PREVENTING TRANSFUSION-ASSOCIATED MALARIA IN NON ENDEMIC COUNTRIES

–

STATE OF THE ART AND QUESTIONS

Congrès suisse de transfusion – Neuchâtel 05/06 septembre 2024

Sophie LE CAM

CONFLICT OF INTEREST DISCLOSURE: NONE

OTHER THAN BEING EMPLOYED BY THE ETABLISSEMENT FRANÇAIS DU SANG (EFS), THE FRENCH TRANSFUSION PUBLIC SERVICE.

EFS,
IN A FEW FIGURES

EFS is about

10,000 BLOOD DONATIONS

needed every day to meet the needs of all patients


13 establishments across France


Over **100** fixed donation centres


30,000 mobile blood drives organised every year


1.5 million donors per year


1,500 hospitals supplied with blood products


1 million patients treated every year


10,000 colleagues


19 research teams

Malaria and transfusion

Transmission by transfusion

- Caused by a parasite, transmitted by mosquitos
- Five species of Plasmodium infect humans: *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*
- **Because the malaria parasite is found in red blood cells (RBCs), malaria can be transmitted through blood transfusion,** organ transplant, or the shared use of needles or syringes contaminated with blood

Malaria and transfusion

How to appraoch the transfusionnal risk ?

The more you answer YES

↕

The more the transfusionnal risk is HIGH

Donors population

- Endemicity of the pathogen ?
- *P. falciparum* circulation ?
- Duration of exposure especially during the first years of life?
- Close relationships with endemic countries (travels/migrations)?

Recipient

- Not Immunized against the pathogen ?
- Immunocompromised?

Type of blood products and preparation methods

- High RBCs numbers in the blood product?
- No pathogen reduction methods ?

Transfusionnal risk

Malaria transfusion risk in non-endemic countries

Such as Europe , US ,Canada, Australia

- **Blood DONORS: A low risk of parasitemia in blood donors** – at risk donors are :
  - **travellers coming back from endemic countries**
  - **people born in malaria endemic countries** → can develop an immuno-tolerance → low parasitemia (persisting a long time after the return) – asymptomatic – very low level of antibodies
- **RECIPIENT : naïve population - most of the time immunocompromised (leukemia, cancer) or other vulnerable patients (elder, new born …)**
- **Blood products**: risk concentrate on **packed red blood cells** and **whole blood**
  - No risk anymore with platelet (in France) or plasma (very low level of residual erythrocytes / pathogen reduced platelets in some countries)

TTMs in the last 20 years in european countries (2001 - 2021)

Transfusion Medicine and Hemotherapy

Review Article

Transfus Med Hemother
DOI: 10.1159/000525414

Received: March 31, 2022
Accepted: June 7, 2022
Published online: July 15, 2022

Transfusion-Transmitted Malaria and Mitigation Strategies in Nonendemic Regions

Christoph Niederhauser[a, b] Susan A. Galel[c, d]

and; [b]Institute for Infectious Disease, University of Bern,
asanton, CA, USA; [d]Stanford University School of Medicine,

Country	TTMs in the last 20 years reported by survey respondents	Last notified TTM case	Reference for last notified case
Belgium	None	None	na
Croatia	None	1964	na
Denmark	None	None	na
Estonia	None	None	na
Finland	None	None	na
France	4 cases	2015	[58]
Germany	None	1997	[56]
Greece	None*	1987	[81]
Ireland	None	None	na
Italy	3 cases*	2019	[60, 82]
Malta	None	None	na
The Netherlands	1 case	2011	[62]
Norway	None	None	na
Poland			
Portugal	None	None	na
Spain	1*	2002*	[83]
Sweden	None	1980	
Switzerland	None	1999	[84]
UK (England, Scotland, Wales, N. Ireland)	1 case	2003	[59]

10 TTMs cases reported in Europe in the last 20 years ► **rare adverse effect of transfusion**

A huge decrease of the numbers of the cases since the 90's because of the rigorous selection of the donors

TTM : a rare side effect of transfusion but always present…

J Travel Med. 2024 Apr 13:taae059. doi: 10.1093/jtm/taae059. Online ahead of print.

A case of possible transfusion-acquired malaria in Zaragoza, Spain

Antonio Beltrán-Rosel [1 2 3], Jorge Ligero-López [1 3], José María Domingo-Morera [4], Beatriz López-Alonso [5], Ingrid Ferreira-Ferreira [1], Amparo Boquera-Albert [6], José Miguel Rubio-Muñoz [7 8]

Affiliations + expand

PMID: 38613442 DOI: 10.1093/jtm/taae059

European regulation: European commission directive 2004/33/EC → mandatory (minimal requirement)

- **Prevention of TTM based on the principle of differing the donation of « at risk » donors – duration of deferral period depending of the risk**

- **3 years:**
  - after returning from endemic countries for those who spent their little childhood in endemic countries
  - after the resolution of clinical malaria

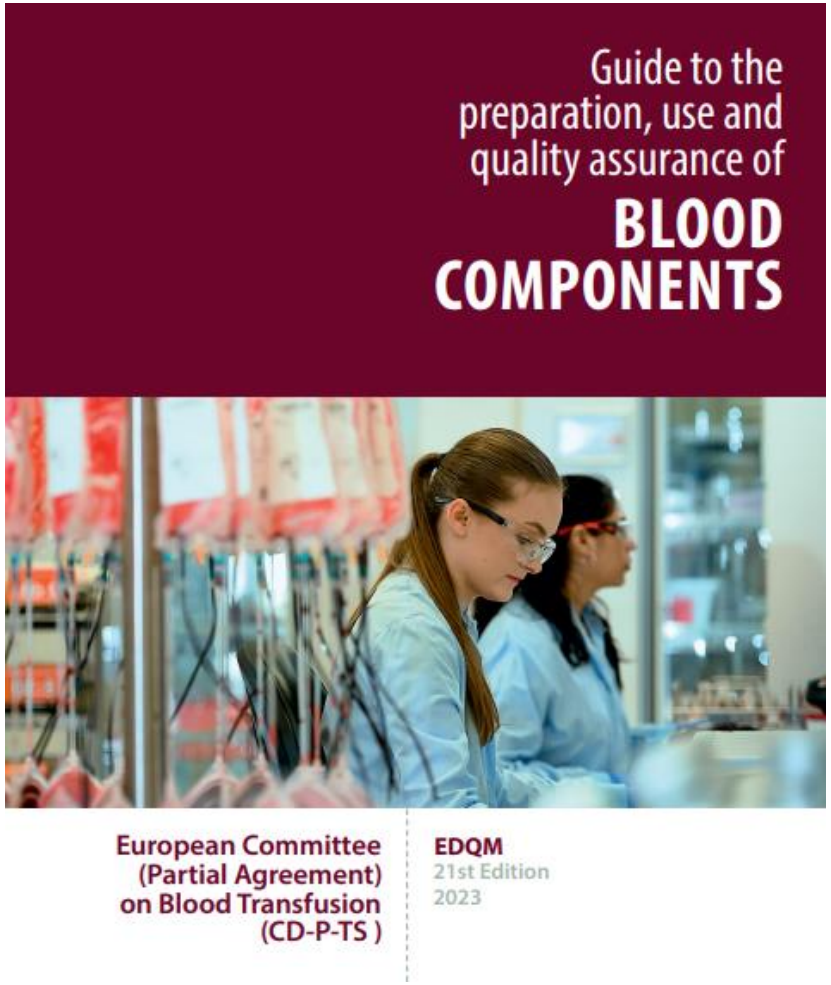
- **6 months**
  - after the return from endemic countries (for “simple travelers”)

Malaria (*)	
— individuals who have lived in a malarial area within the first five years of life	**3** years following return from last visit to any endemic area, provided person remains symptom free; may be reduced to 4 months if an immunologic or molecular genomic test is negative at each donation
— individuals with a history of malaria	**3** years following cessation of treatment *and* absence of symptoms. Accept thereafter only if an immunologic or molecular genomic test is negative
— asymptomatic visitors to endemic areas	**6** months after leaving the endemic area unless an immunologic or molecular genomic test is negative
— individuals with a history of undiagnosed febrile illness during or within six months of a visit to an endemic area	**3** years following resolution of symptoms; may be reduced to 4 months if an immunologic or molecular test is negative

Possibility to reduce the deferral duration by testing the donors with an immunologic or molecular genomic test

European recommandations – EDQM guide

Guide to the preparation, use and quality assurance of blood components.
21st Edition (2023)



- **Prevention of TTM also based of deferral period …**
  BUT deferral period are reduced and the place of immunological test is promoted
- **4 months + negative immunological test**
  - after returning from endemic countries for those who spent their little childhood in endemic countries
  - after the resolution of clinical malaria
    (and 3 years if no testing or positive results)
  - after the return from endemic countries (for “simple travelers”)
    (and 12 months if NO testing)

European Countries policies

- Each European (EU) country has to apply the 2002 European directive (minimal requirement)
- EDQM guide contains recommendations (at this time … will become mandatory until 2028…)
- **But specific rules can be added , depending <u>of the local risk</u>**

Country	Selective testing for donors at risk	Assays used	If tested negative, permission for donating blood		
			travelers	former residents of endemic areas	donors with a history of malaria
Austria	No	na	No	No	No
Belgium	Yes	Malaria EIA (Bio-Rad)	Yes	Yes	Yes
Croatia	Yes	Captia Malaria Total Ab EIA (Trinity Biotech) Malaria EIA (Bio-Rad) ELISA Malaria Ab (Diapro)	Yes	Yes	No
Denmark	No	na	No	No	Yes[1]
Estonia	Yes	Anti-*Plasmodium* (IgG) (Euroimmun)	Yes	Yes	Yes
Finland	Yes	S-PlasAb; EIA (performed in an external lab)	Yes	Yes	Yes
France	Yes	ELISA Malaria Ab (Diapro) 1th line ELISA Anti-*Plasmodium* (IgG) (Euroimmun) 2nd line	Yes	Yes	Yes
Germany	No/yes[2]	na	No/yes	No/yes	No
Greece	Yes	NovaLisa™ Malaria Elisa (NOVATEL Immundiagnostics GmbH)	No	Yes	Yes
Ireland	Currently not but is planned in the near future	Captia Malaria Total Ab EIA (Trinity Biotech) Planned to implement in the near future	No	No	No
Italy	Yes	Different assays	Yes	Yes	Yes
Malta	No	na	No	No	No
The Netherlands	Yes	Captia™ Malaria Total Antibody EIA (Trinity Biotech)	Yes	Yes	Yes
Norway	Yes	Malaria EIA (Bio-Rad)	Yes	Yes	No
Poland	No	na	No	No	No
Portugal	Yes	Malaria EIA (Bio-Rad)	Yes	Yes	Yes
Spain	Yes/no (dependent on the region)	Malaria EIA (Bio-Rad) Anti-*Plasmodium* (IgG) (Euroimmun) Captia™ Malaria Total Antibody EIA (Trinity Biotech)	Yes/no	Yes/no	Yes/no
Sweden	No	na	No	No	No
Switzerland	Yes	Anti-*Plasmodium* (IgG) (Euroimmun), Malaria EIA (Bio-Rad)	Yes	Yes	Yes
UK (England, Scotland, Wales, N. Ireland)	Yes	Captia Malaria Total Ab EIA (Trinity Biotech)	Yes	Yes	Yes

[1] Donors with a history of malaria but unsure of it being malaria. [2] Some blood banks in Germany test for *Plasmodium* antibodies according to the German Hemotherapy Guidelines.

Transfusion-Transmitted Malaria and Mitigation Strategies in Nonendemic Regions

Christoph Niederhauser[a, b] Susan A. Galel[c, d]

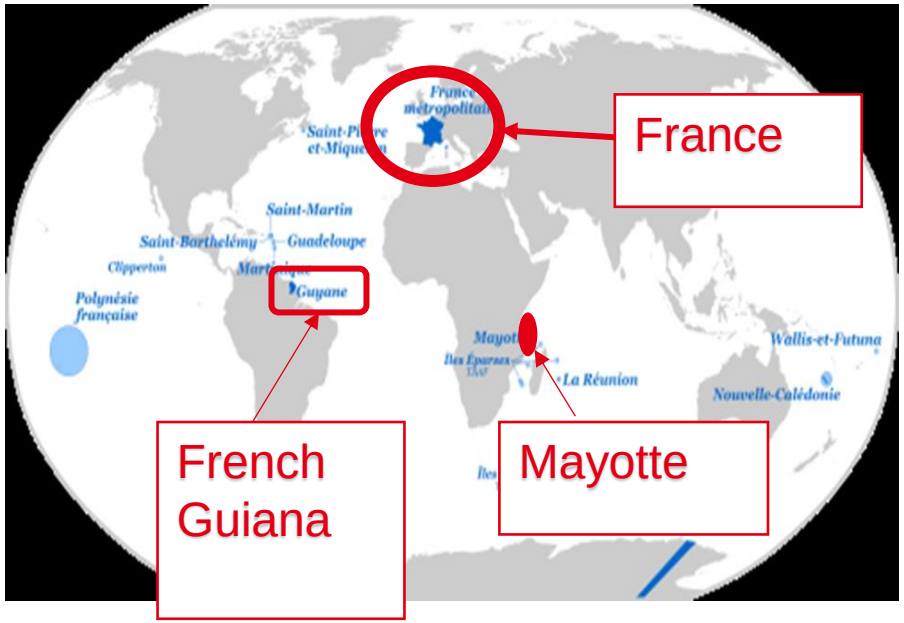
[a]Interregional Blood Transfusion SRC, Bern, Switzerland; [b]Institute for Infectious Disease, University of Bern, Bern, Switzerland; [c]Roche Diagnostics Solutions, Pleasanton, CA, USA; [d]Stanford University School of Medicine, Palo Alto, CA, USA

FOCUS on French strategy

France is free of malaria transmission

→ only imported cases

Exceptions in overseas territories: French Guiana and Mayotte Island



➥ But France has the **highest numbers of imported malaria cases in Europe**:

- -about 4995 cases in 2022
- **88,8% of malaria cases = P. falciparum** (or P. falciparum in association with an other sp.)
- Area of infection= **sub-Saharan Africa in 99,5% of cases**
- **87,6% of cases in former residents or natives of endemic countries** (malaria disease after a travel to visit family in Africa)

(data from Santé Publique France – BEH may 2023)

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021) 116, 943–945

DOI: 10.1111/vox.13097

COMMENTARY

Preventing transfusion-transmitted malaria in France

In 1986 : screening became mandatory for **"at risk donors"** for 3 years after return from endemic countries *(travelers and native)*

Evolution of the screening rules for native donors of endemic areas after a TTM case in 2002

1969-1986

- **≈ 5 cases of TTM / year**

1986-2002

- 5 cases in 16 years
- **≈ 0.3 cases/year**

2003 – 2024

- 3 cases in 21 years
- **≈ 0.15 cases / year**

- Since 2002 = 4 cases of TTM in France
- 3 cases with *P . falciparum* → 3 death
- In 2 cases , ELISA was negative !
- The 4 donors involved were native from West of Africa

French donor selection and screening policies in 2024

Donor status	Delay after returning from an endemic area	
	4 months < Return < 3 years	> 3 years
Born or having lived in a malarial area within the first 6 years of their life (“natives”) OR Individuals who have stayed > 6 consecutive months in a malarial area	- No symptoms AND - a **negative serological test at each donation** during the period	- no symptoms AND - a **negative serological test at first donation**
Others (“travelers”)	- No symptoms AND **- a negative serological test at first donation**	No symptoms

Focus on French strategy

FRENCH donor policy in 2024: management of a positive serology

- **Donors who are native to a malaria-endemic area AND have a positive (or indeterminate) malaria serology → Deferred permanently**

(pending appropriate screening tests to identify immuno-tolerant donors)

- **Donors who are not native to a malaria-endemic area AND have an indeterminate or positive malaria serology:**
  - ✓ **If INDETERMINATE: Deferred temporarily**

    May be re-accepted if the serology becomes negative on a control sample

  - ✓ **If POSITIVE : Deferred for 3 years**

    May be re-accepted after 3 years , if the serology becomes negative on a control sample

French strategy outcomes – 2022 figures

Whole blood donations (ALL)

nb of WB donations en 2022	2 375 558
Nb of WB donations tested for malaria	**101 629**
%of WB donations tested for malaria	**4,3%**

nb of REACTIVE results	3 710
% of REACTIVE results	**3,7%**

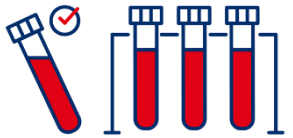
= % of WB donations discarded	**0,16%**

Whole blood donations (donors born in endemics countries)

Nb of WB donations	**13 224**

nb of REACTIVE results	2 621
% of WB donations discarded in this population	**19,8%**

Laboratory testing solutions



➢ What do we need?

- Highly sensitive tests able to recognize the five species of *Plasmodium*
- Highly specific tests
- Tests which are easy to perform on fully automated systems
- Cost-effective solutions

➢ The solutions we have is real life …

- Serological tests : ELISA , IFAT…
- Direct tests: Thin/ Thick film examination, rapid antigenic tests , PCR

Laboratory testing solutions

A large majority of European countries use serological test (ELISA)

- **Advantage: cost effectiveness**
  - ✓ easy to perform on a large sample size
  - ✓ affordable
  - ✓ a correct sensitivity/ specificity balance

- **Disadvantages:**
  - ✓ lack of sensitivity for donors native from malaria-endemic countries with inconsistent antibody titers (but a possible parasitemia !)

  - ✓ Majority of people born in endemic countries have a positive serology : we defer a lot of donors with rare blood phenotype ☹

Laboratory testing solutions: and direct tests?

- **1 dogma persists: 1 parasitized red blood cell in 1 packed red cell could be enough to transmit malaria**

No evidences – No publications

But everyone working in transfusion know this dogma ….!!

- **Sensitivity of the direct tests available (for *P. falciparum*)**
  - Rapid antigenic test ≈ 100 parasites / µl
  - Thick film examination ≈ 10 to 20 parasites / µl
  - Classic PCR from 0,1 to 1 parasites /µl
  - New molecular tests (LOOP test for example) ≈ 0,1 parasites / µL

Laboratory testing solutions

➥ Are molecular tests suitable for TTM risk prevention ?

- Main advantage = **very specific** ►avoids loss of donated blood and donors
- Until a few years ago, PCR was not a suitable solution for blood blank because of the lack of sensitivity
- Since 2023 , new tests **adapted on high throughput automated platforms** with very high sensitivity are available (based on amplification of 18S ribosomal RNA (rRNA))

A novel mitigation strategy for the prevention of transfusion-transmitted malaria

Laura Tonnetti[1] | Jamel A. Groves[1] | Deanna Self[2] | Manisha Yadav[2] | Bryan R. Spencer[3] | Kristin Livezey[2] | Jeffrey M. Linnen[2] | Susan L. Stramer[1]

TABLE 1 Analytical sensitivity of the Procleix Plasmodium Assay.

Plasmodium species	In vitro transcript: 95% LoD in Copies/mL (95% Fiducial Limits)	Infected whole blood: 95% LoD in RBCs/mL (95% Fiducial Limits)
P. falciparum	11.37 (8.88–16.19)	3.50 (2.85–4.62)
P. knowlesi	9.08 (7.21–12.58)	2.10 (1.72–2.87)
P. malariae	8.47 (6.80–11.45)	2.39 (1.85–3.59)
P. ovale	11.16 (8.15–18.01)	6.82 (5.63–8.75)
P. vivax	11.89 (9.04–17.74)	2.85 (1.66–16.75)

2,85 – 4,62 RBCs parasitized / m

↕

≈ 0,003 and 0,005 RBCs parasitized /µL

Laboratory testing solutions

Furthers studies are needed to evaluate:

- The performance of this new molecular tests
- The cost-effectiveness of these solutions vs serological testing

Objective: define a cost-effective STRATEGY to

- ensure safety of transfusion
- avoid the loss of donors native from malaria endemic countries
- enhance the supply of rare phenotype packed red cells

Take home messages

- In Europe, the risk mitigation for TTM is based on a **deferral policy** = **KEY POINT of the mitigation strategy**
- A large number of countries have implemented serological testing **which reduced the deferral time** and **prevented the loss of donation**
- The residual risk is mainly associated to an **identified high-risk population = donors born in malaria-endemic countries**
- The current challenges are to optimize the testing strategy to:
  - minimize the loss of blood products
  - enhance screening sensitivity for the Immuno-tolerant donors
- We will have to imagine the malaria screening strategy for the future:
  - based only on molecular tests ?
  - or mixed strategy with serology AND molecular testing ?

ACKNOWLEDGEMENTS

Etablissement Français du Sang
Dr Valerie Barlet
Dr Claude Maugard
Dr Celine Narboux
Dr Marlène Guillet

Pr Pierre Tiberghien
Dr Pierre Gallian
Dr Syria Laperche

Centre National de Référence
pour le Paludisme
(APHP Hôpital Bichat)
Pr Sandrine HOUZE

THANK YOU !

CONTACT

Sophie LE CAM
sophie.lecam@efs.sante.fr