in vivax veritas

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires

ICBMS UMR 5246 - Université Lyon 1 - CNRS - INSA Lyon - CPE Lyon

Malaria Research Unit, Faculté de Médecine, Lyon

Fig. LVIII. — Soldats japonais munis de la moustiquaire réglementaire.

Vivax malaria issues

Reticulocytes

Hypnozoites

Gametocytes

vivax versus falciparum

- Faster sporogonic development (11-12d /12-14d)
- 1/12 vivax infected mosquitos will live at least 1 day as infective – 1/25 falciparum
- Sporogony completed at 16°C (20°C for Pf)
- Ability to relapse
  - Hypnozoites
  - Gametocytes
- Reticulocytes
  - Dyserythropoiesis
  - RBC & IRBC destruction
  - Severe anemia

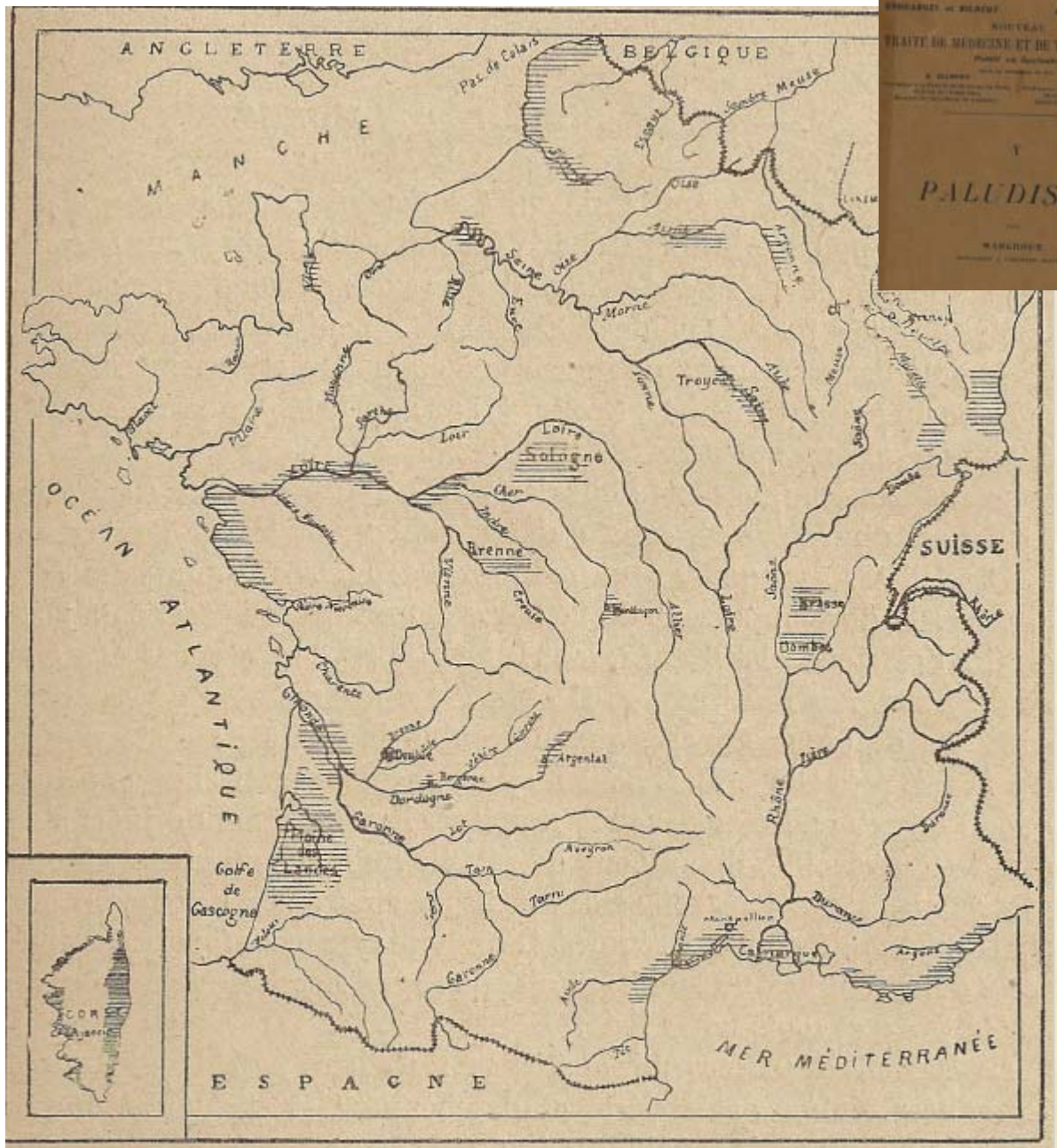


Fig. 129. — Le paludisme en France. En grisé sont indiqués les foyers qui existaient encore au siècle dernier et dont plusieurs se sont réveillés pendant la guerre.

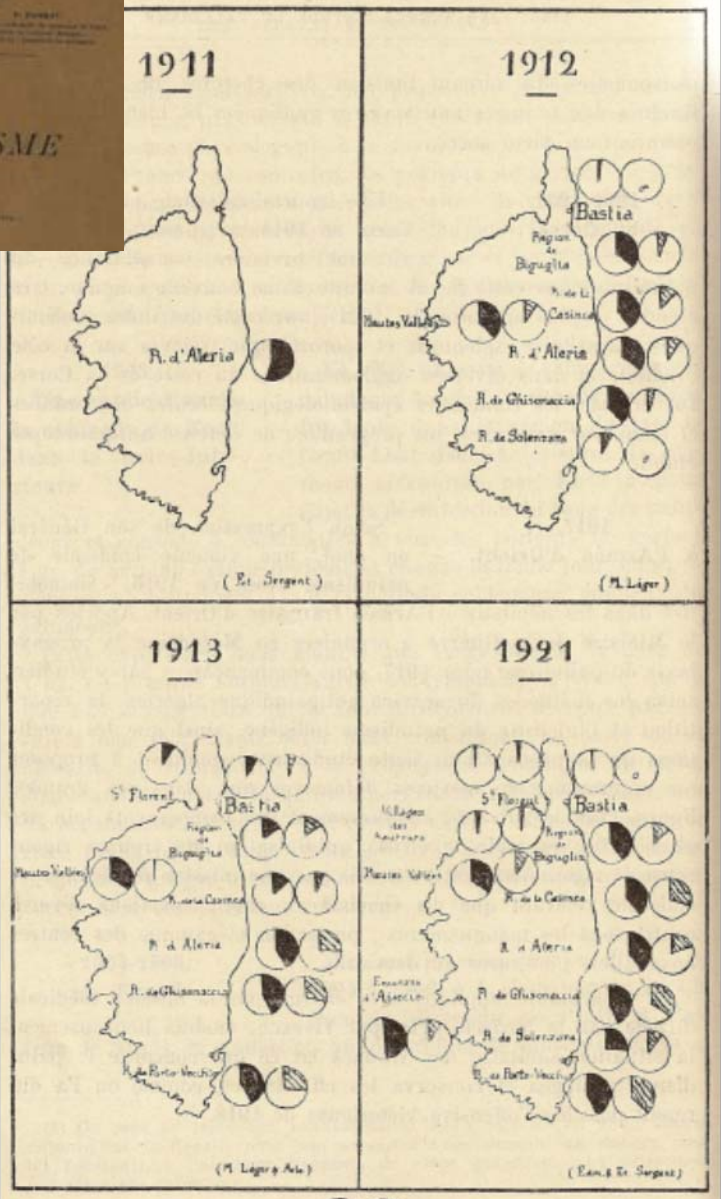


Fig. 7. — Carte du paludisme en Corse d'après l'index splénique et d'après l'index plasmodique, en 1911 (Et. Sergent), 1912 (M. Léger), 1913 (M. Léger et Arlo) et 1921 (Edm. et Et. Sergent).

Arch. Institut . asteur d'Algérie.

1901

Etudes sur les Anophèles des environs de Paris.

En 1901, des recherches effectuées en France nous amenèrent à la constatation suivante : les Anophèles se rencontrent dans certaines localités d'où le paludisme a disparu : vallée de l'Essonne, environs de Paris (bois de Boulogne, Saint-Cloud, Meudon, Clamart, etc.). « L'anophélisme sans paludisme » existait donc en France et la question se posait : pourquoi de deux

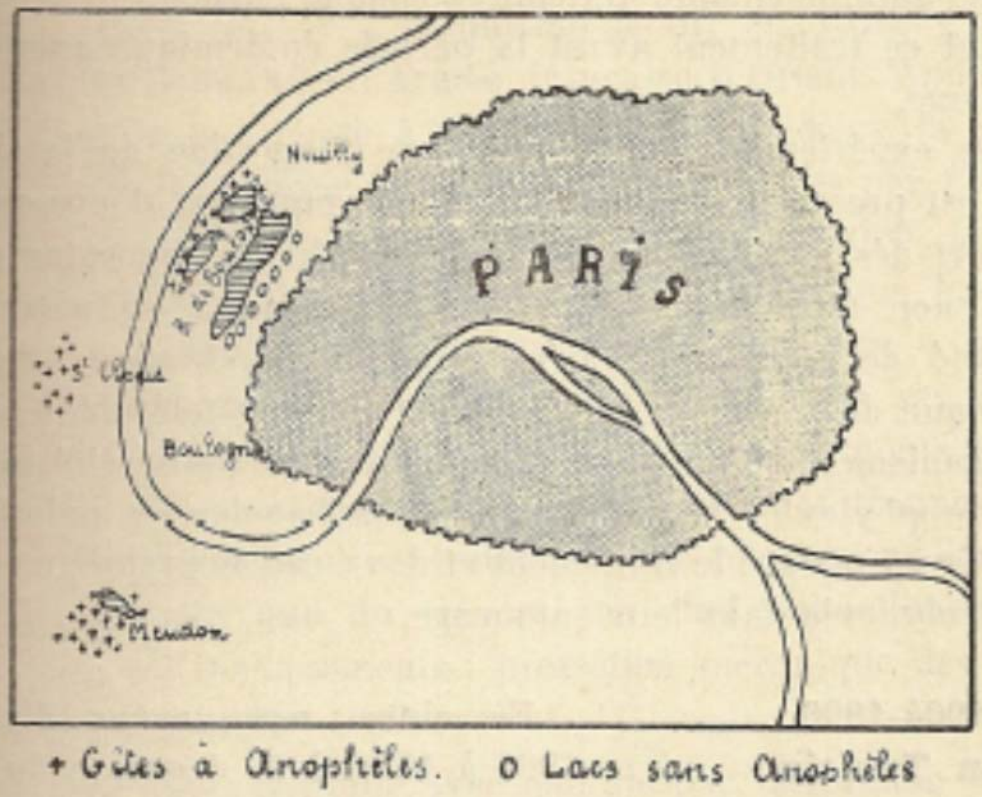


Fig. 6. — Gîtes à Anophèles des environs de Paris.

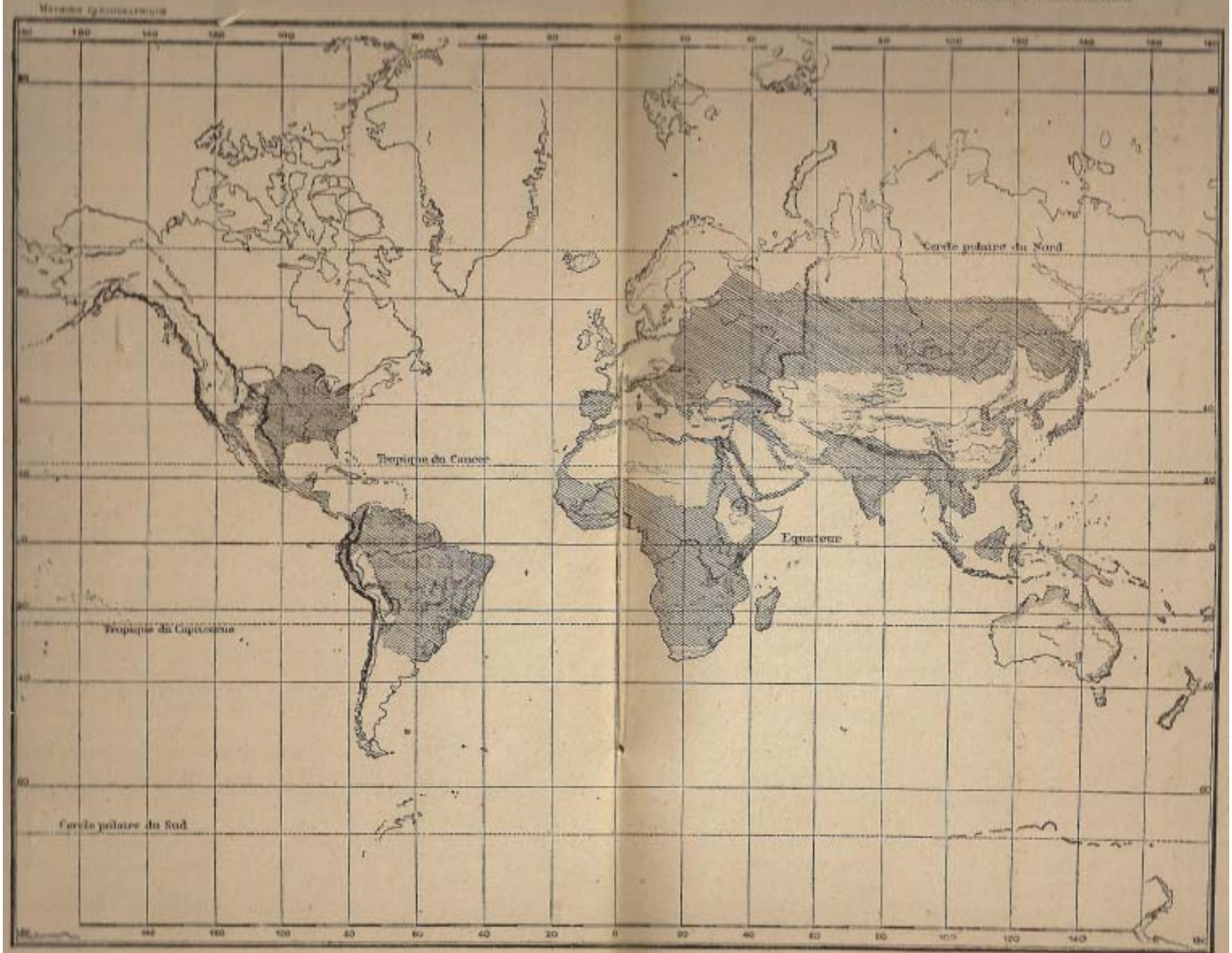
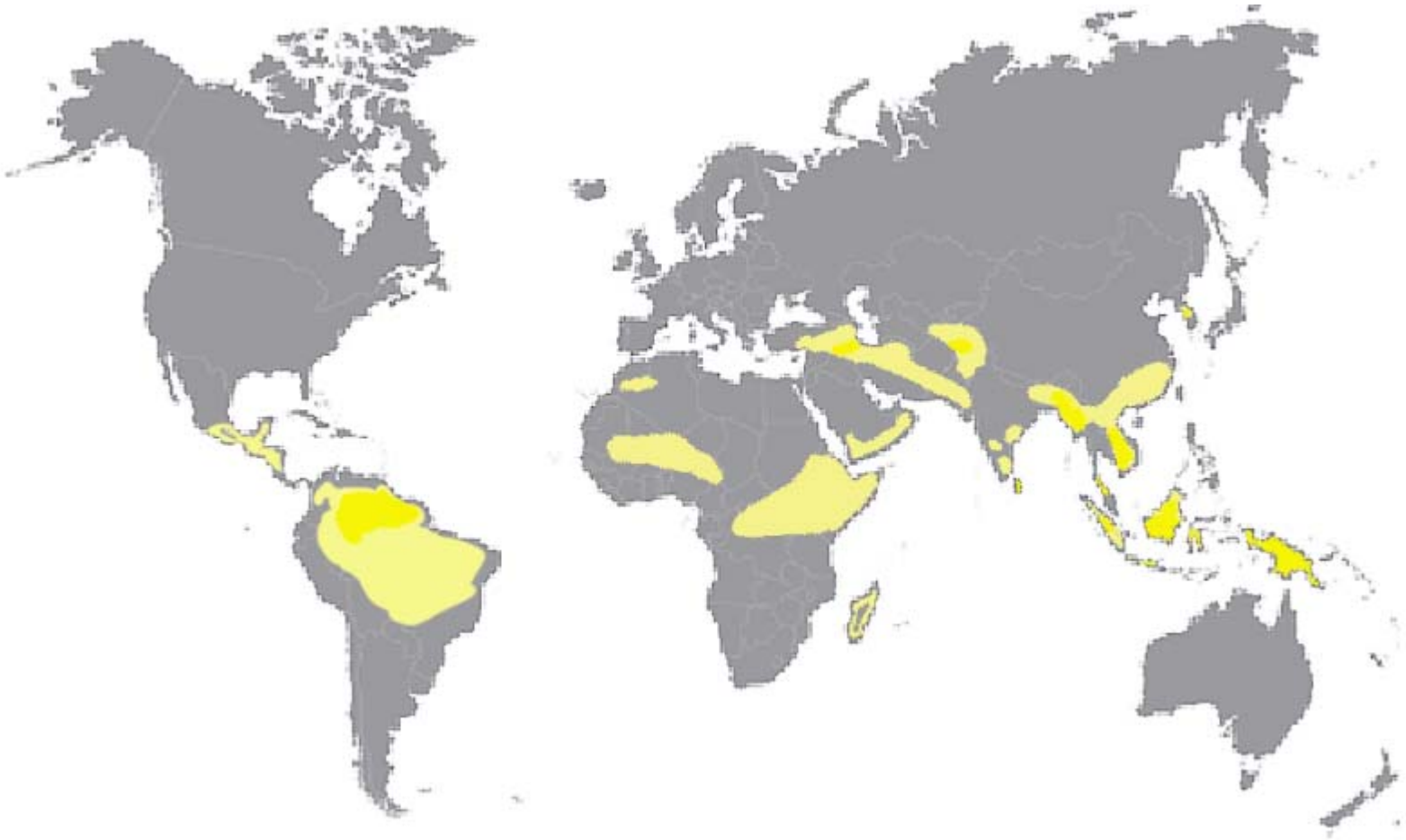


Fig. 128. — Distribution du paludisme dans le monde.

Vivax malaria



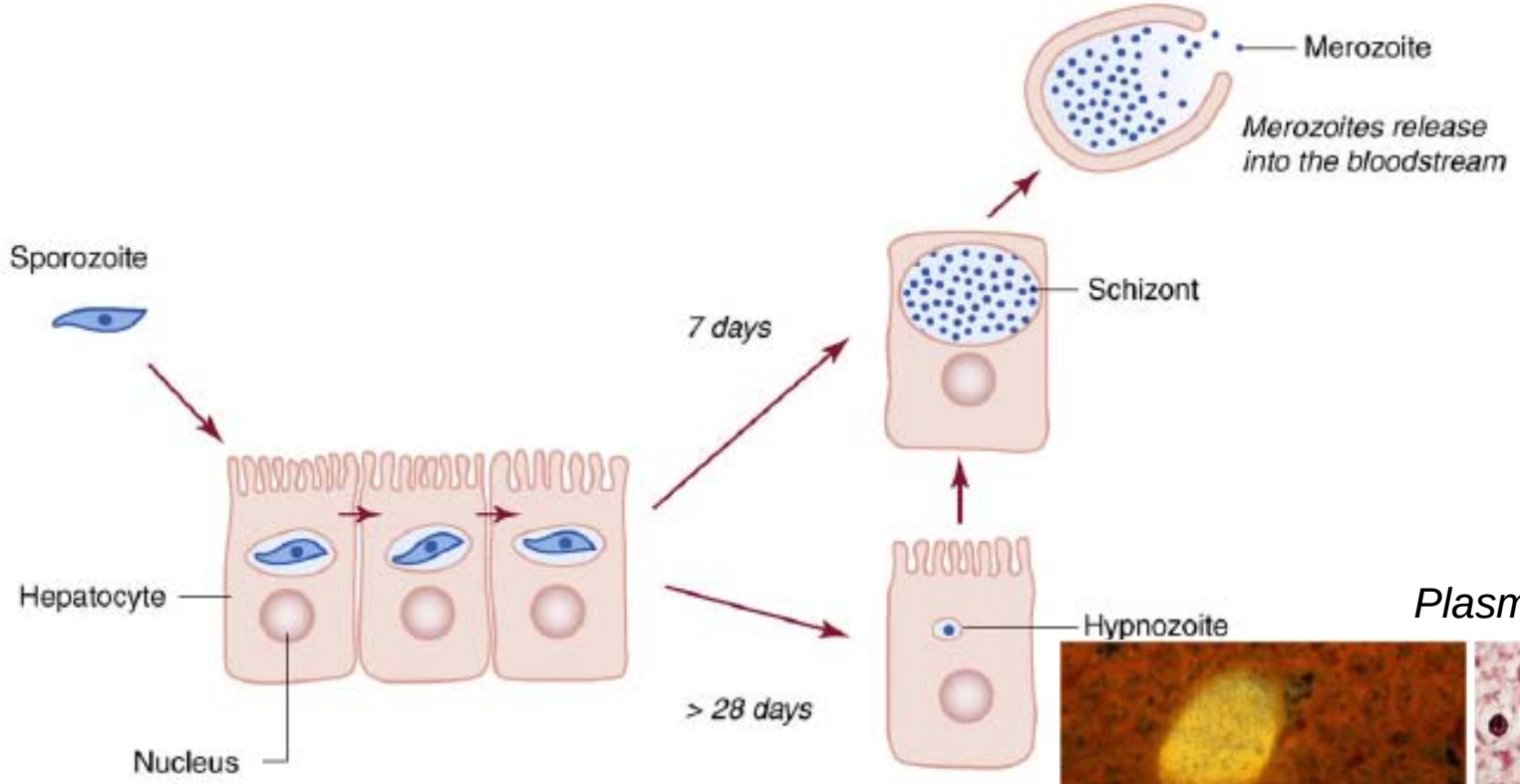
hypothesis

- Pv originated in Africa (FYB^{SE}/FYB^{SE})
  - FYB^{SE} : silent erythroid (FyO phenotype)
  - Drove Duffy negative allele to fixation
  - Disappeared from Africa

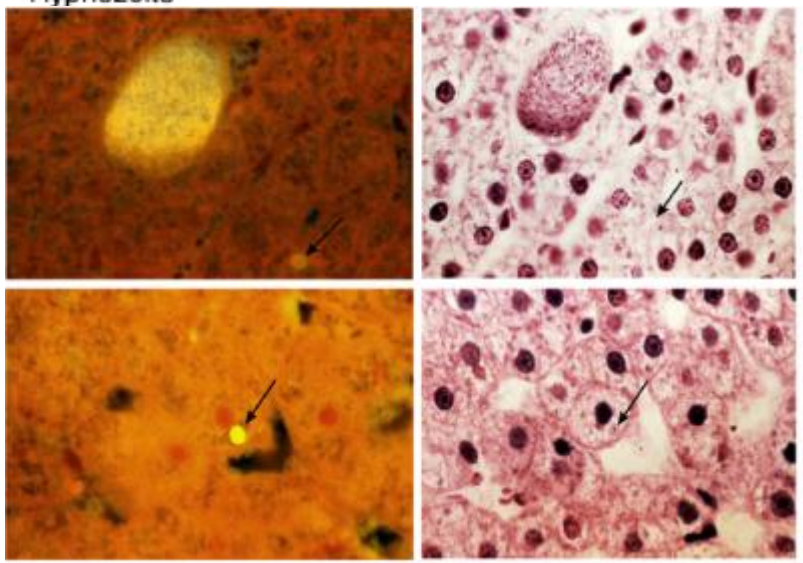
- Implausibility for a non-lethal pathogen having profound selective effect
  - Duffy is a chemokine receptor that could be a target for other, unidentified, selective pressures
- Pv originated in Asia (FYB/FYB)
- Is Pv adaptating to Duffy negative ?

Hypnozoites : hypno-thesis?

- Dormozoites: Dormant form of cystoisospora (Isospora)
  - Miles Markus, TRSTMH, 1976
- Extrapolation to malaria:
  - M. Markus, South African Journal of Sciences, 1978, 75-220
- Hypnozoites: PCC Garnham
- Discovery of two populations of exoerythrocytic stages. Preliminary notes
  - Wojciech Krotowski, British Medical Journal 1980, 1:153-154
- Hypnozoites / chronozoites of *Plasmodium sasai* (lizard)
  - Telford 1989



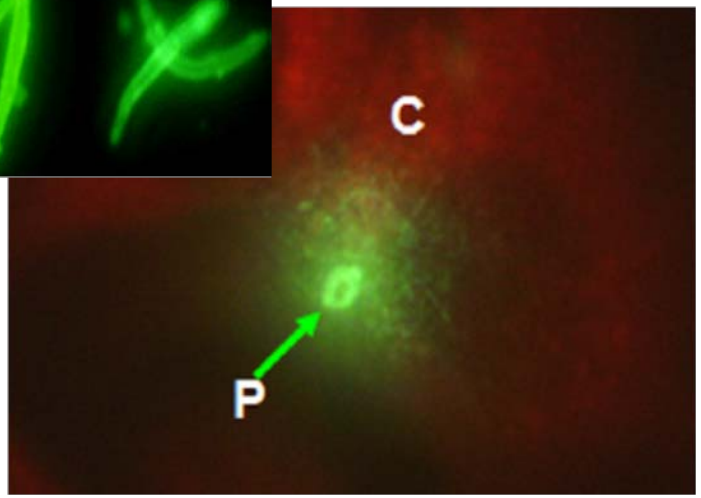
Plasmodium cynomolgi

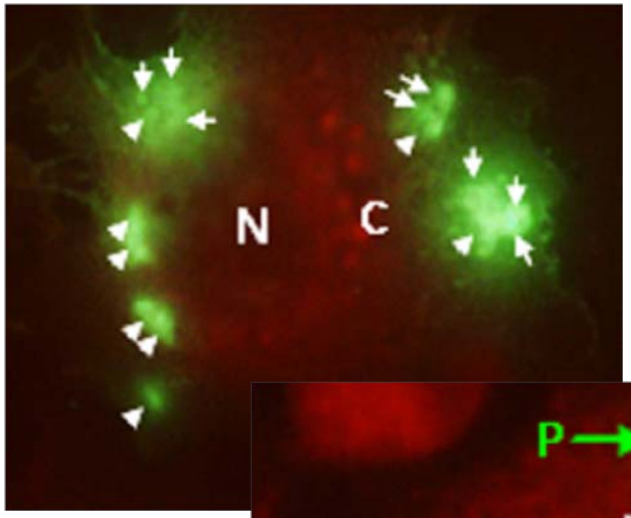


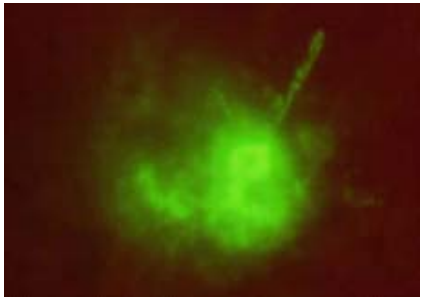
Targeting the hypnozoite reservoir of *Plasmodium vivax*: the hidden obstacle to malaria elimination

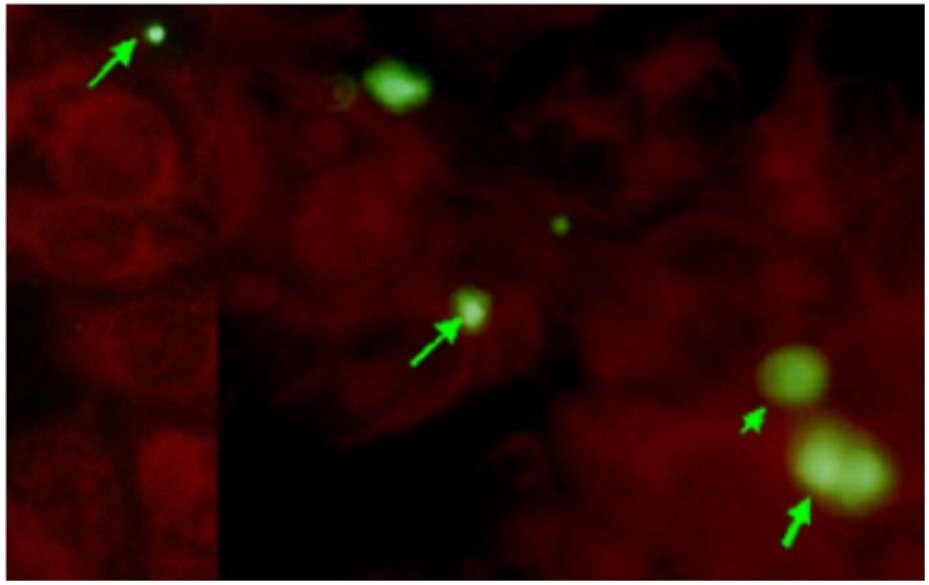
Timothy N.C. Wells[1], Jeremy N. Burrows[1] and J. Kevin Baird[2,3]

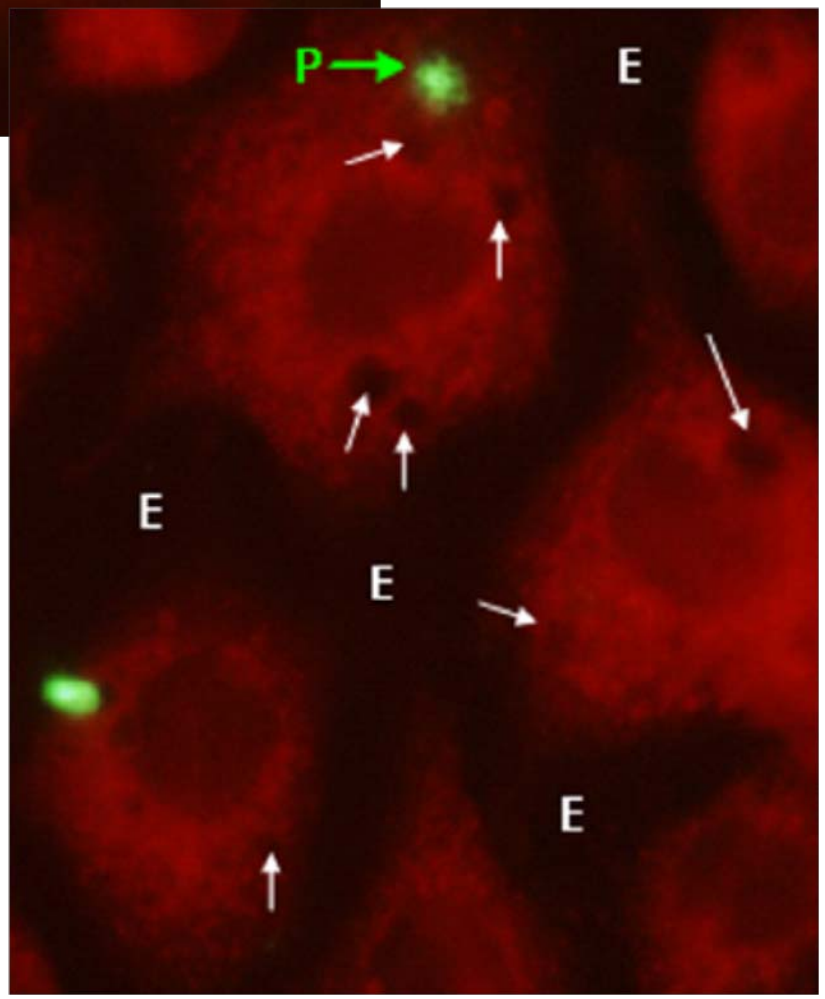
Krotowski, W.A. *et al.* (1982) Observations on early and late post-sporozoite tissue stages in primate malaria. *Am. J. Trop. Med. Hyg.* 31, 211–225





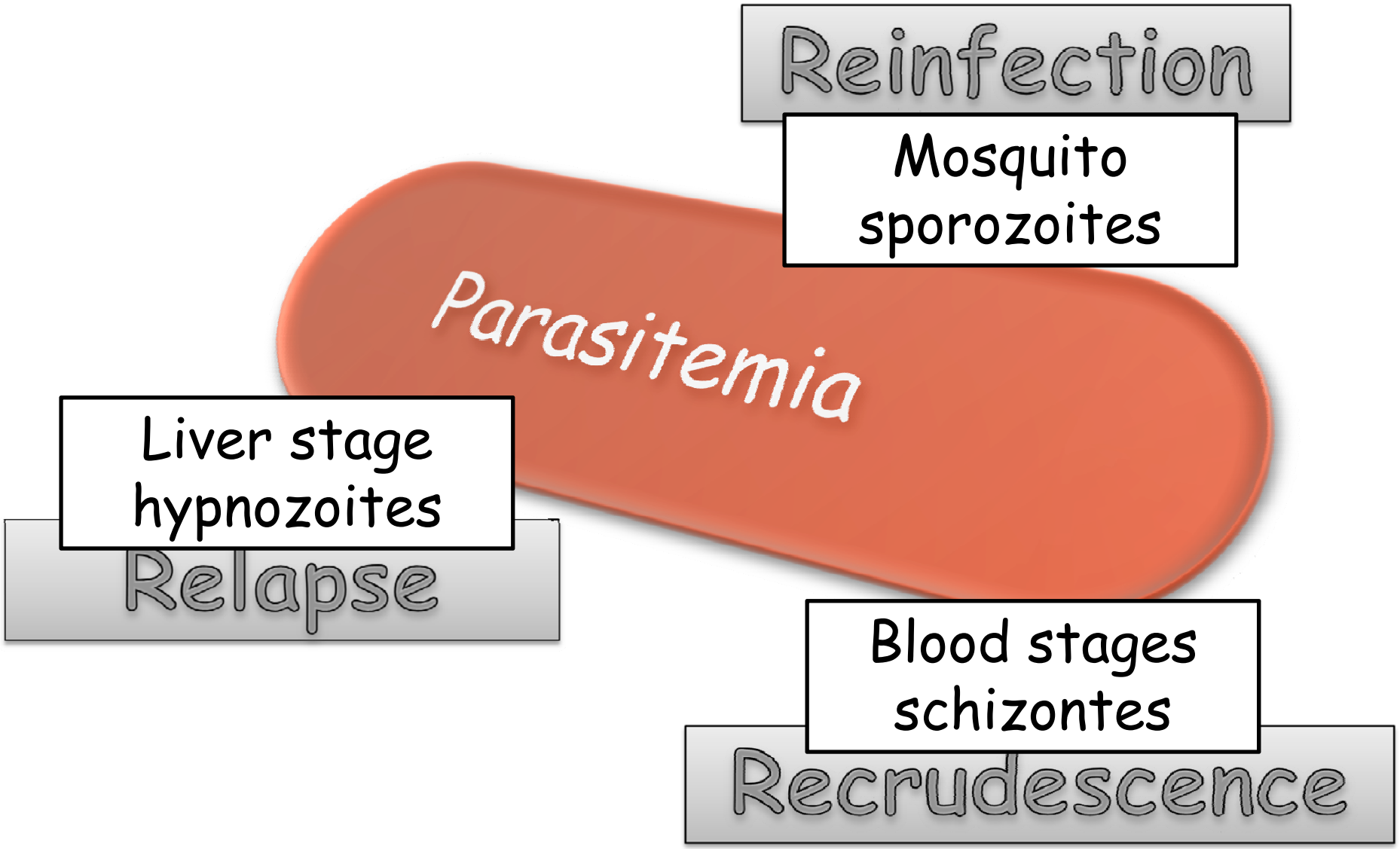






OPEN ACCESS Freely available online PLoS one

Establishment of an *In Vitro* Assay for Assessing the Effects of Drugs on the Liver Stages of *Plasmodium vivax* Malaria


Reinfection
Mosquito sporozoites
Parasitemia
Liver stage hypnozoites
Relapse
Blood stages schizontes
Recrudescence

How to discriminate recrudescence from reinfection during vivax malaria ?

Pv circumsporozoite: Pvcsp (Pvcs)

Merozoite suface protein :Msp

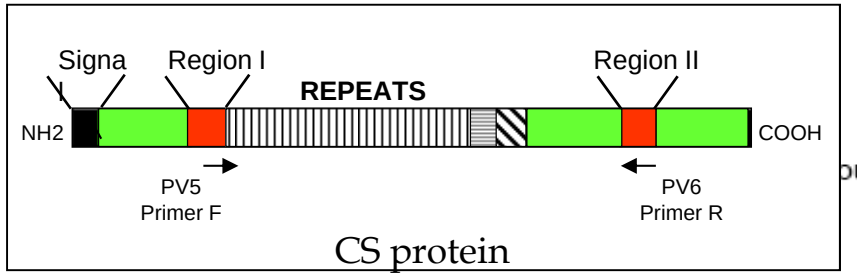
Msp1, Msp3, Msp4

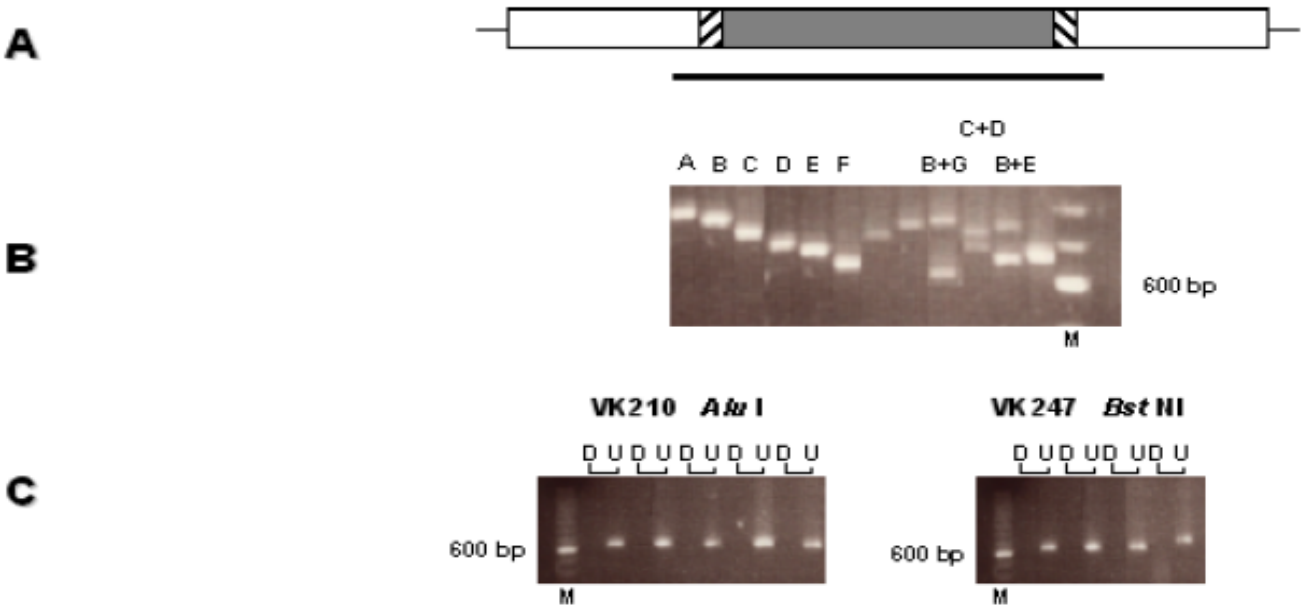
Apical Membrane Antigen : AMA 1

Plasmodium vivax circumsporozoite

Malaria Journal 2005, **4**:20

ournal.com/content/4/1/20





Central variable repetitive domain (27 bp repeat) - Flanked by two conserved regions - Separated by pre- and post-repeat specific sequences (Imwong 2005)

Two types of repeats :

VK210 (type I: Alu1 site) VK247 (type II: BstN1 site).

Merozoite suface protein 1

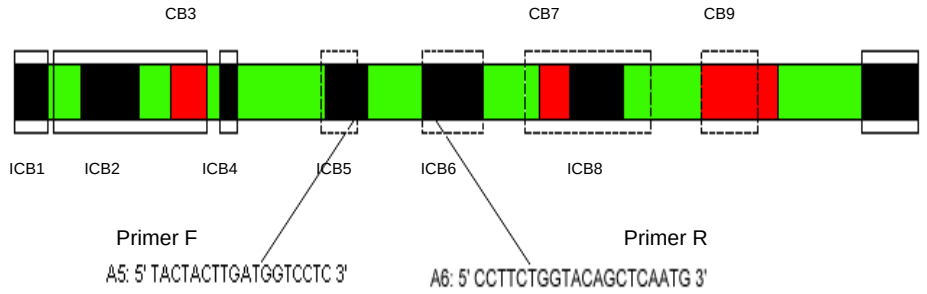
genetic diversity (π)

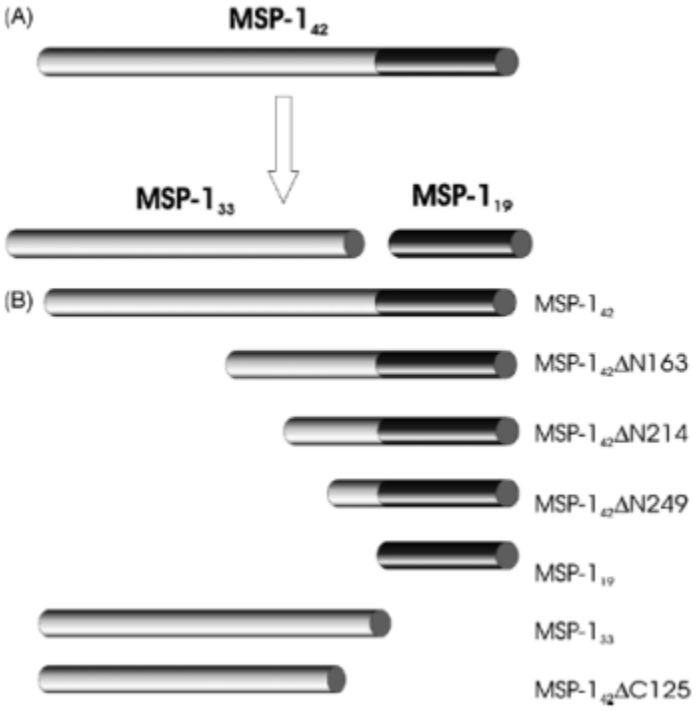
42 kDa : 0.021

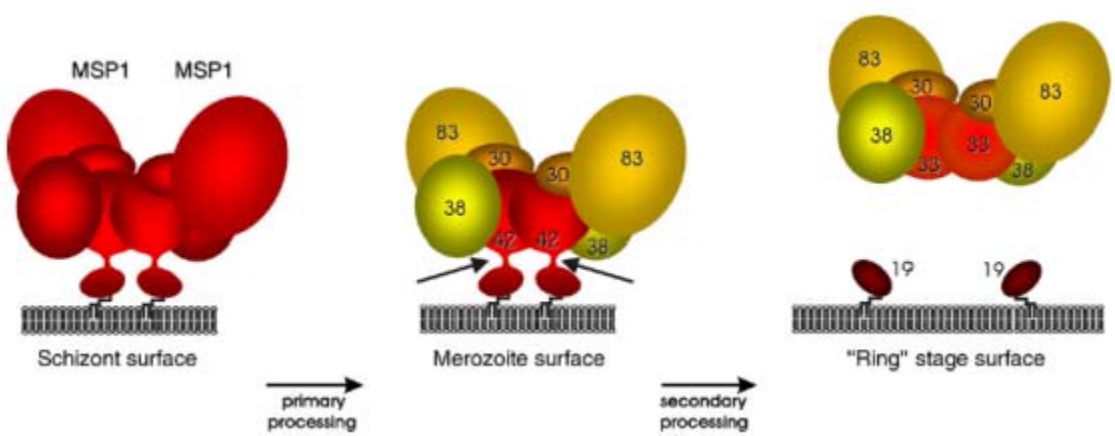
33 kDa : 0.032

19 KDa : 0.0006

(n=75) (Pacheco 2007).







J.J. Babon et al. / Molecular & Biochemical Parasitology 153 (2007) 31–40

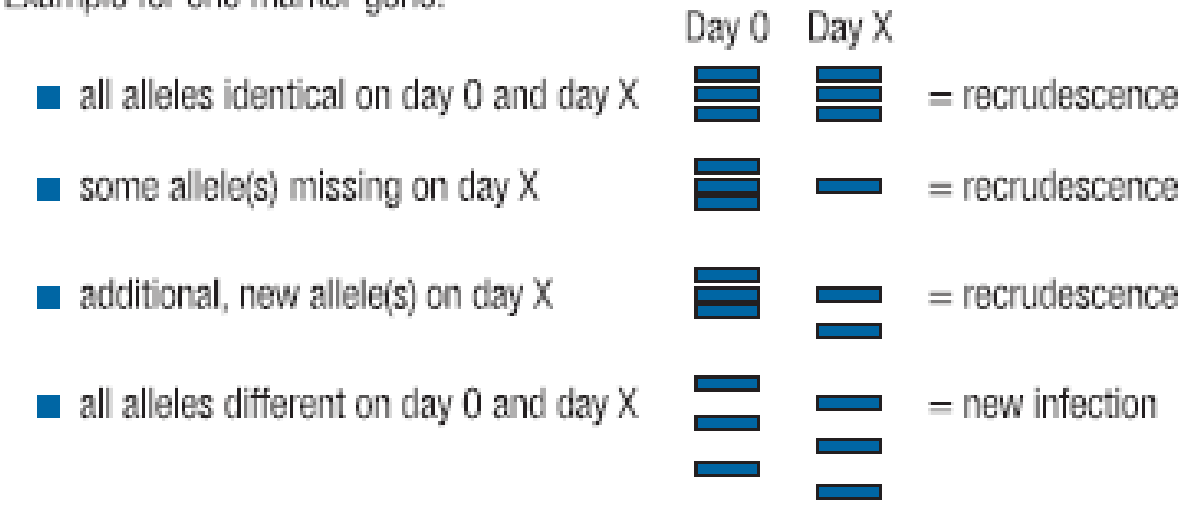
METHODS AND TECHNIQUES FOR CLINICAL TRIALS ON ANTIMALARIAL DRUG EFFICACY:

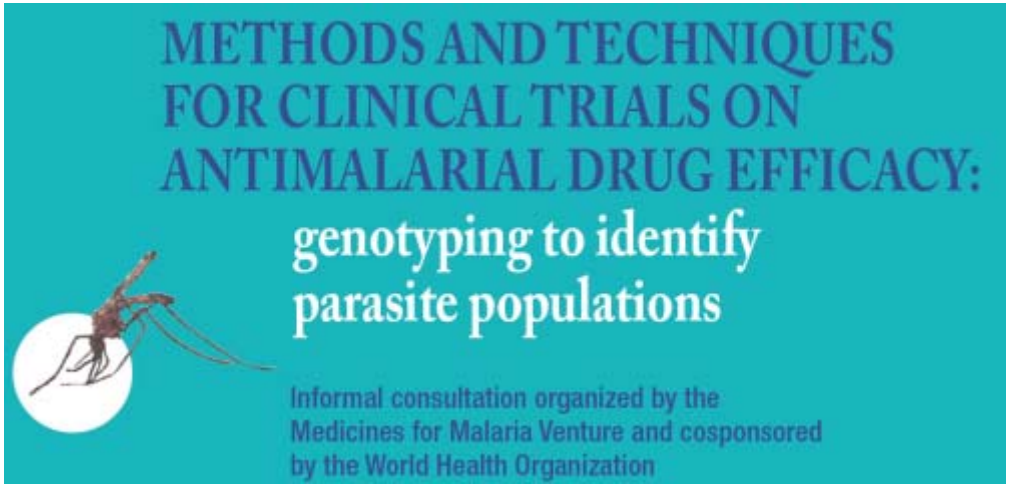
genotyping to identify parasite populations

Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization

CONSENSUS DEFINITIONS OF 'NEW INFECTION' AND 'RECRUDESCENCE'

Example for one marker gene:



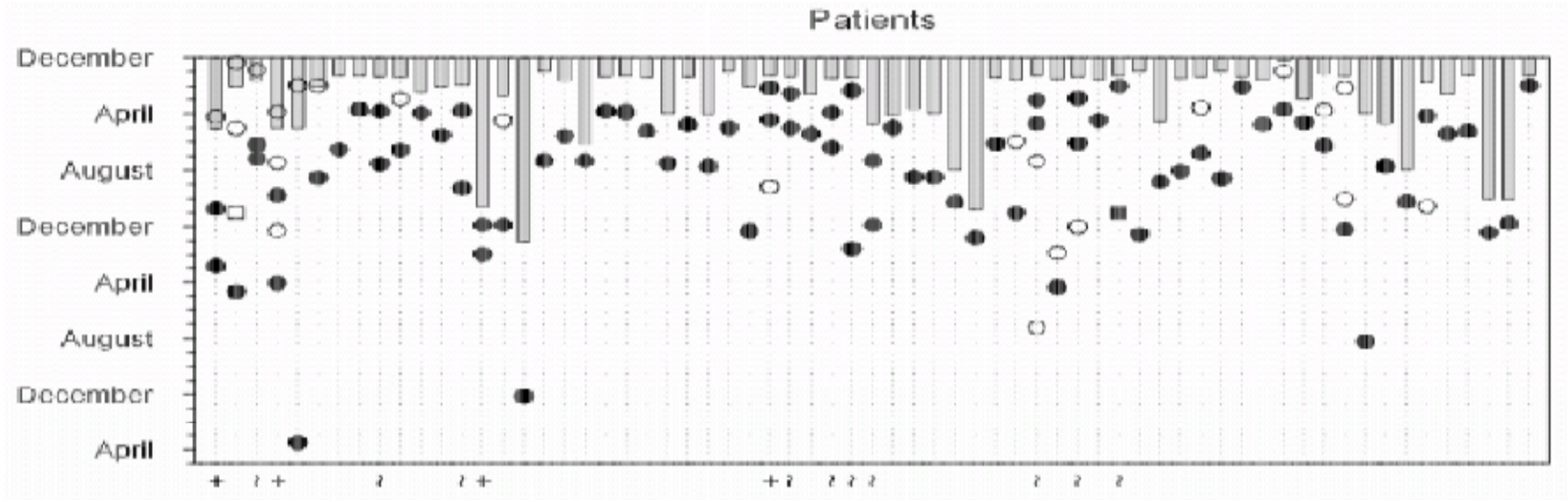


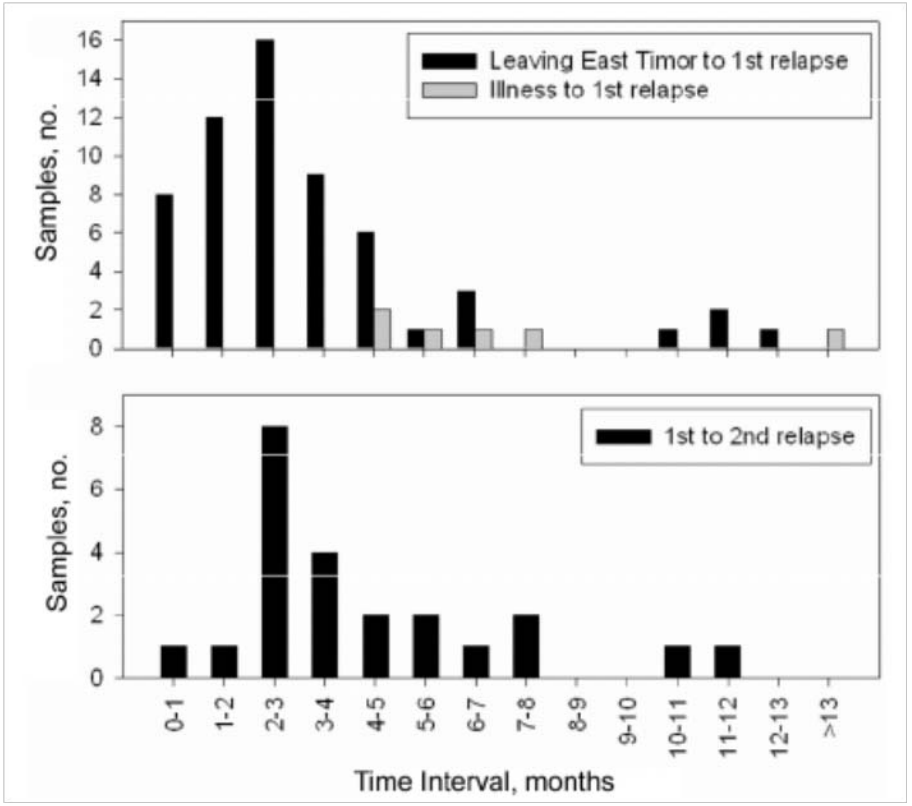
7.5 Recommendation

No recommendation was given for genotyping *P. vivax* in antimalarial drug trials because the interpretation of genotyping in the context of relapsing *P. vivax* infections is uncertain.

7.6 Rationale for not giving a recommendation on *P. vivax* genotyping

Genotyping of *P. vivax* in an antimalarial drug trial is confounded by the occurrence of relapses, which can be due to the same genotype as at baseline or to different genotypes, which will be genotyped as a 'new infections'.

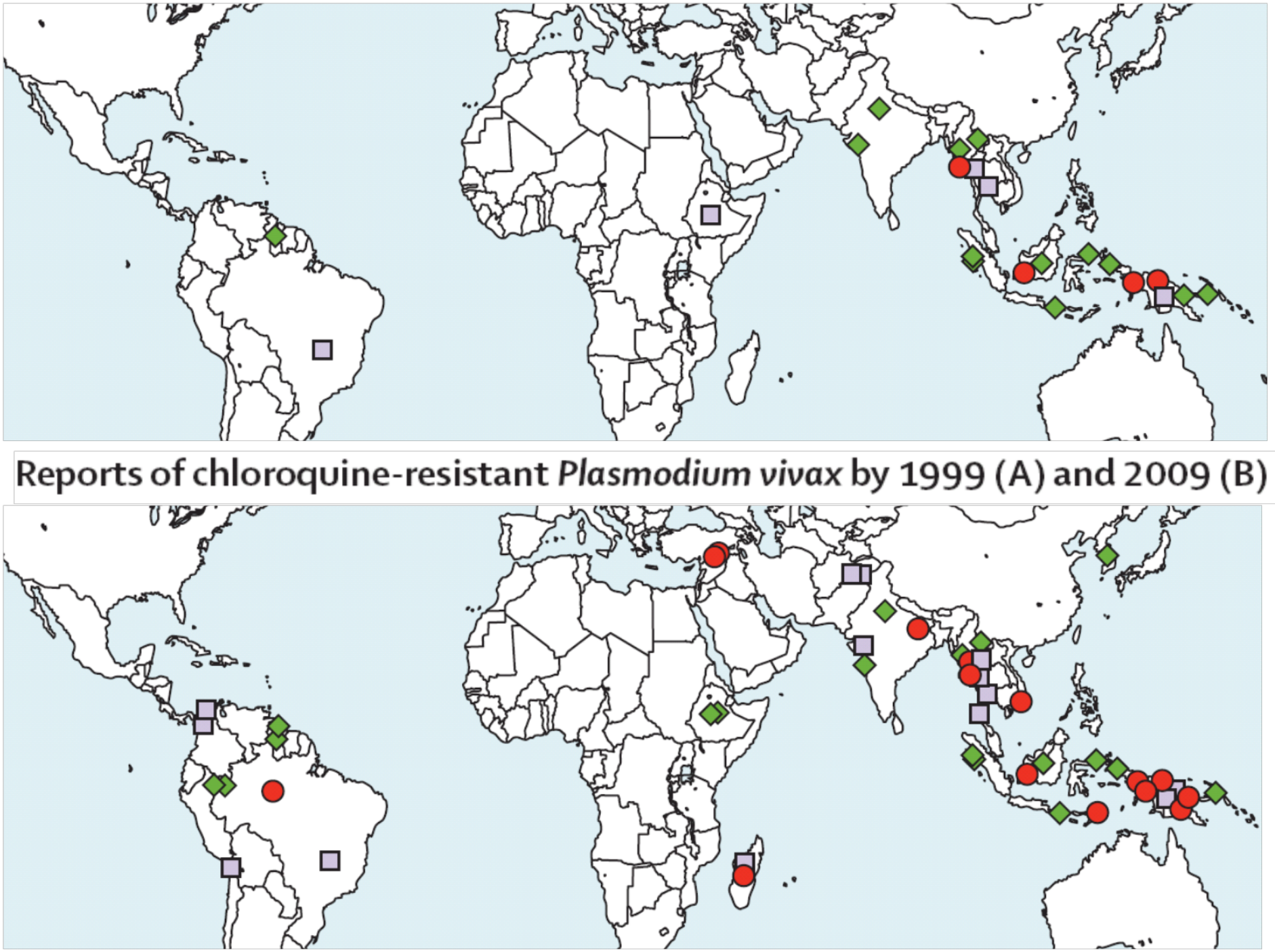




Relapses of *Plasmodium vivax* Infection Result from Clonal Hypnozoites Activated at Predetermined Intervals

Nanhua Chen,[1] Alyson Auliff,[1] Karl Rieckmann,[1] Michelle Gatton,[2] and Qin Cheng[1,2]

JID 2007:195 (1 April)



Reports of chloroquine-resistant *Plasmodium vivax* by 1999 (A) and 2009 (B)

P. vivax resistance: prepare the war

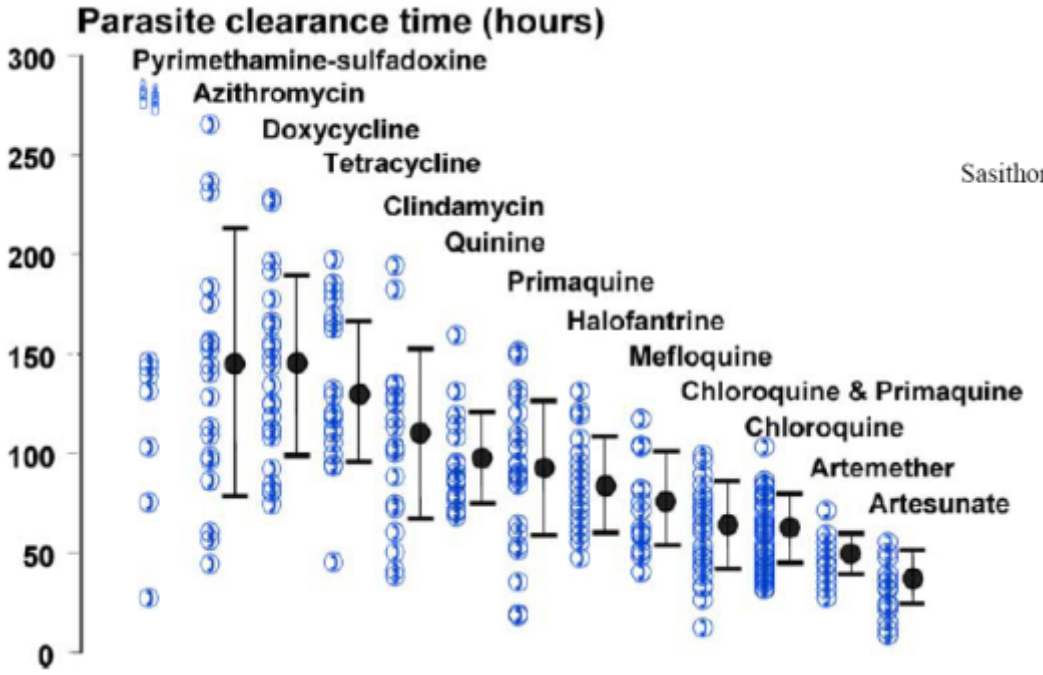
Therapeutic failures known for decades

Emergence of failures in some areas

- Therapeutic failures (India, Turkey, Indonesia, PNG, Thailand…)
- Prophylaxis failures

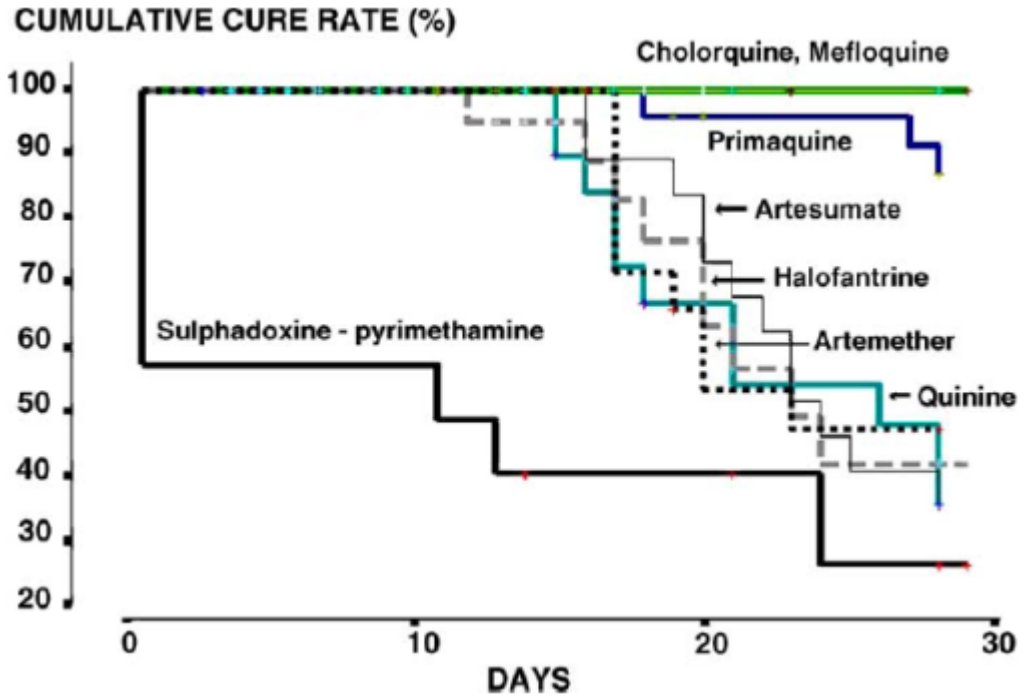
  ATV-PG (Ethiopia, Povinelli 2003. SEA, Jimenez 2006)

  MQ (French Guiana, Picot 2005)
- Decreased primaquine efficacy (Indonesia, PNG, Thailand…)
- Role of falciparum/vivax co-infection (SP)



Therapeutic responses to antimalarial and antibacterial drugs in vivax malaria

Sasithon Pukrittayakamee[a], Malika Imwong[a], Sornchai Looareesuwan[a], Nicholas J. White[a,b,*]

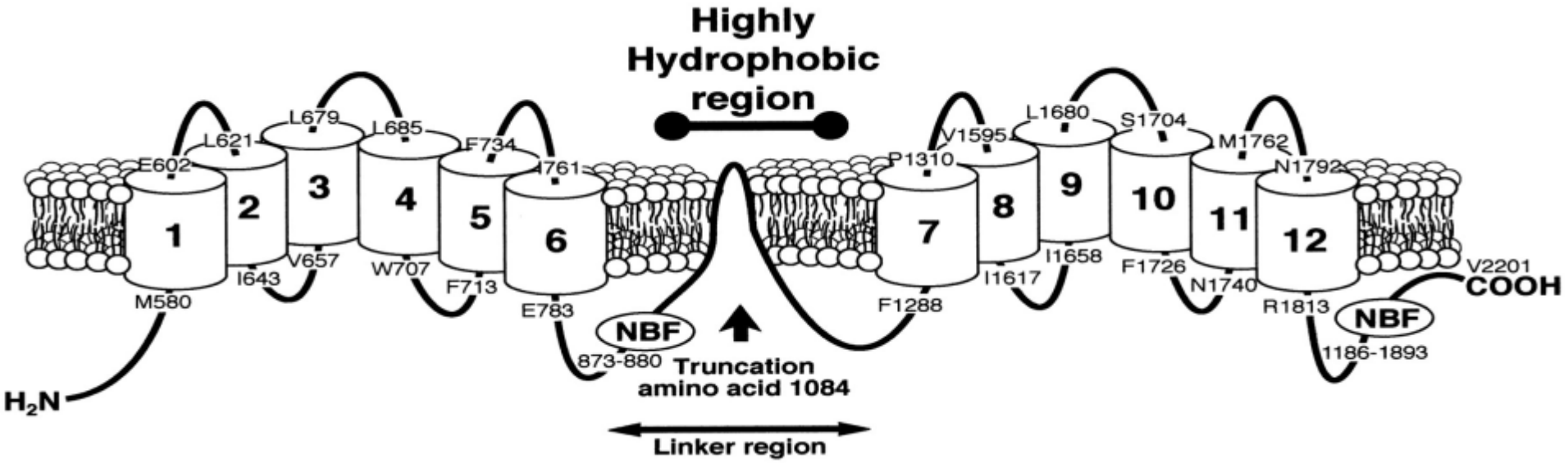


P. vivax chloroquine resistance: pvmdr1

Identification of the *Plasmodium vivax mdr*-Like Gene (*pvmdr1*) and Analysis of Nucleotide Polymorphisms among Isolates from Different Areas of Endemicity

Sara Brega,[1] Benoit Meslin,[1] Frédérique de Monbrison,[1,2] Carlo Severini,[5] Luigi Gradoni,[5] Rachanee Udomsangpetch,[4] Inge Sutanto,[6] François Peyron,[1,3] and Stéphane Picot[1,2]

JID 2005:191 (15 January)



pvdhfr & pvmdr1

Amodiaquine+SP for children in PNG

- Pvdhfr (F57L/I, S58R, T61M, S117T/N, I173F/L)
- Pvmdr1 (Y976F, F1076L)

Treatment failure (D28) : 13,3% (13/98)

- Dhfr 57L (11/12 ; OR = 9)
- Pvmdr1 976F (8/12 ; OR = 3.7)
- Dhfr 57-58-61-117 + mdr 976 (4/12 ; OR = 8.5)

Marfurt et al., JID 2008

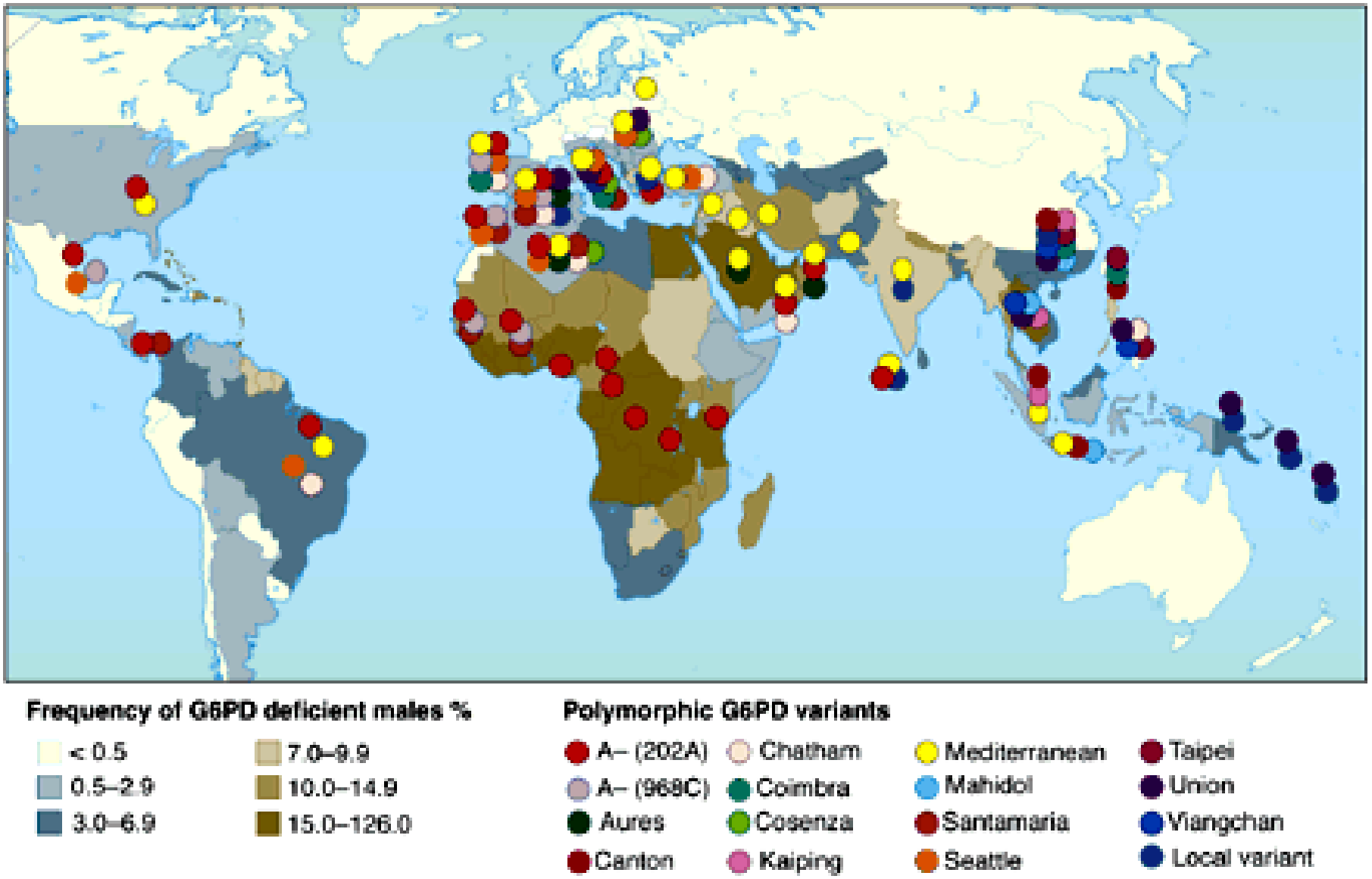
Molecular marker limits in vivax malaria

Pvdhfr, Pvmdr & Pvmdr copy number, Pvcrt-o

- **Duration of the follow-up**
  - D28, D45 …
- **History of drug use in a given area**
  - Role of antibacterial drugs
  - Role of falciparum treatment on vivax resistance
- **Pharmacokinetics**
  - Drugs with long half-life
- **Genotyping reinfection / relapse**
  - Gap of knowledge


ยาเม็ดไพรมาควีน
PRIMAQUINE TABLETS
15 mg
250 เม็ด

Geographic Distribution of G6PD Variants



Mediterranean (B-) Variants

- Serious hemolysis can occur following one dose of 15 mg primaquine base
- Patient may require blood transfusion often hemolyzing > 50% erythrocytes
- Complications include:
  - Acute Renal Failure
  - High Output Cardiac Failure
  - Anoxia and Death

The frequency of the (B-) variant differs markedly among different populations

Caucasian	0.4%
Italians	0.5-1.0%
Hispanic	0.9%
Greek	2-9%
Sardinians	3-35%
Asian	1.8%
African American	7.6%

Treatment	patient 60 kg bw. G6PD OK
Contamination in chloroquine sensitive area:	
1 – Chloroquine Total dose: 25 mg/kg/3 days. D1 : 10mg/kg ; D2 : 10 mg/kg, D3 : 5 mg/kg	**- Chloroquine (100mg)** **6 cp day 1, 6 cp day 2, 3 cp day 3**
2 - Primaquine 0.25 mg/kg/d, 14 days	**- Primaquine (7.5 mg)** **2 cp/day x 14 days**
Contamination in low chloroquine sensitive area (Thaïlande)	
1 – Chloroquine dose totale : 25 mg/kg/3jours. Soit J1 : 10mg/kg ; J2 : 10 mg/kg, J3 : 5 mg/kg	**- Chloroquine (100mg)** **6 cp day 1, 6 cp day 2, 3 cp day 3**
2 - Primaquine 0.50 mg/kg/j, 14 jours	**- Primaquine (cp à 7.5 mg)** **4 cp/day x 14 days**
Contamination in high risk resistance area (Indonesia, PNG)	
Mefloquine : 15 mg/kg, dose unique	**- Mefloquine (250 mg)** **2 cp / day, 1 day**
Primaquine : 0.50 mg/kg/j, 14 jours	**- Primaquine (cp à 7.5 mg)** **4 cp/day x 14 days**

Suppressive Prophylaxis	Causal Prophylaxis	Terminal Prophylaxis
Activity against erythrocytic stages	Activity againts primary liver schizontes and hypnozoïtes	Activity against hypnozoïtes
No action against hypnozoïtes and relapses	Do NOT forget P. falciparum chemoprophylaxis in case of mixed transmission area	Do NOT forget P. falciparum chemoprophylaxis in case of mixed transmission area
Doxycycline, mefloquine (duration of stay + 28 days after return	Primaquine 30 mg/day (0.5 mg/kg/j) : 1-2 days before stay, every day, + 7 days after	Systematic treatment with primaquine after return 15 mg/14 days double dose from PNG
Atovaquone/proguanil (duration of stay + 7 days after return)	Minimun dose in unknown G6PD normal	Asymptomatic patient, Long stay in high risk area (PNG), index case G6PD normal

benign tertian fever ?

The Ghost of the swamp

« The ghost of a man, a sufferer from his cradle to his grave, aged even in childhood and laying down in misery that life which was but one disease »

John Maccinlloch, 1827

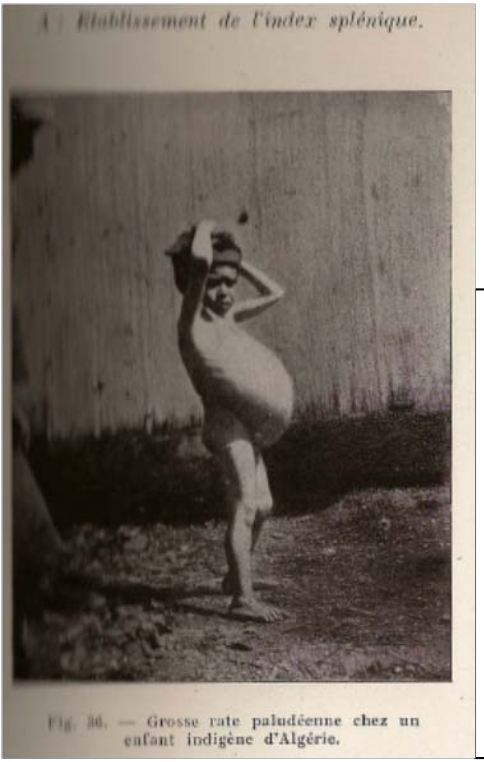


Fig. 36. — Grosse rate paludéenne chez un enfant indigène d'Algérie.

Malariatherapy

Wagner von Jauregg : 1917

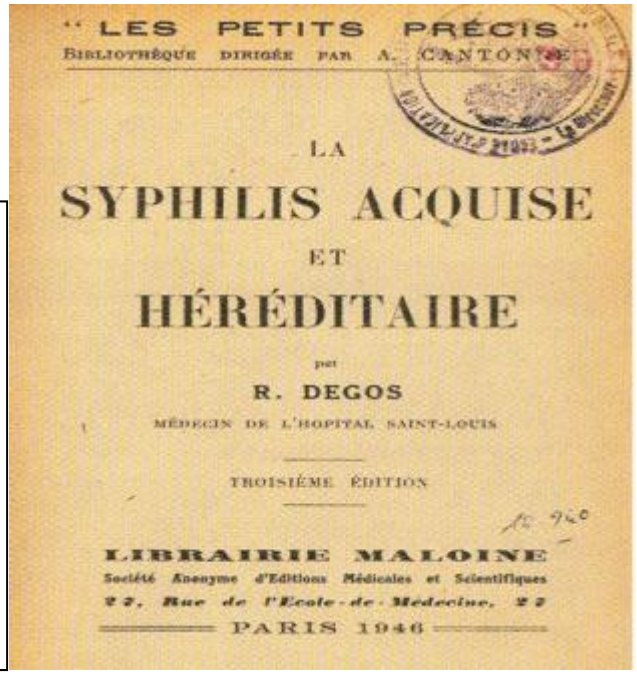
Syphilis

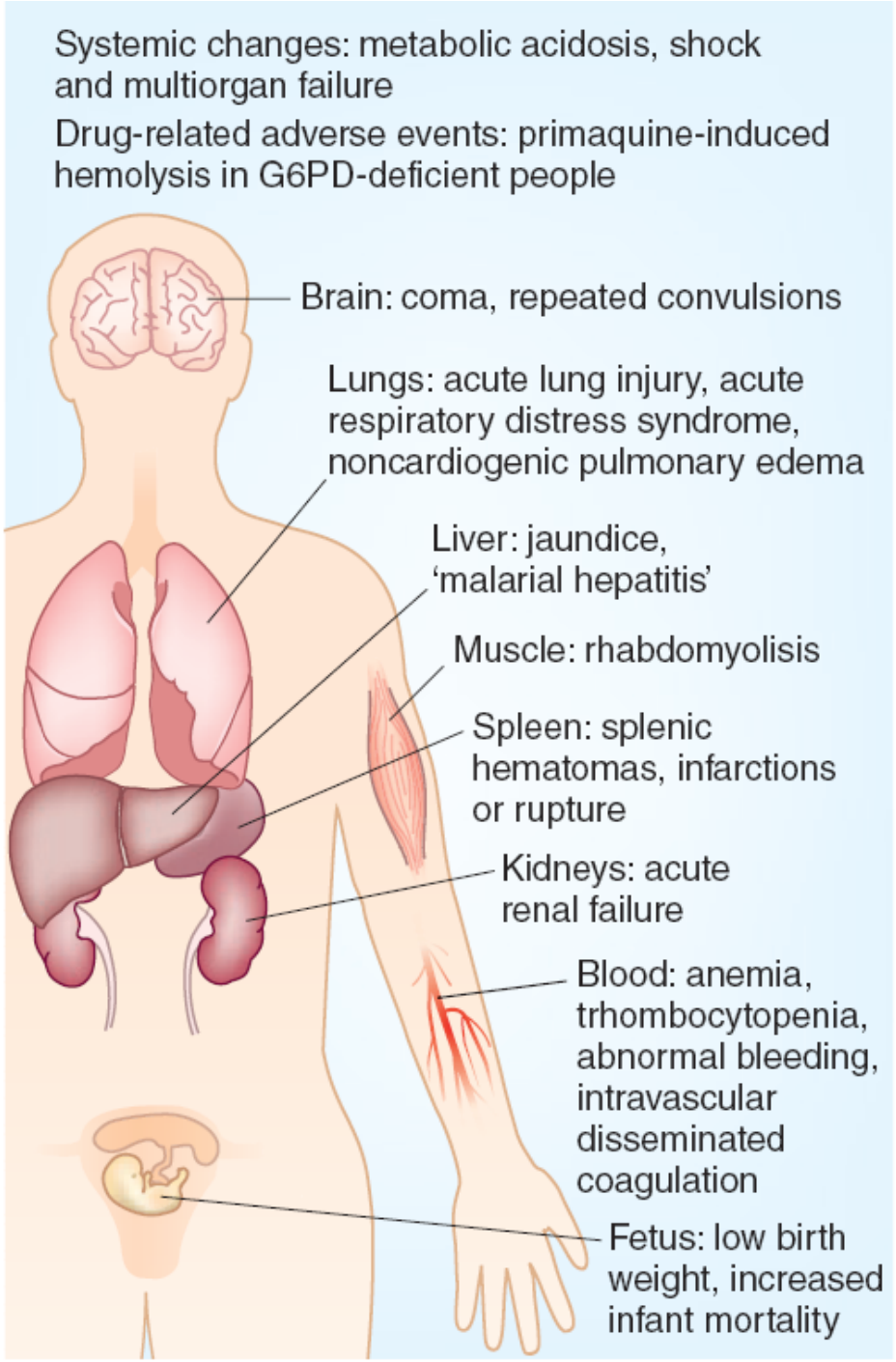
Plasmodium vivax

5-10 ml blood from patient

8 to 12 malaria crisis …

5 % death



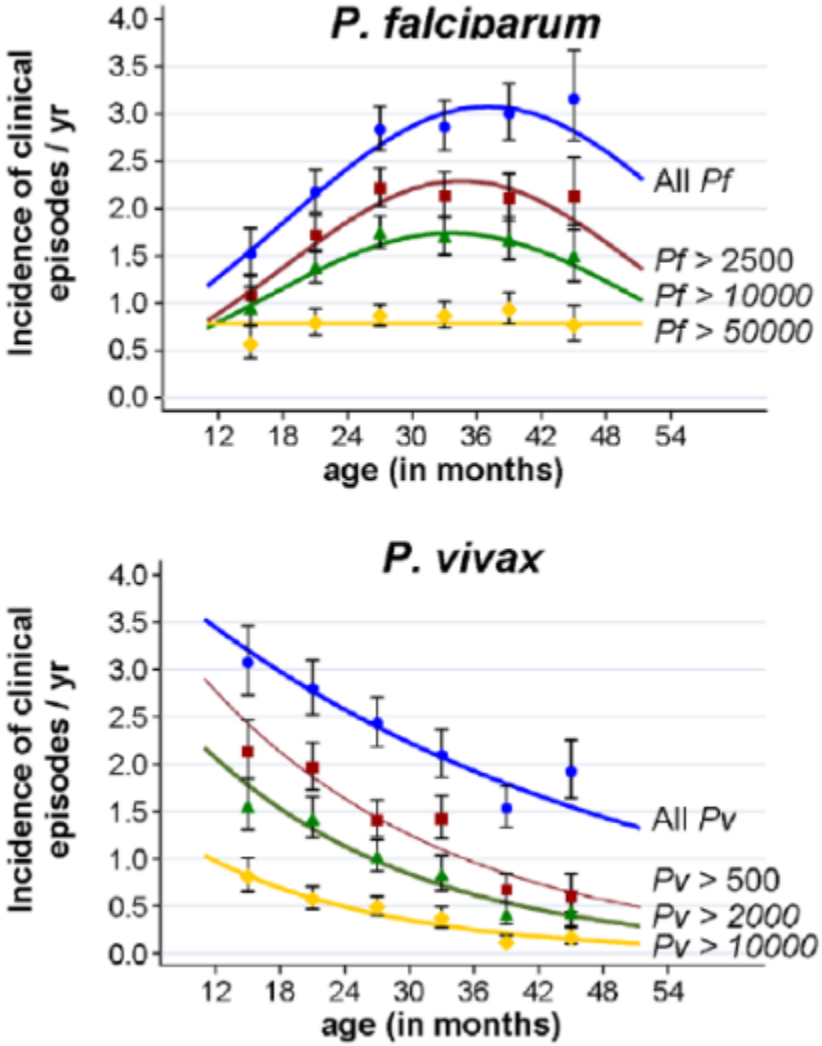


Fathoming severe *Plasmodium vivax* disease

Quique Bassat & Pedro L Alonso

Vivax versus falciparum

- Lower maximum parasitemia (<2%)
- Lower pyrogenic threshold
- Higher inflammatory response
  - Different GPI?
  - Hemozoin associated DNA (higher GC%) stimulate toll-like receptor-9 (TLR9)? (Paroche 2007)
  - Specific toxin-like lipid (Karunaweera 2007)
- Lower cytoadherence
  - Few data from autopsy
  - Chondroitin sulfate (chotinavich 2003)
  - No binding to platelets or CD36



Differential Patterns of Infection and Disease with *P. falciparum* and *P. vivax* in Young Papua New Guinean Children

Enmoore Lin[1], Benson Kiniboro[1], Laurie Gray[2], Stuart Dobbie[1], Leanne Robinson[3,4], Annemarie Laumaea[1], Sonja Schöpflin[5], Danielle Stanisic[1,3], Inoni Betuela[1], Melinda Blood-Zikursh[2], Peter Siba[1], Ingrid Felger[5], Louis Schofield[3], Peter Zimmerman[2], Ivo Mueller[1]*

Table 3. Details of young infants (<3 months) admitted to the hospital with malaria who died.

Patient	Age	Sex	Nutritional status	*Plasmodium* species	Other medical condition
1	6 days	Female	Severely underweight	*Plasmodium falciparum*	Neonatal sepsis (clinical diagnosis)
2	2 months	Male	Not recorded	*P. falciparum*	Bronchopneumonia
3	2 months 17 days	Male	Not recorded	*P. falciparum*	Bacterial meningitis (cerebrospinal fluid confirmed)
4	2 months 21 days	Female	Severely underweight	*P. falciparum*	Coma, severe anemia, hypoglycemia, metabolic acidosis
5	3 months	Male	Normal	*P. falciparum*	Severe anemia with metabolic and respiratory acidosis
6	1 month 11 days	Male	Normal	*Plasmodium vivax*	Coma
7	2 months 16 days	Male	Underweight	*P. vivax*	Respiratory distress and severe anemia

Vivax Malaria: A Major Cause of Morbidity in Early Infancy

Jeanne R. Poespoprodjo,[1,2] Wendelina Fobia,[2] Enny Kenangalem,[1,2] Daniel A. Lampah,[1,2] Afdal Hasanuddin,[3] Noah Warikar,[2,4] Paulus Sugiarto,[3] Emiliana Tjitra,[5] Nick M. Anstey,[6,7] and Ric N. Price[6,7,8]

benign tertian fever ?

Disease severity

618 imported cases europe, 4 (0.6%) severe (Mulhberger, 2003)

1135 cases in PNG, 3.2% severe (Barcus, 2007)

PNG, 9% severe cases (Genton, PLOS Med 2008)

Indonesie, 23% severe cases (Tjitra, Plos Med 2008)

India, 456 malaria cases, 40 severe vivax (9%), 4 cerebral malaria, 4 respiratory distress (Kochar 2009)

Respiratory distress

5.1%, Genton 2008, delayed

6% Tjitra 2008

benign tertian fever ?

Pernicious complications

- Acute respiratory distress syndrome (Tanios 2001, Lawn 2003)
- Acute disseminated encephalomyelitis (Koibuchi 2003)
- Retinal haemorrhages (Choi 2004)
- Spleen rupture
- Severe anemia…

- Cerebral malaria (Beg 2002)
- Death rate: 18% (2/11) (Kochar 2005)

Panel: Outstanding questions on the use of artemisinin-based combination therapies for vivax malaria

- Is the number of *P vivax* relapses predetermined or adaptive?
- Is primaquine as effective at preventing relapses when used in combination with ACTs as when used with chloroquine?
- Is there any increase in inflammatory sequelae, such as lung injury, associated with the use of ACTs for vivax malaria instead of chloroquine?
- What is the additional morbidity and mortality of falciparum malaria caused by inadvertent treatment of *P falciparum* with chloroquine because of separate treatment strategies?
- If a unified treatment strategy was seen as desirable, which artemisinin-based combination would be the most appropriate for use in co-endemic settings?
- What are the operational benefits and disadvantages of a unified versus a separate treatment strategy in co-endemic regions?
- What is the cost-effectiveness of using ACTs for the treatment of both vivax and falciparum malaria in co-endemic areas?

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Artemisinin combination therapy for vivax malaria

Nicholas M Douglas, Nicholas M Anstey, Brian J Angus, Francois Nosten, Ric N Price

P. falciparum dormant forms?

- Late onset of P. falciparum after > 2years
- Lack of Pf hypnozoites
- Nidus of intra-erythrocytic Pf in placenta without evidence of placental infection (Muehlenbachs 2007)
- Rodent malaria : latent merozoites in the lymphatic network : MEROPHORES (Landau 1999)
- MEROSOMES?

Plasmodium vivax drug resistance

Clinical trials (Guyana, Laos, Indonesia)
Molecular markers
Primaquine

Cerebral malaria

vitro, pre-clinical, clinical (Mali, Thailande)
Neuroprotective drugs

Apoptosis

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ERREURS COURANTES ET PRÉJUGÉS

EN MATIÈRE DE PALUDISME

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Edm. et Et. SERGENT

ANOPHELES
Moustique qui transmet le paludisme

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