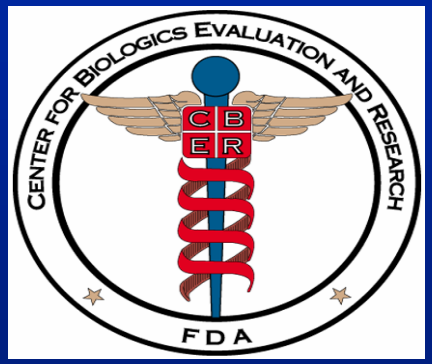

Geography based Donor Deferral to Protect Blood Supply from Malaria Risk

and a Summary of the FDA Workshop on Testing for Malarial Infections in Blood Donors

July 12, 2006

Advisory Committee on Blood Safety and Availability
August 30, 2006

Sanjai Kumar, Ph.D.
Division of Emerging and Transfusion Transmitted Diseases
Office of Blood Research and Review
CBER, FDA

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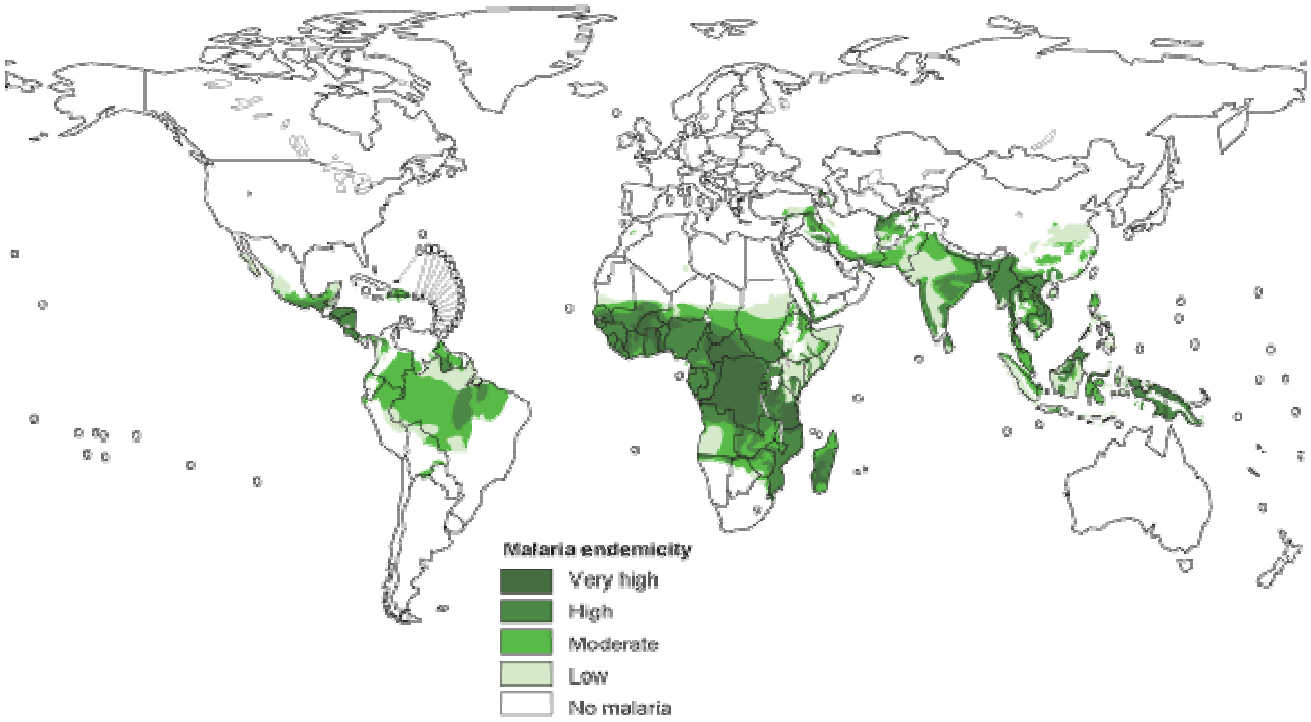
Epidemiology



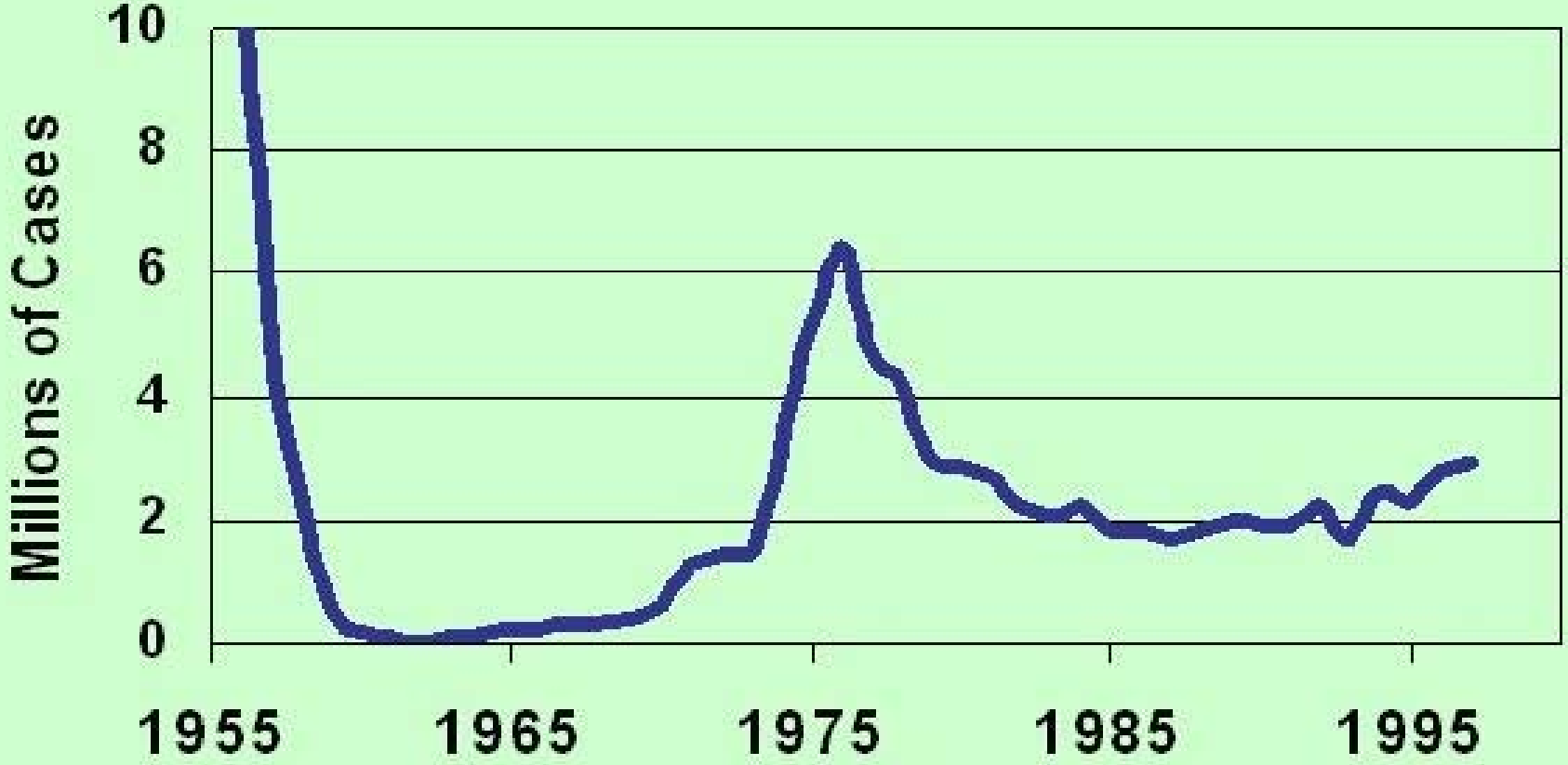
- *Plasmoidum falciparum*, *P. vivax*, *P. ovale*, *P. malariae*
- Occurs in more than 100 countries throughout Africa, Asia, Latin America, and on certain Caribbean and Pacific Islands
- >3.2 billion inhabitants at risk
- 300 – 500 million clinical cases
- ~ 1 – 2 million per year

World Malaria Report, WHO 2005

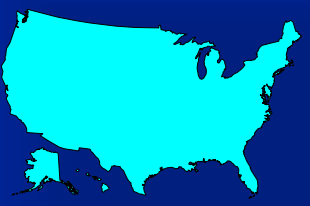
Global Reach of Malaria

- In today's interconnected world, no country is immune from the hazards of malaria
- The problem of malaria is rising. There are more cases of malaria today than 30 years ago
- Major factors attributed to rise in malaria transmission
  - Environmental
  - Human activities
  - Drug resistance in malaria parasites
  - Vector populations

Malaria Incidence in India



Source: Tom Wellems, NIH



Malaria in the United States

- **Approximately 1,000-1,500 cases reported annually**
  - **Imported – 99%**
  - **Locally acquired (up to about 10 cases/year)**

From: Monica Parise, CDC

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Donor populations that cause TTM

- **Travelers**
  - **No prior immunity**
  - **Infection can be acquired shortly before departure**
  - **Infection with a strain of Plasmodium with prolonged latency**
  - **More than 28 millions Americans visit malaria endemic countries each year**
- **Residents**
  - **Born in an endemic country or had a prolonged residence**
  - **Asymptomatic carriers**
  - **Parasite burden in asymptomatic carriers is not known**
  - **-- Millions of immigrants who have been prior residents in endemic countries**
- **History of clinical malaria**
  - **Inadequate treatment**
  - **Relapse from liver form parasites**

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TTM in the US

- TTM is all time low. Approximately 0.5 cases per year or 0.07 cases per million units of blood collected
- No approved laboratory test to detect malaria parasites in blood donors
- Blood safety from TTM is maintained through donor deferral based on residence or travel history

TTM…the last 15 years (1990-2005)

- **16 cases (donor implicated in 14)**
  - **12 – immigrants; two persons born in US but who lived long-term overseas grouped into this category**
  - **1 – US traveler (Kenya)**
  - **1 – VFR (Africa)**
- **12/14 (86%) acquired in sub-Saharan Africa (2 in China due to *Pm*)**
- **71% due to *Plasmodium falciparum***
  - **21% *P. malariae* – China; 7% *P. ovale***
- **Failure of screening process in 71%**

FDA Guidelines for Donor Deferral Based on 1994 Memorandum

- **Three-year deferral:**
  - **History of clinical malaria**
  - **Prior residents of endemic country**
- **One-year deferral:**
  - **Visit to a malaria endemic area by residents of nonendemic countries**

Identification of malaria endemic area as provided by CDC:

www.cdc.gov/travel/regionalmalaria/index.htm

Drawbacks of Deferral Based Safety from the Risk of TTM

- **1.2% loss of donors for potential malaria exposure (range 0.2 - 3.1%) (2006 ABC survey)**
  - **> 120,000 - potential donors/year known to be deferred; representing up to 180,000 donations**
  - **Self-deferral could be much higher**
  - **Deferred donors are difficult to re-recruit (Vox Sang (87) 2004, (150-155).**
  - **Travel deferrals may impact repeat donors disproportionately - impact on donor base is cumulative**
  - **Travel deferrals may impact male donors age 25-39 disproportionately (Transfusion (44) October, 2004**
- **Travel histories are difficult to obtain precisely**
- **Absence of up-to-date mapping utility for malaria risk areas**
- **Endemic areas are subject to change**

Modified from Alan Williams, FDA

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Considerations for improving TTM

- Global transmission and micro-endemicity within a country – identify the source of infection
- Presence of Plasmodium species in an area and its implication for implementation of blood screening test
- Parasite biology and natural immunity

Malaria Mortality: Summary Statistics at the Beginning and End of the 20th Century

Region	Year	Total no. of deaths from malaria	% of all deaths due to malaria
Europe and North America	1900	80,000	0.8
	1997	20	0.0001
Caribbean, Central and South America	1900	42,000	2
	1997	4,000	0.05
Asia, China and Western Pacific	1900	2,800,000	9
	1997	65,000	0.1
Sub-Saharan Africa	1900	210,000	6
	1997	990,000	9
World minus Sub-Saharan Africa	1900	2,900,000	8
	1997	69,000	0.08
Total World	1900	3,132,000	
	1997	1,059,020	
Total World Annual Deaths/10,000	1900	19.4	
	1997	1.84	

Carter and Mendis, Clin Microbiol Rev 2002

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Region of acquisition of malaria cases — United States, 2004

TABLE 5. Number of imported malaria cases among U.S. and foreign civilians, by region of acquisition — United States, 2004*

Area or region	United States No.	United States (%)	Foreign No.	Foreign (%)	Total No.	Total (%)
Africa	548	(70.7)	177	(62.8)	725	(68.6)
Asia	91	(11.7)	53	(18.8)	144	(13.6)
Central America and the Caribbean	73	(9.4)	35	(12.4)	108	(10.2)
South America	24	(3.1)	3	(1.1)	27	(2.6)
North America	6	(0.8)	11	(3.9)	17	(1.6)
Oceania	28	(3.6)	1	(0.4)	29	(2.7)
Europe/Newly Independent States	0	(0)	0	(0)	0	(0)
Unknown†	5	(0.7)	2	(0.7)	7	(0.7)
Total	**775**	**(100.0)**	**282**	**(100.0)**	**1,057**	**(100.0)**

*Persons for whom U.S. or foreign status is not known are excluded.

†Region of acquisition is unknown.

Monica Parise, CDC

Representative Distributions of the Four Recognized Species of Human Malaria Parasites in the World Today

Distribution of species (%) in following areas (total no. of cases)					
Species	Sub-Saharan Africa		Asia (all) (863)	Central America and Caribbean (178,242)	South America (859,480)
	West and Central (858)	East and Southern (297)			
P. falciparum	88.2	78.8	4.2	12.9	29.2
P. vivax	1.2	9.8	95.6	87.1	70.6
P. malariae	2.2	3.0	0.0	0.0	0.2
P. ovale	8.4	8.4	0.2	0.0	0.0

Carter and Mendis, Clin Microbiol Rev 2002

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Considerations for laboratory tests to detect malaria parasites in blood donors

- Direct parasite demonstration (microscopy or DNA detection) is most suitable for all donor groups
  - Window period of exposure in travelers before testing should be allowed and low-parasite burden in asymptomatic carriers
- A surrogate of exposure such as the presence of anti-malaria antibodies can be indicative of a current infection or a previous exposure
  - Time lapse between parasite exposure and first appearance of antibodies in travelers and assay sensitivity in donors with primary infections and asymptomatic carriers
  - A few reports suggest that seroconversion occurs within a few weeks after appearance of blood form parasites
- A screening test should be able to detect all Plasmodium species that frequently cause TTM

Methods to Detect Malaria Parasites

- **Direct parasite demonstration**
  - **Microscopy**
    - **Thick blood film**
    - **QBC method**
  - **Nucleic acid based methods**
    - **PCR test, TaqMan assay, Real-time PCR and Microarray**
- **Antigen detection**
  - **HRP, LDH etc. based dip sticks**
- **Indirect demonstration of parasite exposure**
  - **Antibody based methods: IFAT, ELISA**

TESTING FOR MALARIAL INFECTIONS IN BLOOD DONORS

WORKSHOP

July 12, 2006

Natcher Conference Center
Building 45
National Institutes of Health
Bethesda, MD 20894

Sponsored by
The Food and Drug Administration and
The HHS OS/Office of Public Health Sciences

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Workshop Objective

To seek public discussion of scientific developments that might support donor testing for malarial infections as part of pre-donation testing or as follow-up testing to permit a reduced deferral period for donors deferred for risk of malaria.

Topics for Question

- Malaria in the USA and the main sources of malaria risk to the blood supply
- Risks and benefits of screening donors for malaria infections in lieu of risk-based deferrals
- Available and emerging technologies to test blood donors for malarial infections
- Potential effects of donor testing for malarial infections on the safety and availability of the blood supply under the following scenarios:
  - Universal malaria antibody testing of all blood donors
  - Testing for donors who are deferred based on a history of possible malaria exposure or had experienced clinical malaria in order to accelerate reentry.

Background. Antibody testing in Europe and Australia

- Several European countries and Australia now test deferred at-malaria-risk donors by an EIA that detects antibodies to P. falciparum and P. vivax
- In UK, individuals who had malaria or a history of prior residence in endemic countries are deferred indefinitely, all other prospective donors are deferred for one year after each return
- At-risk donors having no antibodies by EIA at least six months after the last potential exposure or symptom of malaria are allowed to renter
- In France, travelers are allowed to donate if found negative for malarial antibody at least four months after return

FDA Workshop on Testing for Malarial Infections in Blood Donors

Natcher Conference Center
Building 45
National Institutes of Health
Bethesda, Maryland, USA

July 12, 2006
7:30 a.m. – 5:30 p.m.

AGENDA *

7:30 Registration

Workshop Chair: Sanjai Kumar, Ph.D., FDA

8:00 Welcoming Remarks: Jesse Goodman, M.D., M.P.H., FDA

Introduction to the workshop: Hira Nakhasi, Ph.D., FDA

Session I. GLOBAL PROBLEM OF MALARIA AND ITS IMPACT ON THE US BLOOD SUPPLY

Chair: Monica Parise, M.D., CDC

8:20 Global problem of malaria, biology of malaria parasites and implications for transfusion-transmitted malaria and detection methods: Sanjai Kumar, Ph.D., FDA

8:40 Malaria in the United States: Monica Parise, M.D., CDC

9:00 Malaria in the United States military and its implications for safety of the blood supply: Christian F. Ockenhouse, M.D., Ph.D., Walter Reed Army Institute of Research

9:20 Current deferral policies to reduce the risk of transfusion-transmitted malaria and their impact on donor availability: Alan Williams, Ph.D., FDA

9:40 Panel discussion: Moderator: Monica Parise. Panelists: Sanjai Kumar, Christian Ockenhouse, Alan Williams

Q1. What are the main sources of malaria risk to the US blood supply?

Q2. How effective are the current safety interventions?

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Session I: Malaria in USA (Parise, CDC)

- Travel to Africa accounts for only 0.6% of US travel in 2003, yet, 66.2% of all malaria infections and 85.9% of all *P. falciparum* infections were acquired in Africa in 2003
- From 1985-2002, 93% of all malaria deaths in US travelers due to Pf - 73% of those were acquired in sub-Saharan Africa
- TTM in US since (1990-2005)

16 cases; 1 US traveler (Kenya), 1 VFR (Africa), 12-immigrants, 12/14 acquired in Africa, 71% Pf

Session II. TESTING FOR MALARIA INFECTIONS

Chair: Peter Chiodini, M.B.B.S., Ph.D., London School of Hygiene and Tropical Medicine, UK

10:30 Developing a test to detect malaria infections in blood donors: P. Nigel Appleton, Newmarket Laboratories Ltd., UK

10:50 Antigen/antibody diagnostic assays for malaria: A CDRH perspective: Freddie Poole, FDA

11:10 CDC experience with the laboratory tests used to investigate incidents of transfusion-transmitted malaria: Marianna Wilson, M.S., CDC

11:30 Prospects for DNA-based tests to detect malaria infections: Sanjai Kumar, Ph.D., FDA

11:50 Panel discussion: Moderator: Peter Chiodini. Panelists: John Barnwell, Jon Daugherty, P. Nigel Appleton, Freddie Poole, Marianna Wilson, Sanjai Kumar

Q. How sensitive and specific are the available tests for malaria in detecting the infection at different clinical stages, and for different *Plasmodium* species?

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Session II Testing for Malaria Infections (Nigel Appleton, Newmarket Labs)

- EIA sensitivity: Pf: 94%; Pv: 100%. Cross-reactive: Pm: 80%; Po: 67%
- EIA new version:

1 antigen	Sensitivity	69%
2 antigen	Sensitivity	73%
3 antigen	Sensitivity	82%
4 antigen	Sensitivity	99%

Session II Testing for Malaria Infections (Sanjai Kumar, FDA)

- Highly infectious nature of malaria parasites causes a potential risk from a few parasites that could be present in a unit of blood
- Highest sensitivity achieved: 2 to 20 parasites/ml or 1000 parasites in a unit of blood
- Minimum number of infectious parasites present in a unit of blood: Not known (biggest roadblock)
- Possible solutions:

  - A technology for parasite concentration

  - An accurate knowledge of the minimum parasite burden in infected donors would allow to determine the required assay sensitivity

Session III. PERSPECTIVES ON TESTING FOR MALARIA INFECTIONS IN BLOOD DONORS

Chair: Roger Dodd, Ph.D., American Red Cross

1:30 United Kingdom experience regarding malaria antibody tests and their contribution to blood safety: Peter Chiodini, M.B.B.S., Ph.D., London School of Hygiene and Tropical Medicine, UK

1:50 French experience with malaria antibody testing: Olivier Garraud, M.D., Ph.D., University of Saint-Etienne, France

2:10 (a) Australian experience with malaria antibody testing; and
(b) Feasibility of implementing a malaria test for the U S blood donors: Susan Stramer, Ph.D., American Red Cross

2:40 Enhancing U S blood availability by testing for *Plasmodium* spp. infection: David Leiby, Ph.D., American Red Cross

3:00 Estimated risks and benefits of blood donor screening for malaria compared with donor deferrals for geographical exposure: Steven Anderson: Ph.D., M.P.P., FDA

3:20 Panel discussion: Moderator: Roger Dodd. Panelists: Celso Bianco, Peter Chiodini, Olivier Garraud, Susan Stramer, David Leiby, Steven Anderson, Louis Katz, Steven Kleinman

Q1. What are the lessons learned from testing for malarial antibodies amongst blood donors in Europe and Australia?

Q2. What are the pros and cons of universal donor screening compared with testing only for donor reentry?

Session III Testing for Malaria Infections in Blood Donors

- Prof Chiodini, UK
  - Donor testing for malarial antibodies in at-risk populations

2004	42947 tested	1209 RR	2.82%
2005	66994	1368	2.04%
J-M 06	11988	236	1.97%

- Prof Garraud, France
  - **# of donations tested: 75,016 (≈3.5%)**

Négatives: 97.42%

Positives: 1%

Indeterminate: 1.59%

Session III Testing for Malaria Infections in Blood Donors (Susan Stramer, ARC)

- Total malaria deferrals (23, 611, 536 presenting donors)

2000-2005 (mean donation rate 1.69)

	No.	%	Projected total lost donor
Travel	241,777	1.01	410,844
Resident	25, 339	1.69	42, 635
Malaria	495	.002	831
Total	267,611	1.13	454,310

- Australian EIA experience- at risk donors (7/17/05-3/30/06)

26, 356 donors screened (visitors/residents/infection)

2.28% RR

Session III Testing for Malaria Infections in Blood Donors (David Leiby, ARC)

- EIA Newmarket testing of Non-deferred donors

N	3,229
1R	21 (0.65%)
RR	11 (0.34%)

11 RR Donors: 2-no travel; 2-born or lived in Africa; 1 travel to India; 4-previously dx/tx for malaria > 3 years ago, at least 3 lived/born in Africa

Confirmatory testing: CDC

Session IV. ROUND TABLE DISCUSSIONS

Moderator: Jay Epstein, M.D., FDA

1. What are the desirable characteristics of laboratory tests to detect malaria infections in blood donors?
2. What are the risks and benefits of donor screening for malaria infections in lieu of risk-based deferrals?

C. What are the prospects for the use of a malaria antibody test in the US?

I. To screen blood donors;

II. To reenter deferred blood donors.

D. What are the prospects for the use of DNA-based methods as blood screening tests in the US?

Panelists: Hira Nakhasi, Monica Parise, Matthew Kuehnert, Alan Williams, Peter Chiodini, Roger Dodd, Jerry Holmberg, Tom McCutchan, Louis Katz, Olivier Garraud, Steven Anderson

4:45 **OPEN DISCUSSIONS**

5:25 Closing Remarks: Jay Epstein, M.D.

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Summary of Panel Discussion: Session IV

- Donor deferral: A broad consensus regarding the deferral of donors who have traveled to or were prior residents of Africa. However, serious reservations were raised regarding the deferral of travelers who visit the resorts in Mexico or travel to some of the Caribbean countries.

- Parasite detection-

  -DNA based tests: Technology deemed to be not ready due to its inability to detect a few parasites that could be present in a unit of blood

  -Antibody testing: Data presented from experiences in UK, France and Australia based on testing of potentially exposed individuals to allow the donor reentry with reduced deferral period were found to be satisfactory. This test is based on the detection of antibodies to *P. falciparum* and *P. vivax* malarias.

Summary of Panel Discussion: Session IV

- Antibody testing in the US-

  - Universal testing: There was no clear response on the question whether all collected blood units should be tested for the presence of infections with malaria parasites.

  - Testing in at-risk populations: There was a general agreement that careful data analysis is needed to determine the geography based acquisition of infections and area wise species prevalence to decide the number of Plasmodium species to be detected by a laboratory test.

  - Some members of blood banking industry expressed concern regarding the logistics related to database configuration to accommodate donor testing in a selected population for donor reentry.

Lessons from the Workshop and Possible Future Direction

- FDA recognizes that antibody testing is becoming increasingly feasible for reentry purposes. We are willing to facilitate the development of antibody tests to reenter a donor. However, based upon the European experience, reentry to permit the subsequent donation of transfusable components appears to be most efficiently achieved "on-the-spot" at the time of prior donation by an otherwise eligible donor who is deferred for travel to a malaria area.
- Implementation of on-the-spot reentry would depend, among other considerations, on whether the blood banks can obtain and validate software to support that reentry.

Lessons from the Workshop and Possible Future Direction

- **FDA may consider reentry based upon a test that may not detect all 4 Plasmodium species, if the test detects all species known to be associated with malaria in a CDC-defined risk area.**

Lessons from the Workshop and Possible Future Direction

- **We are discussing internally possible modification of the deferral criteria, including deferral for travel; however, our current consideration is that relaxing any deferral criteria would be premature at this time.**

Acknowledgements

- FDA
  - Hira Nakhasi
  - Paul Mied
  - Jay Epstein
- CDC
  - Monica Parise

The full workshop transcript and majority of the presentations are available online.