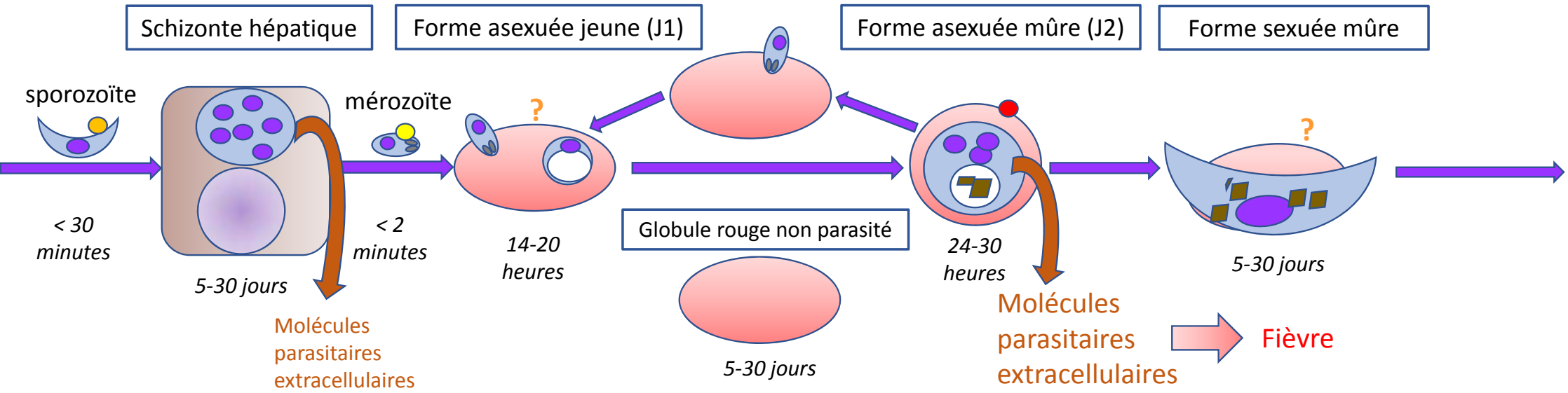


Le sporozoïte et plus encore le mérozoïte sont nus (donc exposés, immunologiquement visibles) mais « furtifs »

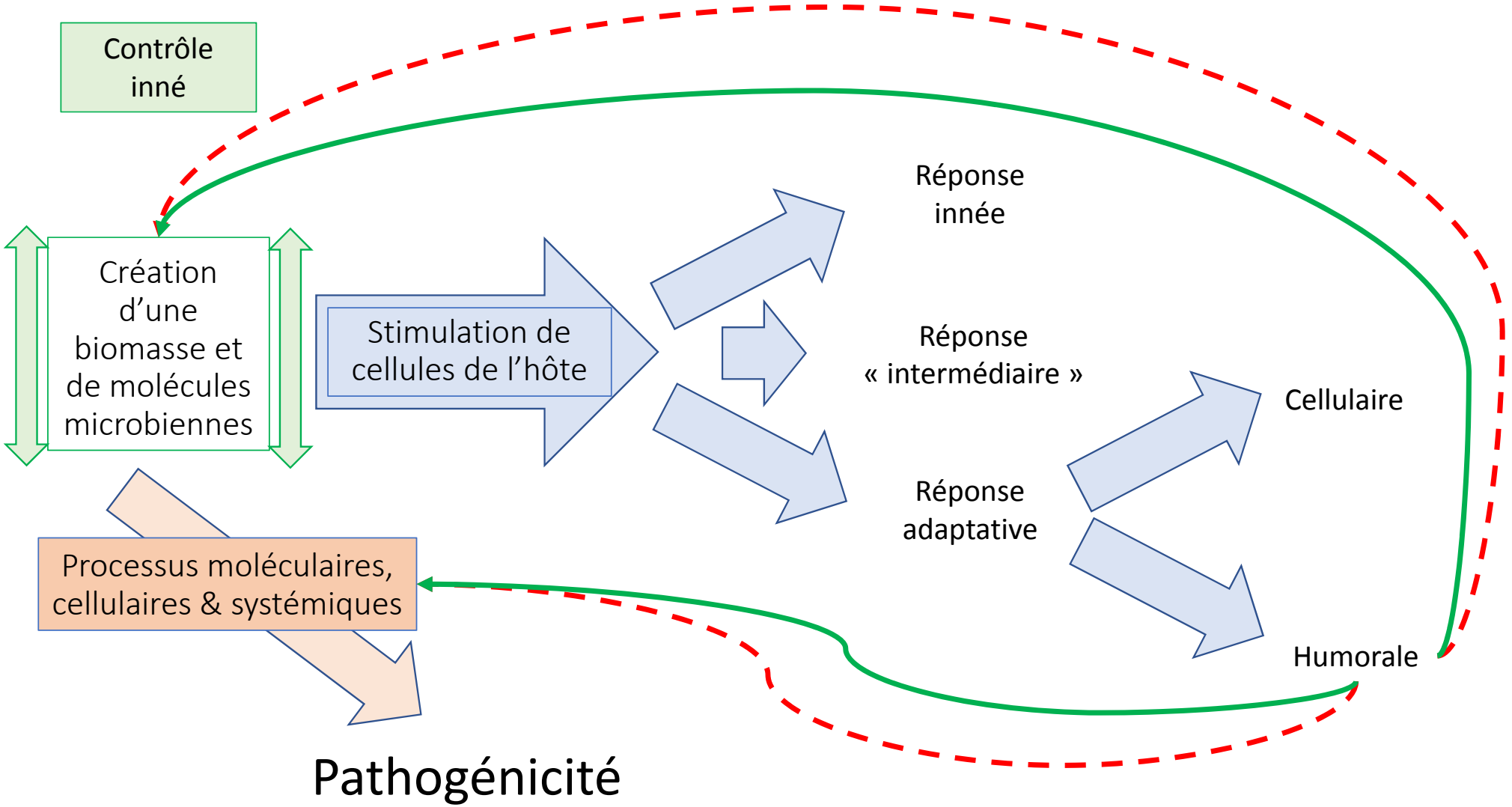
En nombre et en durée de présence extracellulaire

Les formes intra-érythrocytaires sont … intra-érythrocytaires

Les formes asexuées jeunes (anneaux ou rings) et sexuées matures (gamétocytes circulants)
sont <u>probablement</u> immunologiquement furtifs

Les formes asexuées matures exposent des antigènes à la surface de leur cellule hôte

Une part probablement prédominante de la réponse innée et adaptative est dirigée contre des antigènes relargués (hémozoïne, …)
n'ayant aucun impact en termes de contrôle de la croissance parasitaire (écran de fumée)


Contrôle inné
Création d'une biomasse et de molécules microbiennes
Stimulation de cellules de l'hôte
Réponse innée
Réponse « intermédiaire »
Réponse adaptative
Cellulaire
Humorale
Processus moléculaires, cellulaires & systémiques
Pathogénicité

SIDELIGHTS ON MALARIA IN MAN OBTAINED BY SUBINOCULATION EXPERIMENTS.

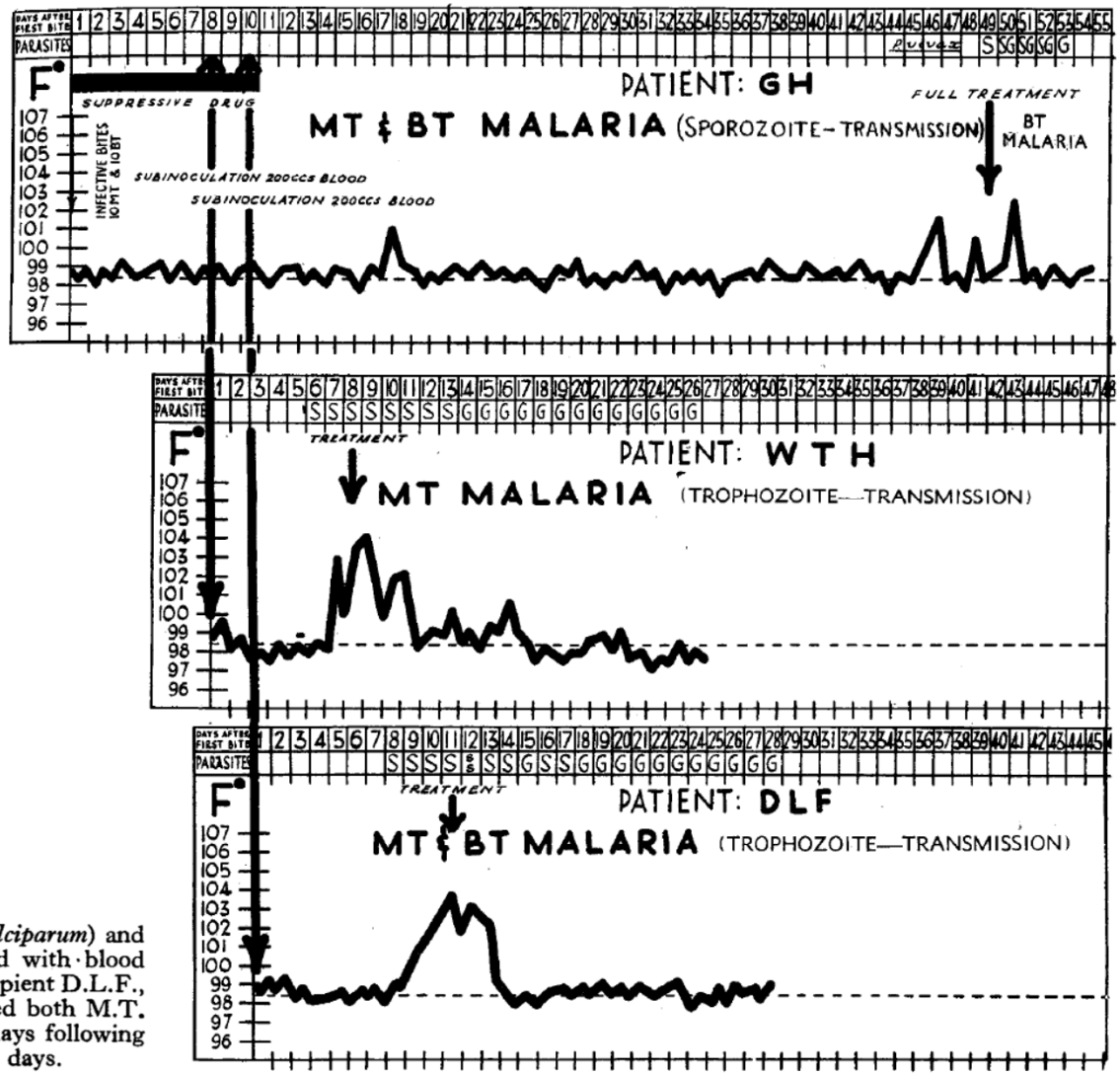
BY

Brigadier N. HAMILTON FAIRLEY, C.B.E., F.R.S., *et al.**

(*From the Land Headquarters. Medical Research Unit (A.I.F.), Cairns, Australia*).

CHART 8.

SUBINOCULATIONS FOLLOWING MIXED INFECTION. (*P. falciparum* AND *P. vivax*).



Subinoculation results in volunteer G.H. receiving ten infective bites (*P. falciparum*) and ten infective bites (*P. vivax*) on zero day. Recipient W.T.H., transfused with blood from donor G.H. collected on the 8th day, developed M.T. malaria only : recipient D.L.F., transfused with blood from donor G.H. collected on the 10th day, developed both M.T. and B.T. malaria. The donor received atebrin 0·1 grammes daily for 10 days following infection ; prior to exposure he had received 0·4 grammes daily for 4 days.

Typical evolution of a first infection in a (non immune) human subjects

Part 1
Mechanical retention of ring-infected RBC

Asymptomatic blood stage

Symptomatic blood stage

Part 2
Stiffening mature gametocytes to interrupt transmission

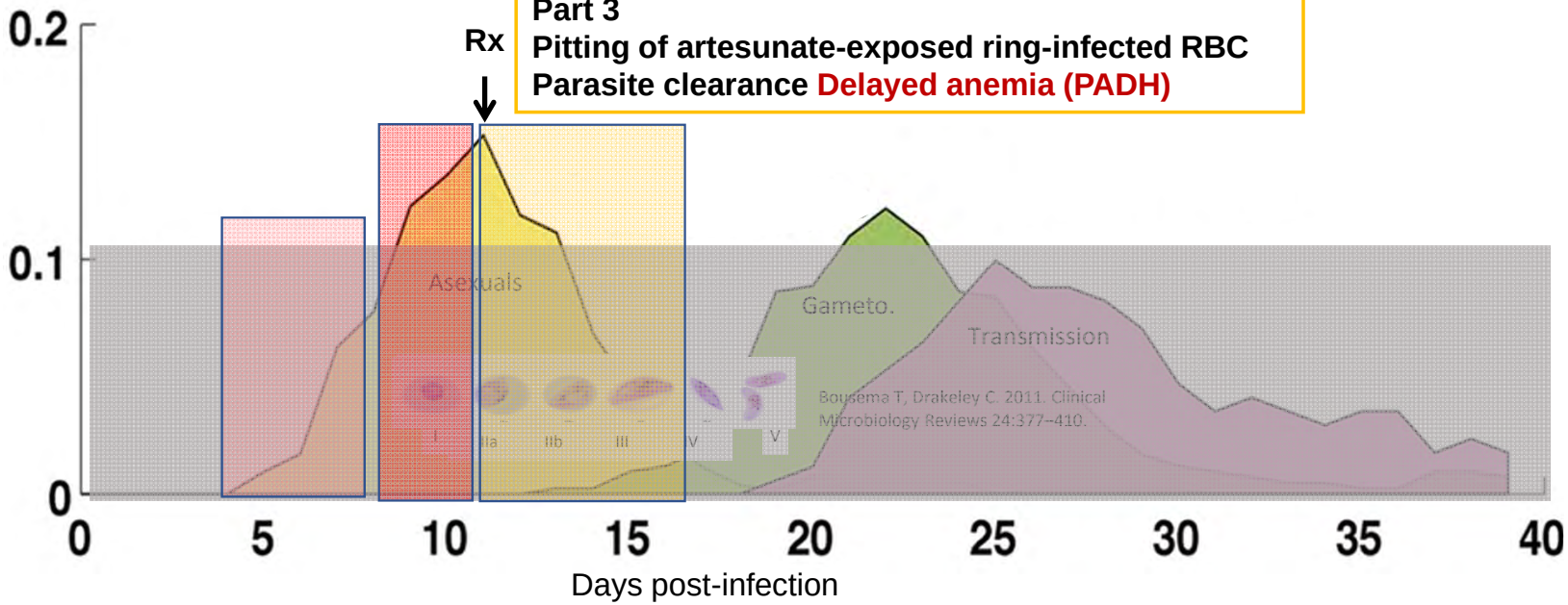
Gametocyte carriage & transmission

Parasite clearance & recovery

Recrudescence & delayed adverse events

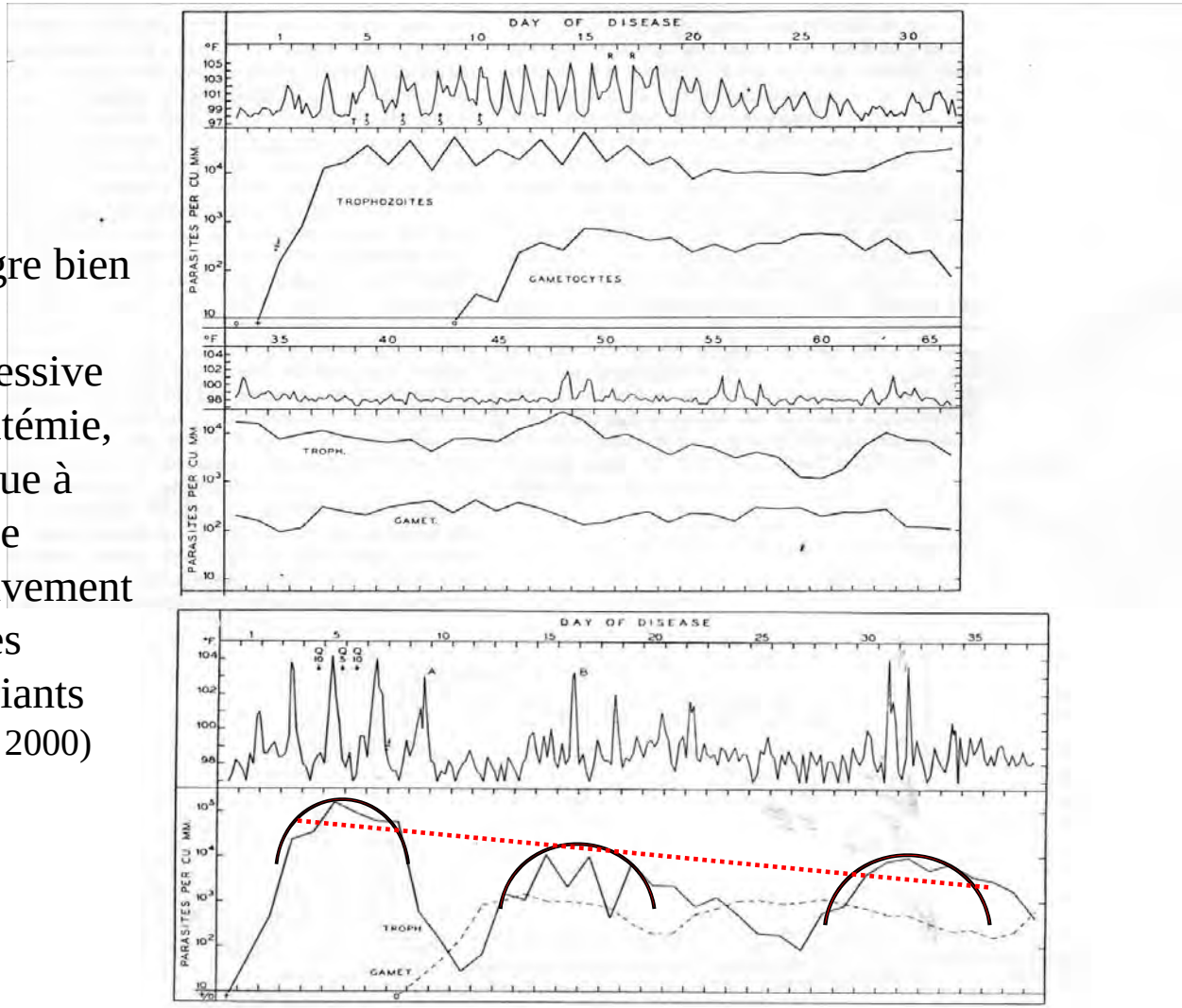
Chronic asymptomatic carriage

Part 3
Pitting of artesunate-exposed ring-infected RBC
Parasite clearance Delayed anemia (PADH)



Nilsson SK, et *al.* 2015. PLOS Pathogens 11:e1004871.

L’hypothèse intégre bien la notion d’une atténuation progressive des pics de parasitémie, potentiellement due à l’émergence d’une réponse progressivement efficace contre des antigènes peu variants
(Pérignon et Druilhe 2000)



The rise and fall of malaria in a west African rural community, Dielmo, Senegal, from 1990 to 2012: a 22 year longitudinal study

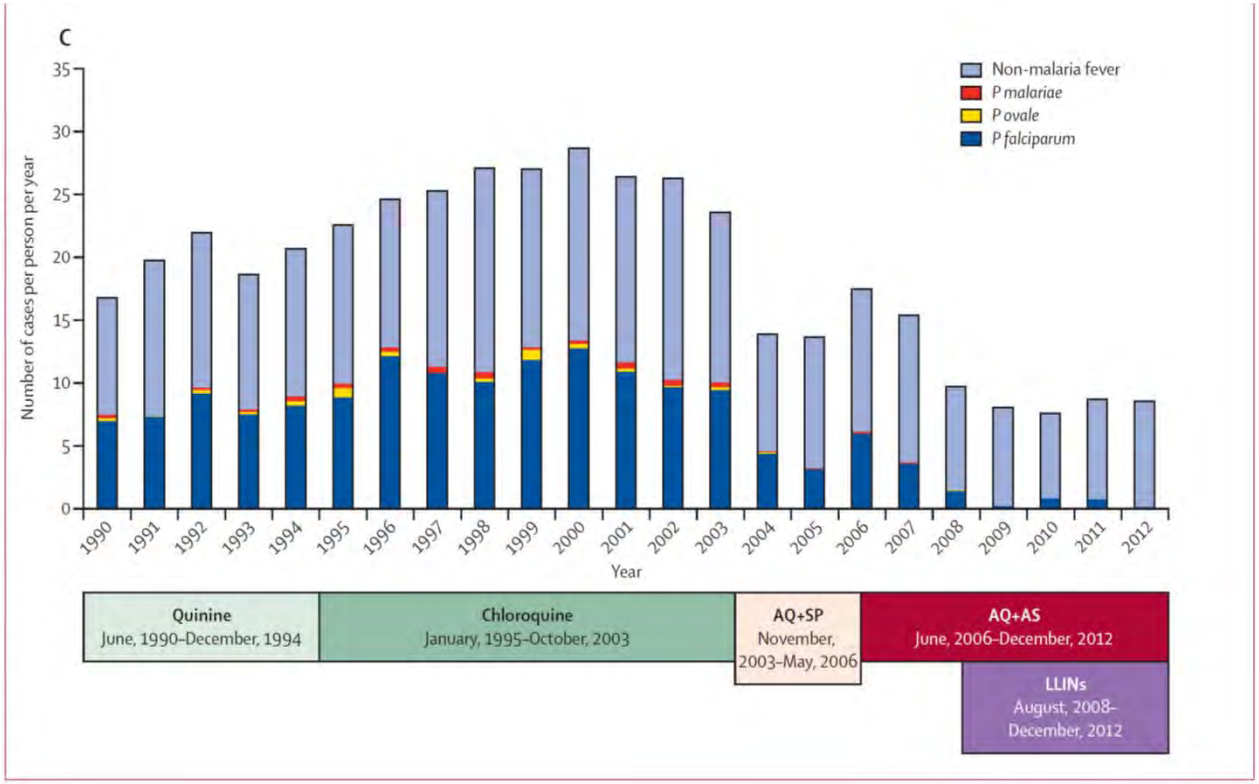
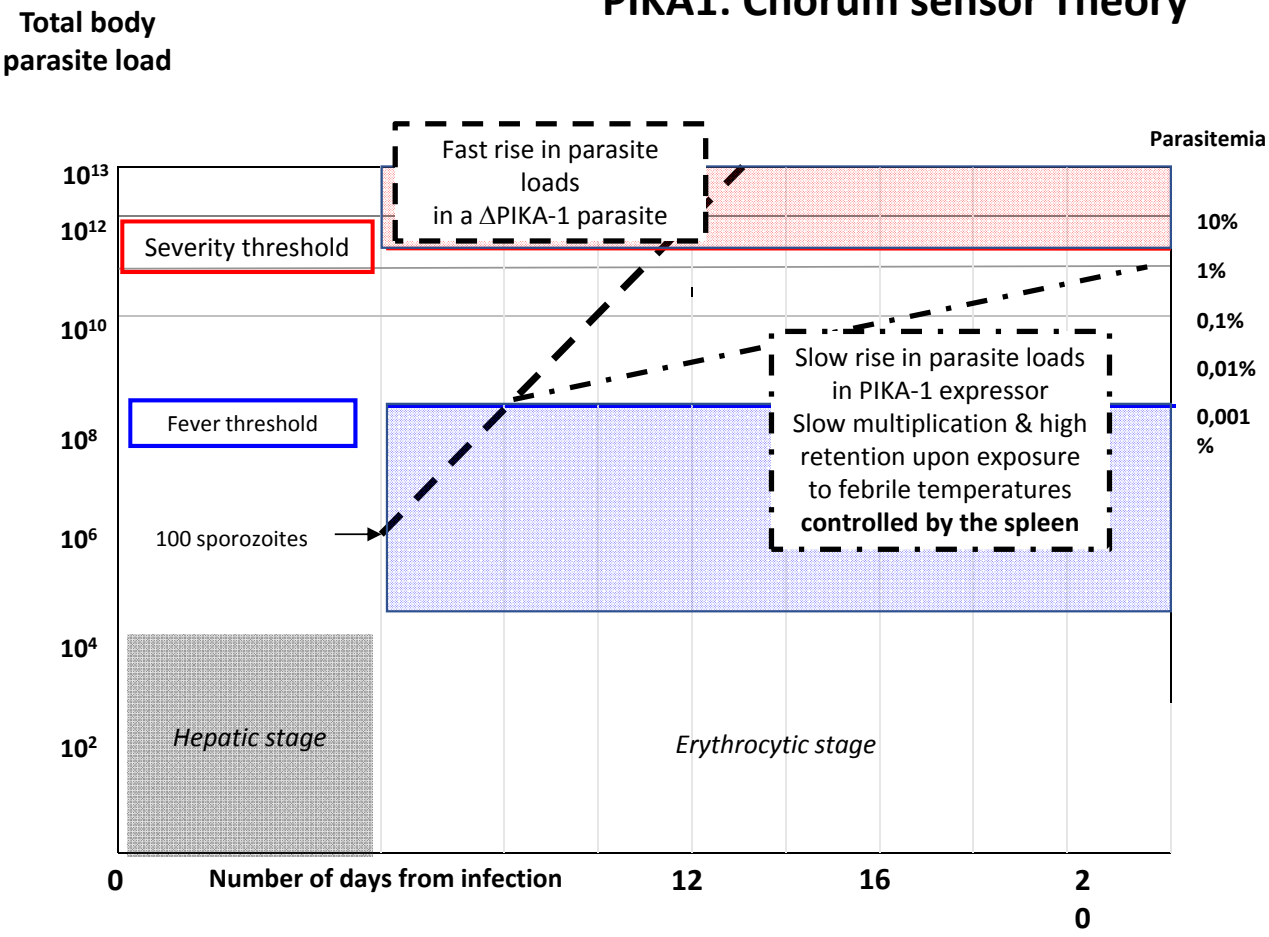


***Figure 3*: Treatment periods and annual trends in *Anopheles* species human biting rates, entomological inoculation rates, malaria prevalence, mean numbers of non-malaria fever and clinical attacks per person, Dielmo, Senegal, 1990–2012**
(A) *Anopheles* species human biting rates, entomological inoculation rates. (B) Malaria and *Plasmodium falciparum* gametocytes prevalence during cross sectional surveys. (C) Mean numbers of non-malaria fever and clinical attacks due to *P falciparum*, *Plasmodium malariae*, and *Plasmodium ovale* per person. AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AQ+AS=amodiaquine plus artesunate. LLINs=long-lasting insecticide-treated nets.

PIKA1: Chorum sensor Theory



Very high parasite loads
Many gametocytes
but premature death of the host
Small contribution to transmission

High parasite loads
Many gametocytes and host survives
Large contribution to transmission

Low parasite loads
Few gametocytes
Small contribution to transmission

Questions & paradoxes

Une multiplication intrinsèque rapide est indispensable (et peu néfaste) en cas d'infection de sujets immuns

Une multiplication intrinsèque rapide peut être néfaste chez le sujet naïf

Un mécanisme inné de contrôle très efficace confère un avantage sélectif à l'hôte et indirectement au parasite, sauf s'il persiste chz les immuns.

- Le contrôle adaptatif n’est par essence pas stable, même si il dépend de l’environnement
- Intuitivement le contrôle inné est considéré comme stable
- en réalité s ’il est couteux il serait avantageux qu’il diminue des lors que le contrôle adaptatif est en place

in the peripheral blood. All volunteers who did not receive treatment on the 17th or 18th day after exposure showed clinical evidence of hyperinfection, either incipient cerebral malaria or characteristic clinical features of an advanced septicaemia with rapid drop in haemoglobin values.

It was evident that in these heavy malignant tertian infections in volunteers, anti-malaria treatment could not be withheld later than the 19th day after the inoculation of sporozoites without endangering life. Hyperinfection, with or without cerebral malaria, would develop and death would take place from the 21st day of the infection onwards (Chart 7).

No volunteer at Cairns died from malaria despite the intensity of the infections and the large number of volunteers experimentally infected. This was due to continuity of clinical observation from the commencement of the infection and repeated examination of blood films for parasites; in the heavier infections blood smears were sometimes searched two or three times daily. These results show that if treated in time, falciparum malaria in otherwise healthy people should not end fatally. Once hyperinfection is established, however, the prognosis becomes uncertain and any delay in therapy may lead to death owing to alarmingly rapid increase in parasite density and tissue anoxia, resulting from blockage of capillaries and small vessels with parasitized cells.

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TABLE VII.

GROUP C CONTROLS.* SUBINOCULATIONS PERFORMED DURING THE FIRST 9 DAYS AFTER EXPOSURE OF THE DONOR TO INFECTIVE MOSQUITOES (*P. falciparum*). SINGLE EXPOSURE ON DAY 0.

Donor.			Subinoculation.			Recipient.
Name.	Number of infective bites.	First parasites in thick blood films (days after infection).	Time after biting ceased (days/hrs.).	Volume in c.c.	Result. Positive (+). Negative (O).	First parasites in thick blood films (days after receiving blood).
Stw.	12	9	1	500	O	0
Aus.	12	11	2	500	O	0
Tre.	7	11	3	500	O	0
Fis.	8	10	4	200	O	0
Bak.	100	8	4/16	500	O	0
Ken.	20	7	5	500	O	0
Cro.	20	8	5/16	200	O	0
Rim.	19	7	5/16	200	O	0
Bak.	100	8	5/16	500	O	0
Fis.	8	10	5/20	200	O	0
O'D.	20	(15)	6	500	O	0
Bly.	19	9	6	500	O	0
Cro.	20	8	6/16	200	+	4
Rim.	19	7	6/16	200	+	4
Rob.	20		6/18	20	+	7
Rim.	19	7	7/16	200	+	4
Stv.	7	11	8/14	200	+	5

* No treatment was given to any of these volunteers until overt malaria had developed, except Rob. who received paludrine on the 7th day after exposure.

TABLE VI.

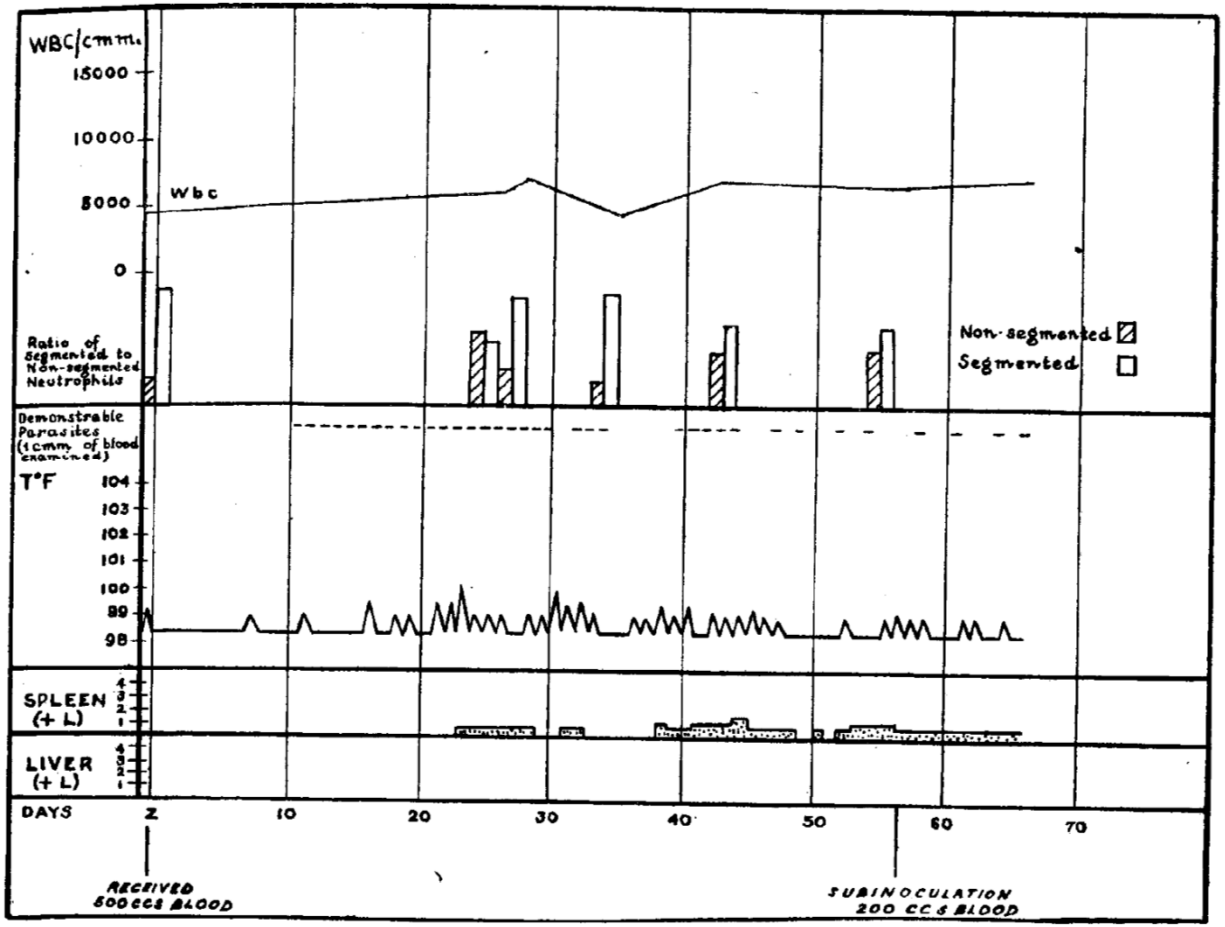
P. falciparum MALARIA. SUBINOCULATIONS PERFORMED DURING THE FIRST 2 HOURS AFTER EXPOSURE OF DONORS TO INFECTIVE MOSQUITOES. SINGLE EXPOSURE ON DAY 0.

Donor.				Subinoculation.			Recipient.
Name.	Number of infective bites.	Duration of biting in minutes.	First parasites in thick blood films (days after infection).	Minutes after biting ceased.	Volume in c.c.	Result. Positive (+). Negative (O).	First parasites in thick blood films (days after receiving blood).
Stw.	12	5–8	9	during biting	500	O	0
Bri.	18	8	*	during biting	500	+	11
Aus.	12	5–8	11	7	500	+	13
Stu.	15	15	10	10	500	O	0
Tre.	7	7	11	15	500	O	0
McD.	14	13	*	18	150	+	14
Stv.	7	10	11	20	500	O	0
Ash.	24	8	9	60	500	+	12
Jac.	18	8	8	60	500	O	0
O'D.	20	6	(15)*	120	500	O	0

* Given paludrine before the development of demonstrable parasites.

The primary attacks of malaria in the positive recipients did not differ significantly from those of the donors beyond showing a longer incubation period. *P. falciparum* were demonstrated in the blood of donors between the 8th and 11th days after exposure, and between the 11th and 14th days after the recipients received their inocula.

CHART 6.



Atypical clinical syndrome in a recipient following a direct transfusion of 500 c.c. of blood made 2 hours after the donor had been bitten by 20 infected mosquitoes (*P. falciparum*). The donor developed overt malaria and parasites 15 days after exposure.

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Stw.	12	9	1	500	O	0
Aus.	12	11	2	500	O	0
Tre.	7	11	3	500	O	0
Fis.	8	10	4	200	O	0
Bak.	100	8	4/16	500	O	0
Ken.	20	7	5	500	O	0
Cro.	20	8	5/16	200	O	0
Rim.	19	7	5/16	200	O	0
Bak.	100	8	5/16	500	O	0
Fis.	8	10	5/20	200	O	0
O'D.	20	(15)	6	500	O	0
Bly.	19	9	6	500	O	0
Cro.	20	8	6/16	200	+	4
Rim.	19	7	6/16	200	+	4
Rob.	20		6/18	20	+	7
Rim.	19	7	7/16	200	+	4
Stv.	7	11	8/14	200	+	5

* No treatment was given to any of these volunteers until overt malaria had developed, except Rob. who received paludrine on the 7th day after exposure.

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Une multiplication intrinsèque rapide est indispensable (et peu néfaste) en cas d'infection de sujets immuns

Une multiplication intrinsèque rapide peut être néfaste chez le sujet naïf

Un mécanisme inné de contrôle très efficace confère un avantage sélectif à l'hôte et indirectement au parasite, sauf s'il persiste chz les immuns.

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- en réalité s ’il est couteux il serait avantageux qu’il diminue des lors que le contrôle adaptatif est en place

Remerciements

A longitudinal study of children in Mali (P.D. Crompton, unpublished data) provides some insight into these questions. A systems biology approach (25) was used to analyze leukocytes sampled from children before the malaria season and seven days after treatment of their first febrile malaria episode of the ensuing season when symptoms had resolved. Leukocytes were stimulated with iRBC lysates in vitro, and various immune parameters were measured. This analysis revealed that before the malaria season the children's immune cells responded to the iRBC lysates by producing proinflammatory mediators such as IL-1β, IL-6, and IL-8. Following febrile malaria, there was a marked shift in the response to iRBCs, with the same children's immune cells producing lower levels of proinflammatory cytokines and higher levels of anti-inflammatory cytokines (IL-10, TGF-β). In addition, molecules involved in phagocytosis-mediated killing and activation of adaptive immunity were upregulated after febrile malaria as compared to before. This shift was accompanied by a marked increase in *P. falciparum*–specific $CD4^+Foxp3^-$ T cells that coproduced IL-10, IFN-γ, and TNF; however, *P. falciparum*–inducible IL-10 production remained upregulated only in children with persistent asymptomatic infection. These findings suggest that in the face of *P. falciparum* reexposure, children rapidly acquire exposure-dependent *P. falciparum*–specific immunoregulatory responses that dampen potentially pathogenic inflammation while enhancing antiparasite effector mechanisms that control parasite replication. These data provide mechanistic insight into the observation that *P. falciparum*–infected children in endemic areas commonly experience a mild febrile illness or no symptoms at all and often keep parasite numbers in the blood in check (112, 113).

The development of a vaccine that would confer protection against malaria by inducing immunity to clonally variant *P. falciparum* antigens is a formidable challenge. However, evidence from studies in malaria-endemic areas suggests that the clonally variant PfEMP1 family is a major target of humoral immunity to malaria (133) and that repeated *P. falciparum* infections may elicit a protective repertoire of PfEMP1-specific antibodies (134). How might this immunity be replicated through vaccination? One approach may be to immunize with whole killed blood-stage parasites that have been genetically modified to express the entire PfEMP1 repertoire of a given parasite simultaneously (135). This approach could complement ongoing efforts to develop killed or attenuated whole-parasite blood-stage vaccines (136), which intriguingly appear to mediate protection through $CD4^+$ T cells, IFN-γ, and NO rather than through antibodies (137).

133. Chan JA, Howell KB, Reiling L, Ataide R, Mackintosh CL, et al. 2012. Targets of antibodies against *Plasmodium falciparum*-infected erythrocytes in malaria immunity. *J. Clin. Investig.* 122:3227–38
134. Bull PC, Lowe BS, Kortok M, Molyneux CS, Newbold CI, Marsh K. 1998. Parasite antigens on the infected red cell surface are targets for naturally acquired immunity to malaria. *Nat. Med.* 4:358–60

Cerebral malaria associated with

rapid evolution (3-4 days of fever)

Bruneel 05, Giha 08

high parasite loads

Giha 05, Dondorp 08

no splenomegaly

Giha 08

Severe malarial anemia associated with

. relatively slow evolution (7 days of fever)

Giha 08, Sowunmi 09

. relatively low parasite loads

Giha 08, Sowunmi 09

. splenomegaly

Looareesuwan 87, Price 01, Giha 08, Sowunmi 09

Malaria first infection is

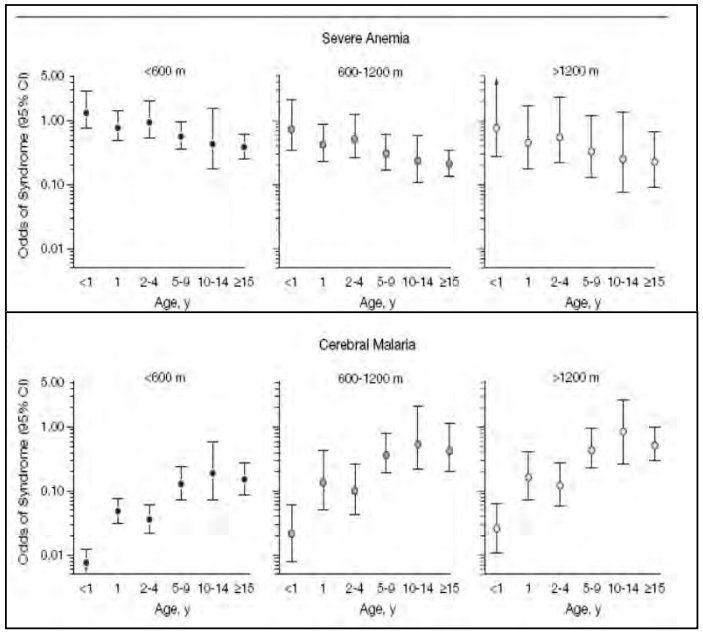
more frequently **severe**

more frequently **fatal**

in **adults** than in children

Bastien 85, Baird 98, Muhlberger 03, Dondorp 08, Legros 09

Reyburn et al. JAMA 05



Price et al. AJTMH 01

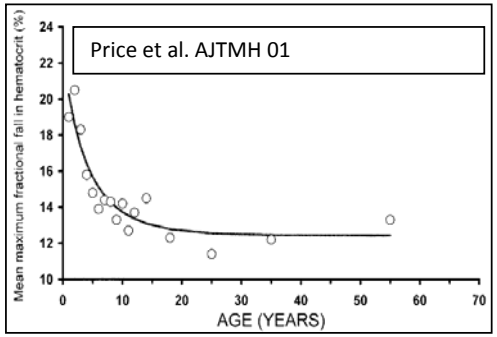
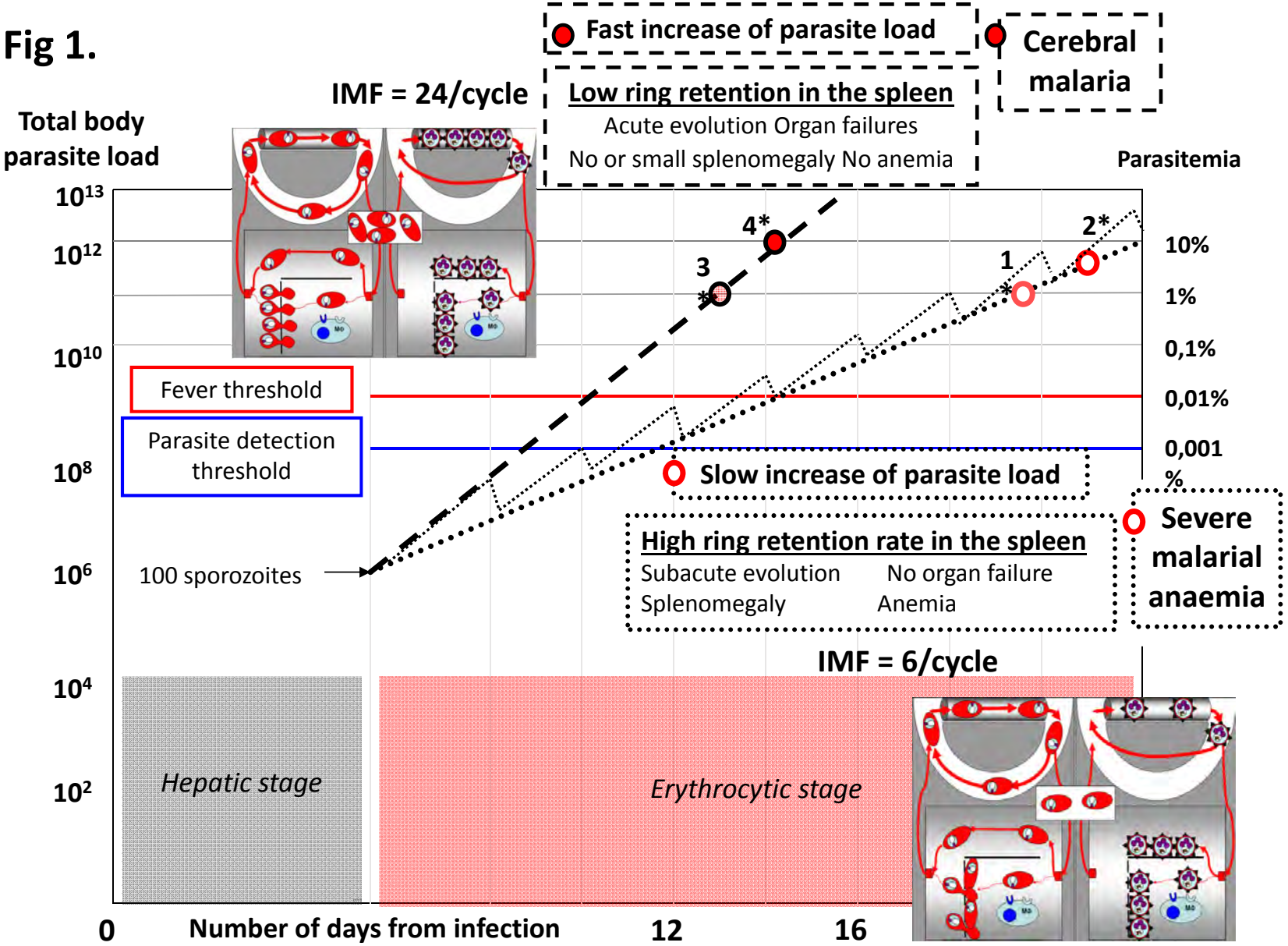
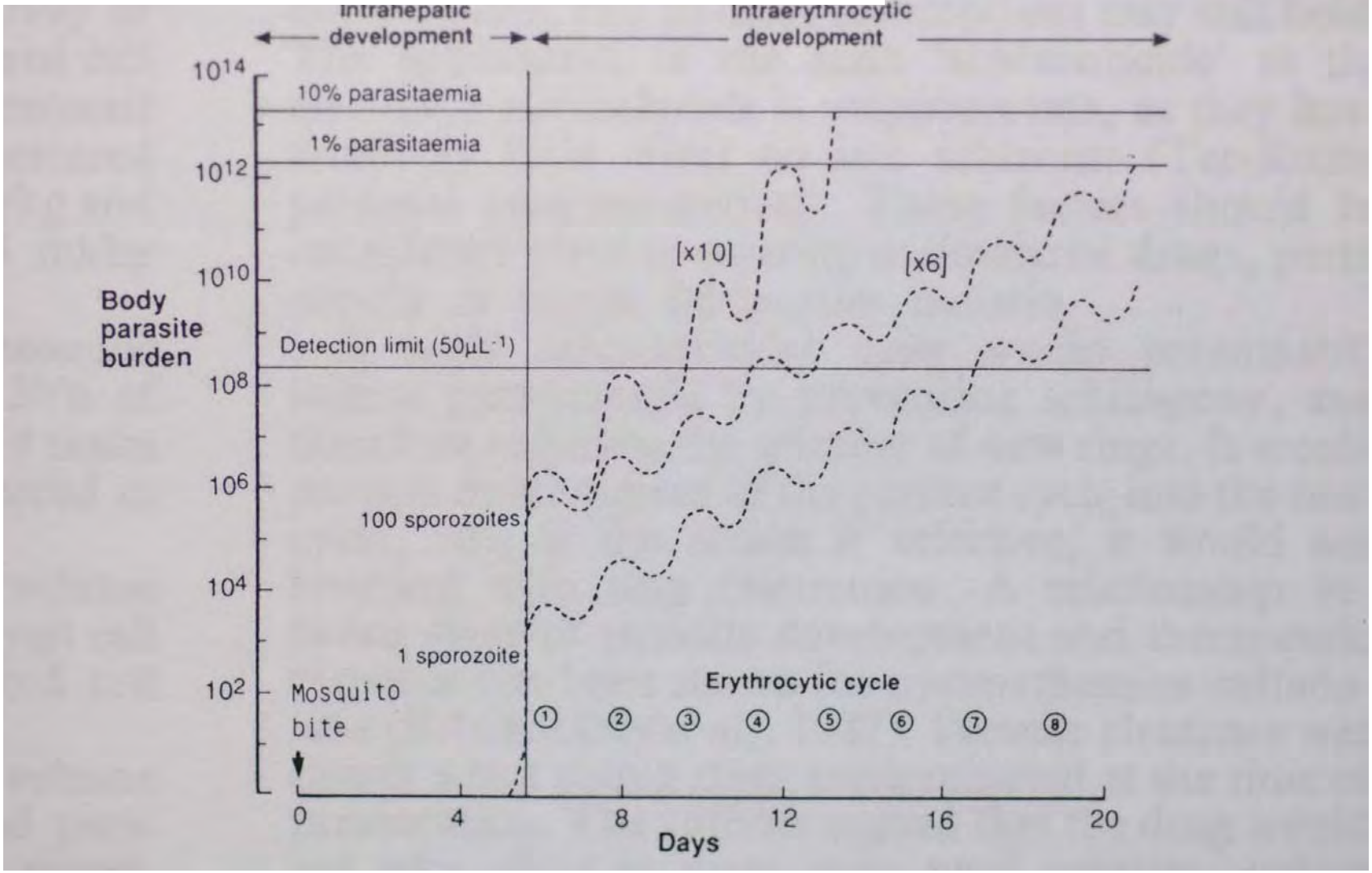


Fig 1.


Fast increase of parasite load
Cerebral malaria
IMF = 24/cycle
Low ring retention in the spleen
Acute evolution Organ failures
No or small splenomegaly No anemia
Total body parasite load
Parasitemia
10^{13}
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10%
1%
0,1%
0,01%
0,001 %
4*
3
2*
1
Fever threshold
Parasite detection threshold
Slow increase of parasite load
Severe malarial anaemia
High ring retention rate in the spleen
Subacute evolution No organ failure
Splenomegaly Anemia
100 sporozoites
IMF = 6/cycle
Hepatic stage
Erythrocytic stage
0
Number of days from infection
12
16

What about the « general » population ?



White N, Chapman D, Watt G. The effects of mutltiplication and synchronicity on the vascular distribution of parasites in falciparum malaria. Trans R Soc Trop Med Hyg 1992;86(6):590

Fig 1 B

Point # on Panel A	1 	2 	3 	4 
In vivo multiplication factor (IMF)	X 6	X 6	X 24	X 24
Ring retention rate	80%	80%	20%	20%
Parasitemia	1%	4%	1%	10%
Days with fever	6	7	3	4
Spleen volume Corresponding Hackett grade	380% 2-3	1100% 4-5	117% 0	270% 0-1
Hb (g/dl)	7.8	3.5	9.2	8.3

Clinical pattern of severe *Plasmodium falciparum* malaria in Sudan in an area characterized by seasonal and unstable malaria transmission

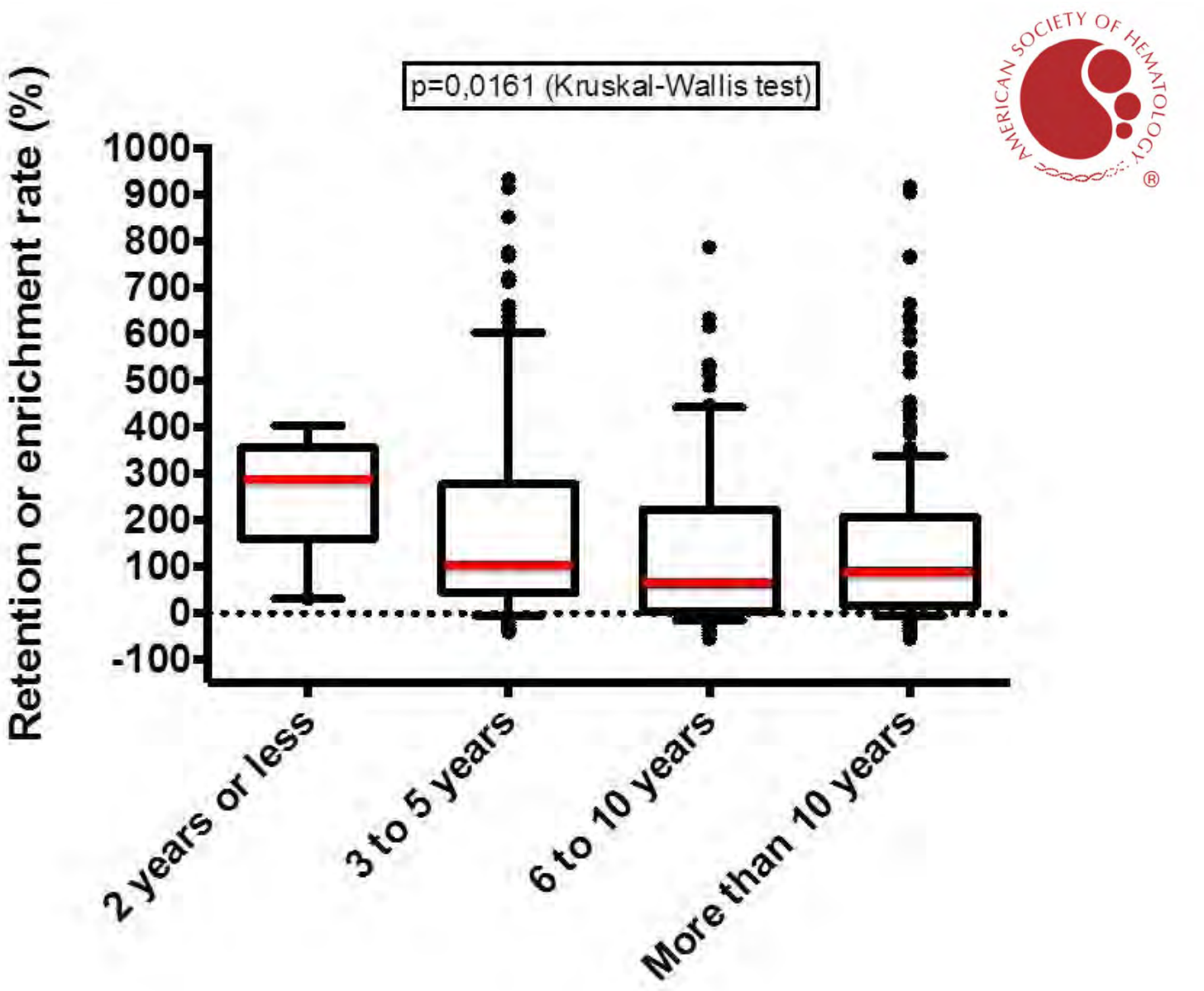
H.A. Giha[a,*], G. ElGhazali[a], T.M.E. A-Elgadir[a], I.E. A-Elbasit[a], E.M. Eltahir[a], O.Z. Baraka[b,c], M.M. Khier[c], I. Adam[d], M. Troye-Blomberg[e], T.G. Theander[f], M.I. Elbashir[a]

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-008-0665-5
2008

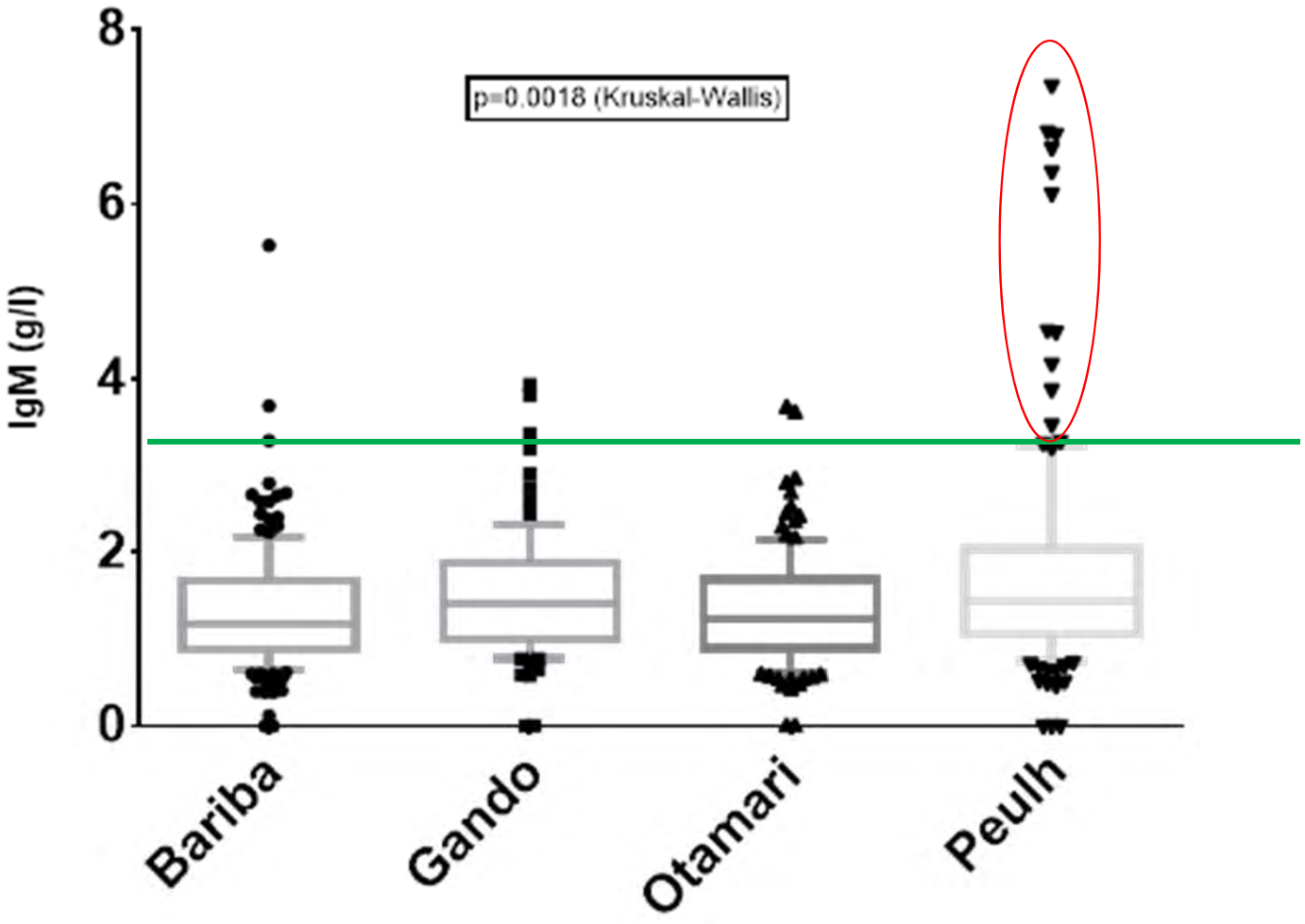
Table 1 Clinical characteristics (history and examination) of patients with severe malarial anemia (SMA) and cerebral malaria (CM)

Parameters	SMA (n = 94)	CM (n = 55)	P value
Gender	57/37	30/25	
Age in years, median [25%–75%]	3 [2–5]	6 [4–10]	<0.001, MW
Mean± SD	4.6±6.2	10.5±11.4	
Hemoglobin level	3.9 [3.15–4.5]	7.58 [6.98–9.0]	<0.001, MW
History of UM	0.91 (86)	0.89 (49)	0.874, χ^2
Number of UM episodes	1[1–3]	1 [1–1]	<0.051, MW
History of SM	0.07 (3/44)	0.22 (8/37)	0.107, χ^2
Fever duration	7 [4–15]	3 [3–4]	<0.001, MW
Convulsions	0.09 (4/44)	0.92 (34/37)	<0.001, χ^2
Splenomegaly	0.57 (54)	0.11 (6)	<0.001, χ^2
Spleen size	3.5 (1–5)	0 (0–0)	<0.001, MW
Hepatomegaly	0.36 (34)	0.07 (4)	0.003, χ^2
Liver size	1 [0–4]	0 [0–0]	0.001, MW
Hepatosplenomegaly	0.33 (31)	0.04 (2)	<0.001, χ^2

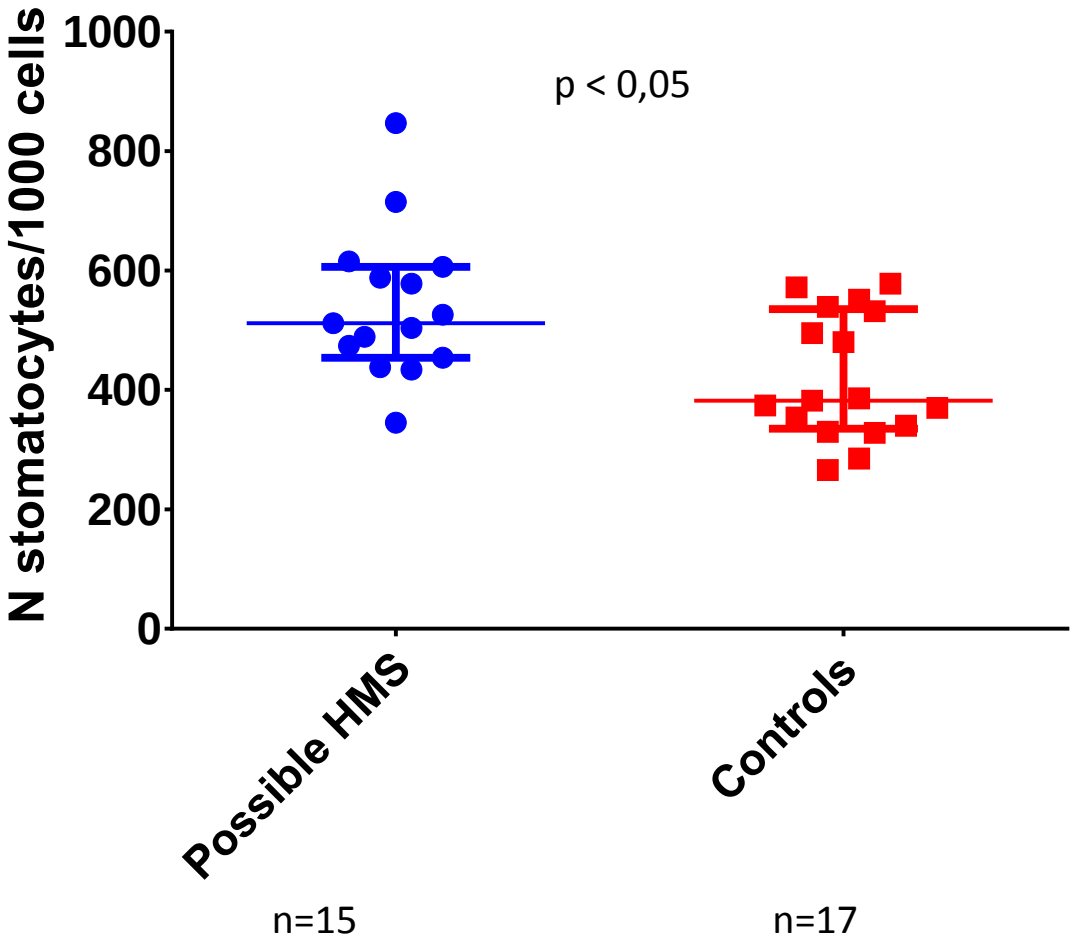
SMA, severe malarial anemia; CM, cerebral malaria; UM, uncomplicated malaria; SM, severe malaria; MW, Mann-Whitney rank sum test (median [25%–75%]); χ^2, Chi-square test


p=0,0161 (Kruskal-Wallis test)
Retention or enrichment rate (%)
1000
900
800
700
600
500
400
300
200
100
0
-100
2 years or less
3 to 5 years
6 to 10 years
More than 10 years

IgM according to ethnicity

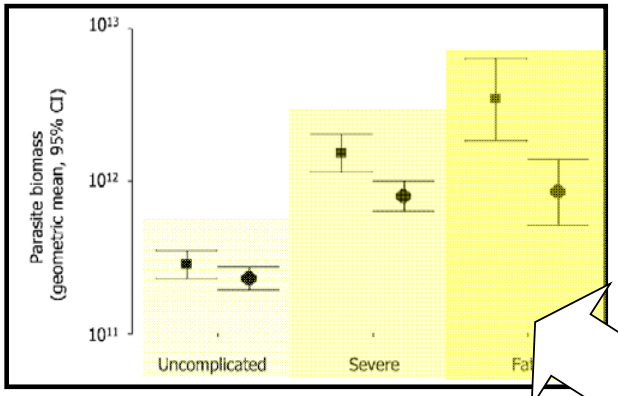


Stomatocytes in excess?



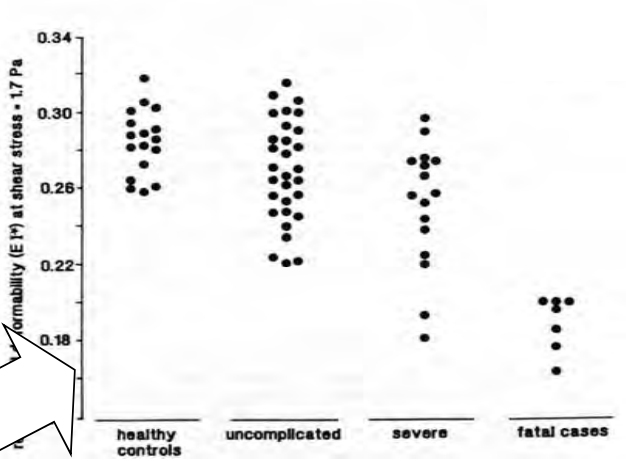
Malaria : Need to integrate the splenic factor

High parasite burden



Dondorp et al. PLoS Medicine 2005;2(8):e204

Elongation index of circulating RBC



Dondorp 97, 99

Poor prognosis

Splenic filtration