detect asymptomatic individuals carrying low-grade *Plasmodium* infection who were prior residents of endemic countries

# Conclusions



- The current FDA's recommendations are insufficient to identify and defer all blood donors with asymptomatic *Plasmodium* infections
- Consequently, TTM continues to occur in the U.S.
- Loss of otherwise eligible donors, particularly those at low-risk of being exposed to *Plasmodium* parasite, adversely affects the blood supply
- Published reports indicate the effectiveness of NAT-based assays in detecting asymptomatic low-grade *Plasmodium* infections among U.S. travelers and prior residents of malaria-endemic countries
- Availability of an FDA-licensed, NAT-based donor screening assay offers the opportunity to further augment blood safety and availability against TTM risk