UNIVERSITÀ DEGLI STUDI DI MILANO

DIPARTIMENTO DI SCIENZE BIOMEDICHE E CLINICHE

Malaria: what's new?

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Centro Congressi StarHotels Ritz

Review

Global Fight against Malaria: Goals and Achievements 1900–2022

Marc Thellier [1,2,*], Ayawovi Arlene Jessicka Gemegah [1] and Ilhame Tantaoui [1]

Nel solo XX secolo si stima che la malaria abbia causato da 150 a 300 milioni di morti, il 2-5% di tutte le morti

Nel 2021 era al 14° posto tra tutte le cause di morte e la quarta in Africa

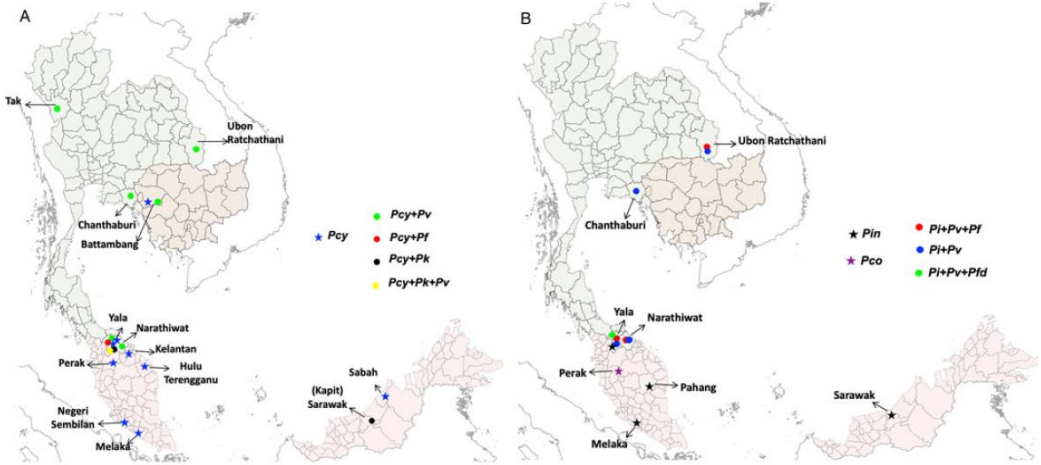
Nel 2022 sono stati stimati in 85 paesi e territori 249 milioni di casi (con un incremento dell'8% rispetto al 2015) nel mondo con circa 600,000 morti

Il 77% delle morti si sono verificate in bambini di età inferiore a 5 anni

J Clin Med 2024; 13:5680

The threat of increased transmission of non-*knowlesi* zoonotic malaria in humans: a systematic review

Rini Chaturvedi[1], Shibani Biswas[1,2,3], Kanika Bisht[2,3] and Amit Sharma[1,3]



Parasitology
2023;150:1167-77

Plasmodium sp.	Erythrocytic Cycle duration (in Hours)	Most common region	Similarity to other Plasmodium sp.	Natural Hosts
P. cynomolgi	48 h (Tertian)	Asia	*P. vivax*	
P. inui	72 h (Quartan)	South Asia	*P. malariae*	
P. fieldi	48 h (Tertian)	South Asia	*P. simiovale*	
P. coatneyi	48 h (Tertian)	South Asia	*P. falciparum*	
P. brasilianum	72 h (Quartan)	South America	*P. malariae*	
P. simium	48 h (Tertian)	South America	*P. vivax*	
P. knowlesi	24 h (Quotidian)	South Asia	*P. falciparum* *P. malariae*	
P. Ovale	48 h (Tertian)	Global	*P. vivax*	
P. malariae	72 h (Quartan)	Global	.....	
P. vivax	48 h (Tertian)	Global	.....	
P. falciparum	48 h (Tertian)	Global	.....	

Old world monkeys | New world monkeys | Chimpanzees | Gorillas | Humans

Locally acquired malaria: a retrospective analysis of long-term surveillance data, European France, 1995 to 2022

Hugues Delamare[1], Arnaud Tarantola[2], Marc Thellier[3,4], Clémentine Calba[5], Olivier Gaget[6], Paul-Henri Consigny[7], Frederic Simard[8], Sylvie Manguin[9], Elise Brottet[10], Marie-Claire Paty[1], Sandrine Houze[4,11], Henriette De Valk[1], Harold Noël[1]

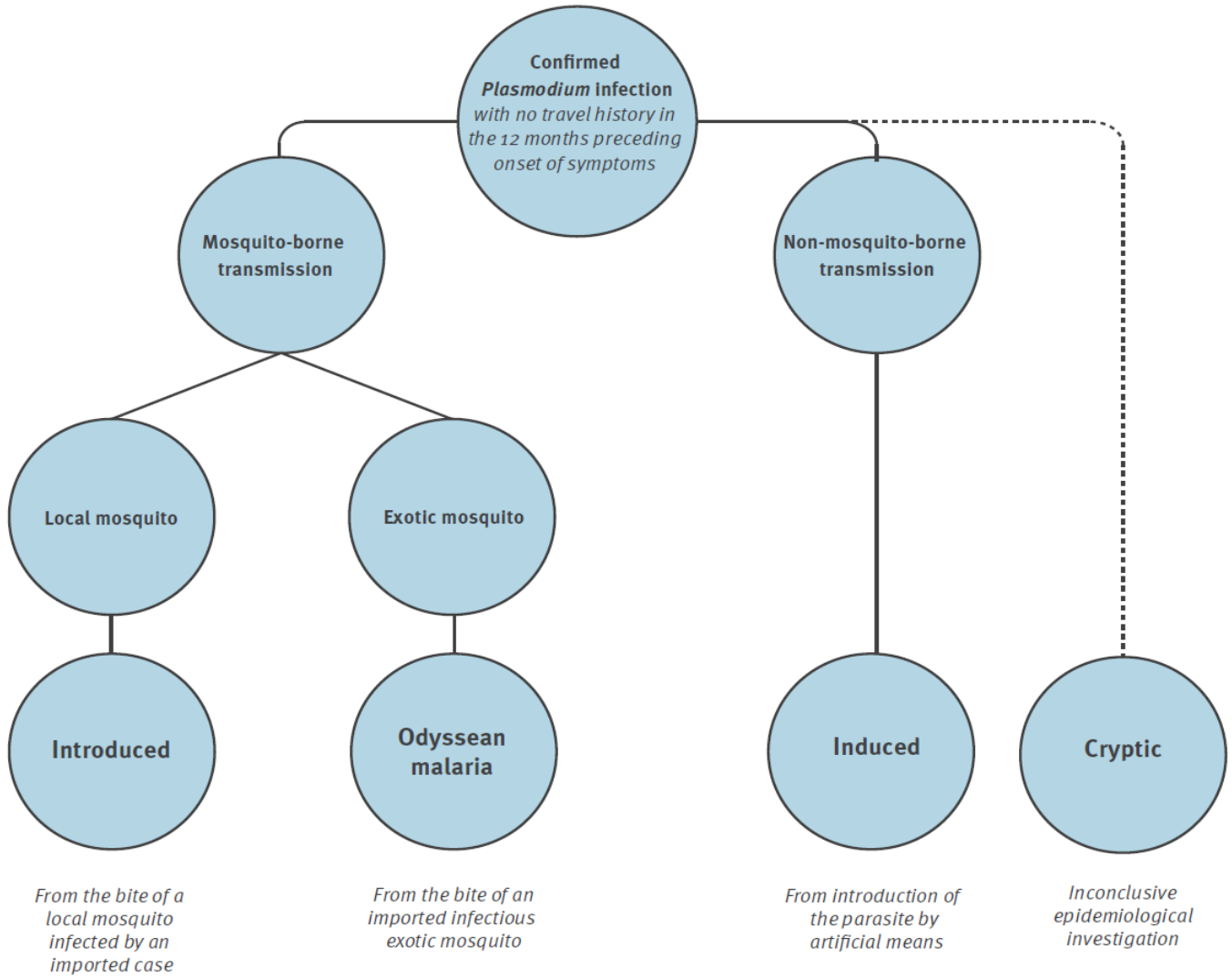
In the previous decade 2012 to 2022, <0.2% of confirmed malaria cases in the EU were locally acquired [5]. Most locally acquired cases were reported in four countries: France, Greece, Italy and Spain [5-13]. In addition to sporadic cases, clusters of locally acquired *P. vivax* cases occurred repeatedly in Greece between 2009 and 2012 [14], while other countries reported sporadic cases involving mainly *P. falciparum* [6-8].

Surveillance data

We retrieved locally acquired malaria cases from three different surveillance databases: the national database of mandatory notification of locally acquired malaria cases from 1995 to 2022, the register of epidemiological investigations of locally acquired malaria from 1998 to 2022, and the NRCm database from 1996 to 2021 (Figure 2).

FIGURE 1

Classification of locally acquired malaria cases by mode of transmission

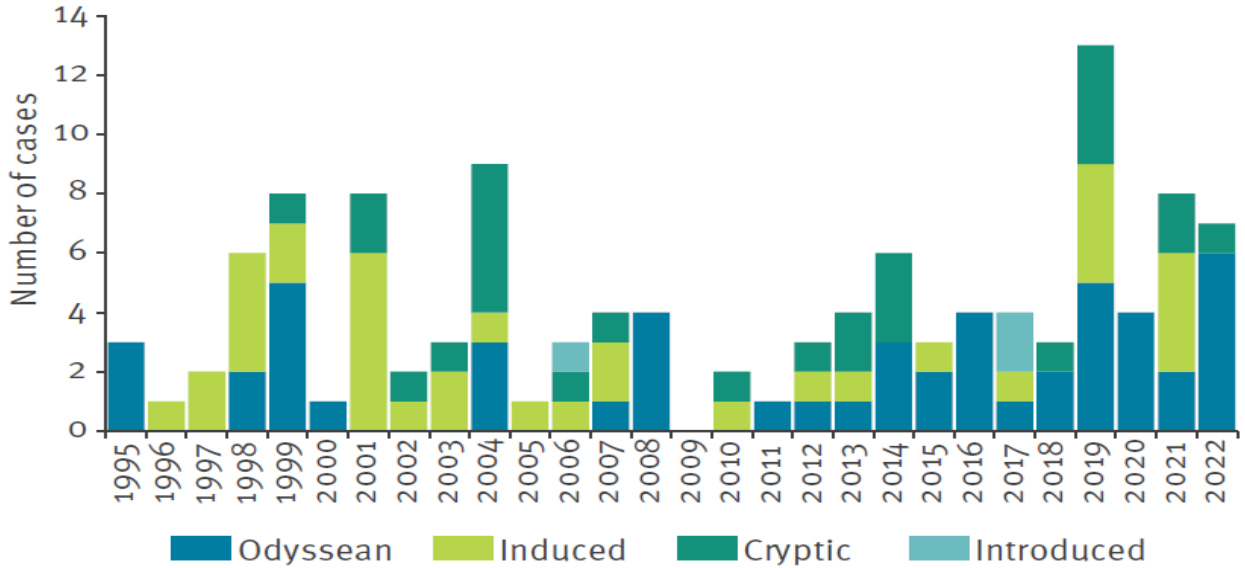


Introduction by artificial means refers to: accidental blood exposure, blood transfusion, mother-to-child transmission, organ transplant, or nosocomial transmission.

Locally acquired malaria: a retrospective analysis of long-term surveillance data, European France, 1995 to 2022

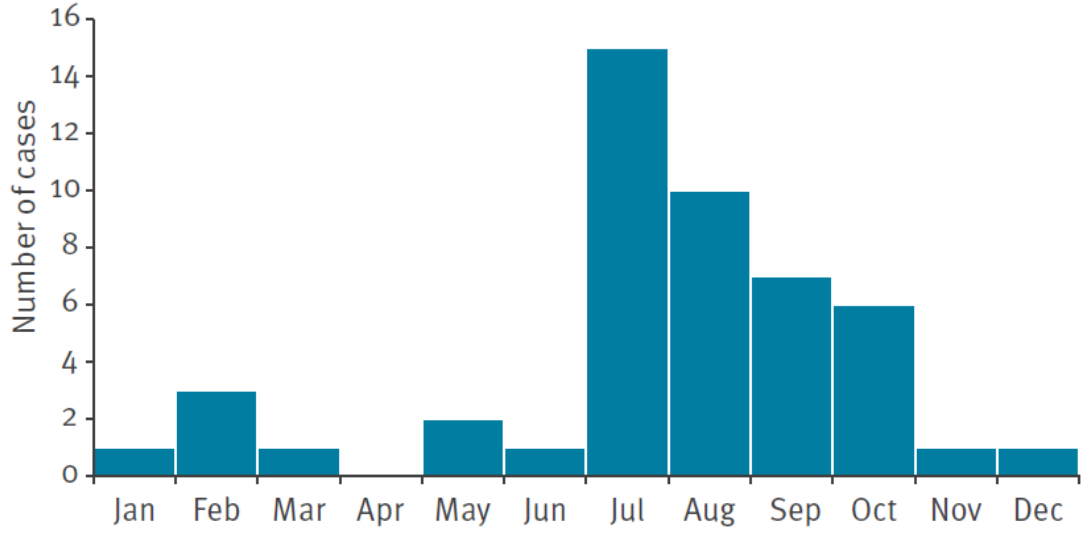
Hugues Delamare[1] , Arnaud Tarantola[2] , Marc Thellier[3,4] , Clémentine Calba[5] , Olivier Gaget[6] , Paul-Henri Consigny[7] , Frederic Simard[8] , Sylvie Manguin[9] , Elise Brottet[10] , Marie-Claire Paty[1] , Sandrine Houze[4,11] , Henriette De Valk[1] , Harold Noël[1]

Locally acquired malaria cases by mode of transmission, European France,1995–2022 (n = 117)



Odyssean malaria is also referred to as airport, port or suitcase malaria.

Odyssean malaria seasonality, European France,1995–2022 (n = 48[a])



[a] Three of the 51 Odyssean malaria cases had missing data on seasonality.

Locally acquired malaria: a retrospective analysis of long-term surveillance data, European France, 1995 to 2022

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Cryptic cases

Cryptic malaria cases (n=27) with inconclusive epidemiological investigations were almost exclusively caused by *P. falciparum* (n=26). For those with available information on place of birth, the proportion of patients born in Africa was significantly higher among cryptic malaria cases than other modes of contamination with 18 of 23 patients born in Africa vs nine of 31 and 21 of 36 among induced and Odyssean malaria cases, respectively (p<0.001). No temporal trend was associated with the occurrence of cryptic malaria cases over the course of the study (proportion ratio: 1.04; 95% CI: 0.97–1.10; p=0.30).

The classification of cryptic malaria cases encounters complexity and limitations. In the absence of an exact mode of contamination, we cannot rule out that cryptic cases may include rare chronic and asymptomatic carriers [38,39]. Moreover, socio-administrative impediments, including linguistic challenges or deliberately omitted travel history were significant obstacles during the investigation of cryptic malaria cases. This may lead to inaccuracies, resulting in imported cases being misclassified as locally acquired cryptic cases [40].

Plasmodium falciparum Recrudescence Two Years after Treatment of an Uncomplicated Infection without Return to an Area Where Malaria Is Endemic

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February 2018 Volume 62 Issue 2 e01892-17

Denis Malvy,[a] Marylin Torrentino-Madamet,[b,c,d] Coralie L'Ollivier,[e,f] Marie-Catherine Receveur,[a] Fakhri Jeddi,[e,f] Laurence Delhaes,[g] Renaud Piarroux,[e,f] Pascal Millet,[g] Bruno Pradines[b,c,d]

an increase in parasitemia. This clinical case of *P. falciparum* malaria, manifested 2 years after exposure and after the first-treated uncomplicated infection, raises questions about the chronicity and activation of *P. falciparum* infection. The presence of late trophozoites (50%), which are not normally detected in the peripheral blood of patients, suggests altered sequestration. Recent studies suggested that *P. falciparum* infection may induce dormant stages, such as persisting nidus of sequestered parasites described in the placenta (19). Some recurrences of *P. falciparum* malaria may be caused by dormant erythrocytic forms that are newly activated as a consequence of decreased immunity.

TABLE 1 Genotyping of two samples obtained from a patient from 2014 and 2016 using eight polymorphic microsatellite markers specific for *P. falciparum*

	Microsatellite allele length[a] (bp) for:							
Sample yr	PfPK2	TA109	Poly α	ARA2	TA42	Pfg377	TA1	TA81
2014	162.21	**166.56**	156.44	67.72	**191.43**	101.68	169.26	121.73
	168.21	169.58	**159.65**	**73.60**	206.12	**107.40**		**136.52**
	177.03	181.51	168.83					
	191.60		174.94					
2016	**177.03**	**166.56**	**159.65**	**73.59**	**191.38**	**107.41**	166.26	**136.63**

[a]Alleles present in both samples are shown in boldface.

Recrudescence of *Plasmodium falciparum* malaria 5 years after treatment in an HIV migrant: a case report with a peculiar presentation

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CASE PRESENTATION

A 28-year-old man, originating from Ivory Coast, was admitted to the emergency department of the tertiary-care University-hospital of Pisa, Italy, in August 2021. He complained of fever, headache and abdominal pain starting 72h earlier. The patient had suffered from malaria, treated with unspecified drugs, five years before, when he was still living in Ivory Coast. He moved to Italy in 2016 and had not travelled abroad since then. Moreover, in 2019, the patient was diagnosed with human immunodeficiency virus (HIV) infection, with initial CD4+ T-cell count and HIV viral load of 40,3/mm^3 (2,7%) and 1010000 copies/

DISCUSSION

We described a case of recrudescent *P. falciparum* malaria, occurring five years after the first episode, in a HIV-infected man originating from Ivory Coast. The patient denied any travel abroad since he moved to Italy, any use of intravenous drugs and did not receive any solid organ transplant or blood transfusion. Luggage malaria was excluded, because the patient denied any contact with people recently coming from endemic areas. Local transmission, with the patient's cohabitants representing a potential source of infection, appears unlikely. *Anopheles labranchiae*, regarded as the main malaria vector in Italy, is present in Tuscany. Nonetheless, recent entomological investigations, conducted for suspected locally-transmitted malaria cases, failed to demonstrate *Anopheles* species presence in several Italian areas, including Tuscany [13]. Besides, previous work suggested that *A. labranchiae* shows a low tropism for tropical *P. falciparum* strains, further reducing the probability of local transmission [14].

SYSTEMATIC REVIEW

Airport and luggage (Odyssean) malaria in Europe: a systematic review

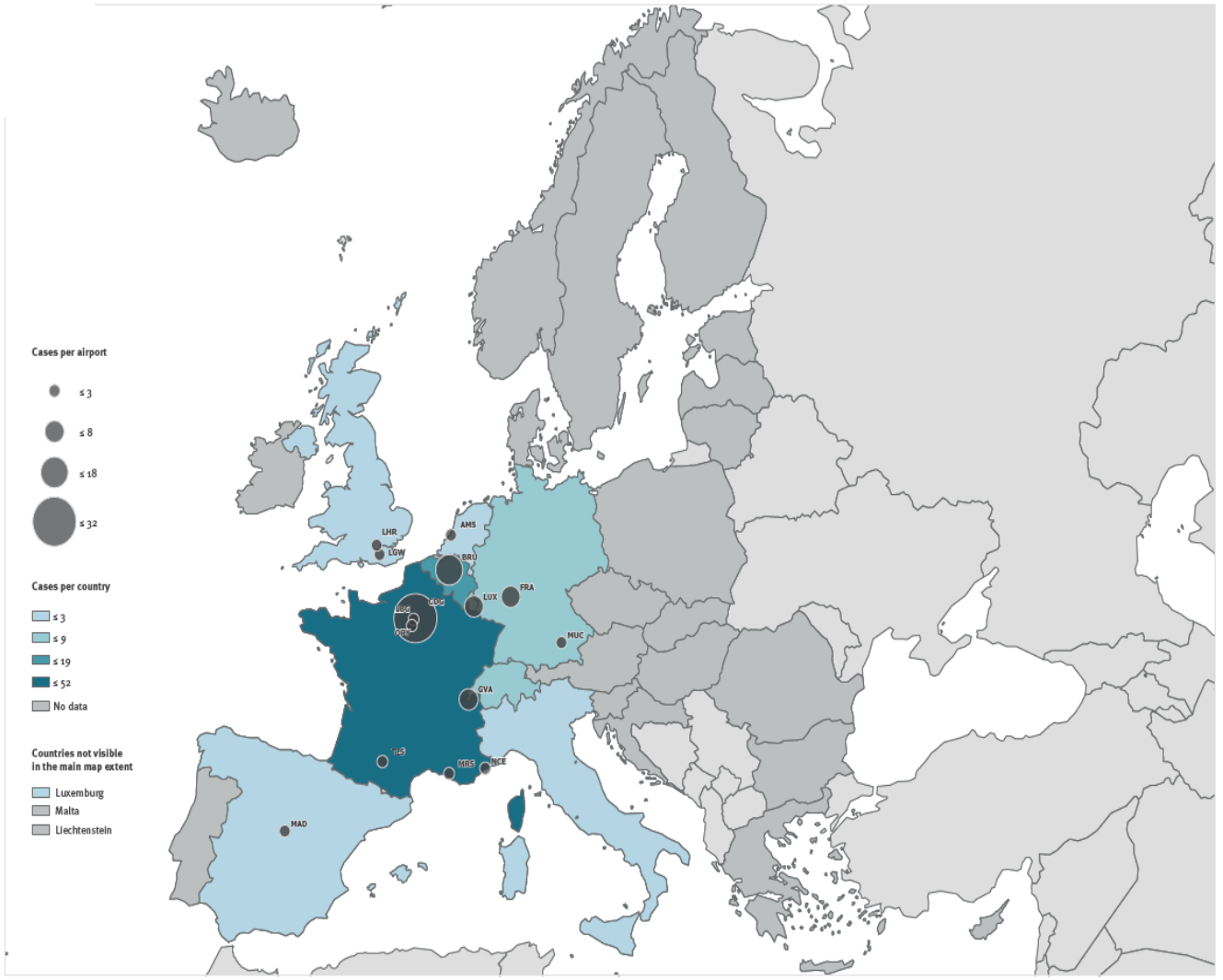
Luisa K Hallmaier-Wacker[1], Merel D van Eick[2], Olivier Briët[1], Hugues Delamare[3], Gerhard Falkenhorst[4], Sandrine Houzé[5], Harold Noël[3], Javiera Rebolledo[6], Wim Van Borte[7,8], Céline M Gossner[1]

Airport malaria

Of the 105 cases of airport malaria, 83 cases occurred between June and September, with a peak in August (Figure 2B). Eight cases were described outside this range, with three cases described in February (two cases infected in a hospital 3 km from the airport [36], one with an occupational link to the airport [46]) and one in December with unknown link to the airport (Supplementary Table S3)). For 11 cases, no month of infection was specified.

All cases of airport malaria were reported in western Europe, with most cases reported in France (49.5%, n = 52), followed by Belgium (18.1%, n = 19) and Germany (8.6%, n = 9) (Figure 3). Six airports in France were associated with airport malaria cases, more than in any other country. Paris Charles de Gaulle airport reported most cases (n=32), with Marseille Provence airport, Nice Côte d'Azur airport, Paris–Le Bourget airport, Paris-Orly airport and Toulouse-Blagnac airport associated with sporadic case reports (Figure 3). Brussels airport was the airport with the second highest number of cases (n = 18), followed by Frankfurt airport (n = 8), Geneva airport (n = 5) and Luxembourg airport (n = 5). Three studies described the possibility

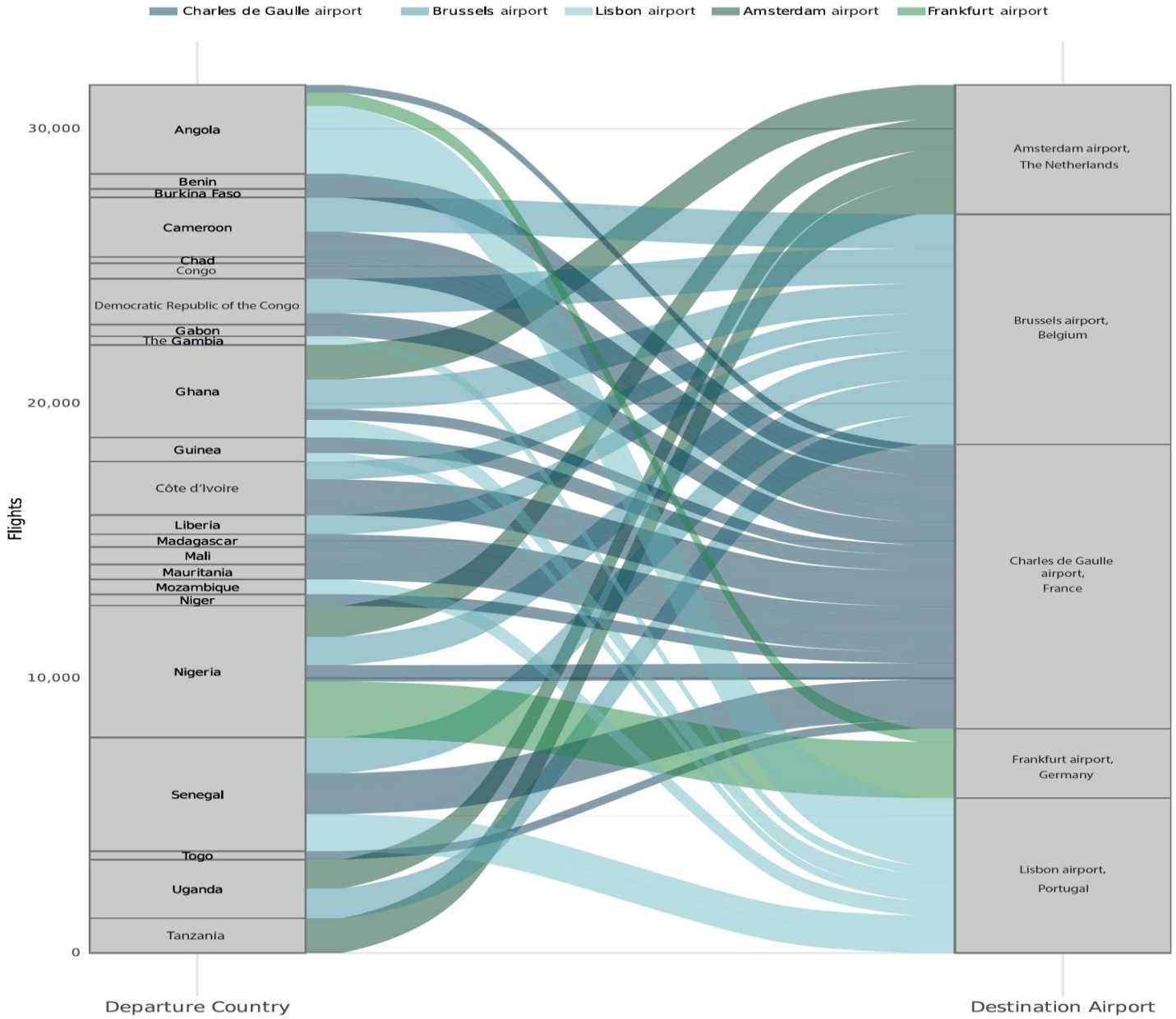
Map of airport malaria cases by airport[a] and country, European Union/European Economic Area countries, Switzerland and the United Kingdom[b]



[a] Amsterdam airport Schiphol (AMS, n = 3), Brussels airport (BRU, n = 18), Charles de Gaulle airport (CDG, n = 32), Frankfurt airport (FRA, n = 8), Geneva airport (GVA, n = 5), Paris–Le Bourget airport (LBG, n = 3), London Gatwick airport (LGW, n = 2), London Heathrow airport (LHR, n = 2), Luxembourg airport (LUX, n = 5), Madrid–Barajas airport (MAD, n = 1), Marseille Provence airport (MRS, n = 2), Munich airport (MUC, n = 1), Nice Côte d'Azur airport (NCE, n = 1), Paris-Orly airport (ORY, n = 3), Toulouse Blagnac airport (TLS, n = 2).

Euro Surveill. 2024;29(41):pii=2400237.

Flights between countries with malaria endemicity[a] and the top five destination airports in the European Union/European Economic Area for 2021 and 2022



Euro Surveill. 2024;29(41):pii=2400237.

Hospital-acquired malaria infections in the European Union

30 April 2018

On 5 September 2017, Italy reported a fatal case of malaria in a four-year-old girl with no travel history to a malaria-endemic country [47].

She had been admitted to a hospital in the Veneto region on 13 August 2017 and diagnosed with diabetes mellitus. After returning from the Veneto region, she had been admitted to a hospital in the Trento region for diabetes from 16 to 21 August 2017, and diagnosed with pharyngitis on 31 August 2017.

On 2 September 2017, she was admitted and diagnosed with *P. falciparum* malaria and subsequently transferred to the tropical diseases reference centre in Lombardy where she died on 4 September 2017. Epidemiological investigations identified two patients infected with *P. falciparum* who were hospitalised in the same ward during her stay in the Trento hospital between 16 and 21 August 2017; both cases were imported. The investigation at the Trento hospital did not identify breaches in medical procedures that could have resulted in transmission.

Molecular sequencing of the *Plasmodium* isolates from the girl and the other two children hospitalised concomitantly, performed by the National Institute of Health in Rome, indicated that the *Plasmodium* isolates of the girl and one of the two children were genetically identical, confirming with reasonable certainty that it was hospital transmission and excluding the involvement of a vector, either from local *Anopheles* mosquitoes or luggage malaria.

Table 1. Cases of hospital malaria transmission in the EU, by country, 2016–2018

Country of report	Age (years)	Date of onset	Place of infection	Suspected mode of transmission	Possible exposure	Outcome	*Plasmodium* species
Germany	33	2016	Nordrhein-Westfalen, Germany	Hospital transmission	Shared room with a malaria case	Alive	*P. falciparum*
Greece	39	18–20 Jul 2017	Ipeiros, Greece	Vector or hospital transmission	Shared ward with a malaria case	Alive	*P. falciparum*
Italy	4	29 Aug 2017	Trento, Italy	Hospital transmission	Shared ward with two malaria cases	Dead	*P. falciparum*
Italy	13	28 Oct 2017	Tuscany, Italy	Hospital transmission	Shared ward with a malaria case	Alive	*P. falciparum*
Spain	64	9 Mar 2016	Galicia, Spain	Hospital transmission	Stayed in emergency ward with a malaria case	Alive	*P. falciparum*
Spain	<1 (3 months)	19 Feb 2018	Madrid, Spain	Hospital transmission	Shared ward with a malaria case	Alive	*P. malariae* and *P. ovale*

Probable autochthonous introduced malaria cases in Italy in 2009–2011 and the risk of local vector-borne transmission

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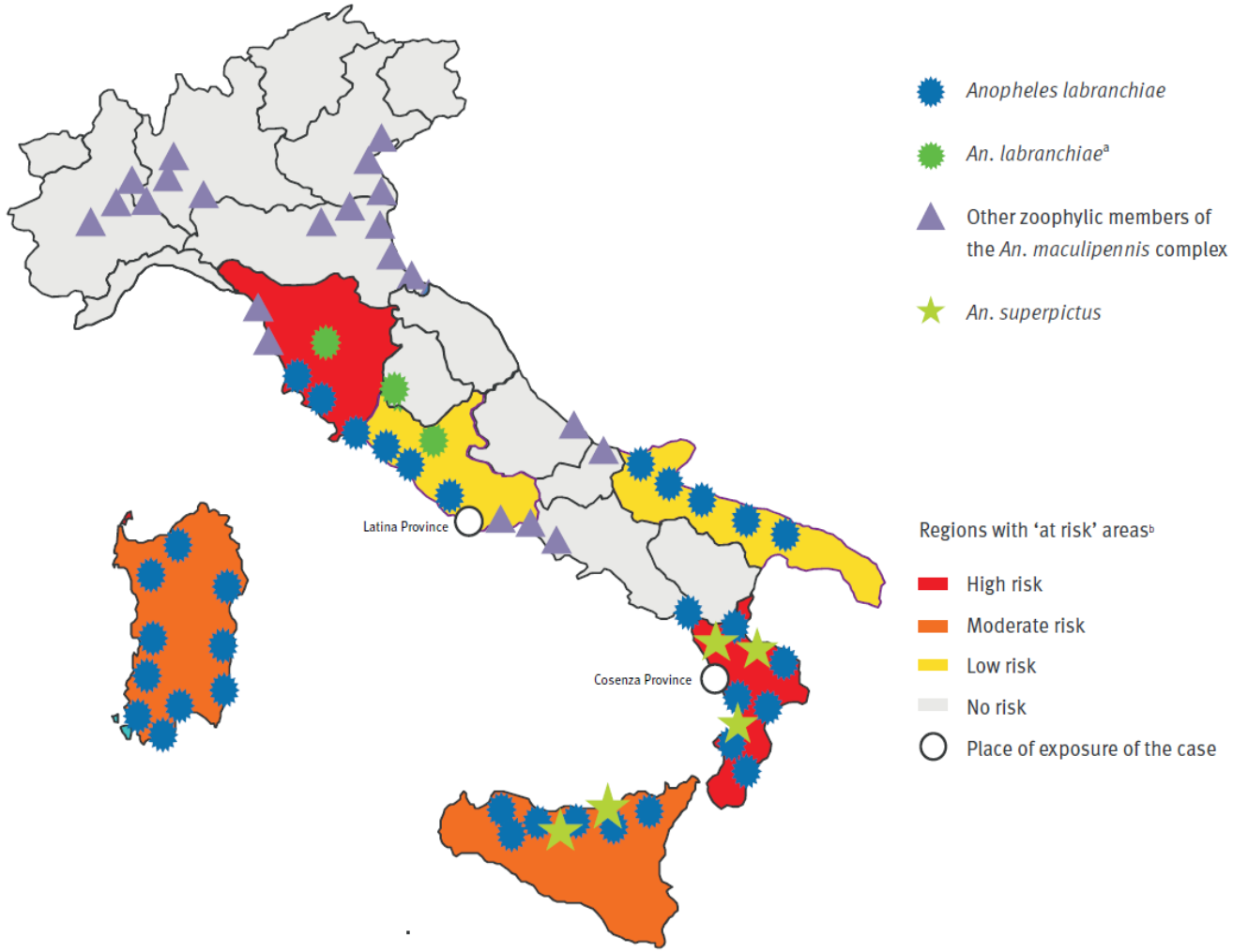
Discussion

During the last 15 years (1997-2011), a total of 17 possible autochthonous cases of malaria occurred in Italy. Only one of them was likely transmitted by local vectors, thus fitting the criteria for an introduced case [5]. Other 14 cases were attributed to either iatrogenic transmission (nosocomial infection (n=7), post-transfusion (n=3), and post-transplant (n=1)) or bites from infected mosquitoes imported with baggage (n=3) [11]. The remaining two cases, discussed in this report, were classified as autochthonous [5]. In fact, although they can potentially be considered cases of introduced malaria transmitted by indigenous vectors, the source of infection remains undefined.

In Italy, as well as in other Mediterranean countries recently investigated for the risk of malaria reintroduction, the return to a situation of endemic malaria is unlikely, but the occurrence of sporadic, isolated cases of introduced *P. vivax* malaria may still be considered

FIGURE 2

Distribution of the potential malaria vectors and regions considered at risk of malaria reintroduction, Italy, 2005-2011



[a] First detected in 2010–2011 in northern-central Italy.

[b] Areas with presence of foci and seasonal abundance of the potential vector and with seasonal climatic conditions favourable to malaria transmission.

Non-imported malaria in Italy: paradigmatic approaches and public health implications following an unusual cluster of cases in 2017

Table 1 Annual incidence and references of non-imported malaria cases reported in Italy in 2000–2018

Years	N. of non-imported cases	*Plasmodium* species	Event definition	Reference	% (Total cases)
2000	1	*P. falciparum*	Induced (nosocomial)	40	0.10 (977)
2001	0	–	–		0.00 (888)
2002	0	–	–		0.00 (733)
2003	1	*P. falciparum*	Induced (suspected)		0.15 (681)
2004	2	*P. falciparum*	Induced (post-transplant)		0.30 (673)
		P. falciparum	Cryptic		
2005	1	*P. malariae*	Induced (transfusional)	41	0.16 (637)
2006	0	–	–		0.0 (630)
2007	2	*P. falciparum*	Induced (suspected)		0.35 (575)
		P. falciparum	Induced (suspected)		
2008	2	*P. vivax*	Cryptic		0.34 (583)
		P. falciparum	Induced (suspected)		
2009	2	*P. vivax*	Introduced (suspected)	21	0.31 (636)
		P. falciparum	Induced (suspected)		
2010	2	*P. ovale*	Cryptic		0.29 (700)
		P. malariae	Induced (suspected)		
2011	1	*P. vivax*	Introduced (suspected)	21	0.14 (701)
2012	1	*P. falciparum*	Cryptic		0.16 (642)
2013	2	*P. malariae*	Induced (suspected)		0.30 (677)
		P. falciparum	Induced (suspected)		
2014	2	*P. falciparum*	Cryptic		0.28 (705)
		P. malariae	Cryptic		
2015	1	*P. malariae*	Cryptic		0.14 (706)
2016	0	–	–		0.00 (888)
TOTAL	**20**				**0.17 (12,032)**
2017	7	*P. ovale*	Cryptic		43,44 / 0.84 (831)
		P. falciparum	Induced (nosocomial)		10,11
		P. falciparum	Induced (nosocomial)		11
		P. falciparum	Cryptic		42,45
		P. falciparum	Cryptic		42,45
		P. falciparum	Cryptic		42,45
		P. falciparum	Cryptic		42,45
2018	3	*P. falciparum*	Cryptic		51 / 0.42 (722)
		P. falciparum	Cryptic		
		P. falciparum	Cryptic		
TOTAL	**10**				**0.64 (1553)**

Case	Region	Locality	*Anopheles* spp. collections
a	Veneto	Bibione	No larvae; *An. maculipennis* s.s. (5 females); *An. messeae* (2)
	Trentino Alto Adige	Trento	No larvae nor adults
b	Tuscany	Florence	No larvae nor adults
c	Marche	Pesaro	No larvae nor adults
d (four cases)	Apulia	Ginosa	Presence of larvae; *An. labranchiae* (102 females)

Fig. 1 Geographical distribution of non-imported malaria cases occurred in 2017 in Italy (grey regions), and associated findings from entomological investigations targeting *Anopheles* vectors species (The map shown in Fig. 1 is an original drawing created by the authors and has not been taken from other sources)

Cryptic *Plasmodium* chronic infections: was Maurizio Ascoli right?

Wuelton Monteiro[1,2*], José Diego Brito-Sousa[1,2], Aleix Elizalde-Torrent[3,4,5], Camila Bôtto-Menezes[1,2], Gisely Cardoso Melo[1,2], Carmen Fernandez-Becerra[3,4], Marcus Lacerda[1,6] and Hernando A. del Portillo[3,4,7*]

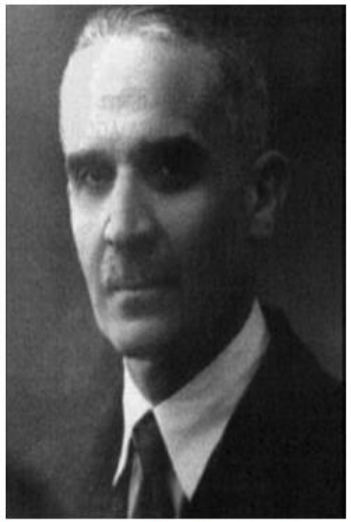


Fig. 2 Maurizio Ascoli (Trieste, July 14, 1876 to Palermo, August 4, 1958). Source: https://it.wikipedia.org/wiki/Maurizio_Ascoli

Abstract

Cryptic *Plasmodium* niches outside the liver possibly represent a major source of hypnozoite-unrelated recrudescences in malaria. Maurizio Ascoli, an Italian physician and scientist, suggested that infection was maintained as a result of the persistence of endoerythrocytic parasites in the circulatory bed of some internal organs, mainly the spleen. This would explain a proportion of the recurrences in patients, regardless of the *Plasmodium* species. Ascoli proposed a method that included the co-administration of adrenaline, in order to induce splenic contraction, and quinine to clear expelled forms in major vessels. Driven by controversy regarding safety and effectiveness, along with the introduction of new drugs, the Ascoli method was abandoned and mostly forgotten by the malaria research community. To date, however, the existence of cryptic parasites outside the liver is gaining supportive data. This work is a historical retrospective of cryptic malaria infections and the Ascoli method, highlighting key knowledge gaps regarding these possible parasite reservoirs.

Monteiro *et al. Malar J* (2020) 19:440
https://doi.org/10.1186/s12936-020-03516-x

The biology and pathogenesis of vivax malaria

Nicholas M. Anstey [1,*], Wai-Hong Tham [2,3,4], G. Dennis Shanks [5], Jeanne R. Poespoprodjo [1,6,7,8], Bruce M. Russell [9], and Steven Kho [1,7]

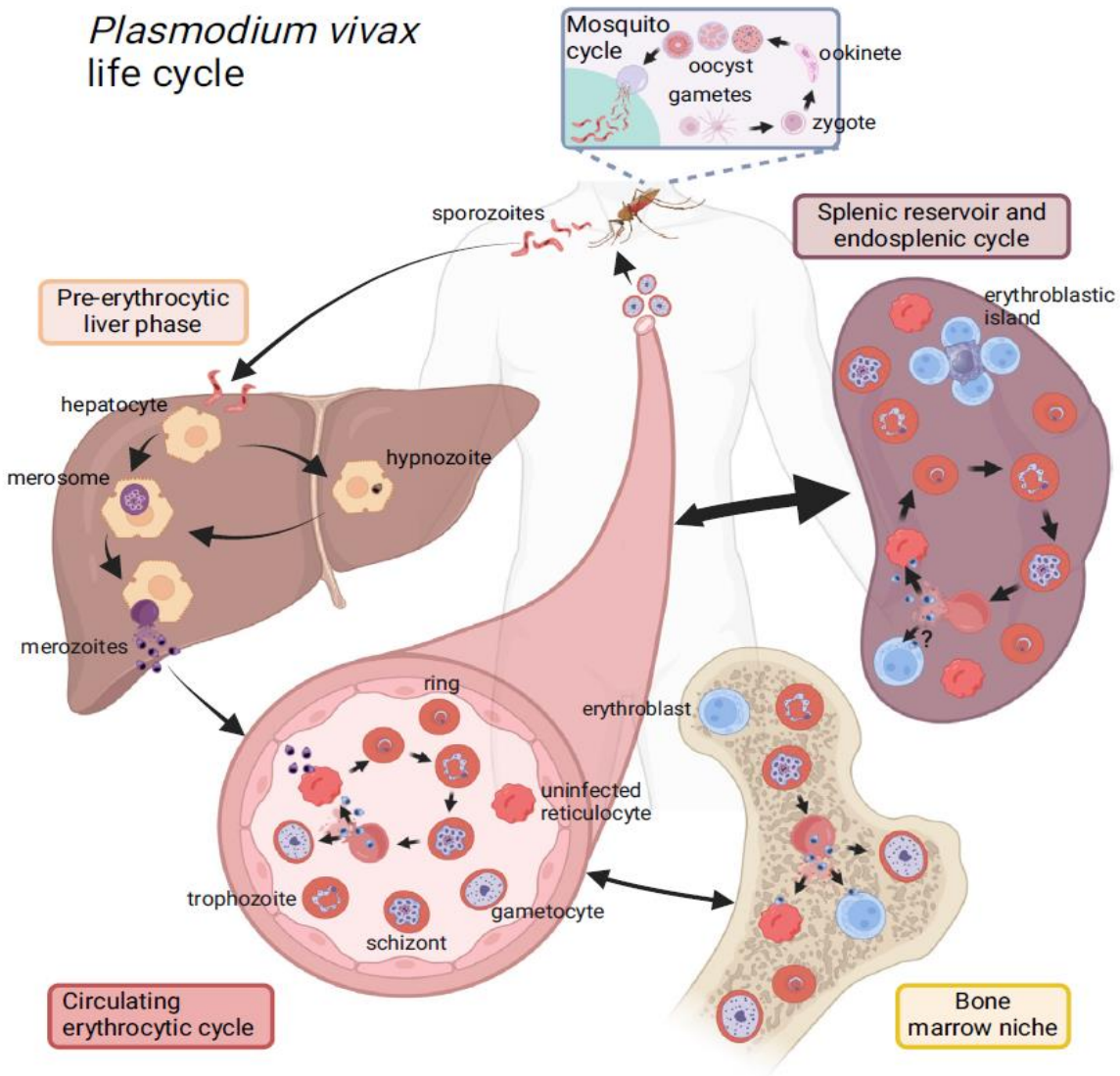
Asexual replication in the reticulocyte-rich spleen

Recent studies show that *P. vivax* asexual stages are not confined to the peripheral circulation as long thought. Indeed, vivax malaria is predominantly an infection of the spleen, with only a small circulating intravascular component [12]. In chronic infection, over 98% of total-body *P. vivax* parasites are found in the spleen [12], sustained by an endosplenic asexual-stage life cycle [12,13] (Figure 1). Multiple lines of evidence support the existence of a major cycle of intrasplenic replication. The magnitude of asexual-stage *P. vivax* biomass accumulating in the spleen is inexplicable

Asexual stages in the bone marrow

The bone marrow is another primary site for accumulation of *P. vivax* asexual stages [20–22] (Figure 1). Parasite densities approximate those in peripheral blood [20,21], though parasites can sometimes be found in individuals whose peripheral blood is microscopy-negative [23]. In asymptomatic infections, the relative contribution of bone marrow parasites to total-body *P. vivax* asexual biomass has been estimated to be 0.1% [13]. Direct comparison of matched human blood, spleen,

The *Plasmodium vivax* life cycle



The biology and pathogenesis of vivax malaria

CD71: also known as transferrin receptor 1 (TfR1), a receptor predominantly present on nascent reticulocytes and absent on mature ones, playing a key role in invasion by *P. vivax* merozoites.

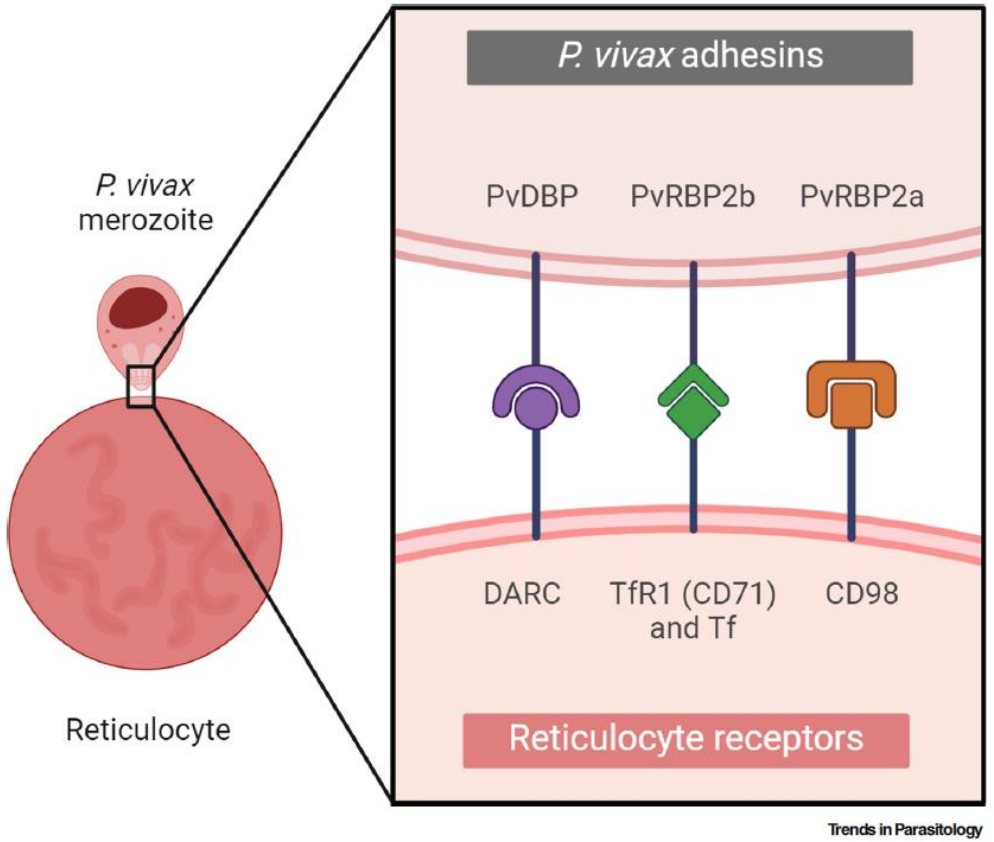
CD98: also known as 4F2 cell-surface antigen heavy chain or CD98hc, a multifunctional transmembrane protein with a key role in reticulocyte invasion by *P. vivax* merozoites. Expressed in various cell types, such as erythrocyte progenitors and nascent reticulocytes.

Complement receptor 1 (CR1): a complement regulatory protein on the RBC surface and an RBC receptor for *P. vivax* erythrocyte binding protein (PvEBP).

Duffy antigen receptor for chemokines (DARC): a reticulocyte receptor for Duffy-binding protein (DBP), that mediates merozoite invasion of reticulocytes.

Trends in Parasitology

Nicholas M. Anstey [1,*], Wai-Hong Tham [2,3,4], G. Dennis Shanks [5], Jeanne R. Poespoprodjo [1,6,7,8], Bruce M. Russell [9], and Steven Kho [1,7]



***P. vivax* Duffy binding protein (PvDBP):** a protein that binds to DARC and is a leading vaccine candidate.

***P. vivax* reticulocyte binding protein 2a (PvRBP2a):** a protein that binds to CD98 on nascent reticulocytes, mediating invasion.

***P. vivax* reticulocyte binding protein 2b (PvRBP2b):** a protein that binds to CD71 (TfR1) on nascent reticulocytes, mediating invasion.

Trends in Parasitology, July 2024, Vol. 40, No. 7 https://doi.org/10.1016/j.pt.2024.04.015

Trends in Parasitology

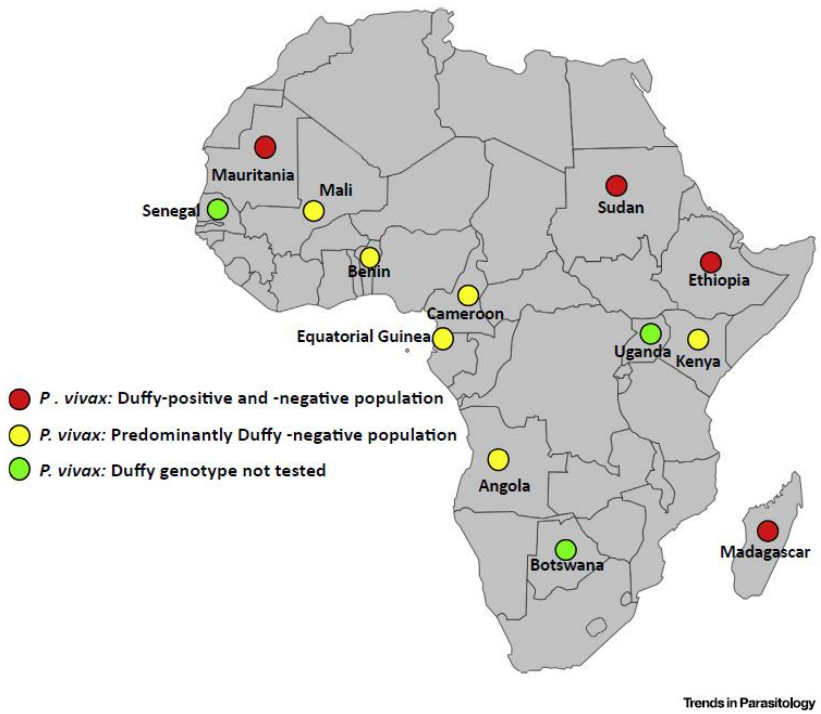
2018;34:420-29

CellPress REVIEWS

Review

Plasmodium vivax Infections of Duffy-Negative Erythrocytes: Historically Undetected or a Recent Adaptation?

Karthigayan Gunalan,[1,3,*] Amadou Niangaly,[2,3] Mahamadou A. Thera,[2] Ogobara K. Doumbo,[2] and Louis H. Miller[1,*]



Receptors: erythrocyte molecules to which parasite ligands bind for invasion. The Duffy blood group is the receptor for DBP1.
Reticulocyte: the immature stage of erythrocytes. Reticulocytes contain residual RNA but not the nucleus. *P. vivax* preferentially invades reticulocytes compared to mature erythrocytes.

Figure 1. *Plasmodium vivax* Infection in Duffy-Negative Populations in Africa. Regions on the African continent in which *P. vivax* infection in Duffy-negative people occurs. Red circles represent *P. vivax* infection in countries where both Duffy-positive and Duffy-negative people live side by side. Yellow circles represent molecular evidence of *P. vivax* infection in Duffy-negative individuals living in predominantly Duffy-negative populations in sub-Saharan Africa. Green circles represent populations with *P. vivax* infection, but in which the Duffy status has not been checked. The map has been adapted from Wikimedia.

Table 1. Latest Findings on Duffy-Negative *Plasmodium vivax* Infections in Africa and the Molecular Tools Used

Countries with *P. vivax* infection in Africa	Number of Duffy-negative infections	Diagnostic tools		Year	Refs
		P. vivax	Duffy genotyping		
Cameroon	27	Nested PCR[a], sequencing	PCR – melting curve analysis	2017	[19]
Mali	25	Microscopy, qPCR[b]	Nested PCR, sequencing	2017	[20]
Uganda	4	Microscopy, RDT[c], Nested PCR	Not tested	2017	[18]
Ethiopia	2	Microscopy, nested PCR, sequencing	PCR, sequencing	2016	[14]
Benin	13	Microscopy, serology, nested PCR, sequencing	Nested PCR, sequencing	2016	[15]
Sudan	4	Microscopy, RDT, PCR	PCR-RFLP[d]	2016	[17]
Botswana	169	Nested PCR	Not tested	2016	[16]
Cameroon	10	Nested PCR, sequencing	PCR, sequencing	2016	[11]
Ethiopia	4	Nested PCR, qPCR	PCR, sequencing	2015	[10]
Senegal	4	Nested PCR, sequencing	Not tested	2015	[12]
Cameroon	8	Nested PCR, sequencing	PCR, sequencing	2014	[9]
Cameroon	6	Microscopy, nested PCR, sequencing	PCR-RFLP, sequencing	2014	[8]
Mauritania	1	qPCR	PCR, sequencing	2011	[7]
Equatorial Guinea	8	Nested PCR, RFLP	PCR-RFLP, sequencing	2011	[13]
Angola	7	Nested PCR, RFLP	PCR-RFLP, sequencing	2011	[13]
Madagascar	42	Microscopy, RDT, PCR, qPCR, sequencing	PCR, LDR-FMA[e], sequencing, flow cytometry	2010	[6]
Kenya	9	Microscopy, nested PCR, sequencing	Flow cytometry	2006	[5]

[a]PCR, Polymerase chain reaction.
[b]qPCR, Quantitative PCR.
[c]RDT, Rapid diagnostic test.
[d]RFLP, Restriction fragment length polymorphism.
[e]LDR-FMA, Ligase detection reaction–fluorescent microsphere assay.

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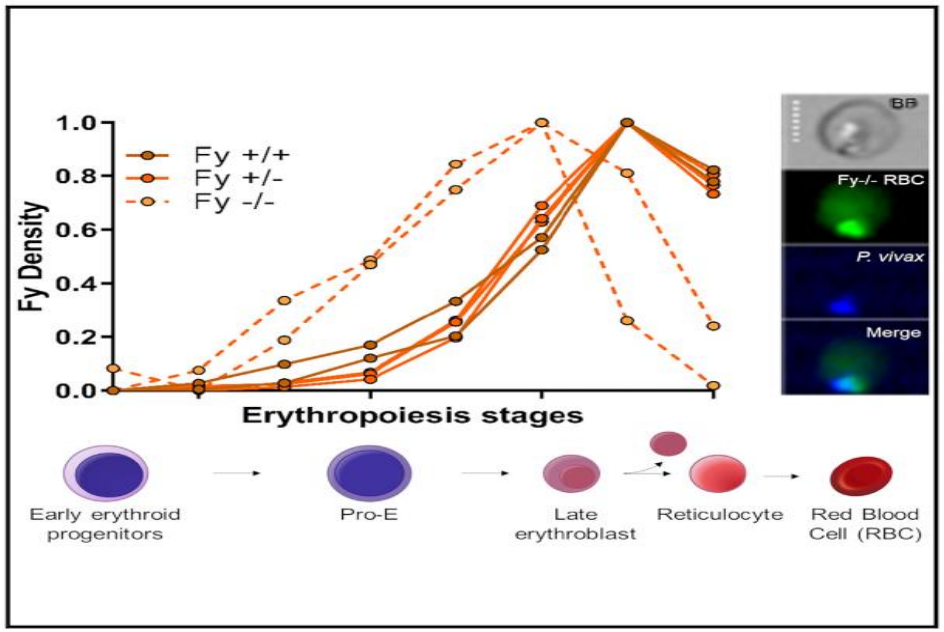
Clinical and Translational Report

Duffy antigen is expressed during erythropoiesis in Duffy-negative individuals

Celia Dechavanne,[1,10,11] Sebastien Dechavanne,[1,10,11] Jürgen Bosch,[1,2,11] Sylvain Metral,[3] Karli R. Redinger,[1] Quentin D. Watson,[1] Arsene C. Ratsimbasoa,[4,5] Brooke Roeper,[1] Sushma Krishnan,[1] Rich Fong,[1] Seth Bennett,[1] Lenore Carias,[1] Edwin Chen,[6] Nichole D. Salinas,[7] Anil Ghosh,[1] Niraj H. Tolia,[7] Philip G. Woost,[8] James W. Jacobberger,[8] Yves Colin,[3] Benoit Gamain,[3,*] Christopher L. King,[1,9,*] and Peter A. Zimmerman[1,12,*]

Graphical abstract



Highlights

- Duffy blood group protein (Fy) is naturally expressed on Fy-negative red blood cells
- Fy expression is higher on erythroid precursors than on red blood cells
- Fy protein is expressed in early erythropoietic stages in Fy-negative individuals
- *P. vivax* invades Fy-positive and Fy-negative erythroid cells *in vitro*

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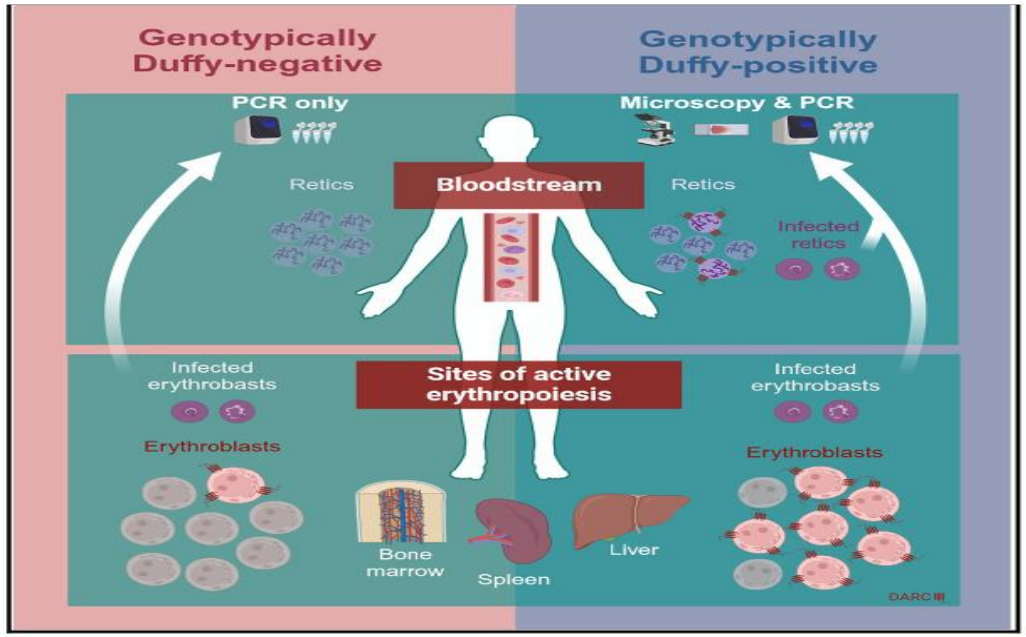
OPEN ACCESS

Clinical and Translational Report

Unveiling *P. vivax* invasion pathways in Duffy-negative individuals

Isabelle Bouyssou,[1,2,3,12] Sara El Hoss,[4,12,*] Cécile Doderer-Lang,[5] Matthieu Schoenhals,[6] Lova Tsikiniaina Rasoloharimanana,[6] Inès Vigan-Womas,[7] Arsène Ratsimbasoa,[8] Andargie Abate,[9] Lemu Golassa,[9] Solenne Mabilotte,[5] Pascal Kessler,[10] Micheline Guillotte-Blisnick,[3] Francisco J. Martinez,[3] Chetan E. Chitnis,[3] John Stroubouli s,[4,*] and Didier Ménard[1,3,5,11,13,*]

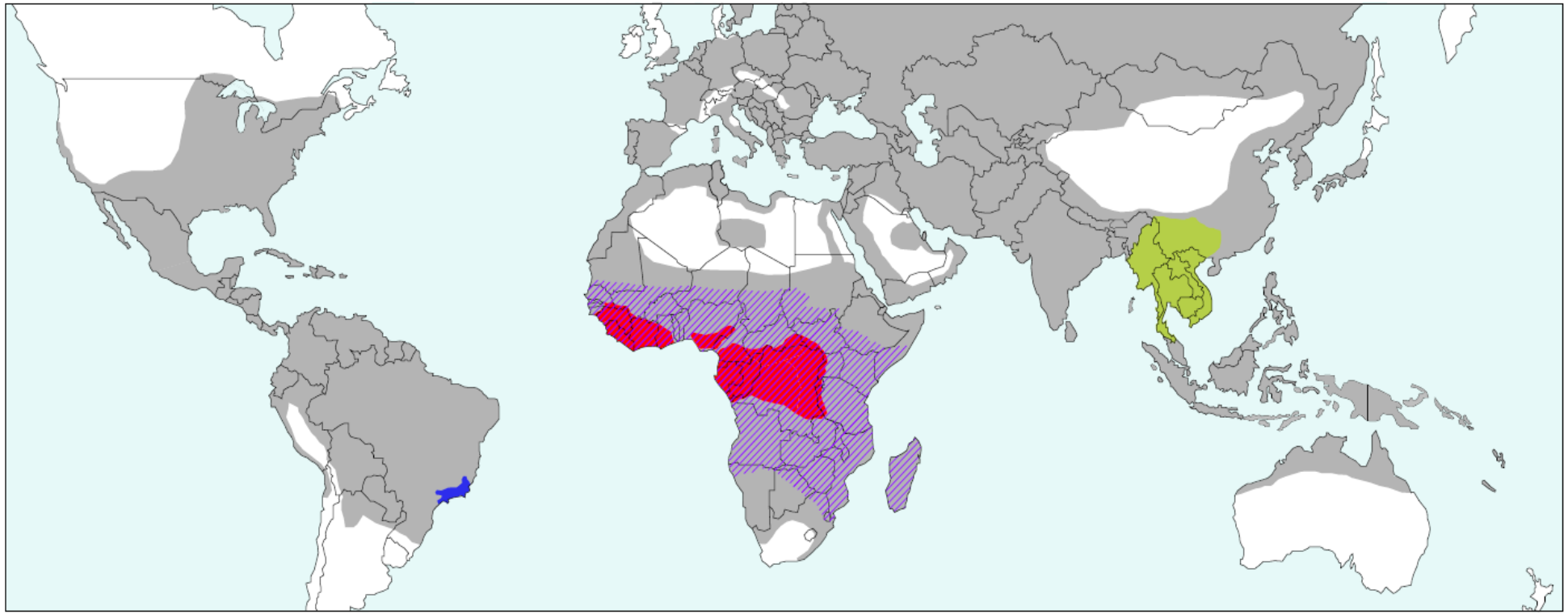


Highlights

- African Duffy-negative (DN) individuals are not fully resistant to vivax malaria
- A subset of DN erythroblasts express DARC during terminal erythroid differentiation
- *P. vivax* can invade DARC+ DN erythroblasts, regardless of their origin
- Deep *P. vivax* infection may be an unconsidered health problem in sub-Saharan Africa

Origin of the human malaria parasite *Plasmodium vivax*

Paul M. Sharp [1,2,*], Lindsey J. Plenderleith [3], Richard L. Culleton [4], and Beatrice H. Hahn [5,6]



Trends in Parasitology

Figure 1. Global distribution of *Plasmodium vivax* and related species found in non-human primates. The approximate areas where human *P. vivax* infections were found over the past few centuries are shown in gray (adapted from [78]). The area where South American monkeys are infected with *Plasmodium simium* is shown in blue [23]. The range of African apes (chimpanzees, bonobos, and gorillas), infected with *P. vivax*-like parasites, is shown in red. The approximate area in southeast Asia previously invoked as the site of origin of human *P. vivax* is shown in green. The area where the Duffy-negative phenotype has a frequency of more than 70% is hatched [62].

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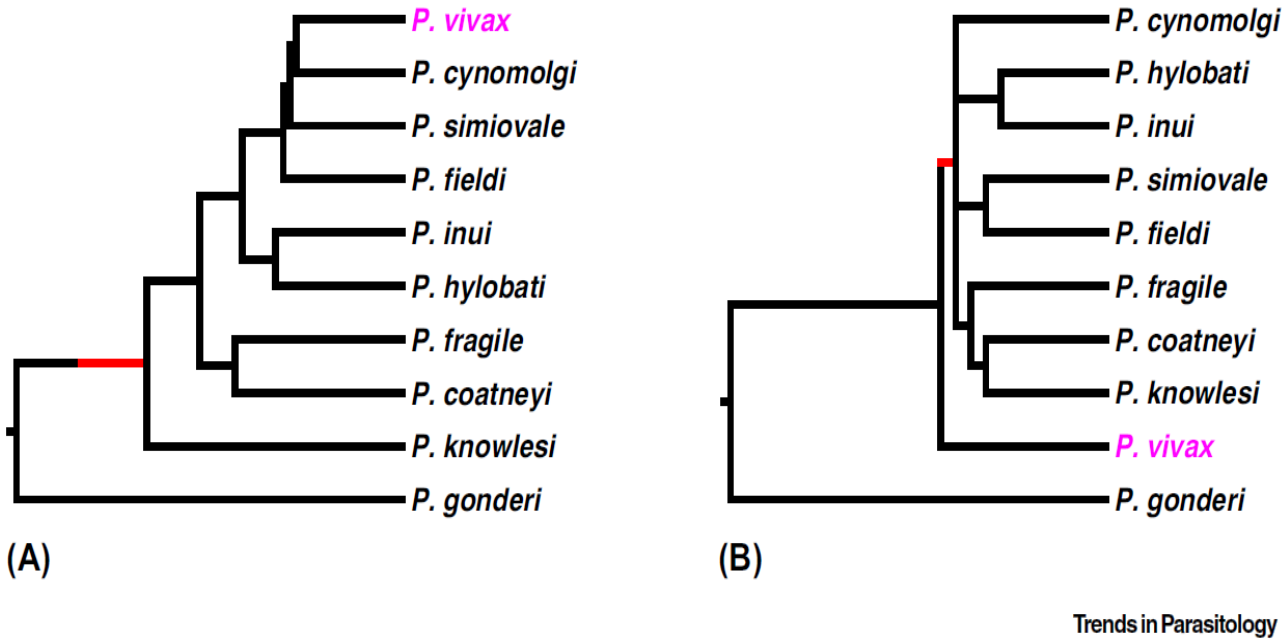

Figure 2. Relationship of *Plasmodium vivax* to southeast Asian parasite species. *P. vivax* from humans is shown in magenta. *Plasmodium gonderi* infects African monkeys; all other *Plasmodium* species shown infect non-human primates in southeast Asia. (A) 'Traditional' phylogeny, as based on analysis of a small number of genes from the mitochondrial genome (adapted from [79]); similar trees were shown in [5,9,10,24,25,27]. (B) Revised phylogeny, based on large numbers of proteins encoded by the nuclear genome (adapted from [44]); similar trees were shown in [6,45]; proteins encoded by the apicoplast genome yielded the same topology [43]. In both trees, the red branch indicates the inferred move from hosts in Africa to hosts in southeast Asia.

The earliest diverging branch among the relatives of *P. vivax* is that of *P. gonderi* (Figure 2), a parasite that infects monkeys in Africa. Thus, it is now clear that the ancestral lineage leading to *P. vivax* need never have left Africa, and that the ancestor of the southeast Asian clade most likely migrated to Asia after its divergence from the common ancestor of *P. vivax*, *P. vivax*-like and *P. carteri* (Figures 2B and 3); this move to Asia may have been with the ancestor of the current Asian macaque species, around 4–5 million years ago [46].

Trends in Parasitology

CellPress

Review

Plasmodium malariae: the persisting mysteries of a persistent parasite

Richard Culleton [1,2], Arnab Pain [3] and Georges Snounou [4,*]

The vexed question of dormancy

The longevity of *Plasmodium* infections is not novel per se, as the parasites have often been found to persist throughout the life of their animal natural hosts. The longevity of *P. vivax* infections is ascribed to the activation of persisting dormant liver stages, hypnozoites, that also occur in a few other species (*P. ovale*, and *Plasmodium cynomolgi*, *Plasmodium fieldi*, and *Plasmodium simiovale* in macaques). The persistence of *P. malariae* over many years, and that of *P. falciparum* [40], is ascribed to continued erythrocytic parasite multiplication since neither species is considered to produce hypnozoites, based on the fact that relapses are not observed in sporozoite-induced *P. falciparum* or *P. malariae* sporozoite infections following chemotherapeutic clearance of the primary episode. However, a recent report of a traveller treated successfully for *P. falciparum* in Germany, who then experienced a *P. malariae* episode 4 months later, led the authors to propose the existence of *P. malariae* hypnozoites [14]. Similar cases of such late recurrences of *P. malariae* a few months after return to Germany despite adequate prophylaxis had been reported [41–43], prompting the authors to re-evaluate the question of dormant stages in *P. malariae*.

Plasmodium malariae Infection in an Asymptomatic 74-Year-Old Greek Woman with Splenomegaly

Joseph M. Vinetz, M.D., Jun Li, M.D., Ph.D., Thomas F. McCutchan, Ph.D., and David C. Kaslow, M.D.

February 5, 1998

We report a case of malaria due to *P. malariae* in a 74-year-old woman from Greece whose illness was reactivated after decades of latency. All manifestations were reversed with a three-day course of chloroquine. Although thick and thin peripheral-blood smears were repeatedly negative, a nucleic acid–based assay detected the infecting species of malaria parasite. Since malaria was eradicated from Greece by about 1950, the patient's infection most likely lasted more than 40 years, possibly as long as 70. Symptoms of malaria began after asymptomatic splenomegaly was mistaken for lymphoma and she was treated with methotrexate. The fevers were in a quartan pattern (recurring every 72 hours). As Hippocrates wrote, "The least dangerous of all [fevers], and the mildest and most protracted, is the quartan."[5]

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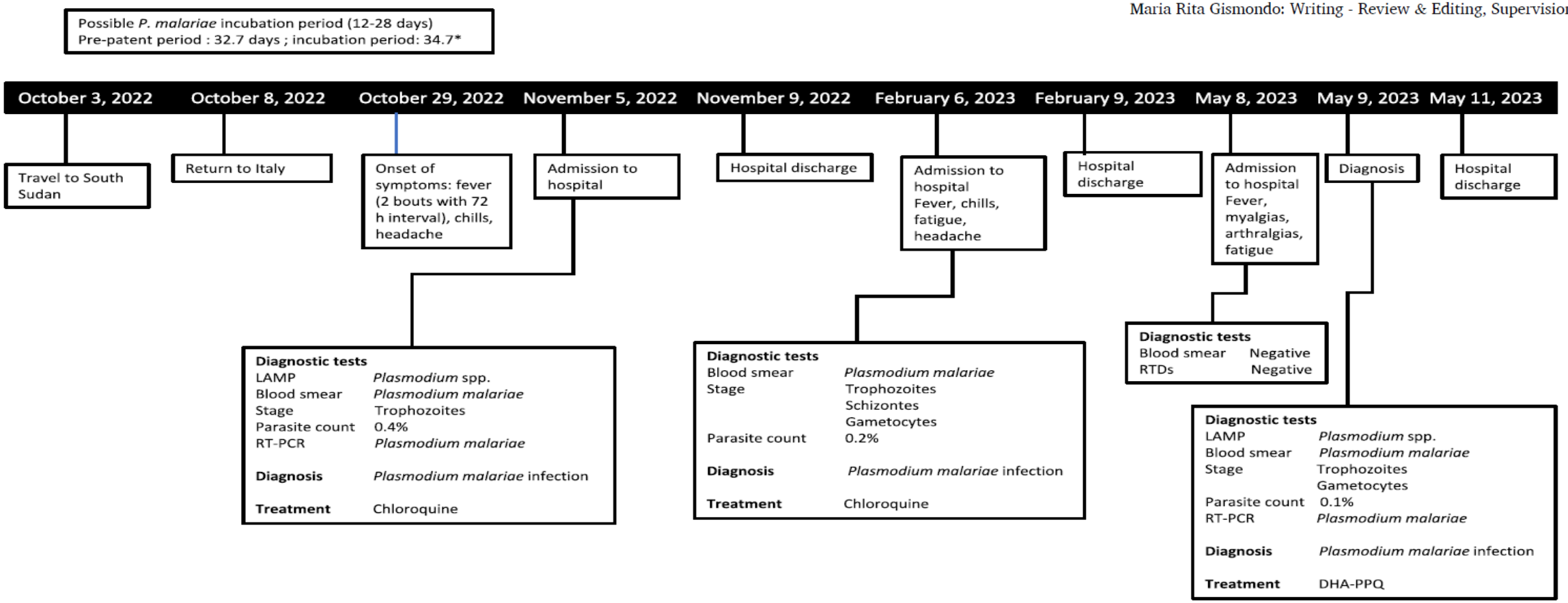
Multiple episodes of *Plasmodium malariae* despite antimalarial treatment: "Quartana te teneat"?



The two parasite species formerly known as *Plasmodium ovale*

Georges Snounou [1,*] Paul M. Sharp [2] and Richard Culleton [3,*]

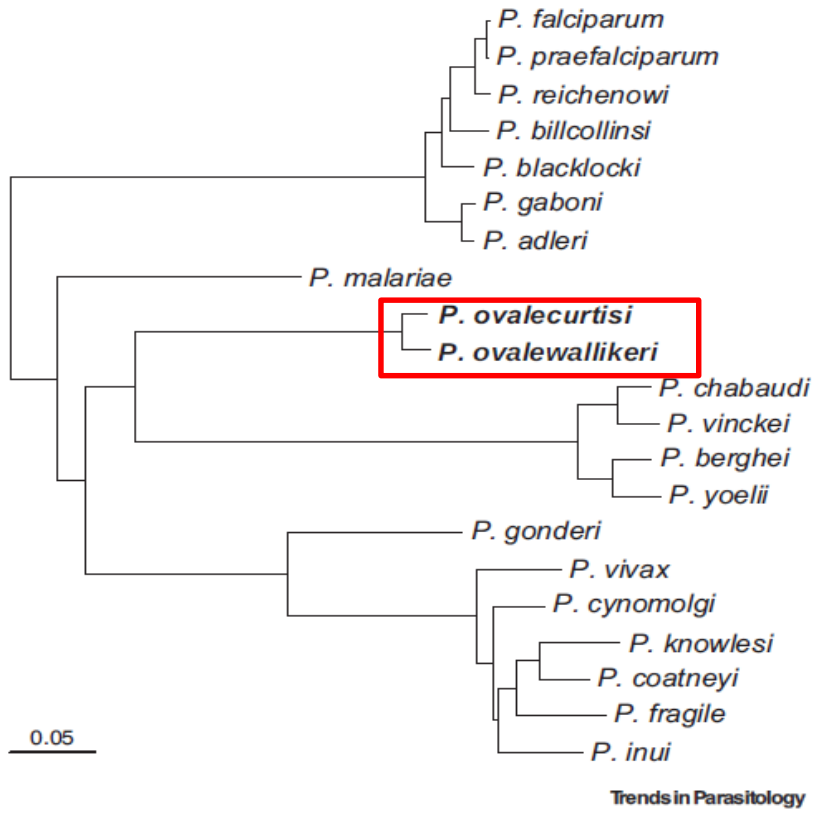


Figure 1. Evolutionary relationships among mammalian *Plasmodium* species. Horizontal branch lengths are drawn to scale, indicating that *Plasmodium ovalecurtisi* and *Plasmodium ovalewallikeri* are more divergent than, for example, *Plasmodium gaboni* (a chimpanzee parasite) and *Plasmodium adleri* (a gorilla parasite), or *Plasmodium falciparum*/*Plasmodium praefalciparum* (from humans and gorillas, respectively), and *Plasmodium reichenowi* (from chimpanzees). The phylogeny was derived from analyses of more than 2700 proteins encoded by the nuclear genome. The scale bar indicates 0.05 amino acid replacements per site. Adapted from [50].

There is some recent, though tentative, evidence to suggest that the latency period of the two species may differ, with several reports documenting a significantly longer latency period for *P. ovale curtisi* than *P. ovale wallikeri* [30–34], although others have found no differences [35]. A meta-analysis considering these and other reports suggested agreement with the former of these two possibilities [36]. Studies on *P. ovale* spp. infections imported into Spain suggested that there was an increased number of parasites per µl of blood in *P. ovale curtisi* infections compared to those of *P. ovale wallikeri*, and that this was associated with higher leucocyte and platelet counts in patients infected with the former species [30,31]. However, numerous other reports do not support this particular finding [37–42]. In terms of prevalence and distribution, the two species do not differ greatly, but it appears that *P. ovale curtisi* may be the more common of the two [36]. To date, nothing is known regarding potential differences between the species relating to their development in mosquitoes.

Nomenclature

The names *P. ovale curtisi* and *P. ovale wallikeri* have been widely used by the malaria research community, despite the taxonomic discrepancy of trinomials, normally used for subspecies, being used for full species. Understandably, this has led to much confusion regarding the status of these parasites, with numerous reports referring to them as 'subspecies'. We have compiled a list of more than 70 peer-reviewed papers published since 2010, in which the two species are referred to as subspecies (see Box S1 in the supplemental information online), as well as additional publications that include the correct species designation at one point but also refer to the two as subspecies elsewhere in the paper (see Box S2 in the supplemental information online).

Trends in
Parasitology

Letter

Calling them names: variants of *Plasmodium ovale*

Jan Šlapeta [1,*]
Colin J. Sutherland [2] and
Hans-Peter Fuehrer [3]

We have read with great interest the opinion by Snounou *et al.* [1] with regard to 'Plasmodium ovalecurtisi' and 'Plasmodium ovalewallikeri' for what represents two cryptic species within *Plasmodium ovale* Stephens, 1922. These authors are correct to highlight the inadequacy of current nomenclature for these malaria parasites. However, it is essential to note that both names, as proposed [1], represent *nomina nuda*, constituting an error within the framework of zoological nomenclature.

The name *Plasmodium ovale* Stephens, 1922 is undisputed

In the context of *P. ovale*, the type consists of blood stages described by Stephens in 1922 [3]. The index case of ovale malaria was a British army private J. [18S817], returning to the UK in 1918 following deployment in 'East Africa', and having reported an episode of symptomatic malaria in December, 1916 [3]. The actual blood smears, the type itself, are either lost or inaccessible. Despite this, the naming of *P. ovale* adheres to all requirements, fulfilling the nomenclature, and thus, the name *P. ovale* Stephens, 1922 remains available for perpetuity. Initially, subjective taxonomy raised questions, but over subsequent decades, *P. ovale* firmly established itself as the fourth species infecting humans, alongside *P. falciparum*, *P. vivax*, and *P. malariae*. While the identity of *P. ovale* remains undisputed, its taxonomy began to undergo erosion when Li *et al.* [4] compared the 18S rRNA of two isolates. Informal genotypes, termed 'classic' and 'variant', were recognized by Win *et al.* [5].

3. Stephens, J.W.W. (1922) A new malaria parasite of man. *Ann. Trop. Med. Parasitol.* 16, 383–388
4. Li, J. *et al.* (1995) *Plasmodium*: genus-conserved primers for species identification and quantitation. *Exp. Parasitol.* 81, 182–190
5. Win, T.T. *et al.* (2004) Molecular analysis of *Plasmodium ovale* variants. *Emerg. Infect. Dis.* 10, 1235–1240
6. Sutherland, C.J. *et al.* (2010) Two nonrecombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. *J. Infect. Dis.* 201, 1544–1550

The two species referred to as *P. ovale* Stephens, 1922 are identical in both morphology and clinical presentation, although they display contrasting latency periods [7,8]. The consensus in the field – that the species differ – is based on sequence dimorphism at all loci examined and an apparent lack of recombination between the dimorphs [6,9,10][ii]. Unfortunately, the type is either missing or inaccessible for additional analysis, making genetic confirmation of the correct dimorph to assign to Stephens' name the crucial missing element in resolving this puzzle.

Box 1. How do we get out of the rabbit hole?

Step 1

The name *P. ovale* Stephens, 1922 has to be retained and cannot be ignored, but we cannot be certain which of the two species recognized since 2010 is represented in the illustration by Stephens [3]. The only solution here is to select a 'neotype' – a new name-bearing type that will be the international reference.

The neotype will comprise a blood smear with *P. ovale*-parasitized erythrocytes of East African origin, photographed, with coordinates of representative infected erythrocytes identified, and the slide deposited in a reputable museum where an accession number can be obtained. DNA sequence data from the parasite isolate represented on the blood film are deposited and accessioned. The DNA sequence obtained will preferably match the 'classic' type according to Win *et al.* [5]. This would most logically allude to the classic nature of the name *P. ovale*.

Step 2

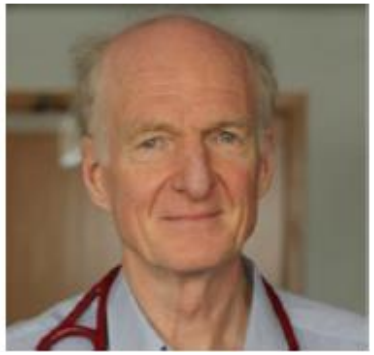
To deal with the 'variant' type according to Win *et al.* [5], we can be rather certain that there is no name introduced correctly according to the ICZN, so we can choose a new name. Before one does that, a blood smear with parasites that appear morphologically identical to *P. ovale* is produced but with accompanying DNA sequence data that matches the 'variant' type. The choice of the name is up to the submitting authors to make the final call. Utility for the malaria community must be carefully considered to ensure that an acceptable and well-recognizable name is chosen.

Step 3

The ultimate stage is to action the nomenclatural act itself by publishing the 'neotype' designation for *P. ovale* and the proposed new name for the other species (informally labelled as *P. ovale* wallikeri – the 'variant' type).

Artemisinin-resistant malaria

N. J. White,[1,2] K. Chotivanich[1,3]



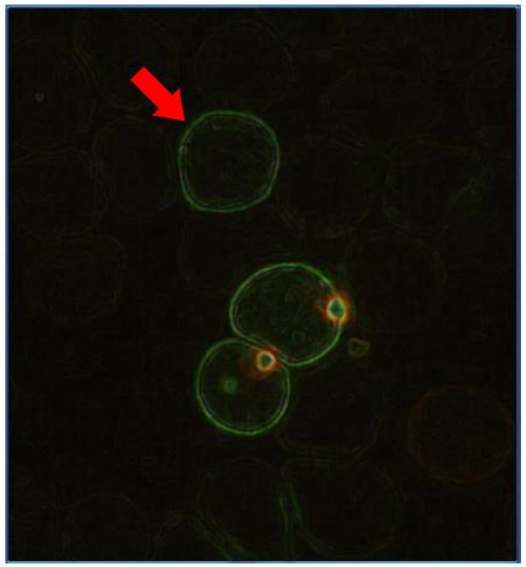
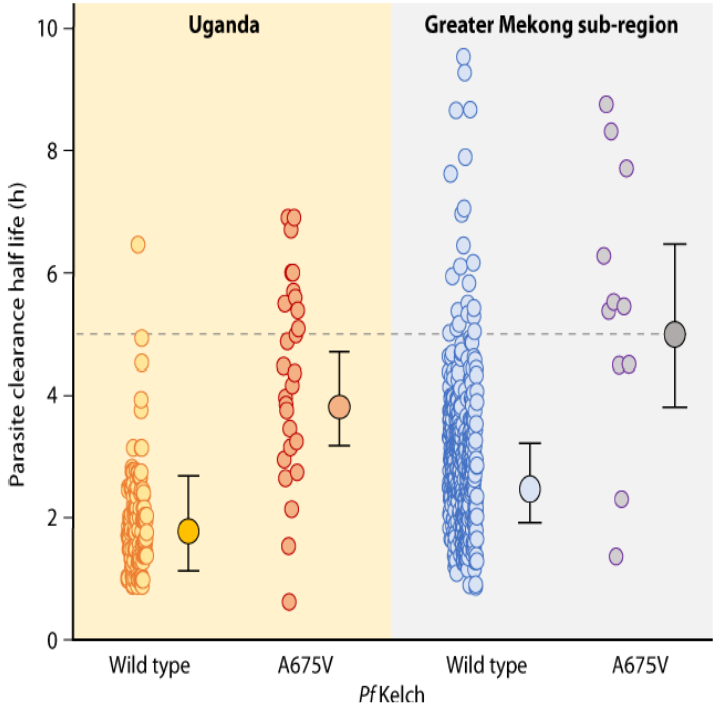


FIG 1 Immunofluorescent labeling of ring erythrocyte surface antigen stained red cells in acute malar In artemisinin-sensitive infections, the ring form parasites are killed by artemisinin drugs and t once-infected erythrocytes (red arrow) are returned to the circulation (19, 20), where they have shorten survival (21). In artemisinin-resistant infections, ring stage susceptibility is lost and this process, call pitting, is markedly reduced.



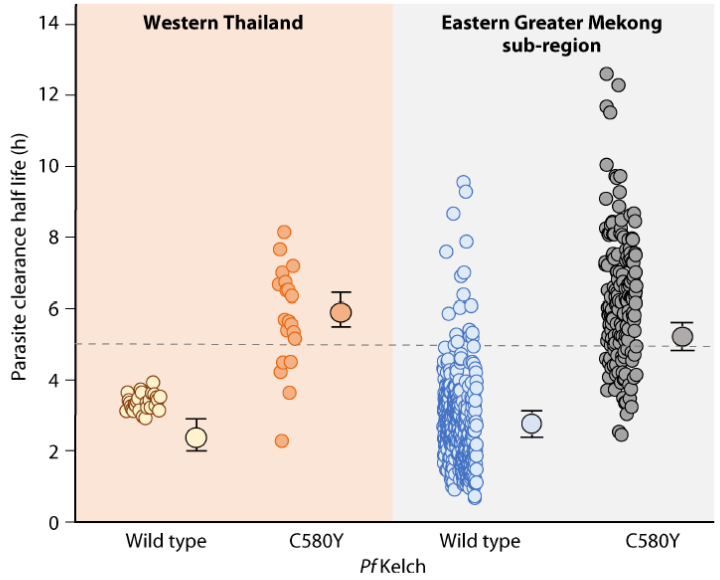
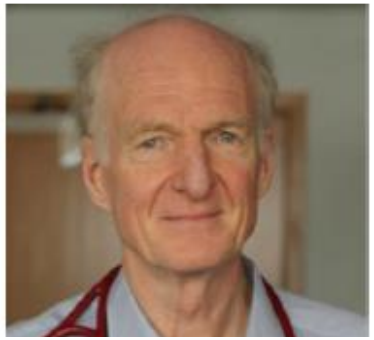


FIG 6 A comparison of parasitological responses in *Pf*Kelch wild-type and C580Y mutant infections. Geometric mean (95% CI) parasite clearance half-lives on the western border of Thailand and in the eastern GMS (34) following artesunate treatment of acute falciparum malaria. The C580Y mutation arose independently in the two locations.

Artemisinin-resistant malaria

N. J. White,[1,2] K. Chotivanich[1,3]



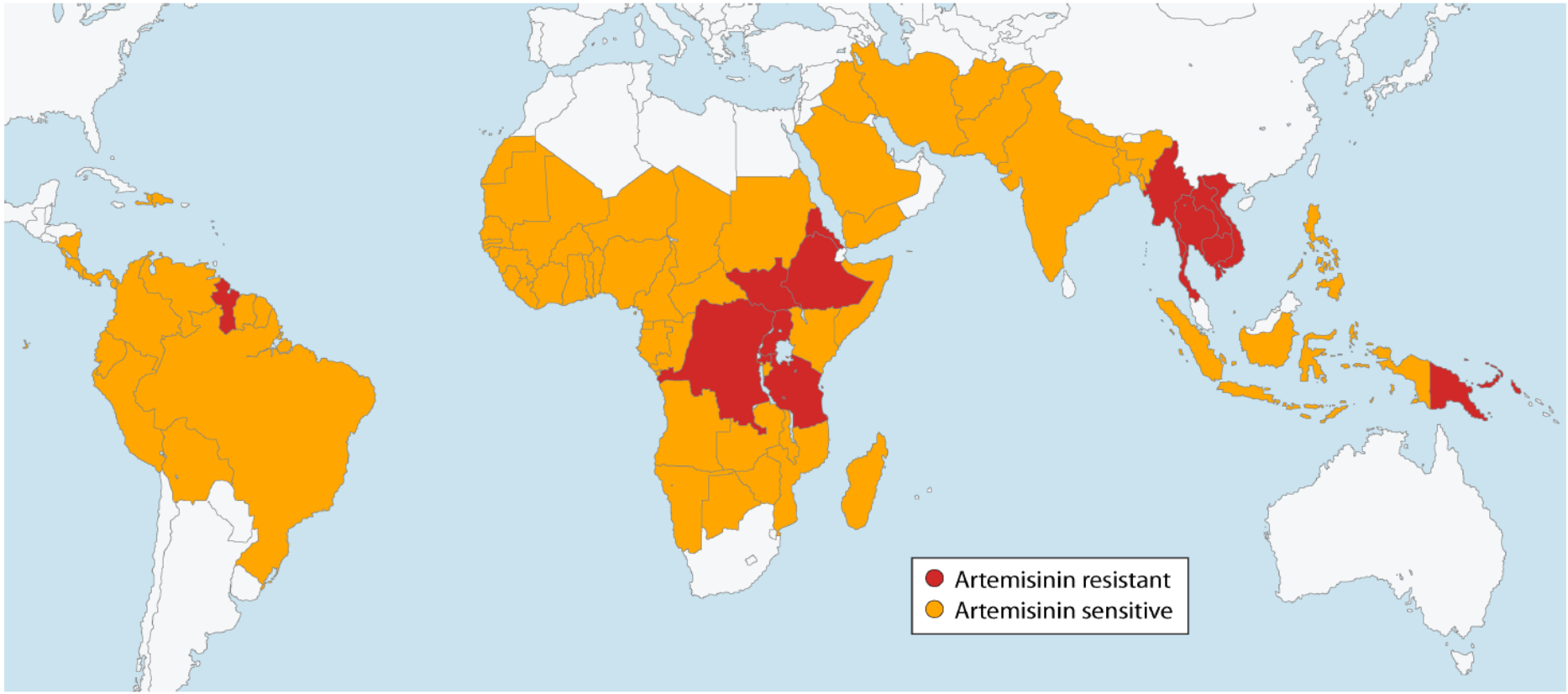


FIG 7 Countries with endogenous *P. falciparum* malaria that have reported artemisinin resistance (as of June 2024).

The emergence of artemisinin partial resistance in Africa: how do we respond?

Philip J Rosenthal, Victor Asua, Jeffrey A Bailey, Melissa D Conrad, Deus S Ishengoma, Moses R Kamya, Charlotte Rasmussen, Fitsum G Tadesse, Aline Uwimana, David A Fidock

	WHO resistance marker status	Principal countries	Clinical evidence	In vitro evidence	
				Field samples	Transfected parasites
Pro441Leu	Candidate	Uganda	No	No	No
Cys469Phe	Candidate	Uganda	No	Yes	No
Cys469Tyr	Validated	Uganda	Yes	Yes	Yes
Arg561His	Validated	Rwanda, Tanzania, and Uganda	Yes	Yes	Yes
Arg622Ile	Validated	Eritrea and Ethiopia	Yes	No	Yes
Ala675Val	Validated	Uganda	Yes	Yes	Yes

Table: **Principal K13 mutations in Africa and evidence for their association with ART-R**

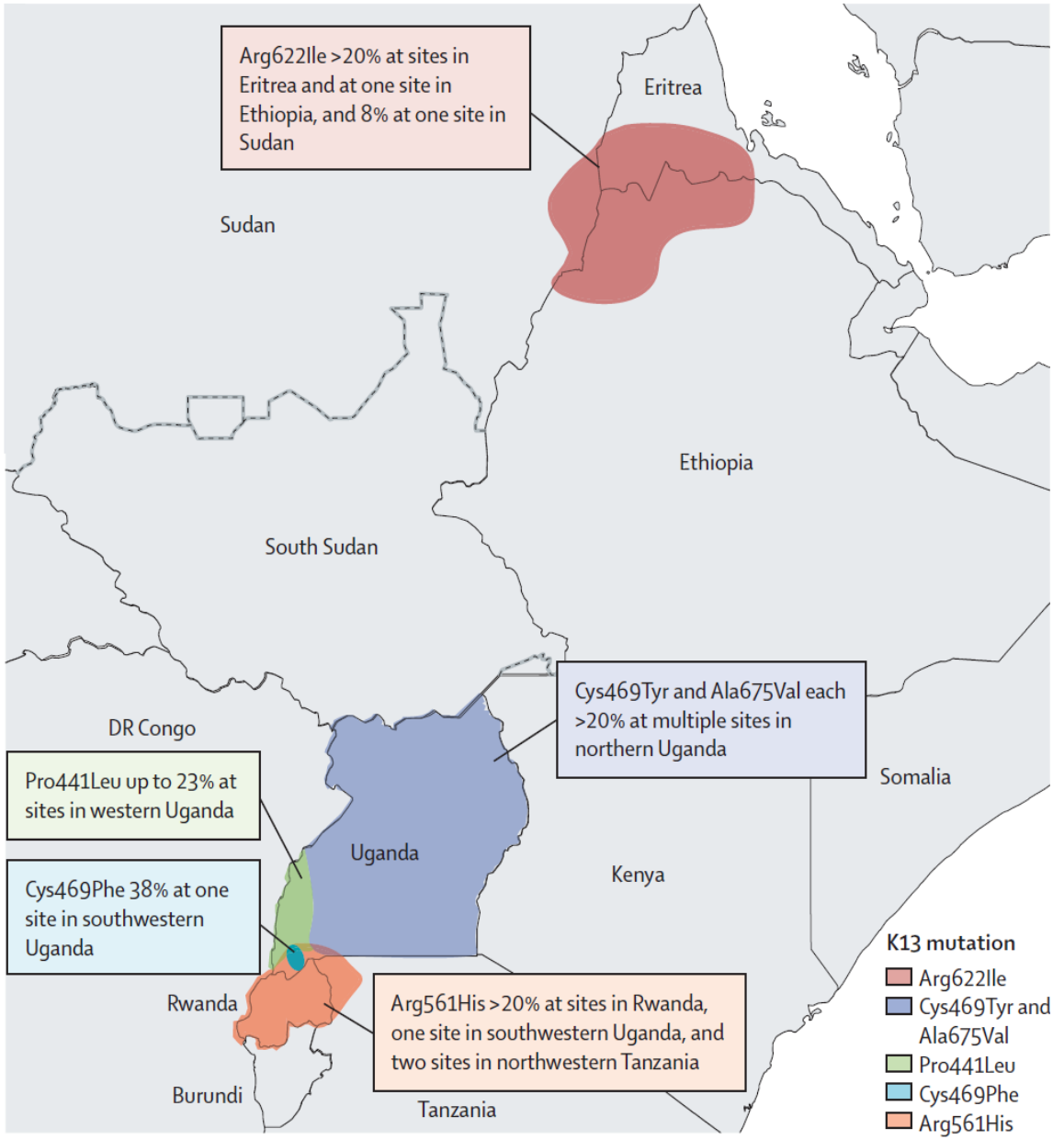
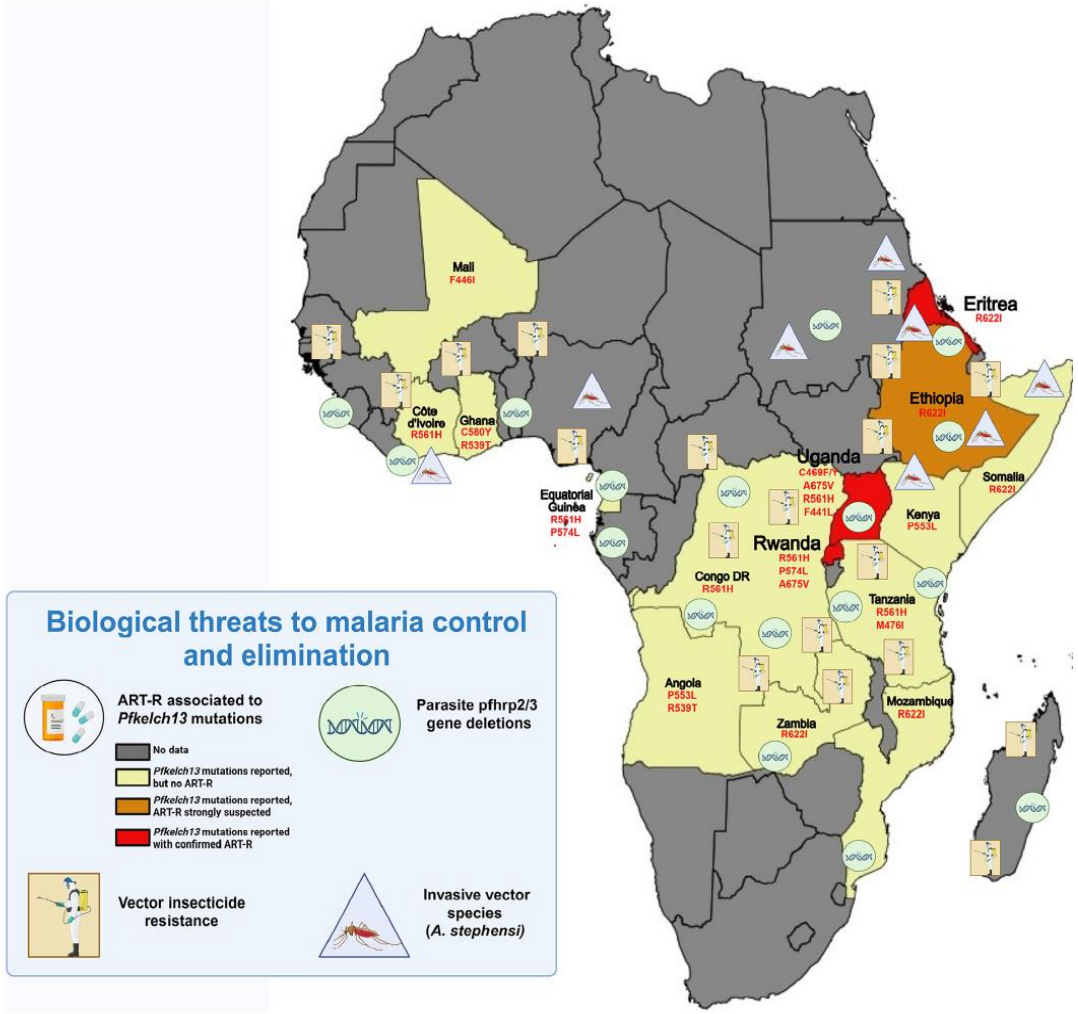


Figure 2: **Areas with established prevalence (>5%) of the indicated validated and candidate K13 mutations associated with ART-R**

The prevalence of the mutations in individuals presenting with malaria or from cross-sectional surveys is shown. Sporadic identification and low prevalences of some of these mutations have been observed in other regions.



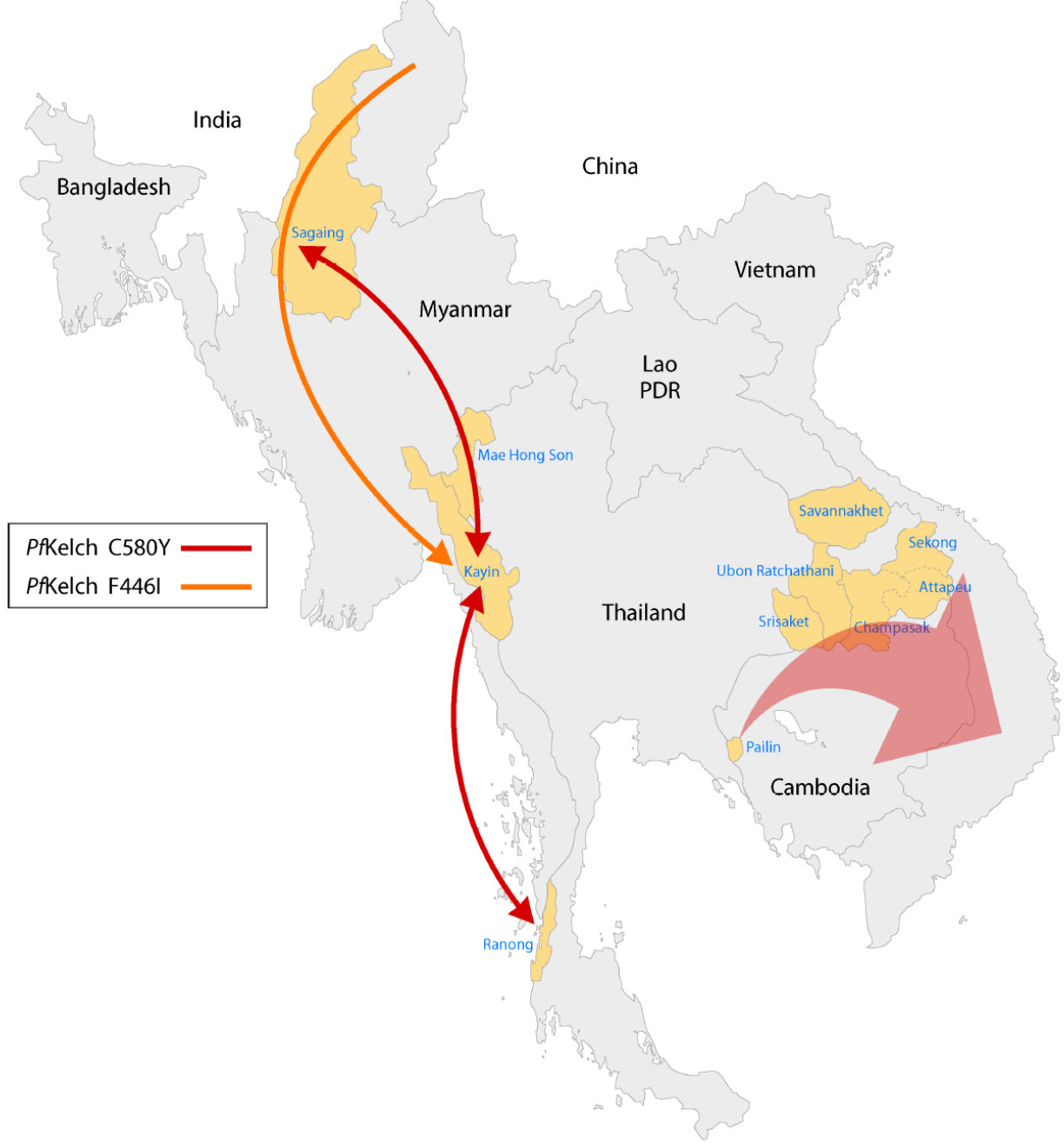


FIGURE 2 **Geographical distribution of malaria-associated biological threats in Africa.** The four malaria-associated biological

3 Transnational spread of artemisinin-resistant *P. falciparum* lineages in the GMS in the previous decade (42, 119). The yellow areas and associated names are provinces from where the genotyped parasites were obtained.

Jejaw Zeleke *et al. Malaria Journal* (2022) 21:26
https://doi.org/10.1186/s12936-022-04051-7

Malaria Journal

RESEARCH Open Access

Plasmodium falciparum histidine-rich protein 2 and 3 genes deletion in global settings (2010–2021): a systematic review and meta-analysis

Ayalew Jejaw Zeleke[1*], Asrat Hailu[1,2], Abebe Genetu Bayih[1,3], Migbaru Kefale[3], Ashenafi Tazebew Amare[4], Yalewayker Tegegne[1] and Mulugeta Aemero[1]

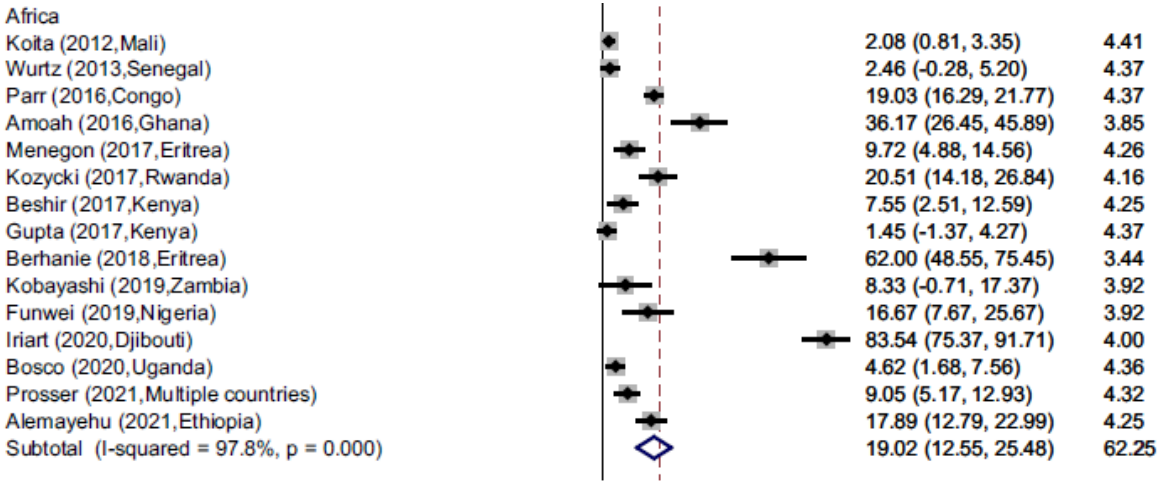
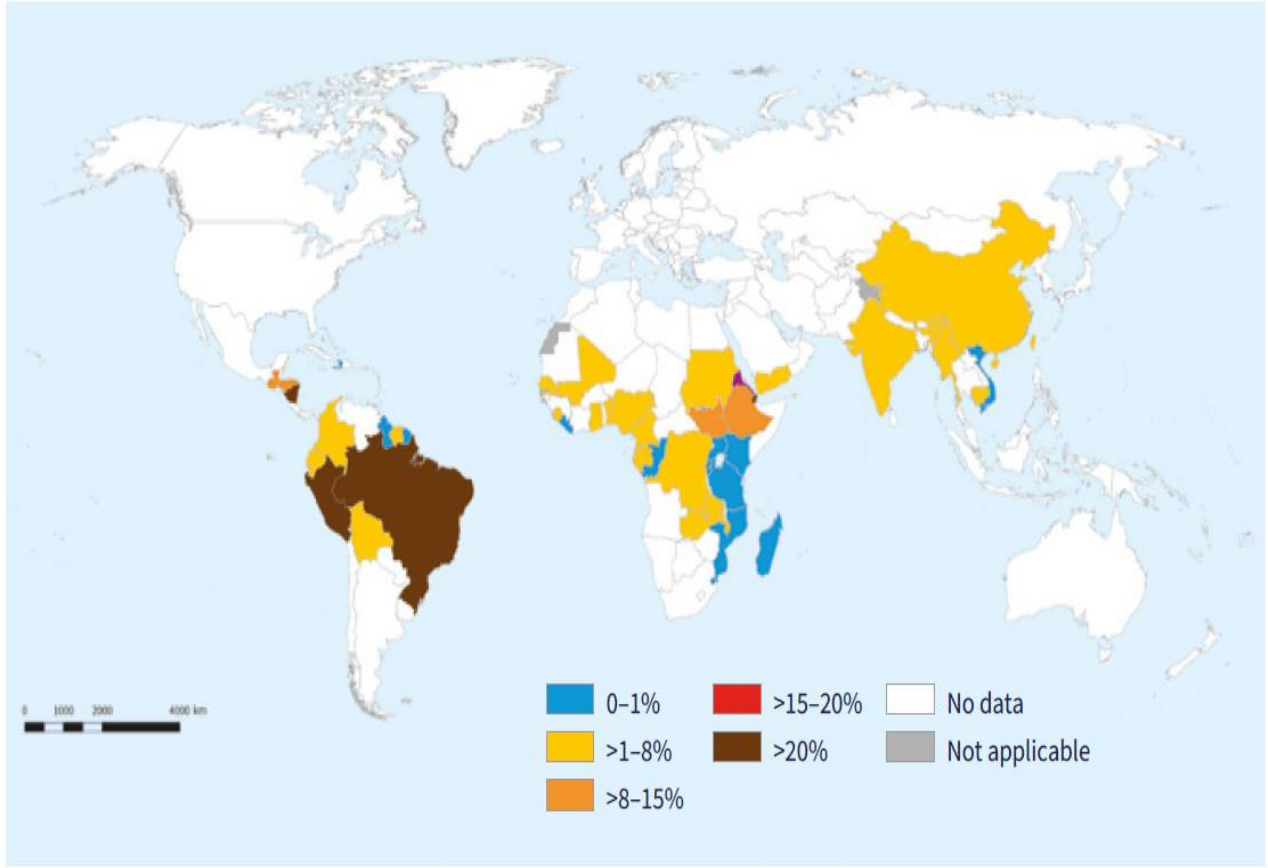


Fig. 9.1.

Estimated prevalence of *Pfhrp2* gene deletions, 2022 *Source: Review of published literature included in the Malaria Threats Map (52).*



Clinical Infectious Diseases

INVITED COMMENTARY

Have You Heard the News? Artemether-lumefantrine is Now Recommended for ALL Uncomplicated Malaria in the United States, Including in Pregnancy

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In late November 2022, following a review of new evidence demonstrating that artemether-lumefantrine is effective and safe in the treatment of malaria in early pregnancy [9], the WHO endorsed artemether-lumefantrine for treatment of uncomplicated malaria during all trimesters of pregnancy. Thus, WHO now recommends ACTs, including artemether-lumefantrine, as the treatment of choice for uncomplicated *Plasmodium falciparum* malaria for all patients (adults, irrespective of pregnancy or breast-feeding, and children, including infants) [10], due to the rapid parasiticidal (parasite killing) action of the artemisinins.

patient data meta-analysis [9]. This publication included 12 cohorts with 34 178 pregnancies, of which 737 were treated with an ACT in first trimester, and 1076 were treated with a non-ACT in first trimester. The risk of adverse pregnancy outcomes (including miscarriage, stillbirth, and major congenital abnormalities) both individually and combined was lower following ACT treatment than non-ACT treatment. Specifically, the risk

Table 1. Considerations for Selecting an Antimalarial Regimen in Pregnancy

Regimen	Adult Dosing	Contraindications	Notes
Chloroquine phosphate or hydroxychloroquine	Loading dose, followed by 3 additional doses at 6, 24, and 48 h Chloroquine phosphate (Aralen): 2 tablets initially (1 gm) followed by 1 tablet (500 mg) at 6, 24, and 48 h Hydroxychloroquine: 4 tablets (800 mg) initially followed by 2 tablets (400 mg) at 6, 24, and 48 h	Can not be used for patients with malaria caused by chloroquine-resistant parasites.	Can exacerbate psoriasis. Both chloroquine and hydroxychloroquine may cause QT prolongation and increased sensitivity to the sun.
Artemether-lumefantrine (Coartem®)	6 doses of 4 adult tablets (250 mg atovaquone and 100 mg proguanil) taken twice daily for 3 d (Day 1: initial dose followed by 2nd dose 8 h later; Days 2 and 3: Doses 12 h apart)	Do not coadminister with strong CYP3A4 inducer such as rifampin, carbamazepine, phenytoin and St. John's wort.	Tablets should be taken with food to improve absorption. If mefloquine was used immediately before treatment, monitor for decreased efficacy and encourage food consumption with medication administration. May cause QT prolongation. Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong QT interval.
Quinine + clindamycin	Quinine sulfate: 2 capsules (648 mg) PO TID × 3 or 7 d PLUS Clindamycin: 20 mg/kg/day po divided TID × 7 d		High rate of adverse effects, in particular cinchonism and gastrointestinal side effects. Quinine may cause QT prolongation.
Mefloquine	2 doses: 3 tablets (750 mg) initially followed by 2 tablets (500 mg) 6 to 12 h later.	Not for use in patients with certain psychiatric disorders, including depression or a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders. Not for use in patients with a seizure disorder.	Mefloquine can be used in all trimesters of pregnancy and during breastfeeding but is recommended only if there are no other suitable options. Mefloquine resistance has been reported among *P. falciparum* in Southeast Asia. May cause QT prolongation. Not recommended for people with cardiac conduction abnormalities.

Abbreviations: *P. falciparum*, *Plasmodium falciparum*; PO, orally; TID, thrice daily.

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