Verona, 15 marzo 2018

La terapia della malaria

Zeno Bisoffi

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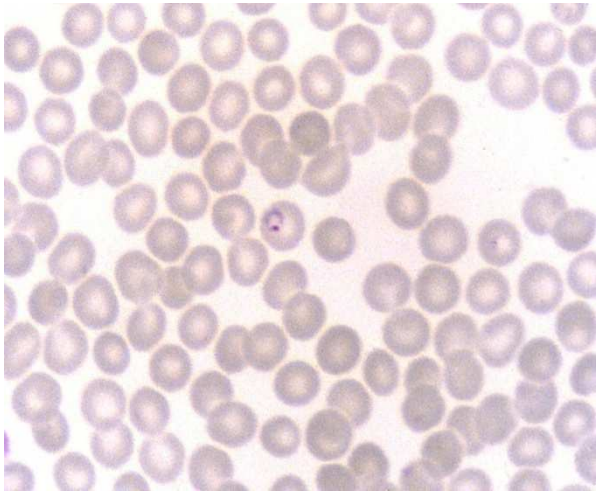
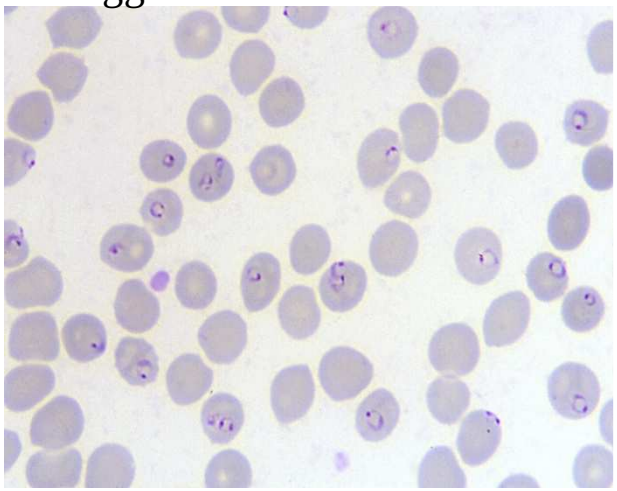
Centro Malattie Tropicali
NEGRAR - VERONA - ITALY
Centre for Tropical Diseases
Ospedale Sacro Cuore Don Calabria
FONDAZIONE DON GIOVANNI CALABRIA PER LE MALATTIE TROPICALI

Ritardo diagnostico e carica parassitaria

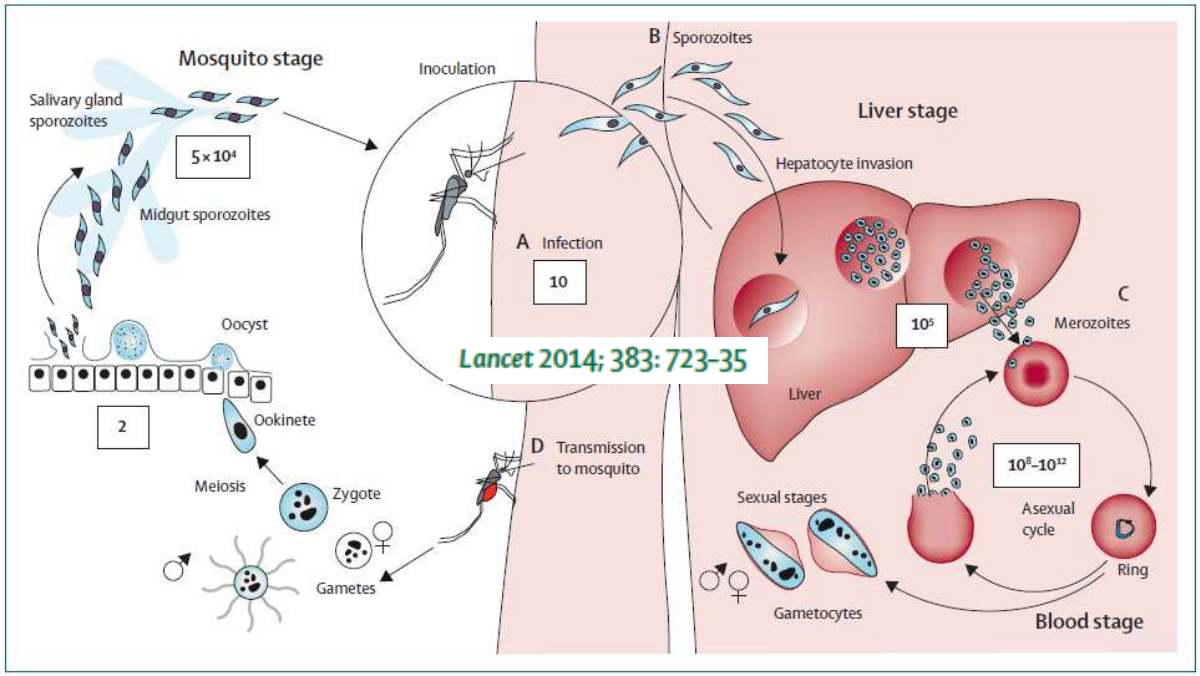
Turista (Kenya), 50 a, febbre da 3 h



Turista (G. Bissau), 36 a, febbre da 8 gg



Ritardo diagnostico prima causa di morte!!



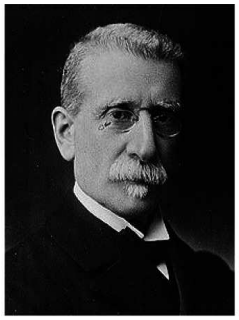
Lancet 2014; 383: 723–35

White N et al. Malaria. *Lancet* 2014;383:732-35

Malaria complicata

Vaso-occlusione o produzione di citochine?

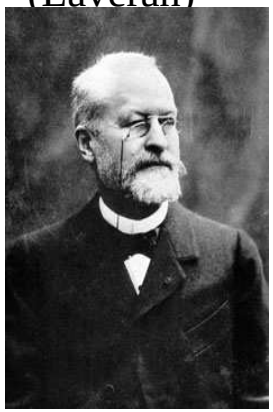
Scuola italiana (Marchiafava, Bignami)



Ettore Marchiafava 1847-1935

Amico Bignami 1862- 1929

Scuola francese (Laveran)



Alphonse Laveran (1845-1922), Nobel price in 1907 for discovering plasmodium as the causative agent of malaria

Efficacia degli interventi medici per malaria grave

Intervention	Result
Urea	No benefit
Aspirin	Harm
Heparin	Harm
Mannitol	Harm
Prostacyclin	No benefit
Corticosteroids	Harm
Plasmapheresis	No benefit
Pentoxyphylline	No benefit (? ↑ mortality)
Desferrioxamine	Harm
Low-dose quinine	Harm
Anti-TNF antibody	Harm
Hyperimmune globulin	No benefit

Intervention	Result
High-dose phenobarbitone	Harm
Exchange blood transfusion	No benefit
Fluid loading	Harm
Albumin	Harm
Erythropoetin	Ongoing
Activated charcoal	Ongoing
L-arginine	Ongoing
Sevuparin	Ongoing
Levamisole	Ongoing
Artesunate	*Reduced mortality by 35%*

The Journal of Infectious Diseases 2013;208:192–8

REVIEW ARTICLE

Lethal Malaria: Marchiafava and Bignami Were Right

Nicholas J. White,[1,2] Gareth D. H. Turner,[1,2] Nicholas P. J. Day,[1,2] and Arjen M. Dondorp[1,2]

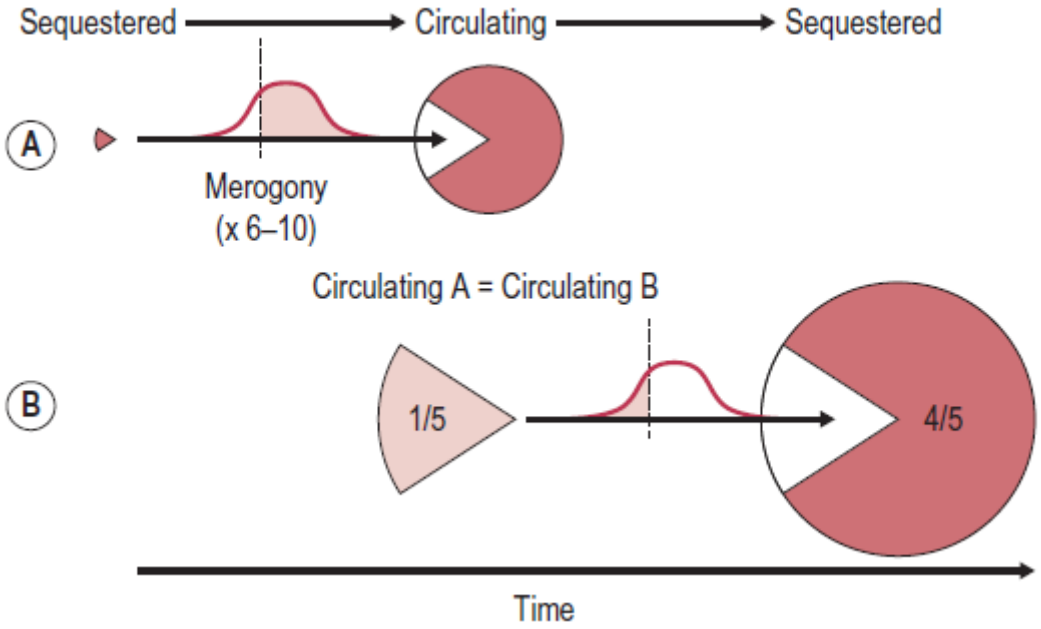
[1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; and [2]Centre for Tropical Medicine, Churchill Hospital, Oxford University, Oxford, United Kingdom

One hundred and twenty years ago, the Italian malariologists Marchiafava and Bignami proposed that the fundamental pathological process underlying lethal falciparum malaria was microvascular obstruction. Since then, several alternative hypotheses have been proposed. These formed the basis for adjunctive interventions, which have either been ineffective or harmful. Recent evidence strongly suggests that Marchiafava and Bignami were right.

Keywords. *P. falciparum*; malaria; cerebral malaria; pathology.

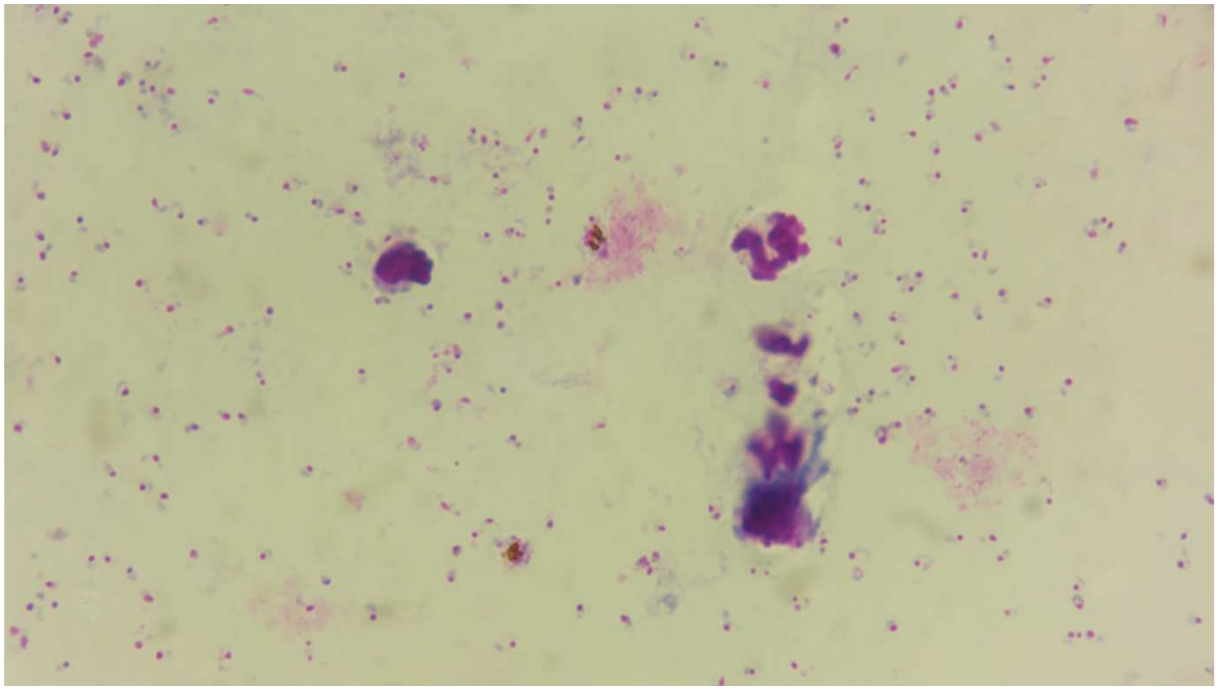
The Journal of Infectious Diseases 2013;208:192–8

Parassitemia periferica e “biomassa”

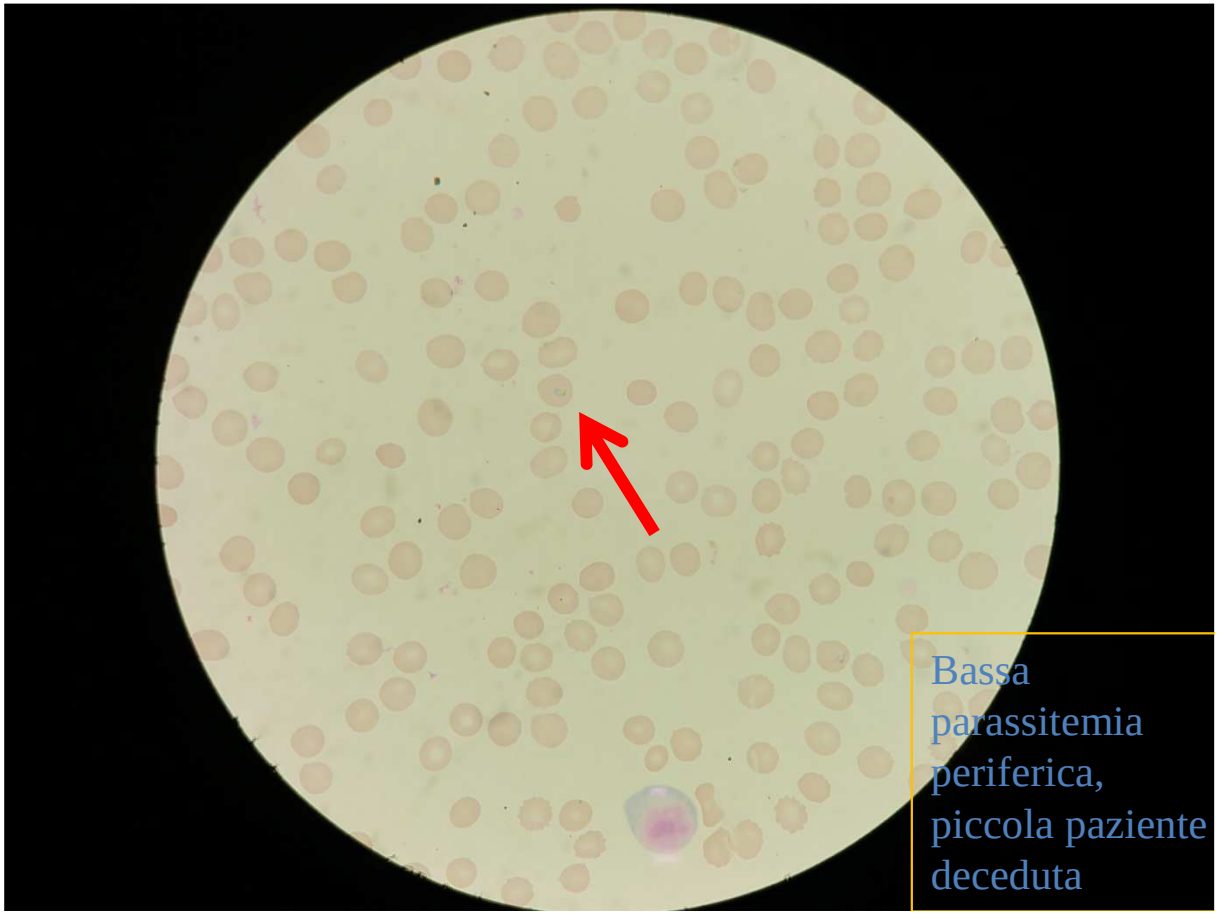


White N. Malaria. In Manson’s Tropical Diseases 2014, **ISBN:** 9780702053061

P. Falciparum parassitemia > 8%



Artesunato e.v., risolta senza complicazioni



Bassa parassitemia periferica, piccola paziente deceduta

Antimalarial drugs

- 4-amino quinolines: chloroquine, amodiaquine, piperaquine, pyronaridine
- Quinine, quinidine, mefloquine, halofantrine, lumefantrine
- Antifolates: pyrimethamine, proguanil, sulfadoxine, dapsone
- Antibiotics
- Artemisinin and derivatives
- 8-amino quinolines: primaquine, tafenoquine

Resistance (Pf) to chloroquine

1960

1965

1978

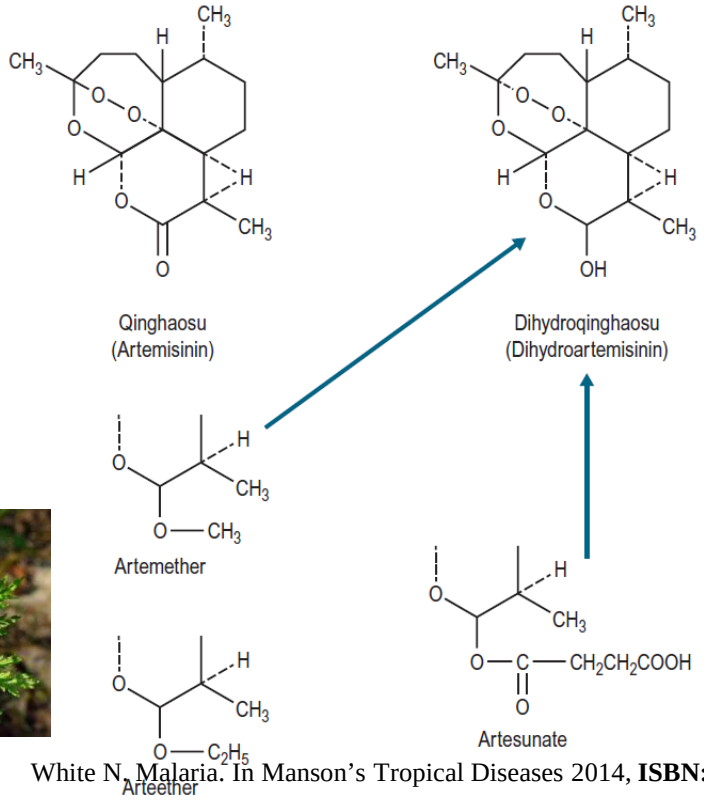
1989

http://www.tigr.org/tdb/edb/pfdb/CQR.html

Treatment: definitions

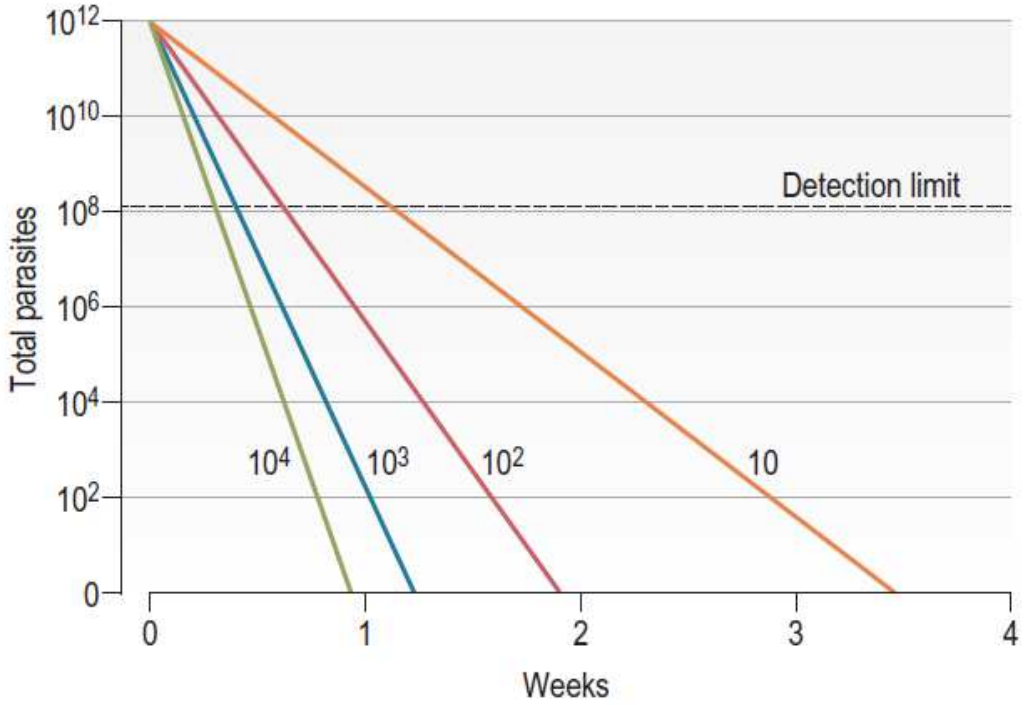
- *Combination therapy (CT)* **: simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite;**
- *Artemisinin-based combination therapy* **(ACT) combination therapy with an artemisinin derivative**; it can be a fixed combination

Artemisinin derivatives



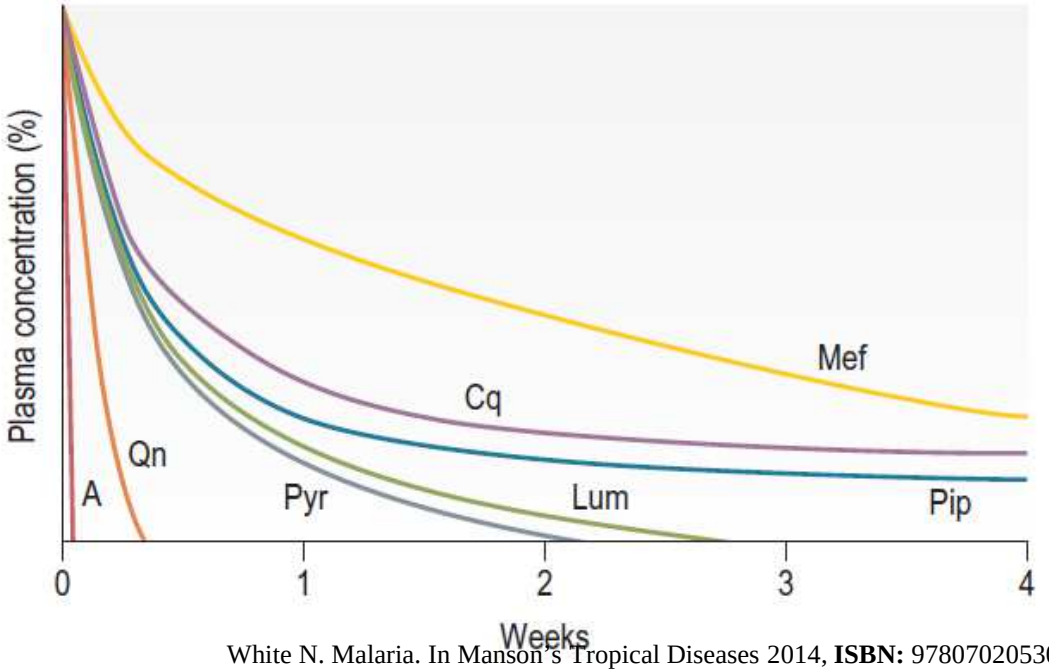
White N, Malaria. In Manson's Tropical Diseases 2014, **ISBN:** 9780702053061

Farmacodinamica dei principali antimalarici

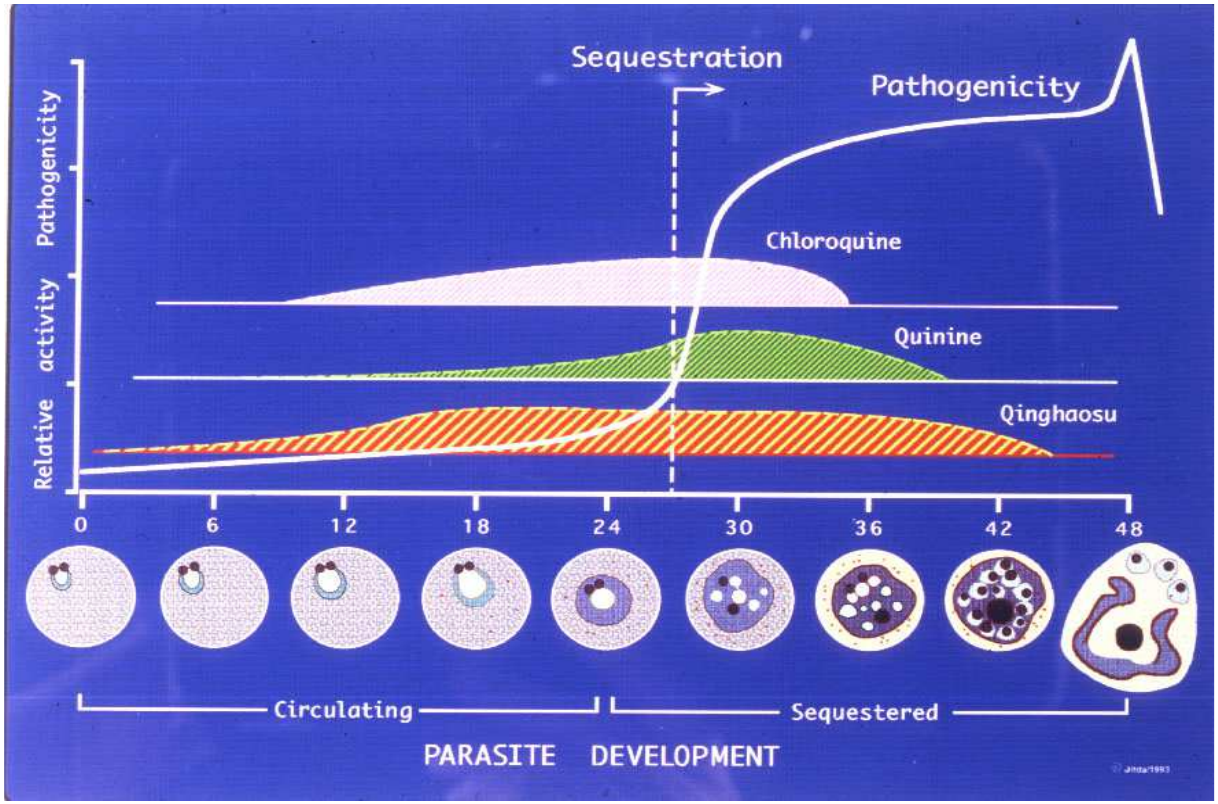


White N. Malaria. In Manson's Tropical Diseases 2014, **ISBN:** 9780702053061

Farmacocinetica



White N. Malaria. In Manson's Tropical Diseases 2014, **ISBN:** 9780702053061

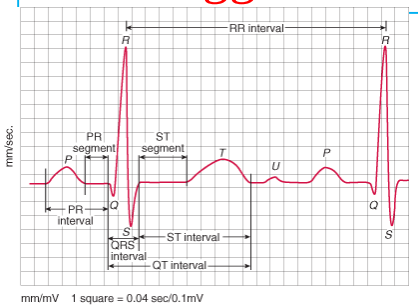


Courtesv Prof. Umberto D'Alessandro. 2018

Malaria da P. falciparum non complicata

Dihydroartemisinin-piperaquine 20-160 mg or 40-320 mg (adulti)

-QTc lungo >440ms
- il dosaggio



Dosaggio (adulti):

<75 kg **3** compresse
>75 kg **4** compresse

Indicazioni WHO:

60-80 kg **4** compresse
80-100 kg **5**

Roseau et al. Malar J (2016) 15:479
DOI 10.1186/s12936-016-1535-8

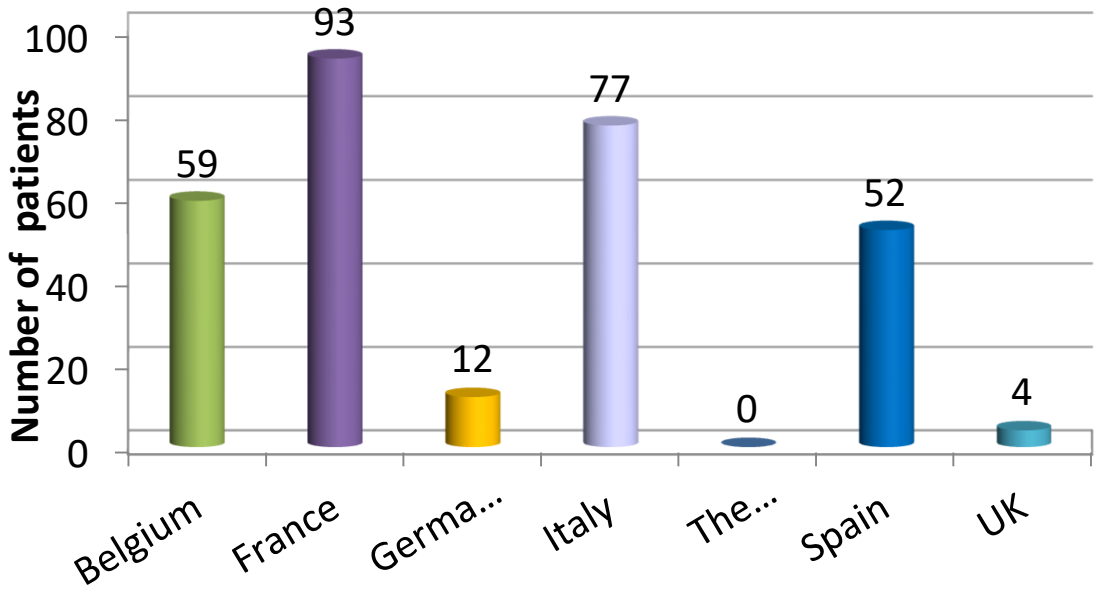
Malaria Journal

CASE REPORT Open Access

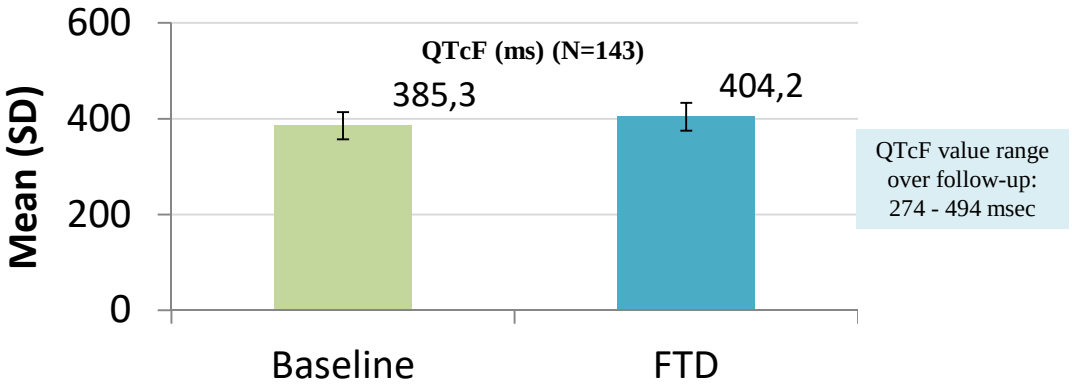
Failure of dihydroartemisinin plus piperaquine treatment of falciparum malaria by under-dosing in an overweight patient

Jean Baptiste Roseau[1,2], Bruno Pradines[3,4,5*], Nicolas Paleiron[2,6], Serge Vedy[2], Marylin Madamet[4,5,7], Fabrice Simon[8,9] and Emilie Javelle[8*]

Eurartesim Safety study
Recruitment by Country (N=297)



QTcF Description in the QTcF Population



QTcF according to ranges at Baseline and at Final treatment day

NB: studio Eurartesim Pregnancy “ongoing” ma… difficile reclutare!!

Normal QTc: value < 430 msec for males and children and < 450 msec for females.
Borderline QTc: value between 430 and 450 msec (included) for males and children and between 450 and 470 (included) msec for females.
Prolonged QTc: value > 450 msec for males and children and > 470 for females.

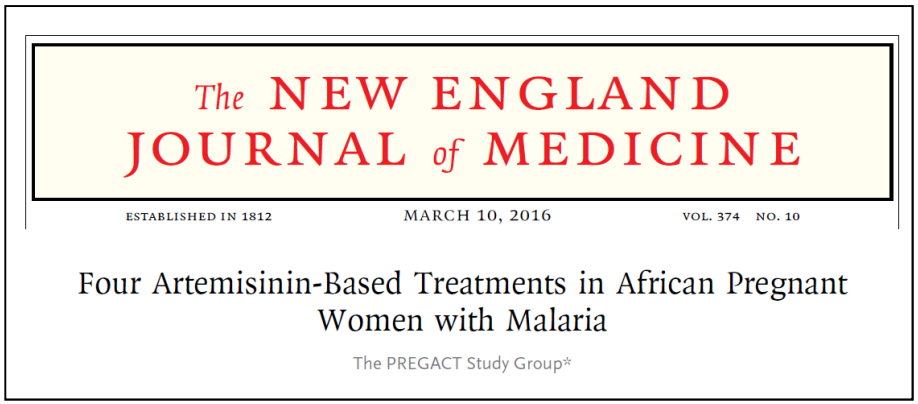
Treating uncomplicated *P. Falciparum* malaria in special risk groups

- Treat pregnant women with uncomplicated *P. falciparum* or chloroquine resistant *P. vivax* malaria in the first trimester with seven days of quinine plus clindamycin (if unavailable use an ACT).

- Treat infants weighing less than 5 kg with uncomplicated *P. falciparum* malaria with an ACT dosed at the same mg/kg target as for children weighing 5 kg.

  Conditional recommendation, Low quality evidence

- Treat adults and children with proven uncomplicated *P. ovale*, *P. malariae*, or *P. knowlesi* malaria with either a three-day course of an ACT known to be effective in the region or chloroquine.



Largest ever clinical trial on malaria during pregnancy in Africa
Results of study involving over 3000 women in Burkina Faso, Ghana, Malawi and Zambia

Conclusion

- DHA-PQ seems the most suitable treatment for uncomplicated malaria in pregnancy (good tolerability, high efficacy and long post-treatment prophylactic period)

Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study

Lancet Infect Dis 2016; 16: 576–83

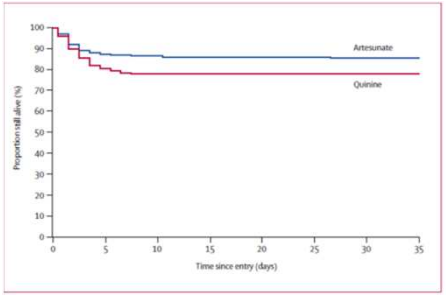
Kerryn A Moore, Julie A Simpson, Moo Kho Paw, Mu Pawjoy Pimanpanarak, Jacher Wiladphaingern, Marcus J Rijken, Podjanee Jittamala, Nicholas J White, Freya J I Fowkes, François Nosten, Rose McGready

Interpretation First-trimester falciparum and vivax malaria both increase the risk of miscarriage. We noted no evidence of an increased risk of miscarriage or of major congenital malformations associated with first-line treatment with an artemisinin derivative compared with quinine. In view of the low efficacy of quinine and wide availability of highly effective artemisinin-based combination therapies, it is time to reconsider first-trimester antimalarial treatment recommendations.

Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group*

Lancet 2005; 366: 717–25



o Multi-centre, open-label, randomised controlled trial
Comparing parenteral artesunate and parenteral quinine in (mostly) adults and children from Bangladesh, Myanmar, India andIndonesia.
Absolute reduction in mortality with artesunate of 34.7%
(95% CI 18.5–47.6; P = 0·0002)

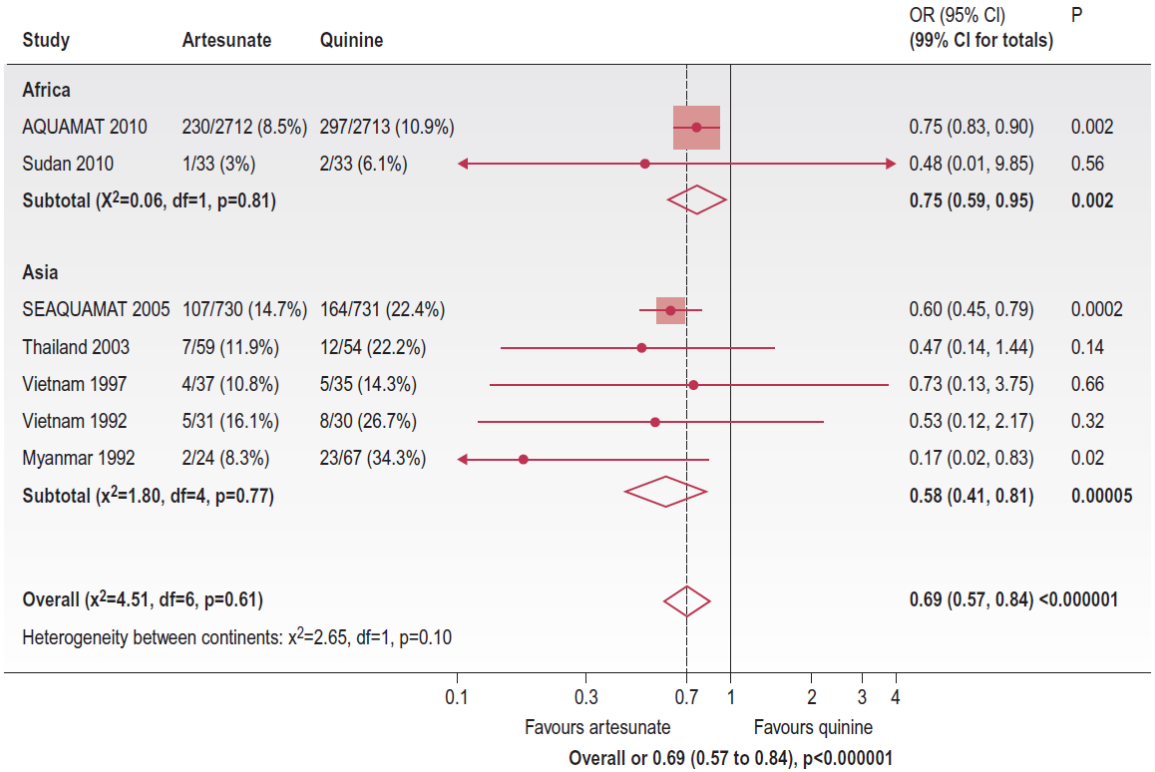
Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

Arjen M Dondorp, Caterina I Fanello, Ilse C E Hendriksen, Ermelinda Gomes, Amir Seni, Kajal D Chhaganlal, Kalifa Bojang, Rasaq Olaosebikan, Nkechinyere Anunobi, Kathryn Maitland, Esther Kivaya, Tsiri Agbenyega, Samuel Blay Nguah, Jennifer Evans, Sa
Catherine Kahabuka, George Mtove, Behzad Nadjm, Jacqueline Deen, Juliet Mwanga-Amumpaire, Margaret Nansumba, Corine Karema, Noella Umulisa, Aline Uwimana, Olugbenga A Mokuolu, Olanrewaju T Adedoyin, Wahab B R Johnson, Antoinette K Tshefu, Marie A Onyamboko, Tharisara Sakulthaew, Wirichada Pan Ngum, Kamolrat Silamut, Kasia Stepniewska, Charles J Woodrow, Delia Bethell, Bridget Wills, Martina Oneko, Tim E Peto, Lorenz von Seidlein, Nicholas P J Day, Nicholas J White, for the AQUAMAT group*

Lancet 2010; 376: 1647–57

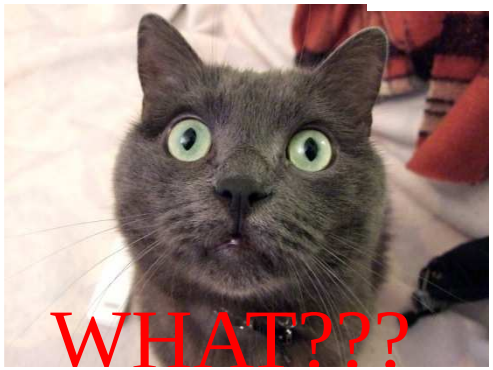
o An open-label, randomised trial comparing parenteral artesunate and parenteral quinine in children (<15 years) from 11 centres in nine African countries.
Relative reduction in mortality with artesunate of 22.5% (95% CI 8.1–36.9; P = 0.0022).
Artesunate also reduced the incidence of convulsions and coma. These are often associated with subsequent neurological sequelae.

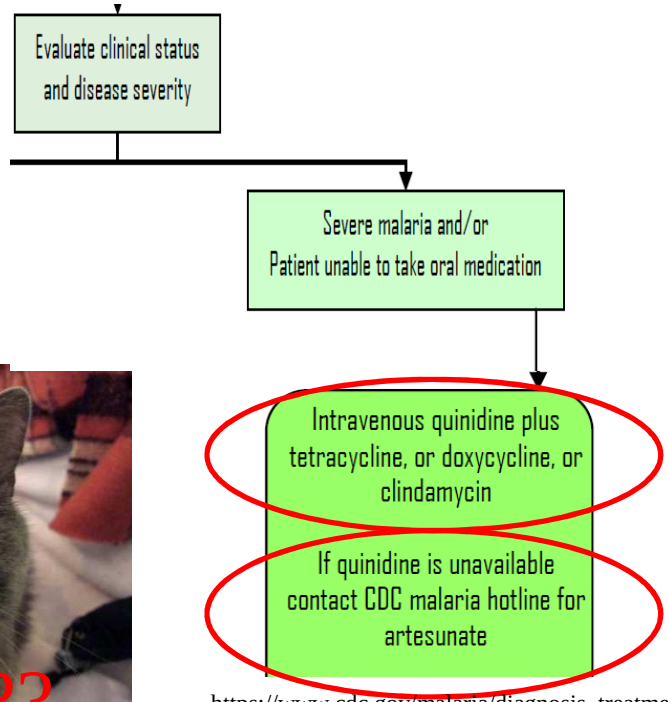
Metanalisi artesunato vs chinino, malaria grave



Cochrane Database Syst Rev. 2012 Jun 13;(6):CD005967. doi: 10.1002/14651858.CD005967.pub4.

Ma artesunato non è GMP… le linee guida del CDC





https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Am. J. Trop. Med. Hyg., 83(2), 2010, pp. 274–276
doi:10.4269/ajtmh.2010.10-0128

Case Report: Combined Intravenous Treatment with Artesunate and Quinine for Severe Malaria in Italy

Alessandro Bartoloni,* Lina Tomasoni, Filippo Bartalesi, Luisa Galli, Spartaco Sani, Sara Veloci, Lorenzo Zammarchi, Alessandro Pini, and Francesco Castelli

Clinica Malattie Infettive, Dipartimento Area Critica Medico-Chirurgica, Università degli Studi di Firenze, Firenze, Italy; SOD Malattie Infettive e Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; Istituto Malattie Infettive e Tropicali, Università di Brescia, Brescia, Italy; Dipartimento di Pediatria, Università di Firenze, Firenze, Italy; UO Malattie Infettive, Spedali Riuniti Livorno, Livorno, Italy

Epidemiologic, clinical, and laboratory data from eight patients with severe falciparum malaria treated with combined intravenous artesunate and quinine, Italy, 2008–2009*

Patient no. (gender/ age in years)	Reason for travel	Country of disease acquisition	WHO severe malaria criteria	Days from symptom onset to therapy	Initial IV therapy†		Follow-on oral therapy		Parasitemia level (%)							Stay in ICU	Supportive care	Length of hospital stay (days)
					Drug	Day	Drug	Day	Day 0	12 h	Day 1	Day 2	Day 3	Day 4	Day 5			
1 (F/32)	Volunteer	Mali	Impaired consciousness, severe anemia, hyperparasitemia	9	AS+Q	1–3	AR+L	4–6	10		0.5	0	0			3	Oxygen; blood transfusion	20 (recrudescence at day 11)
2 (M/40)	Tourism	Ivory Coast	Impaired consciousness, acute renal failure, jaundice, pulmonary edema, hyperparasitemia	4	AS+Q	1–6			10		18	0.1	0.1	0.005	0	15	Oxygen; mechanical ventilation; platelet transfusion	25
3 (F/1)	VRF	Nigeria	Impaired consciousness, severe anemia, hyperparasitemia	9	AS+Q	1–4	AR+L	5–7	8		1		0			0	Blood transfusion	7
4 (F/3)	VRF	Burkina Faso	Impaired consciousness, severe anemia, jaundice, hemoglobinuria, hyperparasitemia	2	AS§+Q‡	1–5	Q	6–9	12	2	0					1		11
5 (F/6)	VRF	Burkina Faso	Impaired consciousness, severe anemia, hemoglobinuria, hyperparasitemia	4	AS+Q‡	1–4	Q	5–8	15	1		0.004		0		2	Blood transfusion	14
6 (M/30)	Volunteer	Guinea Bissau	Coma, pulmonary edema, hyperparasitemia	10	AS+Q	1–2			15	3	0					1	Oxygen; mechanical ventilation	2 (exitus)
7 (M/6)	VRF	Ghana	Impaired consciousness, severe anemia, jaundice, hyperparasitemia	4	AS+Q	1–3	Q	4–8	15	7	3	0				2	Platelet transfusion	8
8 (M/7)	VRF	Burkina Faso	Severe anemia, hyperparasitemia	1	AS+Q‡	1–3	Q	4–7	20	11	3	0				0		7

*WHO = World Health Organization; VFR = visiting friends and relatives; ICU = intensive care unit; AS = artesunate; Q = quinine; AR = arthemeter; L = lumefantrine; IV = intravenous.
† The initial therapy was IV artesunate (2.4 mg/kg at time 0, 12, and 24 hours the first day and then one time daily) and IV quinine (a loading dose of 20 mg/kg followed by 10 mg/kg 3 times a day).

Concerns with safety of i.v. artesunate

International Society of Travel Medicine
Promoting healthy travel worldwide

Journal of Travel Medicine, 2017, 1–2
doi: 10.1093/jtm/tax091
Brief communication

Brief communication

Severe post-artesunate delayed onset anaemia responding to corticotherapy: a case report

Delphine Lebrun, MD[1,2], Thierry Floch, MD[3], Aurélie Brunet, MD[1], Gautier Julien, MD[1], Juliette Romaru, MD[1], Yohan N'Guyen, MD[1], Joël Cousson, MD[3], Aurélien Giltat, MD[1], Dominique Toubas, MD, PhD[4], and Firouzé Bani-Sadr, MD, PhD[1*]

International Journal of Infectious Diseases 29 (2014) 268–273

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

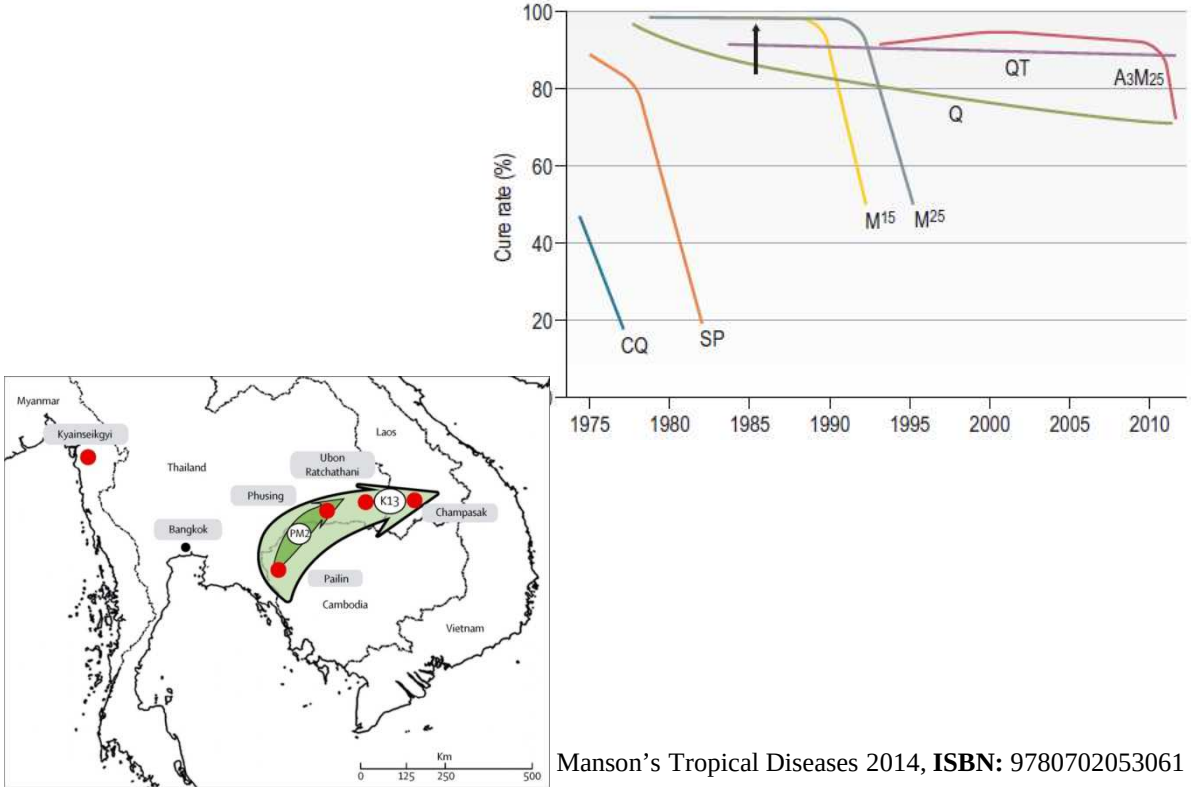
Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence

Khalid Rehman[a], Felix Lötsch[a,b], Peter G. Kremsner[b,c], Michael Ramharter[a,b,c,*]

[a] Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna, Austria
[b] Centre de Recherches Médicales de Lambaréné, Hôpital Albert Schweitzer, Lambaréné, Gabon
[c] Institut für Tropenmedizin, Universität Tübingen, Wilhelm Straße 27, 72074 Tübingen, Germany

"Pitted erythrocytes" the most likely explanation

Il declino dell’efficacia di alcuni antimalarici in Tailandia – Cambogia - Birmania



Manson’s Tropical Diseases 2014, **ISBN:** 9780702053061

Travel Medicine and Infectious Disease 14 (2016) 548–550

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevierhealth.com/journals/tmid

Editorial

The threat of artemisinin resistant malaria in Southeast Asia

In the absence of further information severe falciparum malaria from areas of known artemisinin resistance should be treated with both artesunate and quinine in full doses. NJ White

Am. J. Trop. Med. Hyg., 83(2), 2010, pp. 274–276
doi:10.4269/ajtmh.2010.10-0128

Case Report: Combined Intravenous Treatment with Artesunate and Quinine for Severe Malaria in Italy

Alessandro Bartoloni,* Lina Tomasoni, Filippo Bartalesi, Luisa Galli, Spartaco Sani, Sara Veloci, Lorenzo Zammarchi, Alessandro Pini, and Francesco Castelli

Artemisinin Combination Treatments (ACT): attenzione alle resistenze!

Gobbi et al. Malar J (2016) 15:525
DOI 10.1186/s12936-016-1572-3

Malaria Journal

CASE REPORT Open Access

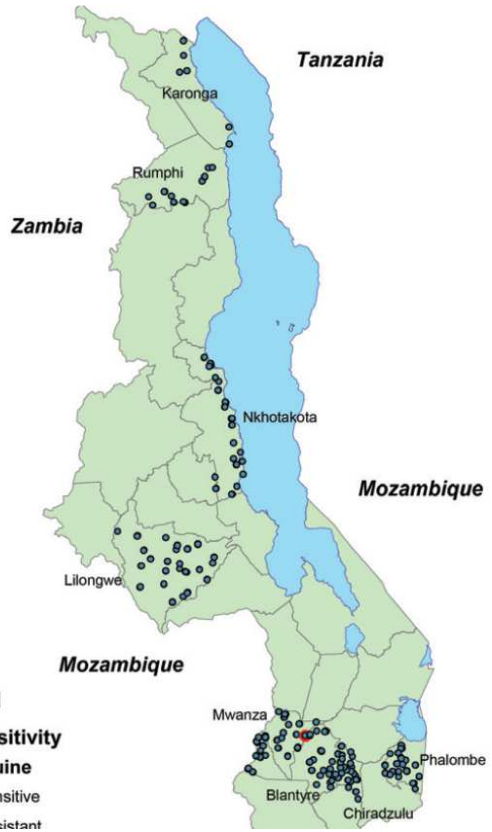
Failure of dihydroartemisinin-piperaquine treatment of uncomplicated *Plasmodium falciparum* malaria in a traveller coming from Ethiopia

Federico Gobbi[1*], Dora Buonfrate[1], Michela Menegon[2], Gianluigi Lunardi[1], Andrea Angheben[1], Carlo Severini[2], Stefania Gori[1] and Zeno Bisoffi[1]

BRIEF REPORT

Return of Widespread Chloroquine-Sensitive *Plasmodium falciparum* to Malawi

Anne E. P. Frosch,[1,2,a] Miriam K. Laufer,[1] Don P. Mathanga,[4] Shannon Takala-Harrison,[1] Jacek Skarbinski,[3,b] Cassidy W. Claassen,[1] Fraction K. Dzinjalamala,[5] and Christopher V. Plowe[1]



The Journal of Infectious Diseases 2014;210:1110–4