CENTRO NAZIONALE SANGUE
Istituto Superiore di Sanità

GLOBAL BLOOD PRODUCT SAFETY

10 aprile 2019 | April 10, 2019

Istituto Superiore di Sanità, Aula Pocchiari
Viale Regina Elena, 299
ROMA

SESSIONE I
10.50 - 11.10

Chagas and Malaria diseases impact on transfusion safety

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IRCCS
Sacro Cuore
Don Calabria
Negrar - Verona

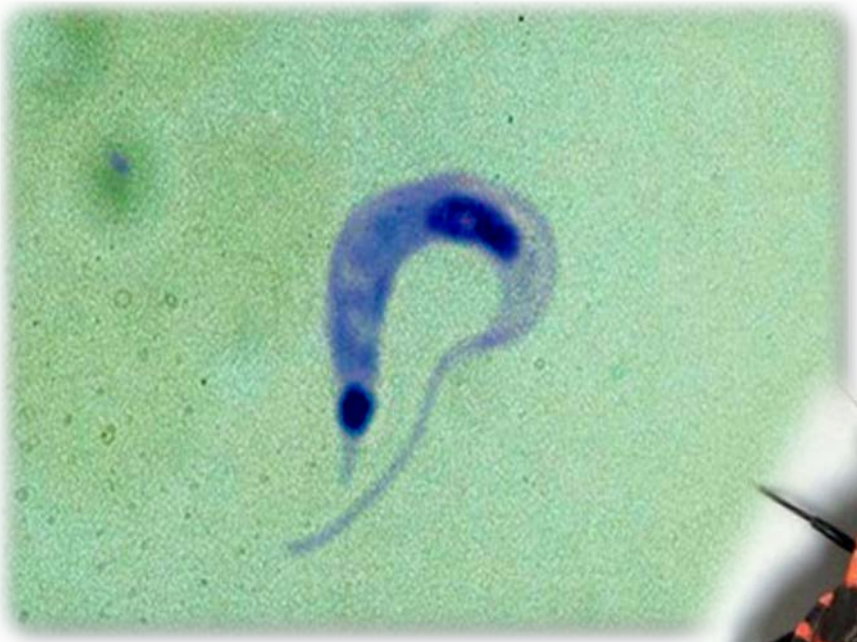
Il sottoscritto, dr. Andrea Angheben, in qualità di Relatore dichiara che
nell'esercizio della Sua funzione e per l'evento in oggetto, NON è in alcun modo portatore di interessi commerciali propri o di terzi.

Ospedale "Don Calabria"
Negrar (VR)
MALATTIE TROPICALI
ANGHEBEN

Chagas disease or American trypanosomiasis

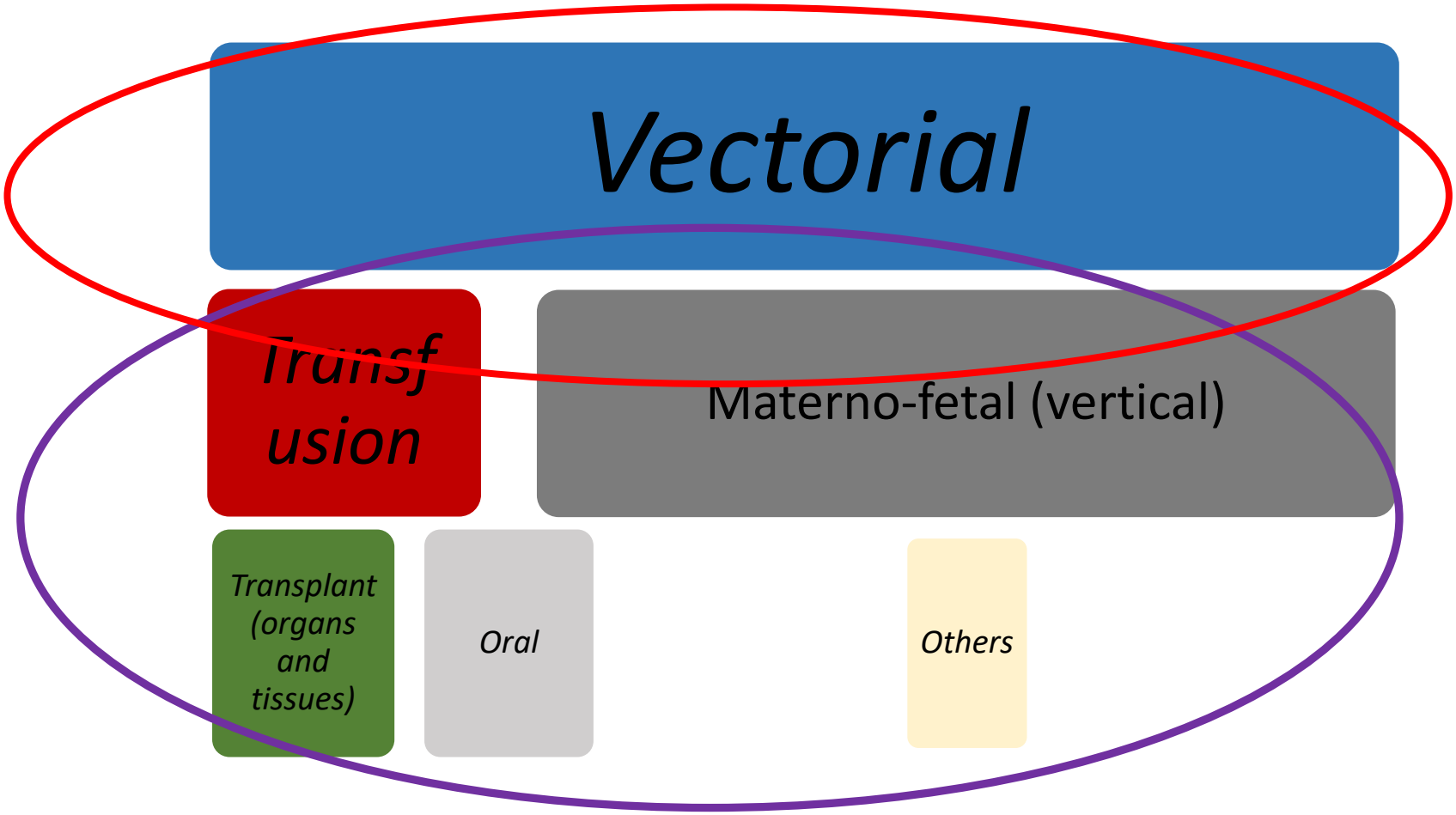
Chagas disease is a zoonosis with a complex ecology* and cycle. Endemic exclusively in the American continent, it was discovered and fully described by the Brazilian doctor Carlos Chagas.

Its cause is the hemoflagellate protozoan *T. cruzi,* which is mainly transmitted to humans by the socalled kissing ugs of the family Triatominae.



*hundred of mammalian hosts, many triatomine vectors

Transmission ways



Transmission risk:

- **Contact with infected triatomine: 0,1%**
- **Single whole blood transfusion (500 ml): 12-20%**
- **Renal trnasplant from an infected donor: 35%**
- **Reactivation in course of immunesuppression: 30%**
- **Vertical: 0,1-12% (4,2% in non endemic countries)**

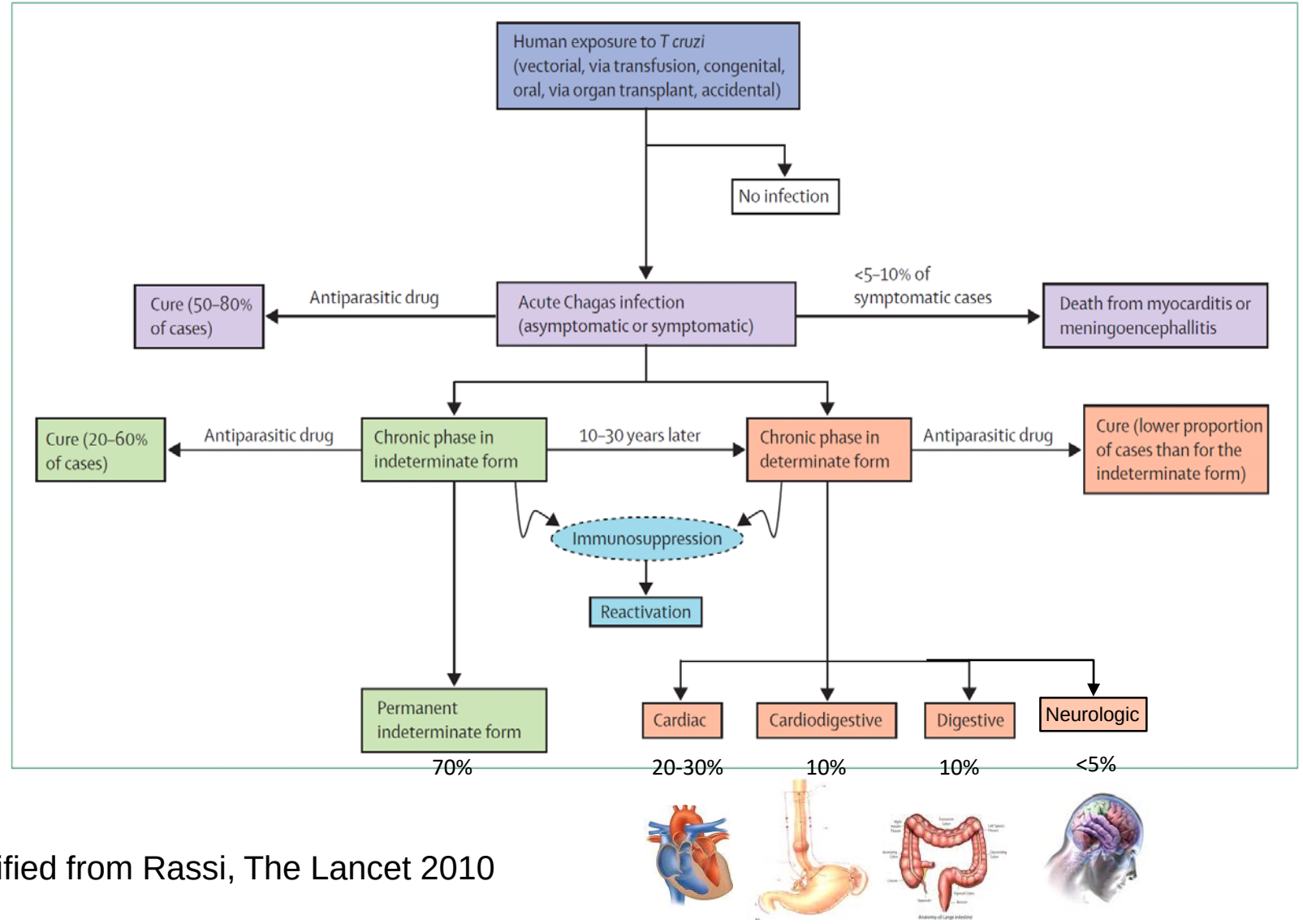
Chagas disease: oral transmission→ foods

Tabla 2. Alimentos asociados a transmisión de la enfermedad de Chagas por vía oral

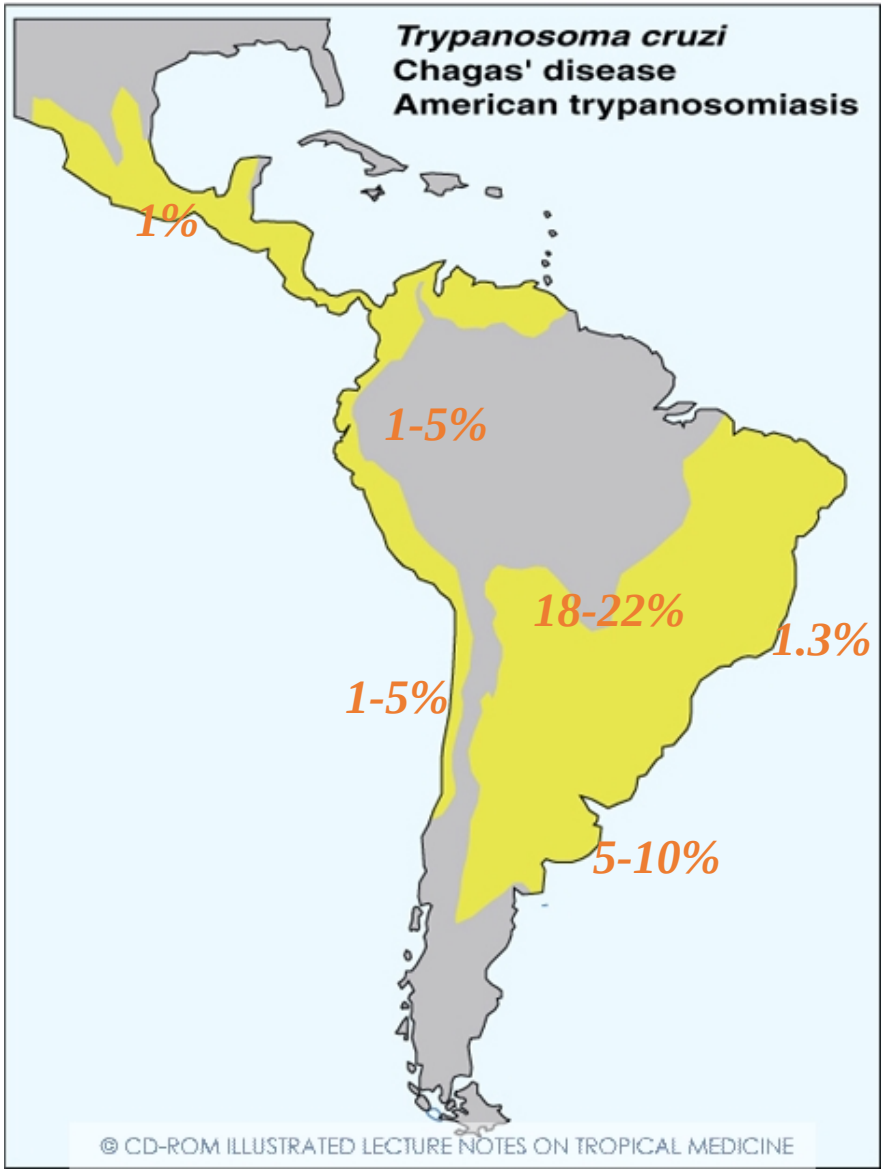
Jugo de caña (Brasil)
Jugo de açai (Brasil)
Jugo de guayaba (Venezuela)
Vino de palma (Colombia)
Carne de animales de caza (Argentina-Ecuador)

Rev Med Chile 2011; 139: 258-266

Natural history of Chagas disease



Modified from Rassi, The Lancet 2010



Endemic in 21 Latin American countries (not Caribbean or Cuba)

(8 Millions of infected people worldwide (12000 deaths per year)

100 Millions at risk (25% of whole Latin Americans)

Huge variability of endemicity across LA

Migration and disease spreading

Clin Res Cardiol
DOI 10.1007/s00392-013-0613-y

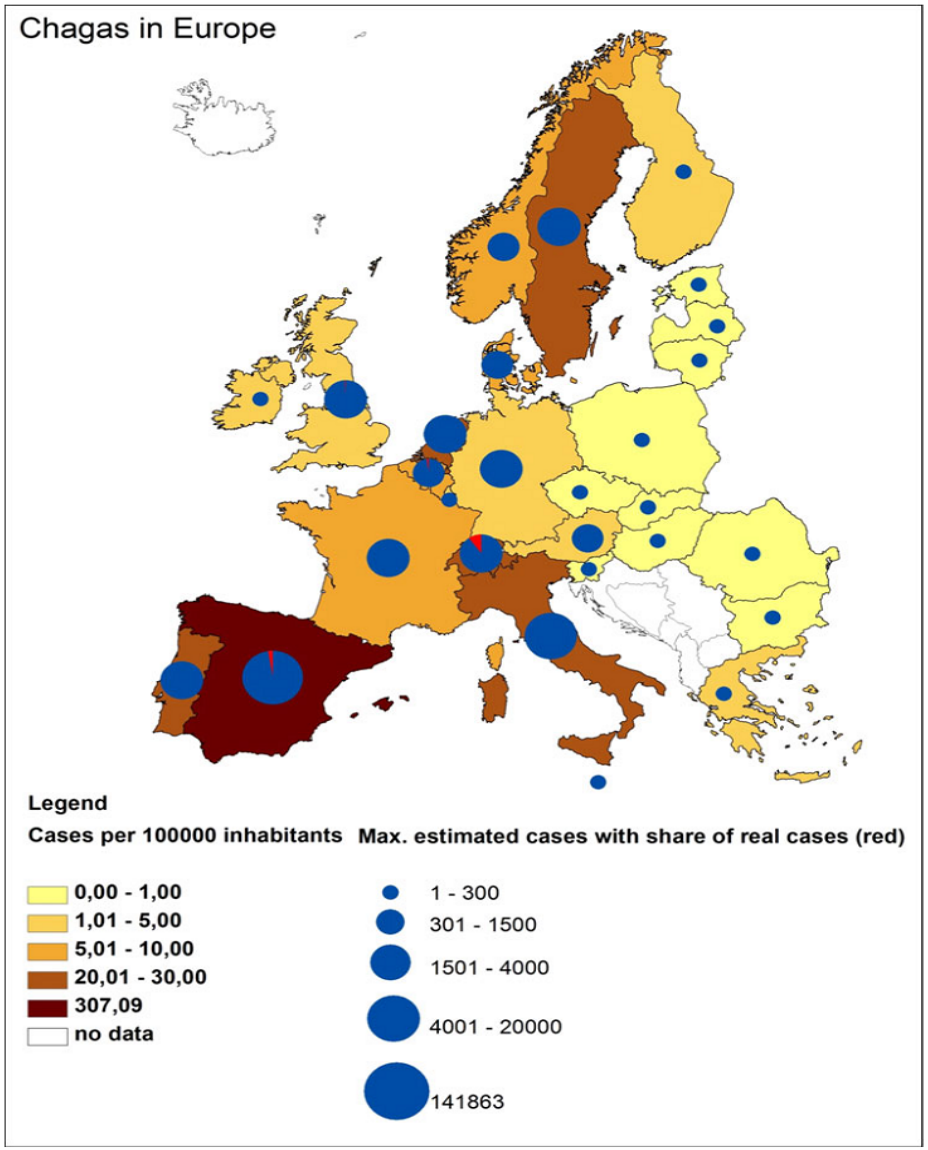
REVIEW

Epidemiology of Chagas disease in Europe: many calculations, little knowledge

Jörn Strasen · Tatjana Williams · Georg Ertl · Thomas Zoller · August Stich · Oliver Ritter

Received: 12 July 2013 / Accepted: 14 August 2013

Fig. 1 Incidence of Chagas disease from *light* to *dark* color, showing the biggest incidences in Spain, followed by Italy and Portugal and, surprisingly, Sweden, Switzerland, and the Netherlands. The maximum absolute number of cases is shown by *blue spots*. By far again Spain is most affected, again followed by Italy and again the Netherlands and then Germany and France. In the *red shares*, the portion of indentified patients is illustrated, showing visible shares only for Switzerland, Spain and Belgium [11] (Tables 2, 3, and 4)



Hotez PJ, Dumonteil E, Betancourt Cravioto M, Bottazzi ME, Tapia-Conyer R, et al. (2013) An Unfolding Tragedy of Chagas Disease in North America. PLoS Negl Trop Dis 7(10): e2300. doi:10.1371/journal.pntd.0002300 http://127.0.0.1:8081/plosntds/article?id=info:doi/10.1371/journal.pntd.0002300

Table 4. Pooled *T. cruzi* prevalence by country of origin in Latin American migrants from European countries.

Country	Number screened	Number of seropositives	Country-specific prevalence* (%)	95% CI	Prevalence in country of origin (National level) PAHO (%)[39]	Prevalence ratio
Argentina	875	16	2.2	0.80–4·13	4.13	0.53
Bolivia	2264	541	18	13.9–22.66	6.75	2.67
Brazil	954	4	0.6	0.16–1.12	1.02	0.59
Chile	290	1	1	0.17–2.36	0.99	1.01
Colombia	1627	6	0.5	0.15–0.92	0.96	0.52
Ecuador	2131	7	0.4	0.18–0.72	1.74	0.23
El Salvador	67	2	3.7	1.62–11.7	3.37	1.10
Honduras	136	3	4.2	1.27–7.36	3.05	1.38
Mexico	166	0	1.5^	0.24–3.76	1.03	1.46
Nicaragua	50	1	4.6	0.76–11.3	1.14	4.04
Paraguay	385	19	5.5	3.46–7.91	2.54	2.17
Peru	1029	4	0.6	0.23–1.18	0.69	0.87
Uruguay	248	0	0.8^	0.08–2.24	0.66	1.21
Venezuela	311	0	0.9^	0.16–2.22	1.16	0.78

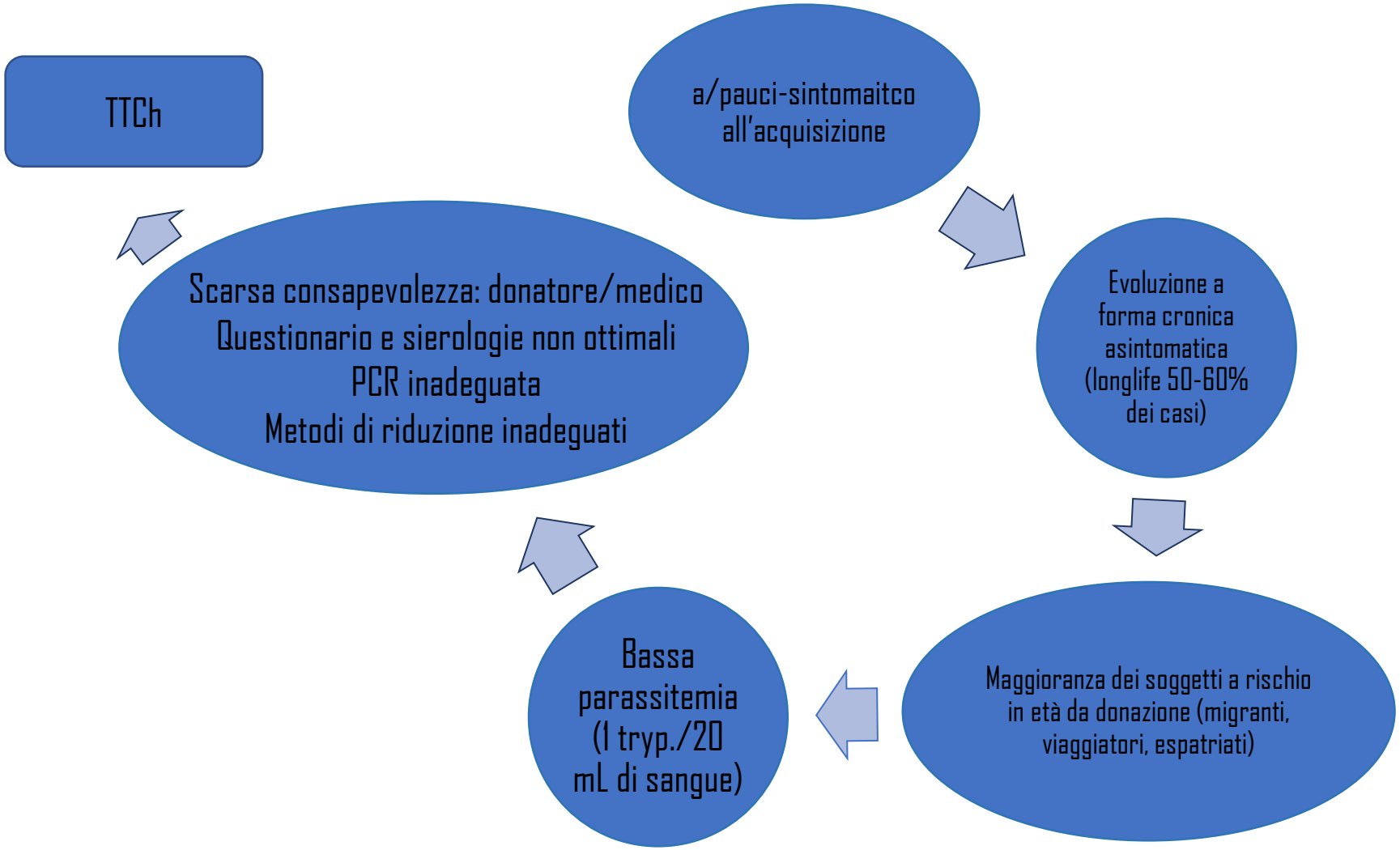
CI: Confidence Interval; PAHO: Pan American Health Organization;

*Weighted prevalence with Random effect model;

^ although there was not any reported case of Chagas disease in migrants coming from this country, the weighted prevalence is not "0" due to the Random Effect model

doi:10.1371/journal.pntd.0003540.t004

Chagas: «insidie trasfusionali»



Chagas disease and blood transfusion

- Firs case decribed in1952; then USA 80s, Spain 1992; **350** cases reported in the literature, at least 800 cases are estimated in the last decades...

Wendel S . Transfusion-transmitted Chagas' disease. Curr Opin Hematol 1998; **5**: 406-11.

Hernande z-Becerril N, Mejia AM, Ballinas-Verdugo MA, et al. Mem Inst Oswaldo Cruz 2005; **100**: 111-6.

Chagas disease and blood transfusion

- After the implementation of screening in LA: 1:200000 units is estimated infected; in non endemic countries about 1:30000;

- All blood components can transmit (***T.cruzi*** **survives 18 days at 4°C, 250 days at room temperature**); **PLT have the highest risk**

- Incubation time TTCh: 20-40 days, (8-120)

- 20% of TTCh is asymptomatic

Alcuni (15) casi di TTCh sono stati descritti in USA, Canada e Spagna, Messico. Tutti da trasfusione di PLT. Non efficacie la leucoriduzione (Benjamin et al. Transfusion 2012;52:1913-21.)

Perché in particolare le piastrine?

Cancino-Faure et al*. Hanno dimostrato ciò che l'esperienza aveva evidenziato e cioè **che le PLT sono l'emocomponente più a rischio per la trasmissione del Chagas**;

Nello studio (donatori PCR+ su sangue periferico → aferesi) le PLT erano al 100% positive alla PCR *T.cruzi*, mentre nel sangue periferico la carica parassitaria era 5X inferiore; plasma neg;

Le dimensioni (16-20 µm) di *T.cruzi* e il suo peso specifico stanno tra quelli delle PLT e dei globuli bianchi

Latinamerican migrants and blood transfusion?

Yves Jackson et al*, Plos NTD 2010 during a survey on Chagas disease among LA migrants living in Geneva, Switzerland, found that 18,5% of enrolled individuals are willing to donate or donated blood in Switzerland.

Chagas and blood donors: international studies

Seroprevalence of *Trypanosoma cruzi* infection among at-risk blood donors in Japan

Yusuke Sayama,[1,#,†] Yasumi Furui,[2] Akiko Takakura,[1] Masazumi Ishinoda,[2] Chieko Matsumoto,[1] Rikizo Taira,[2] Shigeru Igarashi,[2] Shun'ya Momose,[3] Keiji Matsubayashi,[1] Shigeharu Uchida,[1] Satoru Hino,[2] Tadashi Nagai,[1] and Masahiro Satake[1,2]

TRANSFUSION 2018;9999;1–8

TABLE 4. Summary of seroprevalence of *T. cruzi* infection among blood donors in previous studies, including the present one

No.	Country	Donor	Number of donors tested	Number confirmed positive	%	Reference
1	Japan	At-risk donors*	18,076	3	0.017	The present study
2	United States	All	2,940,491	89	0.003	10
3	Canada	At-risk donors*	14,587	13	0.089	12
4	England	At-risk donors*	38,585	3	0.008	11
5	France	At-risk donors*	30,837	3	0.010	13
6	Spain	At-risk donors*	1,770	11	0.622	14

* Definition of at-risk donor differed at each study.

SURVEILLANCE AND OUTBREAK REPORTS

Chagas disease in Italy: breaking an epidemiological silence

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1. Centre for Tropical Diseases, Sacro Cuore – Don Calabria Hospital, Negrar, Italy
2. COHEMI project (COordinating resources to assess and improve HEalth status of Migrants from Latin America)
3. Service of Epidemiology and Laboratory for Tropical Diseases, Sacro Cuore – Don Calabria Hospital, Negrar, Italy
4. Infectious Disease Unit, G. Rummo Hospital, Benevento, Italy
5. Paediatric Division, Sacro Cuore – Don Calabria Hospital, Negrar, Italy
6. Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy
7. Obstetric and Gynaecologic Department, Careggi University Hospital, Florence, Italy
8. Infectious Diseases Unit, Anna Meyer Children's University Hospital, Florence, Italy
9. Immunohaematology and Transfusion Unit, Careggi University Hospital, Florence, Italy
10. Obstetrics and Gynaecology Clinic, L. Mangiagalli Hospital, Milan, Italy
11. Obstetrics and Gynaecology Division, Sacro Cuore – Don Calabria Hospital, Negrar, Italy
12. Infectious Diseases Division, San Raffaele Hospital, Milan, Italy
13. Infectious Diseases Division, G.B. Rossi University Hospital, Verona, Italy
14. Public Health Sciences Department, La Sapienza University, Rome, Italy
15. WHO Programme on Control of Chagas disease, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Citation style for this article:
Angheben A, Anselmi M, Gobbi F, Marocco S, Monteiro G, Buonfrate D, Tais S, Talamo M, Zavarise G, Strohmeyer M, Bartalesi F, Mantella A, Di Tommaso M, Aiello KH, Veneruso G, Graziani G, Ferrari MM, Spreafico I, Bonifacio E, Galera G, Lanzafame M, Mascarello M, Cancrini G, Albajar-Viñas P, Bisoffi Z, Bartoloni A. Chagas disease in Italy: breaking an epidemiological sil
Euro Surveill. 2011;16(37):pii=19969. Available
leId=19969

Article published on 15 September 2011

Chagas disease, a neglected tr
due to population movements i
to Latin America, threatens a wi
ple (travellers, migrants, blood or organ recipients, newborns, adoptees) also in non-endemic countries where it is generally underdiagnosed. In Italy, the available epidemiological data about Chagas disease have been very limited up to now, although the country is second in Europe only to Spain in the number of residents from Latin American. Among 867 at-risk subjects screened between 1998 and 2010, the Centre for Tropical Diseases in Negrar (Verona) and the Infectious and Tropical Diseases Unit, University of Florence found 4.2% patients with positive serology for Chagas disease (83.4% of them migrants, 13.8% adoptees). No cases of Chagas disease were identified in blood donors or HIV-positive patients of Latin American origin. Among 214 Latin American pregnant women, three were infected (resulting in abortion in one case). In 2005 a case of acute Chagas disease was recorded in an Italian traveller. Based on our observations, we believe that a wider assessment of the epidemiological situation is urgently required in our country and public health measures preventing transmission and improving access to diagnosis and treatment should be implemented.

Su 28 donatori testati, 0% di prevalenza…

Jnited States to Mexico and Central
a. In endemic countries it is respon-
est estimated burden of neglected tropical diseases, affecting 8 to 10 million people [1]. As a consequence of migration flows, the disease has been recorded also in non-endemic countries and is becoming a global health problem [2]. In Europe, about 59,000-108,000 cases of Chagas disease are estimated [3] . Italy has a large number of Latin American resident migrants, second in Europe only to Spain, as a result of various migratory waves to Argentina, Brazil, Chile, Uruguay and Venezuela through the last 200 years, until the direction of migration reversed in the 1970s [3].

The majority of Latin American migrants reached Italy in the past ten years, with a growing trend [4] . Migrants from different countries tend to have a patchy distribution in Italian Regions, with a major concentration in the north and in Rome. For instance most Bolivians live in Bergamo Province, Lombardy, Ecuadorians in Liguria Region and Peruvians in big cities such as Milan, Florence and Rome [4].

This new epidemiological scenario prompted the Centre for Tropical Diseases in Negrar (CTDN) and the Infectious and Tropical Diseases Unit, University of

Chagas and blood donors: Italy

Chagas and blood donors: Italy

Surveillance of Chagas disease among at-risk blood donors in Italy: preliminary results from Umberto I Polyclinic in Rome

Simona Gabrielli[1,4], Gabriella Girelli[2,5], Francesco Vaia[3], Mariella Santonicola[2], Azis Fakeri[2], Gabriella Cancrini[1,4]

[1]Parasitological Analyses Unit, [2]Immunohaematology and Transfusion Unit, [3]Sanitary District, Umberto I Teaching Polyclinic; [4]Department of Public Health and Infectious Diseases, [5]Department of Molecular Medicine, "Sapienza" University, Rome, Italy

Background. Chagas disease is a parasitic disease due to *Trypanosoma cruzi*, endemic in Central and Southern America, where the protozoon infects about 8-10 million people. In rural areas the infection is acquired mostly through reduviidae insect vectors, whereas in urban ones it is acquired mainly through the transfusion of blood products, vertical transmission and organ transplantation. The important migratory flows of the last decades have focused attention on possible *T. cruzi* transmission by transfusion also in non-endemic countries, and platelets have been recognised as the main origin of infection for recipients from serologically-positive Latino-American donors.

Materials and methods. In order to avoid the occurrence of transfusion-related cases, in 2010 systematic screening for anti-*T. cruzi* antibodies was started at the Umberto I Polyclinic in Rome, controlling blood donors born and/or coming from Latin-American countries in which the disease is endemic. The aim of this paper is to report the preliminary results achieved since the introduction of this screening.

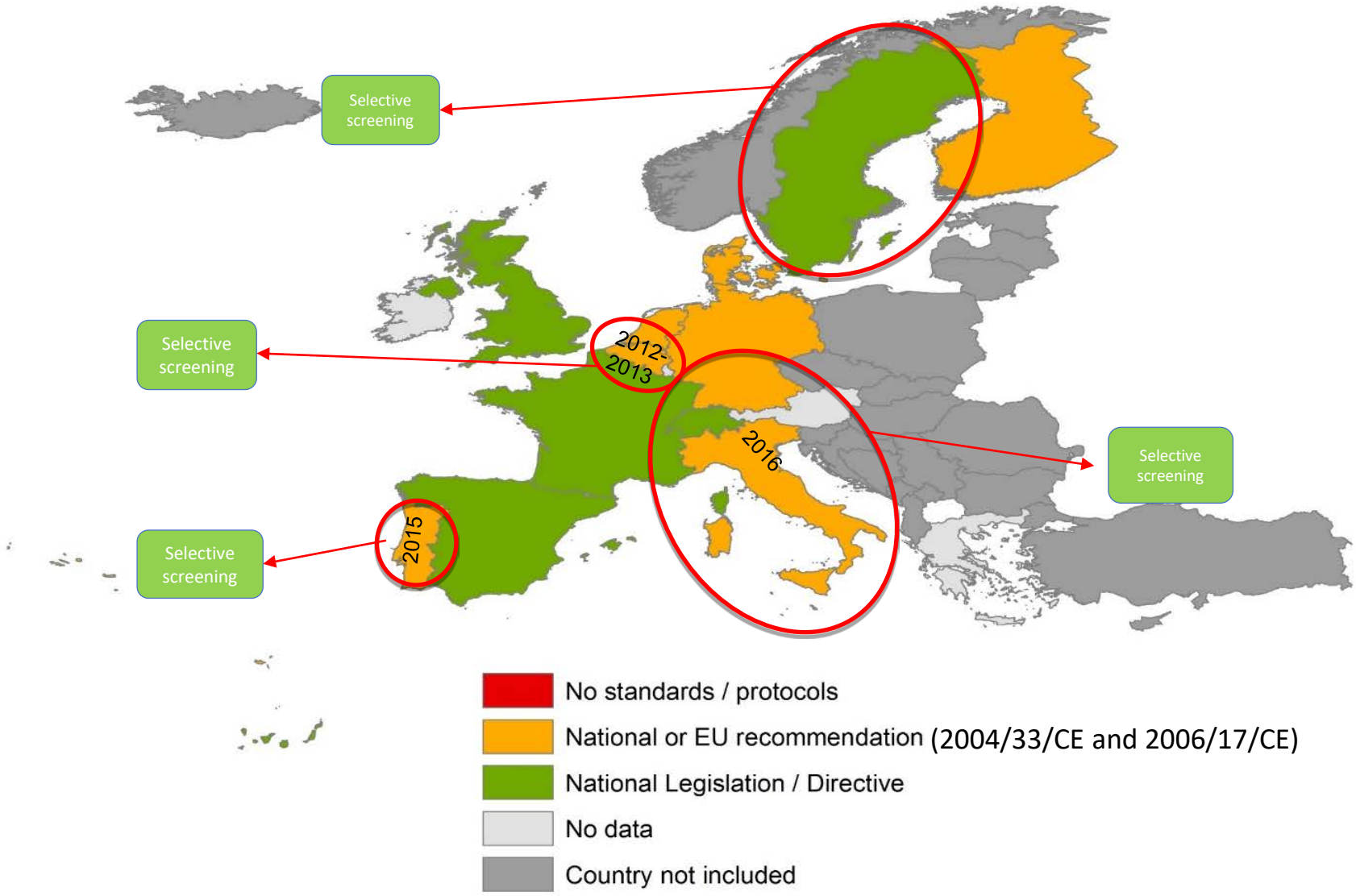
Results. Anti-*T. cruzi* antibodies have been detected to date in 3.9% out of the 128 people examined. A seropositive subject also proved positive by polymerase chain reaction analysis and showed very light parasitaemia.

Su 128 donatori testati, 3,9% di prevalenza…un caso parassitemico

Blood Transfus 2013; 11: 558-62 DOI 10.2450/2013.0055-13

Citation: Requena-Méndez A, Albajar-Viñas P, Angheben A, Chiodini P, Gascón J, et al. (2014) Health Policies to Control Chagas Disease Transmission in European Countries. PLoS Negl Trop Dis 8(10): e3245. doi:10.1371/journal.pntd.0003245

Prevention of blood transfusional transmission of *T. cruzi* in the EU countries and Switzerland



ALLEGATO *III*

CRITERI PER LA SELEZIONE DEL DONATORE DI SANGUE ED EMOCOMPONENTI E PER LA SELEZIONE DELLA COPPIA DONATRICE DI SANGUE DEL CORDONE OMBELICALE

10	Malattia di Chagas o tripanosomiasi americana	I soggetti nati (o con madre nata) in Paesi dove la malattia è endemica, o che sono stati trasfusi in tali Paesi, o che hanno viaggiato in aree a rischio (rurali) e soggiornato in condizioni ambientali favorenti l'infezione (camping, trekking) possono essere ammessi alla donazione solo in presenza di un test per anticorpi anti-Tripanosoma Cruzii negativo.

Critical issues

TABLE 1. Results of seven anti-*T. cruzi* antibody detection tests using WHO international standard

	TcI							TcII						
IU/mL	ELISA	CLIA	ESA	In-house IFA	ICT-1	ICT-2	ICT-3	ELISA	CLIA	ESA	In-house IFA	ICT-1	ICT-2	ICT-3
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.5	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.25	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.125	+	+	+	–	+	–	+	+	+	+	+	+	–	+
0.063	+	+	+	–	–	–	+	+	+	+	–	–	–	–
0.032	–	+	+	–	–	–	–	–	+	–	–	–	–	–
0.016	–	+	–	–	–	–	–	–	–	–	–	–	–	N.T.
0.008	–	–	–	–	–	–	N.T.	–	–	–	–	–	–	N.T.

+ = reactive; – = non-reactive; N.T. = not tested; ELISA = *Trypanosoma cruzi* (*T. cruzi*) whole cell lysate antigen ORTHO *T. cruzi* ELISA test system, ortho clinical diagnostics; CLIA = ARCHITECT Chagas, Abbott; ESA = ABBOTT ESA Chagas, Abbott, ICT-1 = Chagas STAT-PAK Assay, Chembio Diagnostic Systems; ICT-2 = Chagas Detect Rapid Test, InBios; ICT-3 = Chagas Detect Rapid PLUS Test, InBios.

- WHO: one test for transfusion medicine – two test for clinical confirmation
- Donor referral

Wendel, Acta Tropica 2010

- NAT inadequate for Chagas disease detection

- The need of chaotropic agents (guanidine HCl) for better DNA extraction (Avila et al., 1991), associated with variable sensitivity (45–100%) (Zingales et al., 1998; Antaz et al., 1999; Lages-Silva et al., 2001; Marcon et al., 2002; Galvao et al., 2003; Vera-Cruz et al., 2003; Salomone et al., 2003) have precluded the adoption of this method as a gold standard so far.


Screening
Donated Blood
for Transfusion-
Transmissible
Infections
Recommendations
World Health
Organization

Figure 1: A

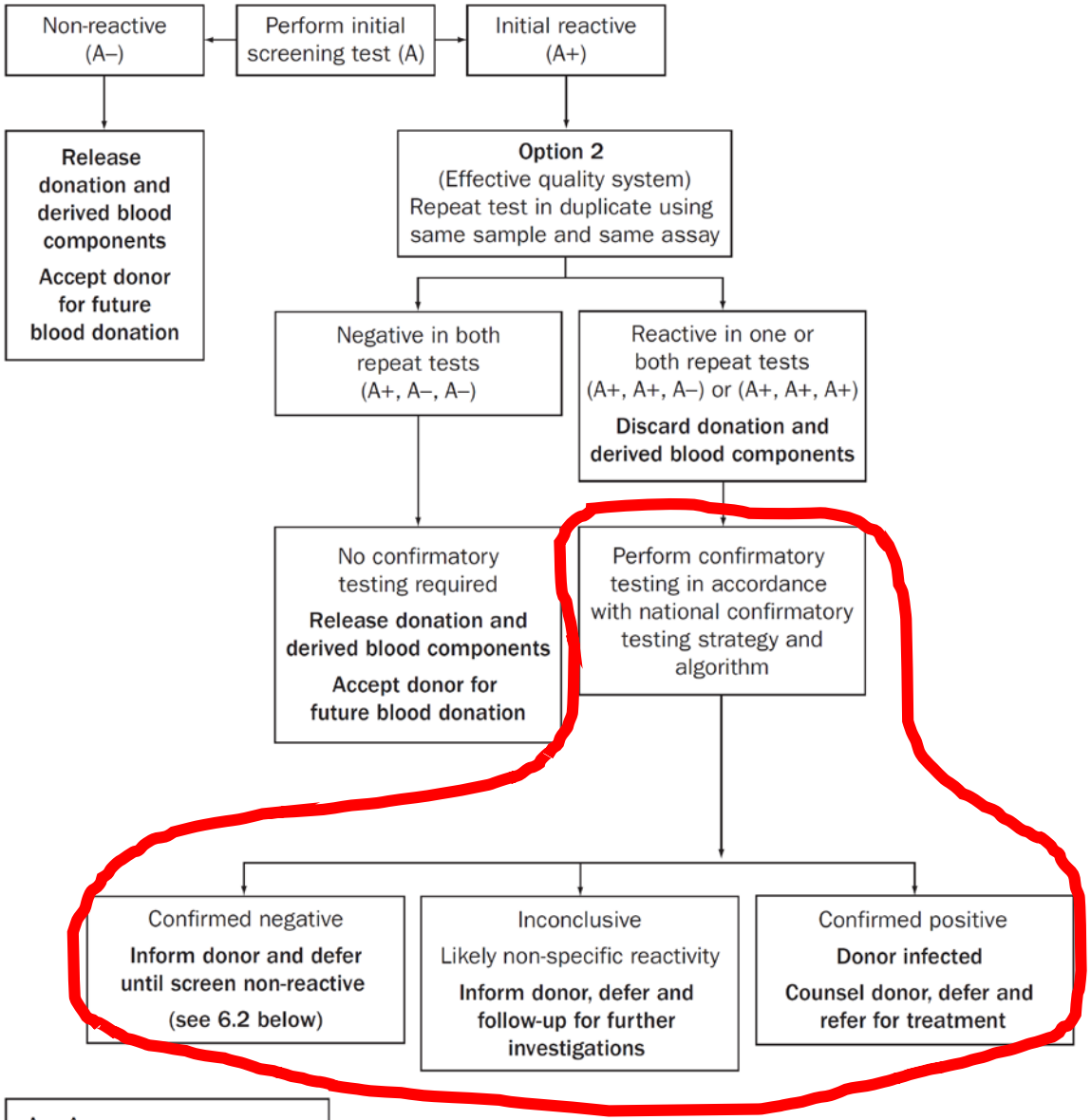
Non-reactive (A–)

Release donation and derived blood components

A = Assay
A+ = Reactive r
A– = Non-reacti

one or
t tests
(A+, A+, A+)
ation and
omponents
atory testing

Figure 2: Algorithm for blood donor management based on screening and confirmatory testing



World Health Organization

Health Topics | Countries

Neglected tropical

- Neglected tropical diseases
- About us
- Diseases
- Preventive chemotherapy and transmission control
- Innovative and intensified disease management
- Vector ecology and management
- Neglected zoonotic diseases
- Water, sanitation and hygiene

WISCENTD

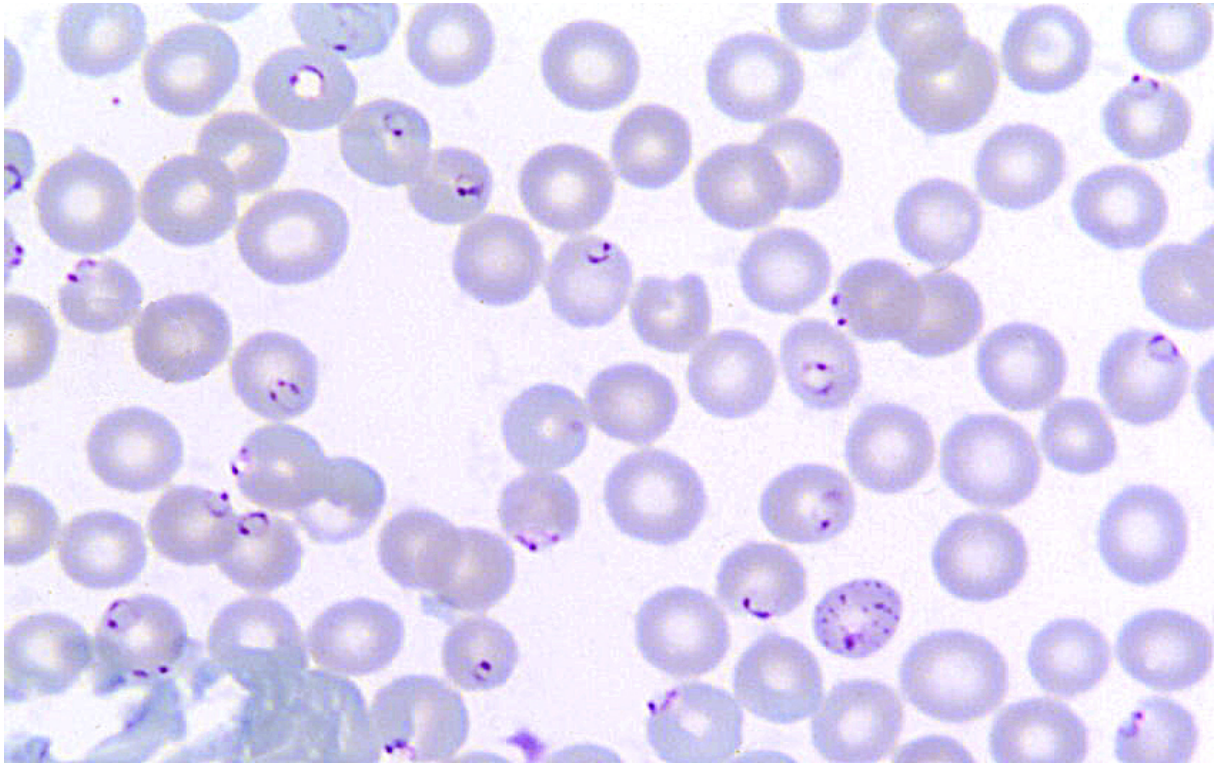
Introduction

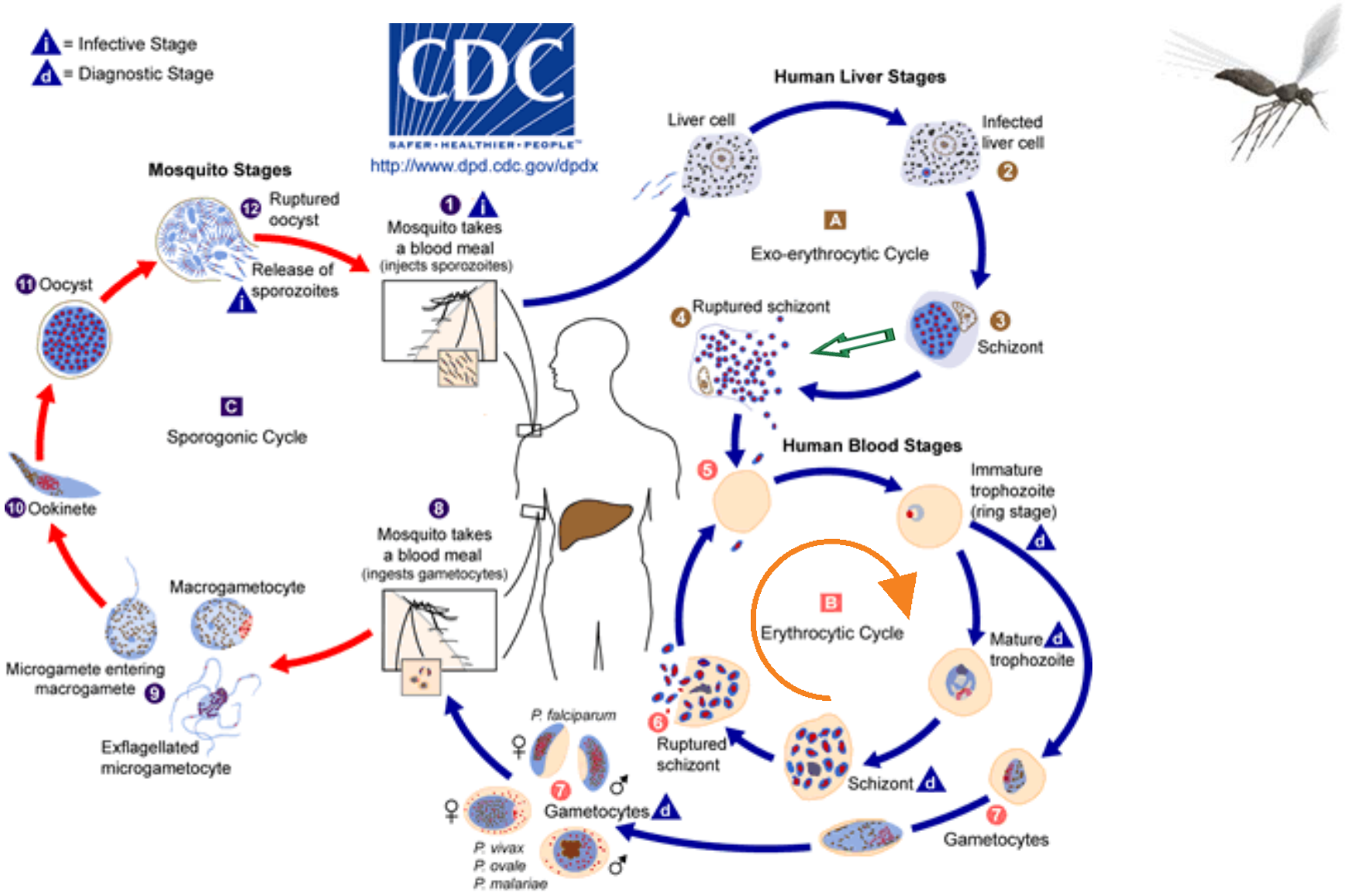
The importance of data

Neglected tropical diseases (NTDs) disfigure and disable, leading to stigmatization and social discrimination. Severe complications and death can result if treatment is not provided early and adequately. This group of diseases largely affects low-income, politically marginalized people living in rural and periurban areas with low visibility and little political voice and with limited access to health care. NTDs are mainly focal and present in remote areas. However, they can be controlled, prevented and possibly eliminated or even eradicated with proven interventions. Strong surveillance systems should be in place in order to understand the burden of NTDs, to describe their geographical distribution and to identify populations at risk in order to best target control interventions in this resource constrained context and take evidence-based decisions.

The WHO Information System to Control and Eliminate NTDs (WISCENTD): an ecosystem

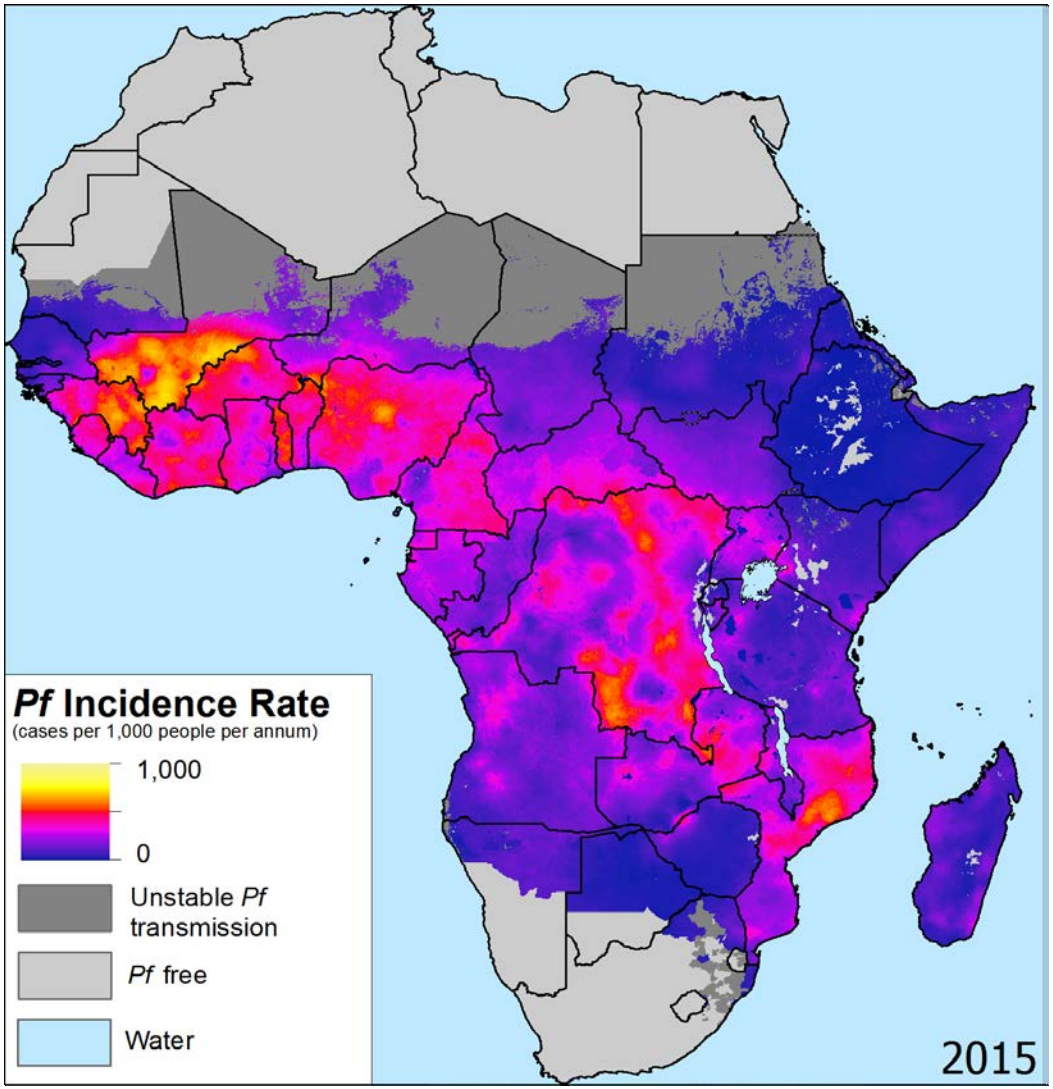
1. Malaria



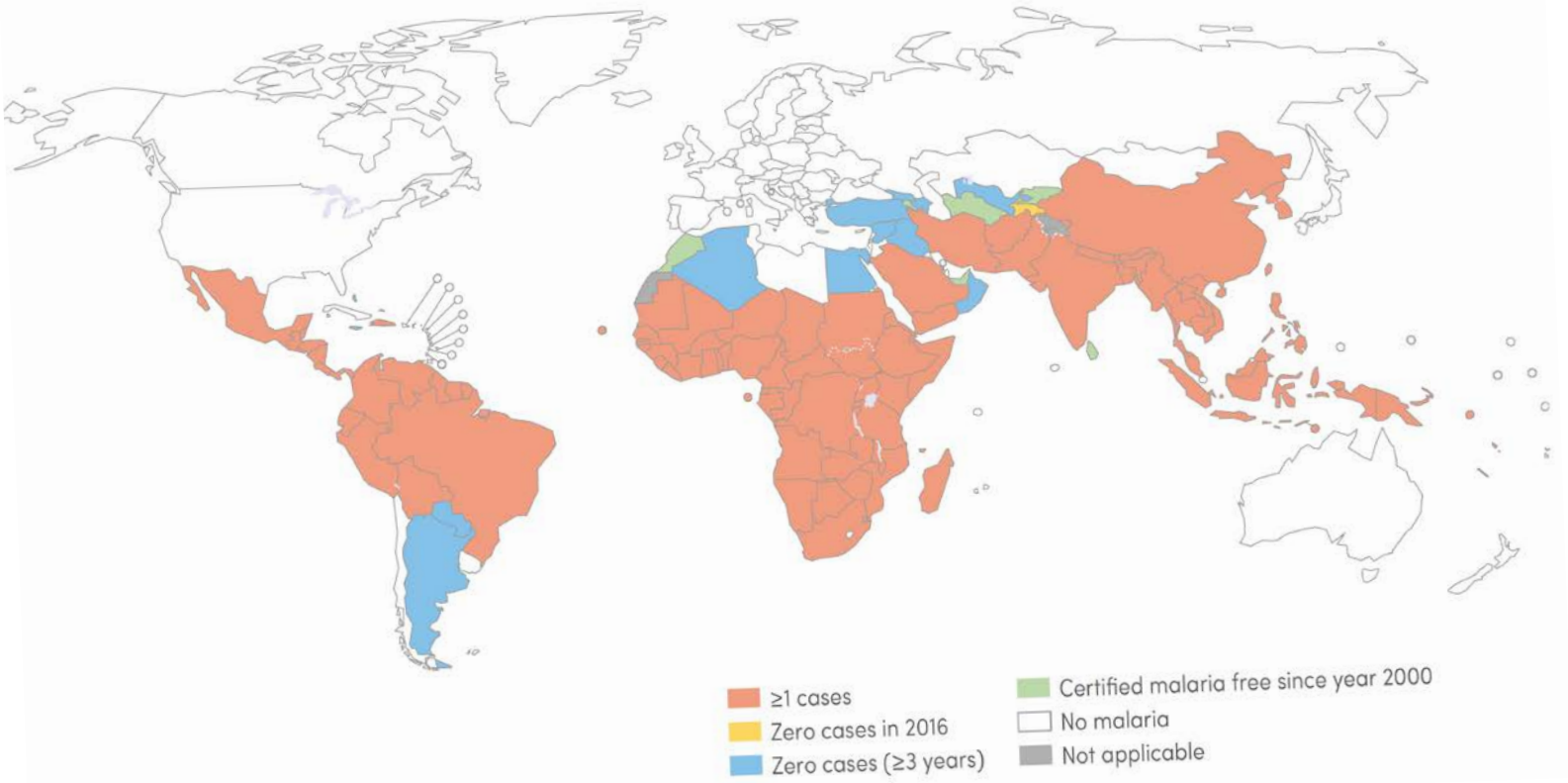

i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx
Mosquito Stages
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
Ruptured schizont
4
3
Schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
B
Erythrocytic Cycle
Mature trophozoite
d
6
Ruptured schizont
Schizont
d
7
Gametocytes
Gametocytes
d
P. falciparum
P. vivax
P. ovale
P. malariae
1
i
Mosquito takes a blood meal
(injects sporozoites)
12
Ruptured oocyst
Release of sporozoites
i
11
Oocyst
C
Sporogonic Cycle
10
Ookinete
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte

Global Malaria - *WHO World Malaria Report 2018*

- 217 Millions of cases in 2017
- 90% of *P. falciparum* in Africa
- 435000 deaths in 2017
- Trend stable


Pf Incidence Rate
(cases per 1,000 people per annum)
1,000
0
Unstable *Pf* transmission
Pf free
Water
2015

Countries and territories with indigenous cases in 2000 and their status by 2016 Countries with zero indigenous cases over at least the past 3 consecutive years are eligible to request certification of malaria free status from WHO. All countries in the WHO European Region reported zero indigenous cases in 2016. Kyrgyzstan and Sri Lanka were certified malaria free in 2016. *Source: WHO database*



World malaria report 2017

ISBN 978-92-4-156552-3

Malaria ed Europa

Figure 1

Nombre de cas importés de paludisme dans les 51 pays de la région Europe de l'OMS - 1971-1999/Number of malaria cases imported in the 51 countries of the WHO European Region, 1971-1999

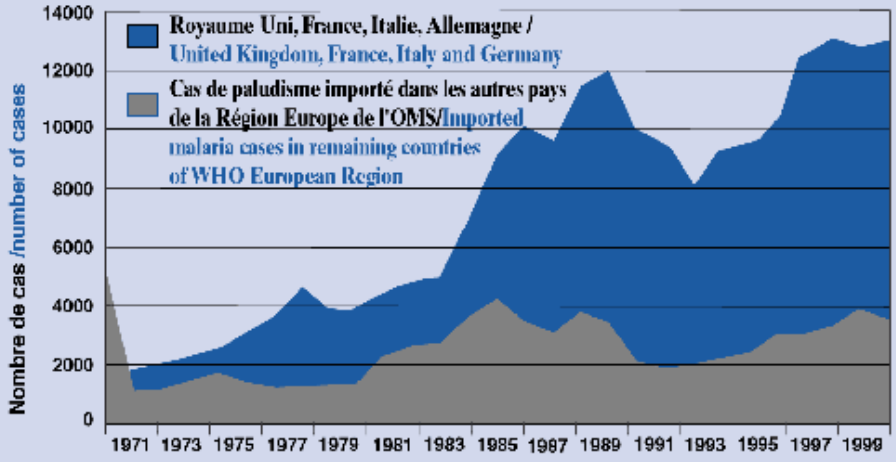
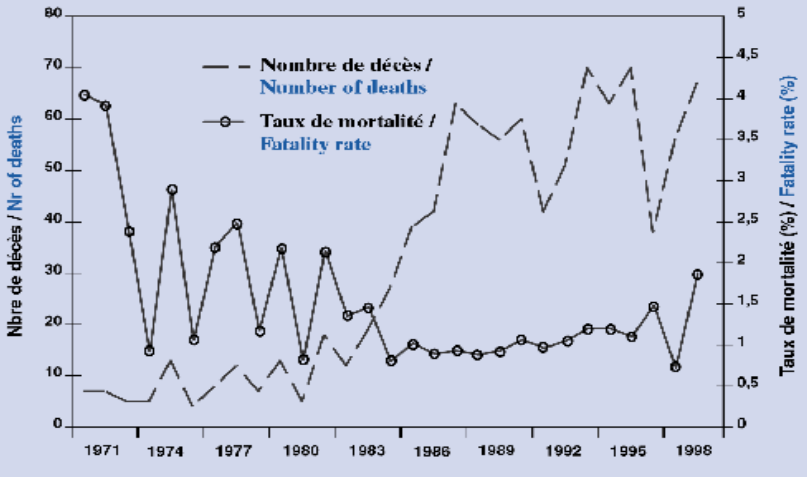


Figure 2

Nombre de décès dus au paludisme et taux de mortalité dans la région Europe de l'OMS, 1971-1999/Number of deaths for malaria and fatality rates in WHO European Region, 1971-1999



Malaria in Italia

Tabella 2 - Lineamenti epidemiologici della malaria d'importazione in Italia nel periodo 2002-2006, tra parentesi sono riportate le frequenze relative calcolate sui casi totali.

Anno	2002	2003	2004	2005*	2006*	Totale
Casi Totali	733	681	673	637	630	**3354**
Italiani	205 (28,0)	233 (34,2)	205 (30,4)	184 (28,9)	147 (23,3)	**974 (29,0)**
Stranieri	528 (72,0)	448 (65,8)	468 (69,6)	453 (71,1)	483 (76,7)	**2380 (71,0)**
Casi importati	733 (100)	680 (99,9)	671 (99,7)	636 (99,8)	630 (100)	**3350 (99,9)**
Casi autoctoni	0	1 (0.1)	2 (0,3)	1 (0,2)	0	**4 (0,1)**
Africa	689 (94,0)	649 (95,4)	621 (93,0)	595 (93,7)	592 (94,0)	**3146 (94,0)**
Asia	29 (4,0)	18 (2,6)	24 (3,0)	23 (3,5)	29 (4,6)	**123 (3,6)**
Amer. Cent. Sud	15 (2,0)	9 (1,3)	21 (3,0)	15 (2,4)	7 (1,1)	**67 (2,0)**
Papua N.G.	0	4 (0,6)	5 (0,7)	3 (0,5)	2 (0,3)	**14 (0,4)**
P. falciparum	607 (83,0)	580 (85,2)	568 (84,4)	535 (84,0)	549 (87,1)	**2839 (84,6)**
P. vivax	59 (8,0)	43 (6,3)	63 (9,4)	49 (7,7)	43 (6,8)	**257 (7,7)**
P. ovale	49 (6,6)	47 (7,0)	35 (5,2)	38 (6,0)	27 (4,3)	**195 (6,0)**
P. malariae	13 (1,8)	8 (1,2)	7 (1,0)	14 (2,2)	10 (1,6)	**52 (1,5)**
Infezioni miste	5 (0,7)	3 (0,4)	0	1 (0,2)	1 (0,2)	**10 (0,3)**
Tot. decessi Tra italiani	4 3	4 3	4 2	1 1	3 2	**16** **11**
Letalità % Tra italiani	0,7 2,0	0,7 1,6	0,7 1,4	0,2 0,8	0,5 1,6	**0,6** **1,5**

* L'analisi dei dati è stata effettuata in collaborazione con il Ministero della Salute

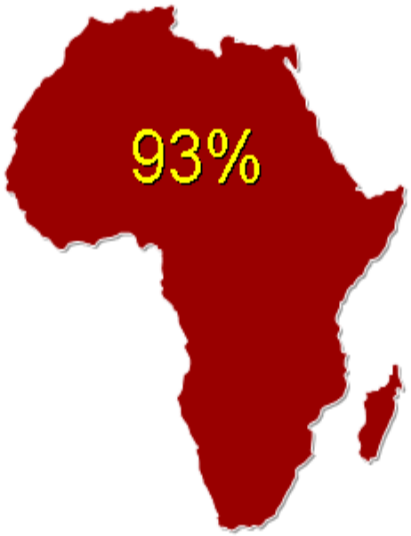
- Circa 700 casi di malaria/anno in Italia
- 85% P. falciparum
- 1-4 decessi anno (soprattutto tra italiani)

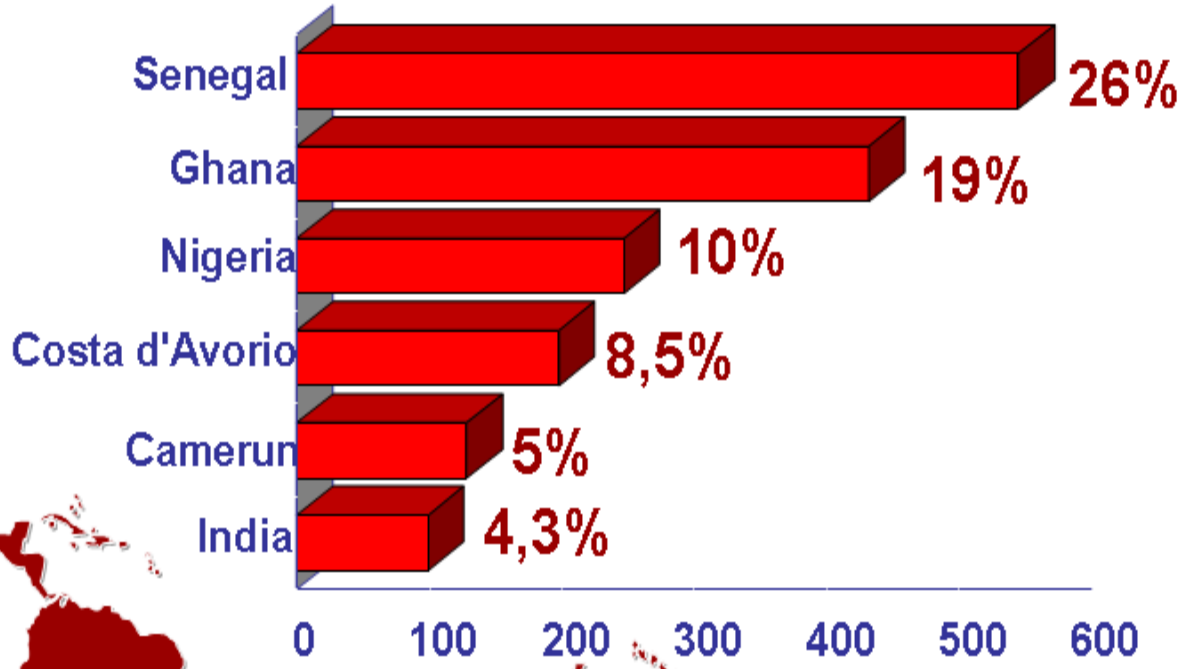
Boccolini et al. G Ital Med Trop, 2007

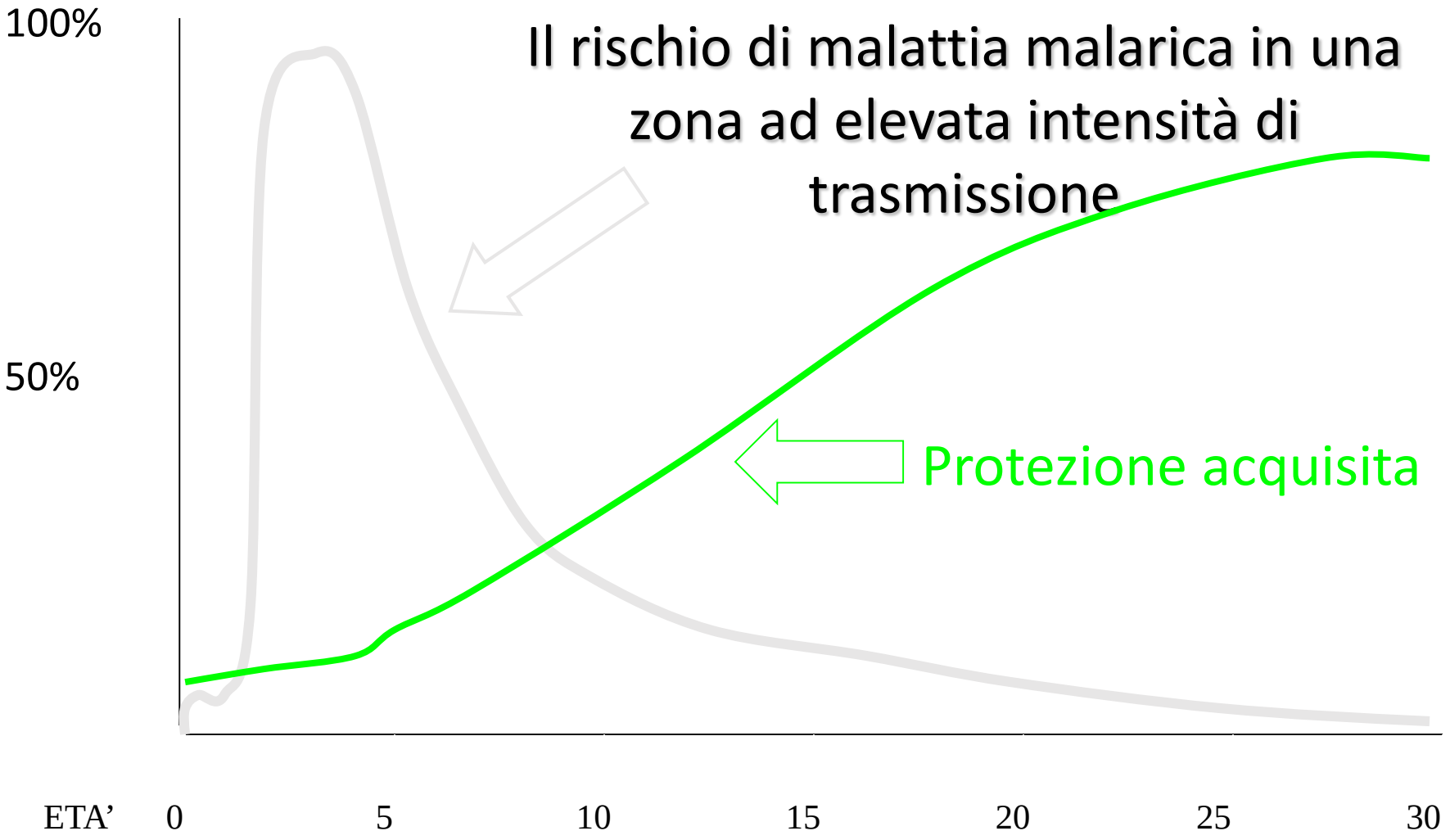
Provenienza dei casi tra stranieri, 2000-04

(oltre 50 paesi di provenienza)

2280 schede






100%
Il rischio di malattia malarica in una zona ad elevata intensità di trasmissione
50%
Protezione acquisita
ETA’ 0 5 10 15 20 25 30

Malaria: scenarios

- Individuals who never had malaria (exemple, a traveller) → no immunity
- Like a newborn when maternal antibodies are lost (>six months)
- Like a child born from migrant woman who returns to the country of origin of the family
- Like the adult migrant who comes back to his/her country afterm many years of permanence on malaria non-endemic areas (specific immunity is lost)

FULL SUSCEPTIBILITY TO MALARIA
INCLUDED SEVERE FORMS

Malaria: scenarios

- On the other side an individual who has had numerous malaria attacks

LESS EVIDENT SYMPTOMS

NO SEVERITY

TROPICAL SPLENOMEGALY =

(HYPERREACTIVE MALARIAL SPLENOMEGALY)

Malaria: transfusion transmitted malaria (TTM)

- Casi di trasmissione trasfusionale (TTM) noti dal 1911[1]
- TTM possibile con globuli rossi concentrati (globuli rossi conservati a 4°C fino a circa 20 gg), piastrine, leucociti, plasma fresco congelato[2]
- Bastano 10 plasmodi per trasmettere la malattia da zanzara
- TTM rara in Paesi non endemici[2]
- Italia: 0-2 casi per milione di donazioni[2]

[1]Woolsey G. Ann Surg 1911
[2]Grande R. Blood Transfus 2011

Malaria da trasfusione di sangue/emocomponenti (TTM)

- Delle cinque specie di *Plasmodium*, il *falciparum* è il più pericoloso in quanto comporta un 10% di mortalità in caso di TTM[1]

[1]Mungai M et al. *N Engl J Med* 2001; **344**:1973–1978

Malaria: TTM

- As a result of the asymptomatic persistence of parasites, transmission of *P. malariae* has been documented as long as 53 years [22], *P. vivax* 27 years [23] and *P. falciparum* 13 years [23] after the last exposure

[22] Gauzzi M, Grazan S: *Trop Dis Bull* 1964; **61**:11–12

[23] Besson P, et al.: *Rev Fr Transfus Immunohematol* 1976; **19**:369–373

Table 1. Reported cases of transfusion transmitted malaria (TTM) in Italy.

Country#	Year	Donor gender & age	Donor origin & last exposure	Recipient gender & age	Recipient incubation (Delayed diagnosis)	Recipient outcome	Blood § component transfused	*Plasmodium* species	Diagnosis Method Recipient (Donor)	Reference
Italy										
Liguria	1963	N/A	N/A	M premature	28-40 days	recovery	WB	*P. malariae*	LM	Sansone & Centa 1967
Liguria	1963	N/A	N/A	F 8 yrs	1-13 days	recovery	WB	*P. vivax*	LM	Sansone & Centa 1967
Liguria	1964	N/A	N/A	F 6 yrs	multiple transfusions (4 months)	recovery	WB	*P. vivax*	LM	Sansone & Centa 1967
Sicily	2005	M	Philippine	F 35 yrs	multiple transfusions (4 months)	recovery	WB	*P. malariae*	LM	Neri et al., 2008
Veneto	2008	N/A	N/A	F 29 yrs Morocco	multiple transfusions (2 weeks)	recovery	RBCs	*P. vivax*	LM	Tagariello et al., 2014

only non-endemic areas of the country if malaria endemic were included; N/A: data not available.

§ WB= whole blood, RBCs= red blood cells, PLTs= platelets, FFP= fresh frozen plasma.

LM: light microscopy; ELISA: enzyme-linked immunosorbent assay; IFAT: indirect immunofluorescent antibody test; PCR: polymerase chain reaction.

Verra F et al, Malaria J, 2018

Verra et al. Malar J (2018) 17:36
https://doi.org/10.1186/s12936-018-2181-0

Malaria Journal

RESEARCH Open Access

A systematic review of transfusion-transmitted malaria in non-endemic areas

Federica Verra[1*†], Andrea Angheben[1†], Elisa Martello[2], Giovanni Giorli[1], Francesca Perandin[1] and Zeno Bisoffi[1]

Table 2 Mean values of transfusion-transmitted malaria (TTM) versus mosquito-transmitted malaria (MTM) incubation time in days

Species	TTM (95% CI)	MTM (95% CI)[a]	p value[b]
P. falciparum	25.7 (7.4–43.9)	13.1 (7–27)	0.172
P. malariae	63.9 (43.5–84.4)	34.8 (27–37)	*0.006*
P. ovale	19.0 (11.7–26.3)	13.6 (8–31)	0.118
P. vivax	29.3 (12.3–46.2)	13.4 (11–16)	0.060
P. knowlesi[c]	15.5 (9.1–21.9)	10.0 (/)	0.058

CI confidence interval

Significance threshold p value <0.05 (in italic)

[a] As reported by Dover and Schultz [9]

[b] Obtained through one sample two-tailed Student's t test, using the MTM mean value for the null hypothesis

[c] A range of the mean incubation time for this species in humans was not available in literature, so a direct comparison of CIs was not possible

Criteri per l'accettazione per la donazione di emocomponenti cellulari e plasma per uso clinico (*):

1. **soggetti che hanno vissuto per un periodo di 6 mesi o più (continuativi) in zona endemica in qualsiasi momento della loro vita** (questi soggetti non possono donare fino a quando non venga
- devono
- possono
- se il t

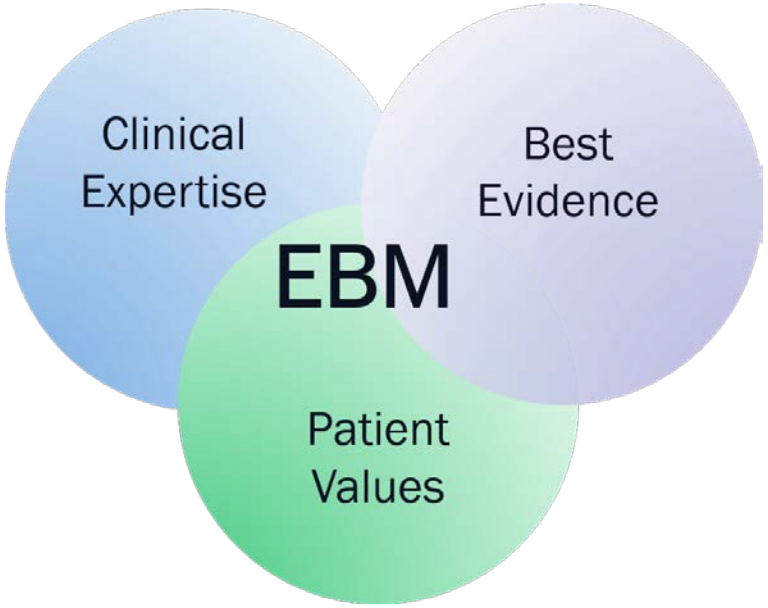
2. **soggetti che hanno sofferto di malaria, soggetti che hanno so**
- devon
- possor
- se il

3. **Tutti gli altri soggetti che hanno visitato un'area ad endemia malarica e che non hanno sofferto di episodi febbrili o di altra sintomatologia compatibile con la diagnosi di malaria durante il soggiorno o nei 6 mesi successivi al rientro:**
- possono essere accettati come donatori se sono passati almeno 6 mesi dall'ultima visita in un'area ad endemia malarica, e se risultano negativi a un test immunologico per la ricerca di anticorpi anti-malarici;
- se il test risulta ripetutamente reattivo, il donatore è sospeso per 3 anni; successivamente può essere rivalutato e accettato per la donazione se il test risulta negativo;
- se il test non viene effettuato, il soggetto può donare se sono passati almeno 12 mesi dall'ultima visita in un'area ad endemia malarica .

estionario: Ha avuto
aria o febbre inspiegata
ante un viaggio in zone
chio o entro 6
?

Disposizioni relative
sicurezza del sangue e de

Quindi perché passare ad una valutazione non solo clinico-anamnestica di selezione del donatore come fatto nel 2015?



Some countries only apply selective epidemiological questionnaires (e.g. Canada, USA), while others reinforce their selection measures with immunological tests and/or molecular techniques (e.g. Australia, France, England, Italy, Spain and Portugal

Table 3
Documented transfusi

Management of TTM at the Australian Red Cross Blood Service (Blood Service) combines the identification of 'at-risk' donors', targeted antibody screening [malaria antibody enzyme-linked immunoassay (EIA)] and, if reactive, exclusion from the manufacture of fresh blood components.
The estimated residual risk of TTM with this strategy is low (<1 in 3,3 million)

France			
West Africa			ıted 2 years ago
			/ of malaria 13-15 years ago
			negative on Lab 21
West Africa			ıted
West Africa			ıted 4 years ago
UK			
West Africa			ıted 15 years ago
			sited Africa 7 years ago
United States			
West Africa			ıted 16 years ago
			tory of malaria
			ent travel
West Africa			n West Africa for 17 years
West Africa			vel in last 4 years
			ıted 5 years ago
West Africa			d for malaria at age 12
			ıted to the United States as a child
			ned malaria as a child
			Recent travel 13-17 months ago
West Africa	2007	*P. falciparum*	Emigrated 5 years ago
			Presumed malaria 19 years ago
West Africa	2003	*P. falciparum*	Emigrated 1 year ago
			Treated for malaria 2 years ago
West Africa	2002	*P. malariae*	Emigrated 8 years ago

There were no transfusion-transmitted cases in Australia or Canada, 2002 to 2013. Data obtained from national reports [24-33,35].

Malaria: TTM

- Grande et al. hanno screenato (EIA Ab totali e Ag pan, Pf e pv) 412 donatori a rischio di malaria (16,8% italiani viaggiatori):

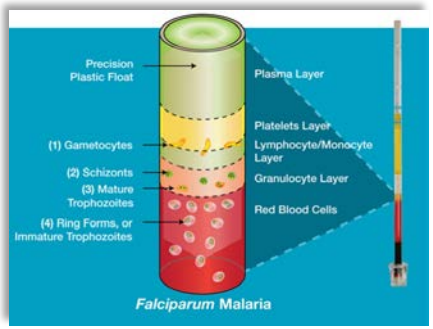
- 91,3% negativi; 8,7% positivi EIA, non Ag: quali vantaggi?

→ Possibile riammissione a 4 mesi nel 90% dei donatori, non affidamento alla sola clinica

Grande R. Blood Transfus 2011

Malaria: diagnosi

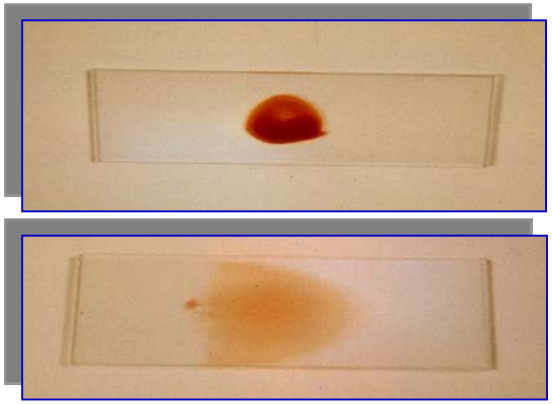
- QBC®



QBC: 1p/µL

- Se p<10/µL dx 50% times earlier than GS

- GS/SS



GS: 1-20 p/µL

SS: 200p/µL

- Antigen malarial test

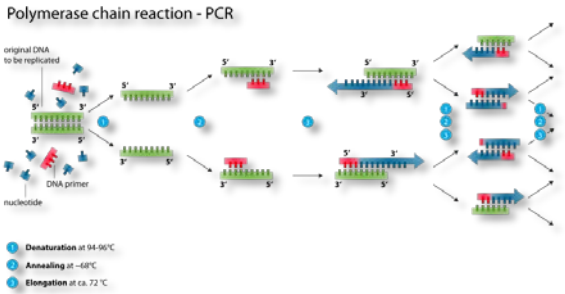
(HRPII → P.falc, pLDH → 4 specie)

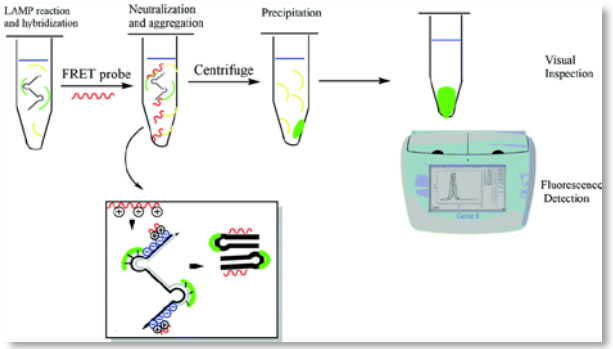
Bassa sensibilità se <100p/µL

Diagnosi di malaria: tecniche molecolari

- Sono disponibili tecniche per infezione mista e diagnosi di specie
- Elevata sensibilità:

- PCR: 3-5 p/µL (parassitemia 0,00006%)
- LAMP: 2 p/µL (parassitemia 0,00004%)





Portugal-Calisto *et al. Malar J (2016) 15:548*
DOI 10.1186/s12936-016-1586-x

Malaria Journal

RESEARCH Open Access

Post-exposure serological responses to malaria parasites in potential blood donors

Daniela Portugal-Calisto[1], Ana Raquel Ferreira[2], Marcelo Sousa Silva[1,3,4*] and Rosa Teodósio[1*]

- Studio su 505 adulti che rispondevano ai seguenti criteri:
- Età 18-65 aa
- Esposizione a rischio (area endemica) indipendentemente da storia di malaria, durata o ragione del viaggio
- Bio-Rad EIA (4 recombinant proteins, total Abs)

Table 2 Frequency of travel characteristics and malaria history and their statistical relations with total anti-*Plasmodium* spp. antibodies

	Presence of antibodies					Crude logistic regression[a]				Adjusted logistic regression[a]			
	Overall n (%)	Yes n (%)	No n (%)	χ^2	p value	β_i	p value	OR	CI 95%	β_i	p value	OR	CI 95%
Birth in endemic areas n = 495													
Yes	120 (24.2)	35 (53.0)	85 (19.8)	34.36	<0.001	1.519	<0.001	4.569	(2.667;7.830)	0.843	0.011	2.324	(1.209;4.464)
No	375 (75.8)	31 (47.0)	344 (80.2)			–	–	Reference category	–	–	–	Reference category	–
First 5 years of life in endemic area n = 86													
Yes	75 (87.2)	24 (92.3)	51 (85.0)	0.89	0.351	0.739	0.365	2.095	(0.423;10.363)	[b]			
No	11 (12.8)	2 (7.7)	9 (15.0)			–	–	Reference category	–				
Previous history of malaria n = 485													
Yes	165 (34.0)	51 (79.7)	114 (27.1)	68.50	<0.001	2.358	<0.001	10.565	(5.539;20.152)	2.183	<0.001	8.872	(4.344;18.118)
No	320 (66.0)	13 (20.3)	307 (72.9)					Reference category	–	–	–	Reference category	–
							0.788[d]						
Number of travels to endemic areas n = 480													
1	220 (45.8)	25 (44.6)	195 (40.6)	0.48	0.787	−0.246	0.541	0.782	(0.356;1.719)	[b]			
2–9	189 (39.4)	21 (37.5)	168 (39.6)			−0.271	0.511	0.763	(0.340;1.711)				
≥10	71 (14.8)	10 (17.9)	61 (14.4)			–	–	Reference category	–				
Length of stay n = 476													
<6 month	306 (64.3)	20 (37.0)	286 (67.8)	19.69	<0.001	−1.274	<0.001	0.280	(0.155; 0.504)	[c]			
≥6 month	170 (35.7)	34 (63.0)	136 (32.2)			–	–	Reference category	–				
Length of time since last stay n = 502							0.274[d]						
<4 month	213 (42.4)	34 (50.7)	179 (41.1)	4.06	0.255	0.204	0.478	1227	(0.697;5.128)	[b]			
4 month–1 year	50 (10.0)	5 (7.5)	45 (10.3)			−0.332	0.523	0.718	(0.259;1.988)				
1–3 years	60 (12.0)	4 (6.0)	56 (12.9)			−0.774	0.169	0.461	(0.153;1.388)				
≥3 years	179 (35.7)	24 (35.8)	155 (35.6)			–	–	Reference category	–				
Age	–	–	–	–	–	0.037	0.001	1.038	(1.016;1.060)	[c]			

β_i coefficient of the independent variables in the model

OR odds ratio; CI 95–95% of confidence interval for odds ratio

p value statistical significant <0.05

[a] Dependent variable: presence of antibodies

[b] Variable not included in the model, because in bivariate analysis it was not statistically significant

[c] Variable excluded from the model, by method forward likelihood ratio (LR)

[d] p value common to all the categories within the same variable

- 75,8% dei soggetti studiati erano nati in Portogallo
- 13,3% erano positivi per anticorpi anti-malaria
- 35% di questi aveva anticorpi oltre tre anni dall'ultima esposizione
- L'essere nati in area endemica è correlato alla presenza di anticorpi anti-malaria
- La pregressa malaria è correlate alla presenza di anticorpi
- Lunghezza del soggiorno in area endemica e l'età NON sono correlate a presenza di anticorpi anti-malaria

Am. J. Trop. Med. Hyg., 62(6), 2000, pp. 720–725

SEROLOGIC RESPONSES OF KOREAN SOLDIERS SERVING IN MALARIA-ENDEMIC AREAS DURING A RECENT OUTBREAK OF *PLASMODIUM VIVAX*

CHAE GYU PARK, YONG-JOON CHWAE, JONG-IL KIM, JI-HO LEE, GANG MIN HUR, BYEONG HWA JEON, JAE SOO KOH, JAE-HEE HAN, SHIN-JE LEE, JAE-WON PARK, DAVID C. KASLOW, DANIEL STRICKMAN, AND CHEON-SEOP ROH

Korean Armed Forces Central Medical Research Institute, Chumok-dong, Yuseong-gu, Taejeon, Republic of Korea; Laboratory of Malaria Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; Fifth Medical Detachment, Eighteenth Medical Command, United States Forces Korea, Yongsan Garrison, Seoul, Republic of Korea

- *P.vivax*
- 4-6 mesi di persistenza anticorpale

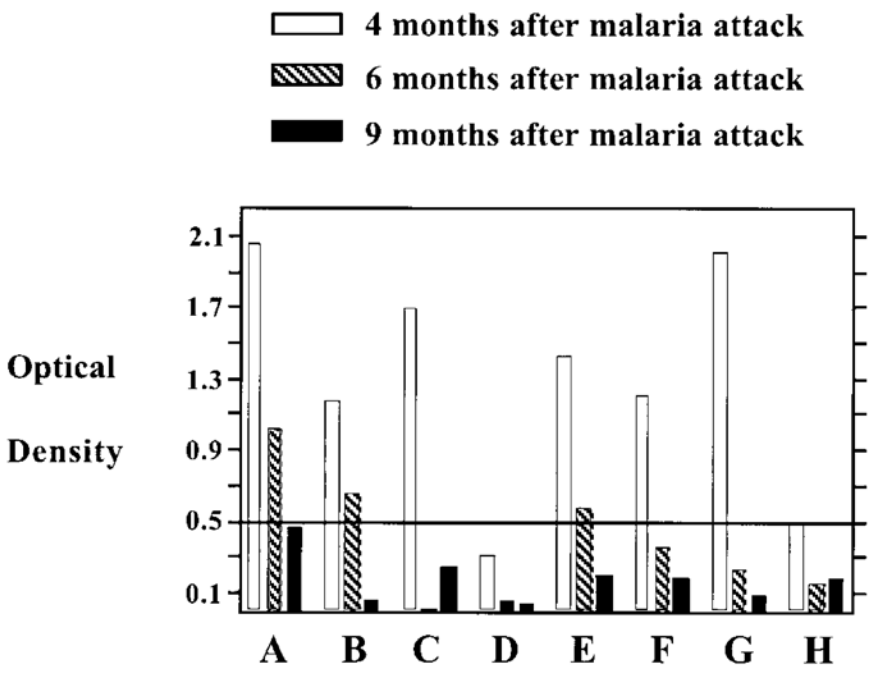


FIGURE 3. Anti-Pv200 antibody levels of 8 individual soldiers (designated A through H) with a history of *Plasmodium vivax* malaria determined by indirect enzyme-linked immunosorbent assay (ELISA). Anti-Pv200 antibody titers of the serum samples from these 8 soldiers were tested at 4, 6, and 9 months after the malaria attack.

New Insights into Acquisition, Boosting, and Longevity of Immunity to Malaria in Pregnant Women

Freya JI. Fowkes,[1,2,4] Rose McGready,[6,7,8] Nadia J. Cross,[1,4] Mirja Hommel,[1,4] Julie A. Simpson,[2] Salenna R. Elliott,[4] Jack S. Richards,[1,3,4] Kurt Lackovic,[4] Jacher Viladpai-Nguen,[6] David Narum,[9] Takafumi Tsuboi,[10] Robin F. Anders,[5] François Nosten,[6,7,8] and James G. Beeson[1,4]

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JID 2012:206 (15 November) • Fowkes et al

- Thailandia – area di malaria stagionale
- Donne gravide divise in «infette» con parassitemia+ e «non infette» = parassitemia sempre-
- Persistenza degli anticorpi anti-malaria (anti-merozoiti) a livello popolazionale 0,8-7,6 anni

Table 3. Longevity of *Plasmodium* species Antibody Responses in Pregnant Women

Antigen	Uninfected control low schizont lysate responder	Uninfected control high schizont lysate responder	*P. falciparum* uninfected case[a]	*P. falciparum* infected case
P. falciparum				
*Pf*VAR2CSA	36.0 (0.1–∞)	50.2 (0.1–∞)	57.6 (0.2–∞)	142.0 (0.4–∞)
*Pf*AMA1	1.8 (0.2–∞)	3.0 (0.3–∞)	2.3 (0.2–∞)	7.6 (0.7–∞)
*Pf*EBA175	2.0 (0.3–∞)	2.6 (0.4–∞)	1.9 (0.3–∞)	5.3 (0.8–∞)
*Pf*MSP2	2.6 (0.4–∞)	3.1 (0.5–∞)	2.3 (0.4–∞)	4.1 (0.6–∞)
*Pf*MSP3	0.8 (0.1–∞)	1.0 (0.1–∞)	0.8 (0.1–∞)	2.2 (0.2–∞)
	Uninfected control low schizont lysate responder	Uninfected control high schizont lysate responder	*P. vivax* uninfected case[a]	*P. vivax* infected case
P. vivax				
*Pv*AMA1	2.6 (0.4–∞)	2.8 (0.4–∞)	5.7 (0.8–∞)	4.0 (0.5–∞)

Values represent the estimated mean antibody response half-life in years with the 95% reference range. The predicted mean half-life was determined from the mixed-effects model with covariates set to the mean. The 95% reference ranges were derived from the estimate and between-woman standard deviation of the slope of the linear mixed-effects model. Multigravida had longer antibody half-lives compared to primigravida for VAR2CSA-DBL5 (64.8 [0.2–∞] compared to 36.0 [0.1–∞]).

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
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ORIGINAL PAPER

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Malaria antibody persistence correlates with duration of exposure

H. M. Faddy,[1] C. R. Seed,[2] M. J. Faddy,[3] R. L. Flower[1] & R. J. Harley[4]

Faddy et al. studied a population of blood donors and concluded that antibodies anti-Plasmodium spp. may persist in the bloodstream up to 19.6 months after the last exposure.

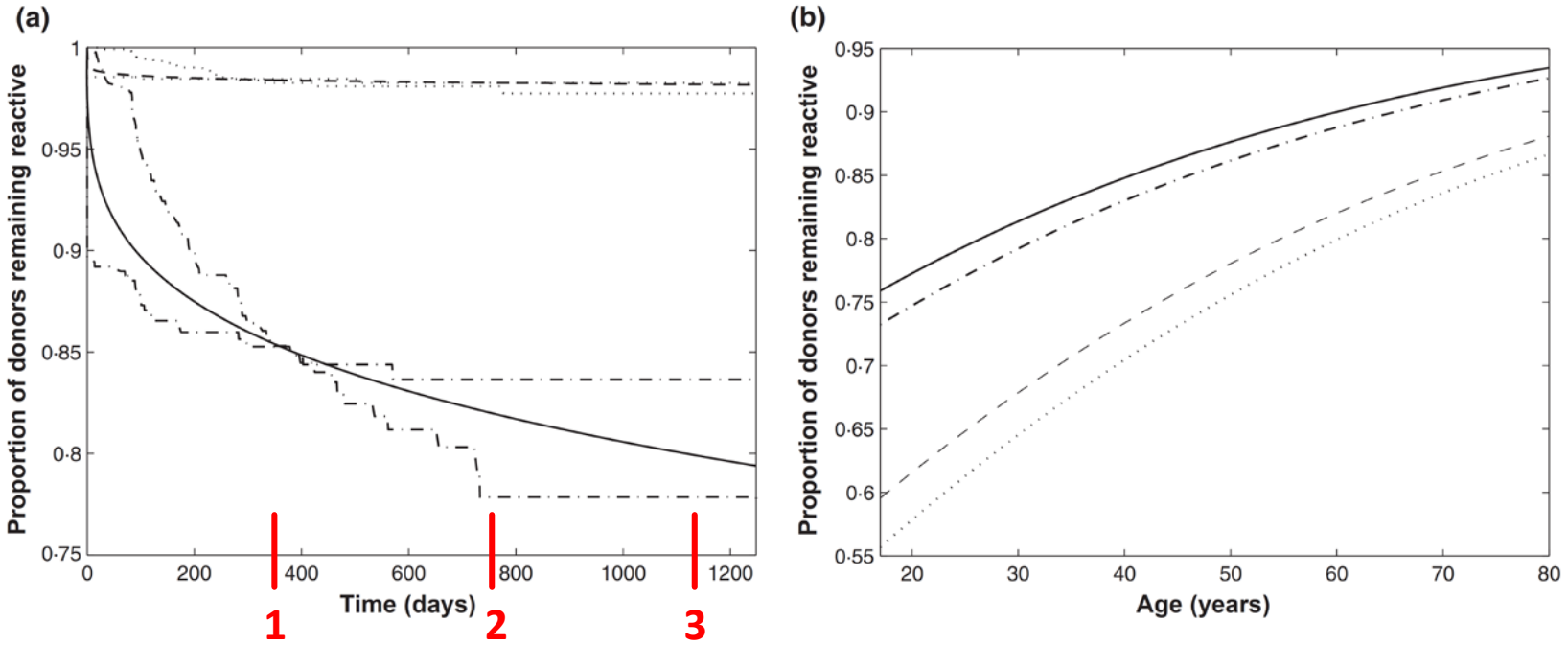

Fig. 3 Malaria-specific antibody survival modelling. Proportion of donors remaining reactive as a function of time; Kaplan–Meier extremes (-.-.-) and Weibull estimate (___) for 'Visitors'; and Kaplan–Meier extremes (….) and Weibull estimate (- -) for 'Residents' (a). Proportion of 'Visitors' remaining reactive as a function of age; Weibull estimates at 2 years for males (___) and females (- -) and at 3 years for males (-.-.-) and females (.....) (b).

Table 1 Proportion of donors predicted to test non-reactive

Time since first reactive EIA (years)	Proportion of 'Visitors' predicted to test non-reactive (%: 95% CI)	Proportion of 'Residents' predicted to test non-reactive (%: 95% CI)
1	15 (12–18)	2 (1–2)
2	18 (14–22)	2 (1–3)
3	20 (15–25)	2 (1–3)
4	21 (16–28)	2 (1–3)
5	23 (17–30)	2 (1–3)

Gli Ab anti-malaria sono utili, persistono a lungo (> negli autoctoni), ma ciò significa che quel donatore è parassitemico?

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Detection of malarial DNA in blood donors – evidence of persistent infection

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Since the implementation of malarial DNA testing, malarial DNA has been found in 14 donations out of a total of 138,782 malaria-risk donations screened (1/10000). Of these, 4302 (3,1%) were seroreactive.

Table 2 Malarial DNA-positive donors identified; serology and DNA results and declared risk

Sample ID	Serology screen result[a]	Confirmatory serology assay results[a]			IFAT titre	Plasm. Spp	Overall risk category
		DiaPro	Cellabs	Diamed			
009839	7·46	6·76/6·90	16·54/17·05	5·21/4·20	1/640	Pf	Previous residency; no history of malaria
100255	7·51	0·69/0·62	19·09/18·79	11·39/13·26	1/640	Pf	Previous residency; no history of malaria
208922	26·61	1·49/1·83	13·94/14·4	NT	1/640	Pf	Previous residency; no history of malaria
204137	86·12	0·44/0·48	25·97/25·83	7·79/8·27	1/640	Pf/Pm	Previous residency; no history of malaria
211908	7·14	0·746/1·0	13·71/13·80	NT	1/640	Pm	Previous residency; no history of malaria
216512	2·75	0·36/0·34	9·89/8·41	NT	1/320	Pm	Previous residency; no history of malaria
103461	1·82	2·39/2·48	0·83/0·92	4·07/3·55	1/80	Po	Previous residency; no history of malaria
114294	19·36	0·37/0·38	9·12/9·64	2·77/3·07	1/160	Po	Previous residency; malaria in 2006
209306	4·65	0·39/0·43	1·88/2·04	NT	Neg	Po	Previous residency; malaria in 2006
102726	94·15	4·73/4·61	23·57/23·57	7·52/6·28	Neg	Pv	Previous residency; no history of malaria
105435	96·89	2·30/2·65	12·37/12·84	4·00/4·46	Neg	Pv	Previous residency; no history of malaria
205176	76·44	5·64/5·77	6·45/8·03	4·70/4·69	Neg	Pv	Previous residency; no history of malaria
302327	99·79	5·05/5·95	9·11/9·32	NT	Neg	Pv	Previous residency; malaria in 2012
312209	76·797	10·5/10·5	5·418/5·976	NT	Neg	Pv	Previous residency; no history of malaria

[a]All immunoassay results expressed as s/co ratios.
NT, not tested.

Quale test immunologico però?

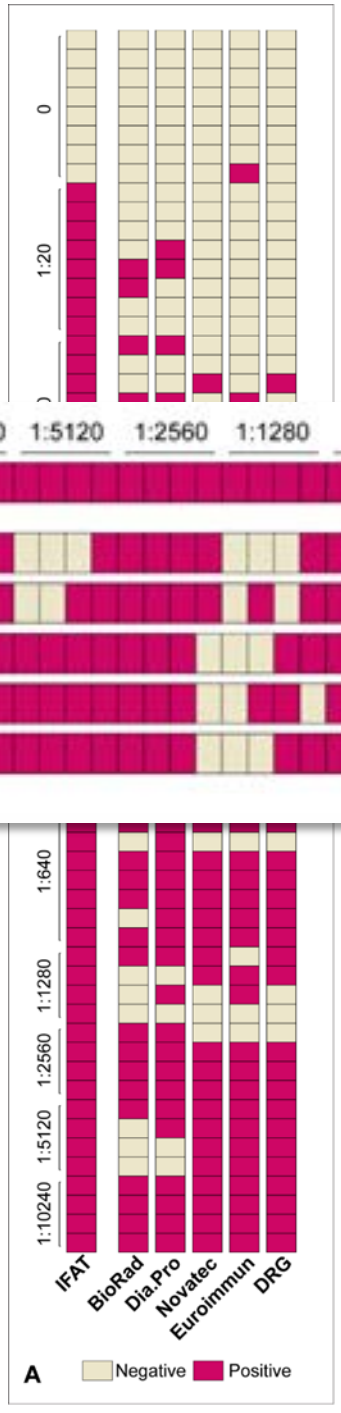
Mangano et al, 2018

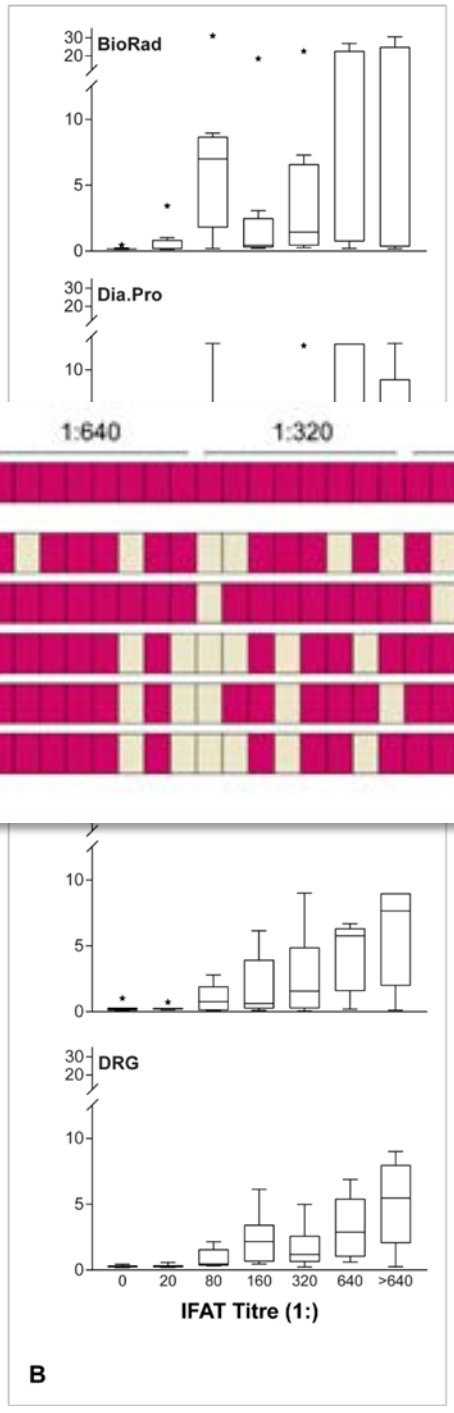
- **Retrospective** study using archived serum samples from subjects recruited in two Italian (Pisa, Negrar).

- In the absence of a gold standard for malaria serology, the aim of this work was to evaluate **five commercial ELISA kits**, in comparison to IFAT assay, and to determine their accuracy and agreement.

- Serum samples (N=64) from **malaria patients** or from subjects with **malaria history**, malaria naive patients with other parasitic infections (N=15), malaria naïve blood donors (N=8) and malaria exposed candidate blood donors (N=36) were tested.

- The specificity of all ELISA kits was 100%, while **sensitivity ranged between 53% - 64%** when compared to IFAT on malaria patients samples.
- When tested on candidate blood donors' samples, ELISA kits showed **highly variable agreement** (42% - 94%) raising the possibility that the same individual could be excluded from donation depending on the test in use by the transfusion centre.





Pair of ELISA kits	Concordance	Cohen's *k*
BioRad *vs.* Dia.Pro	95%	0.89
BioRad *vs.* DRG	78%	0.53
BioRad *vs.* Euroimmun	91%	0.8
BioRad *vs.* Novatec	55%	0.2
Dia.Pro *vs.* DRG	80%	0.57
Dia.Pro *vs.* Euroimmun	91%	0.8
Dia.Pro *vs.* Novatec	51%	0.17
DRG *vs.* Euroimmun	77%	0.49
DRG *vs.* Novatec	57%	0.21
Euroimmun *vs.* Novatec	58%	0.24

C

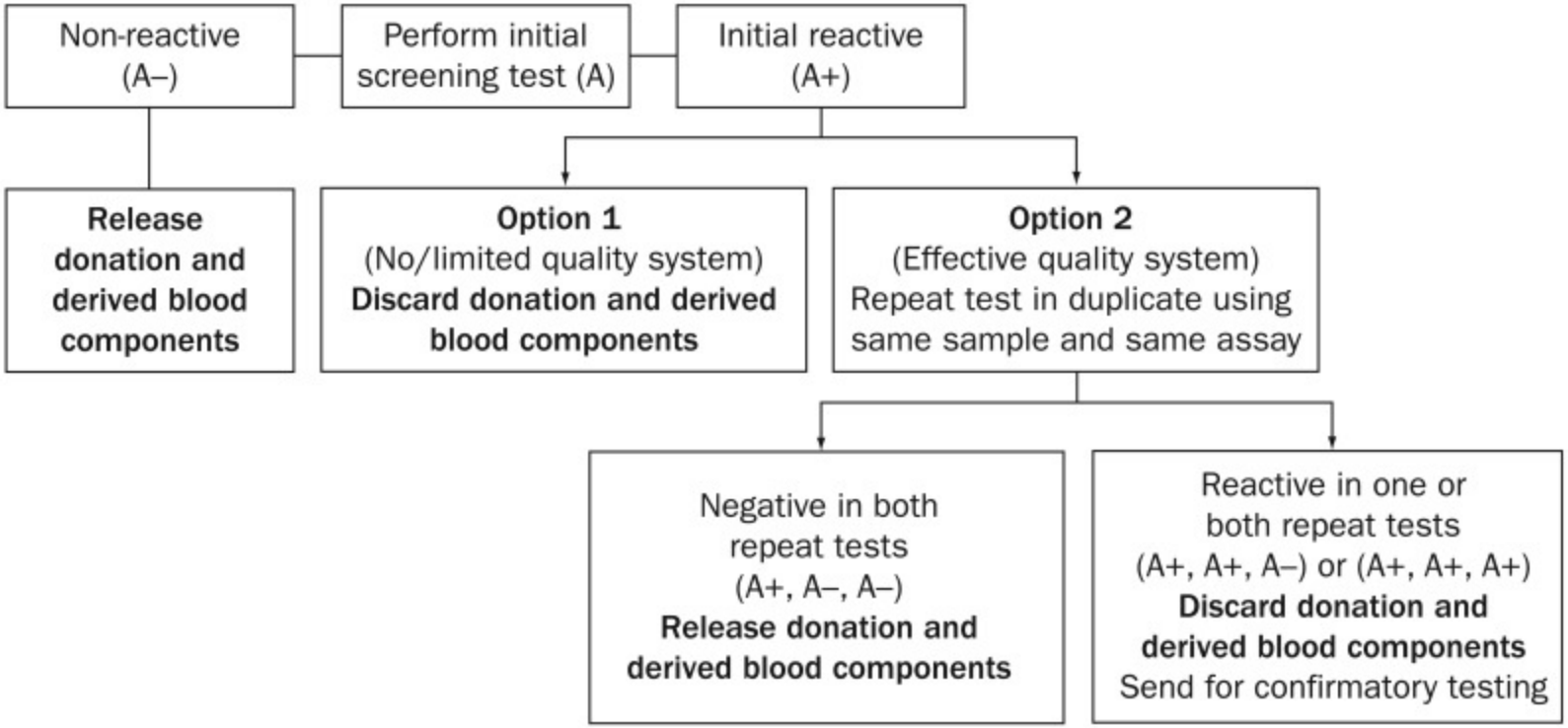
negative with all kits. Contrasting results were instead obtained for 27 samples (48%). **B)** Distribution of ELISA indexes according to IFAT titre (Tukey's boxplot). For Malaria ELISA, Anti-Plasmodium ELISA and NovaLisaTM malaria kits, a trend towards an increased ELISA index at higher IFAT titres was observed. However, for all kits, it was not possible to assign a given IFAT titre to a sample based on the ELISA index. **C)** Agreement of the results obtained with the ELISA kits on candidate blood donor samples (n=43). The concordance ranged from 51% (Cohen's *k*=0.17) for the comparison Malaria Ab *vs.* NovaLisaTM malaria, to 95% (Cohen's *k*=0.89) for the comparison Malaria EIA Test *vs.* Malaria Ab.

Protocollo di gestione (in discussione)

Cosa fare del donatore positivo EIA/IFAT per malaria?

Vari scenari:

- falso+ → da dimostrare
- Pz parassitemico → da trattare
- Pz con splenomegalia iper-reattiva malarica → da trattare



A = Assay
A+ = Reactive result in A
A– = Non-reactive result in A

Protocollo di gestione (in discussione)

Cosa fare del donatore positivo EIA/IFAT per malaria?

- Ripetere in doppio su stesso prelievo la sierologia per malaria (stesso test)
- Se uno dei due test è positivo, procedere a invio a centro di referenza per test di conferma dove:
- il paziente viene sottoposto a:
- Test sierologici (2 diversi, uno solo?)
- Emoc+formula, IgM totali, PCR (o LAMP) per malaria e antigenemia (meglio) oppure QBC/GS e antigenemia
- Inoltre a valutazione clinica per eventuale splenomegalia o pregressa storia di malaria da vivax (nel qual caso primachina?)

Grazie

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