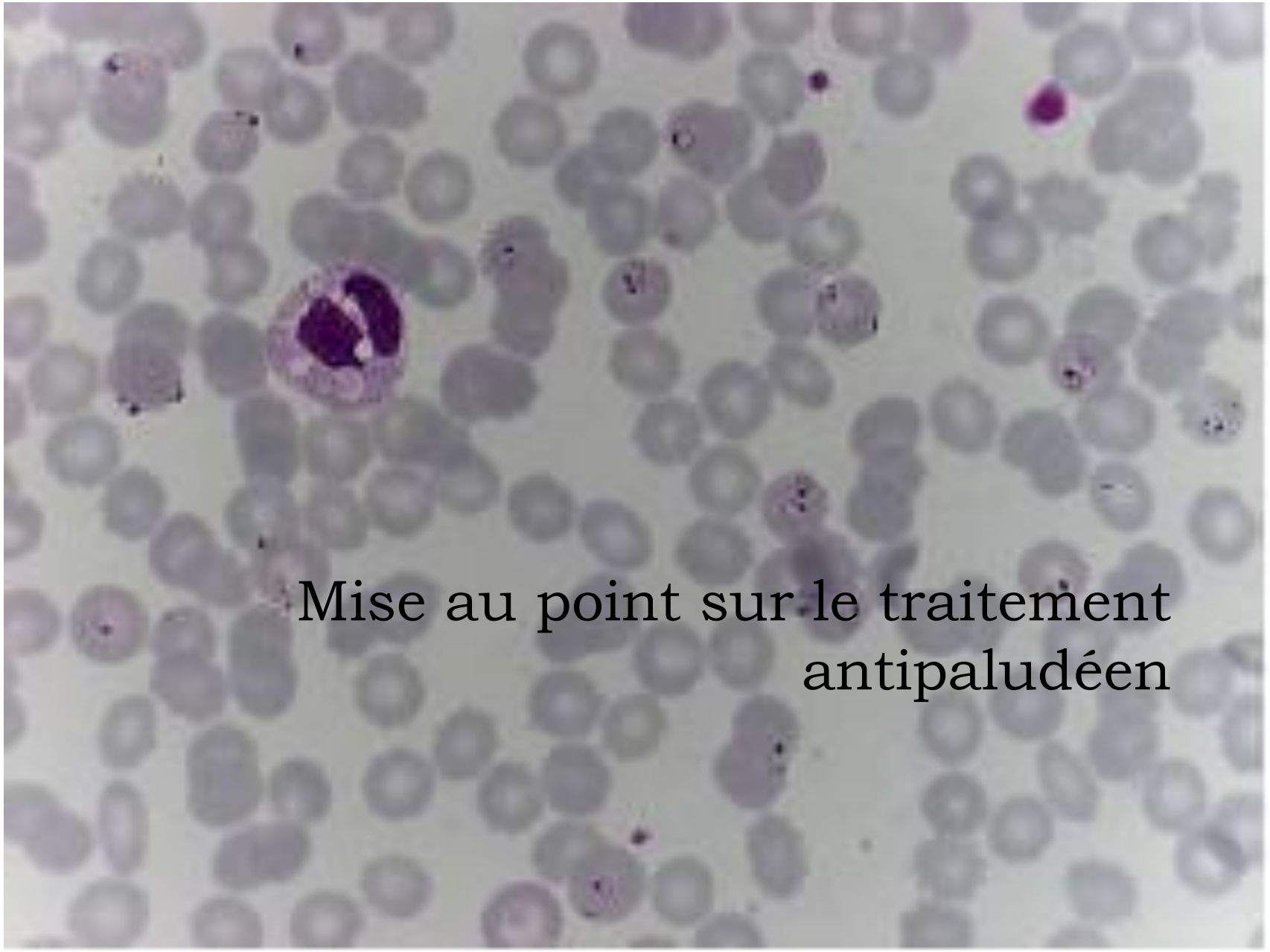
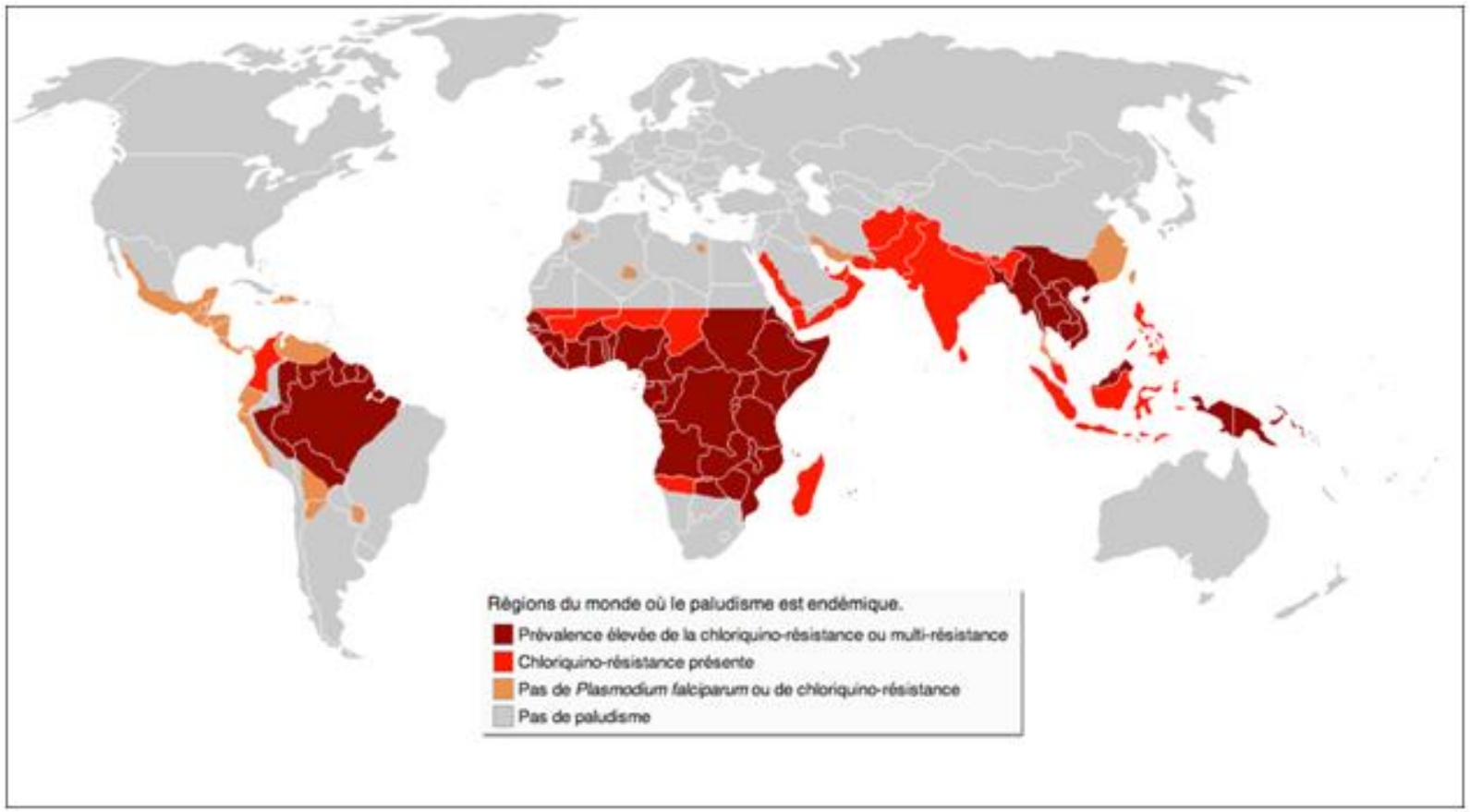


Mise au point sur le traitement antipaludéen

Introduction

- Maladie tropicale et intertropicale
- Déclaration obligatoire
- Urgence diagnostique et thérapeutique
- Ttt changé depuis chloroquinorésistance
- Emergence récente de « résistance » vav artémisinine
- Monothérapie délaissée pour les bithérapies
- Association comprenant un dérivé d'artémisinine est recommandée

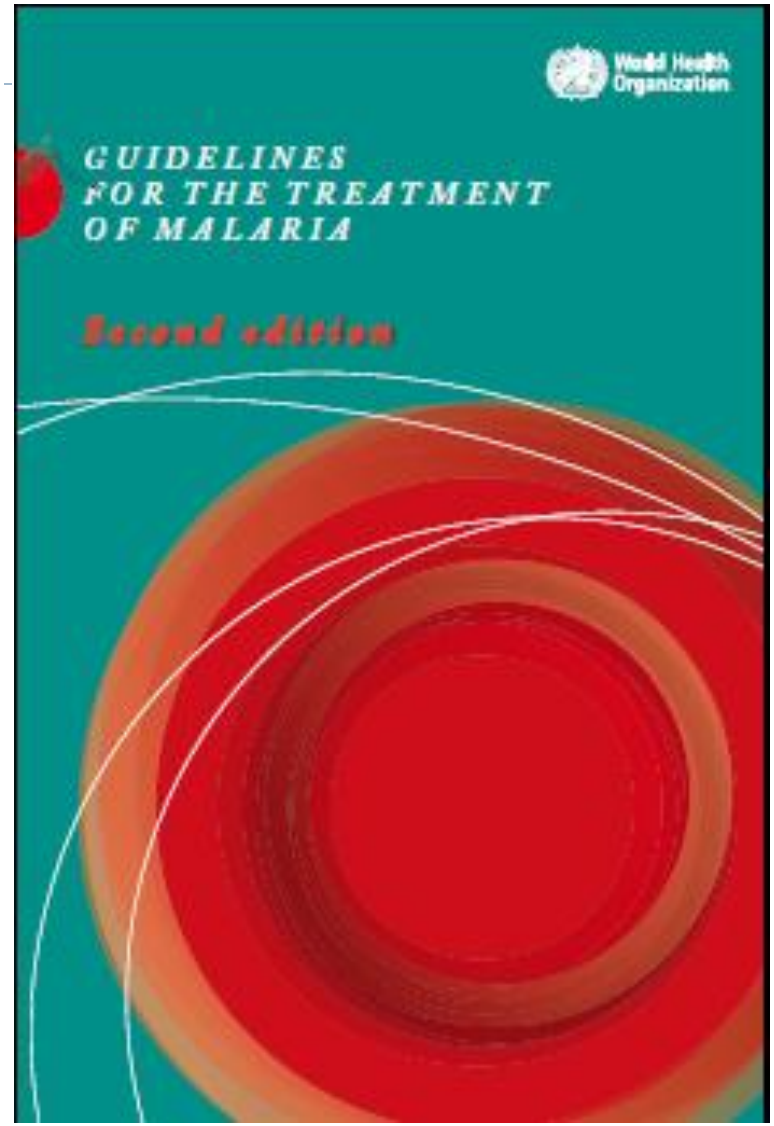
Zones de chloroquinorésistances



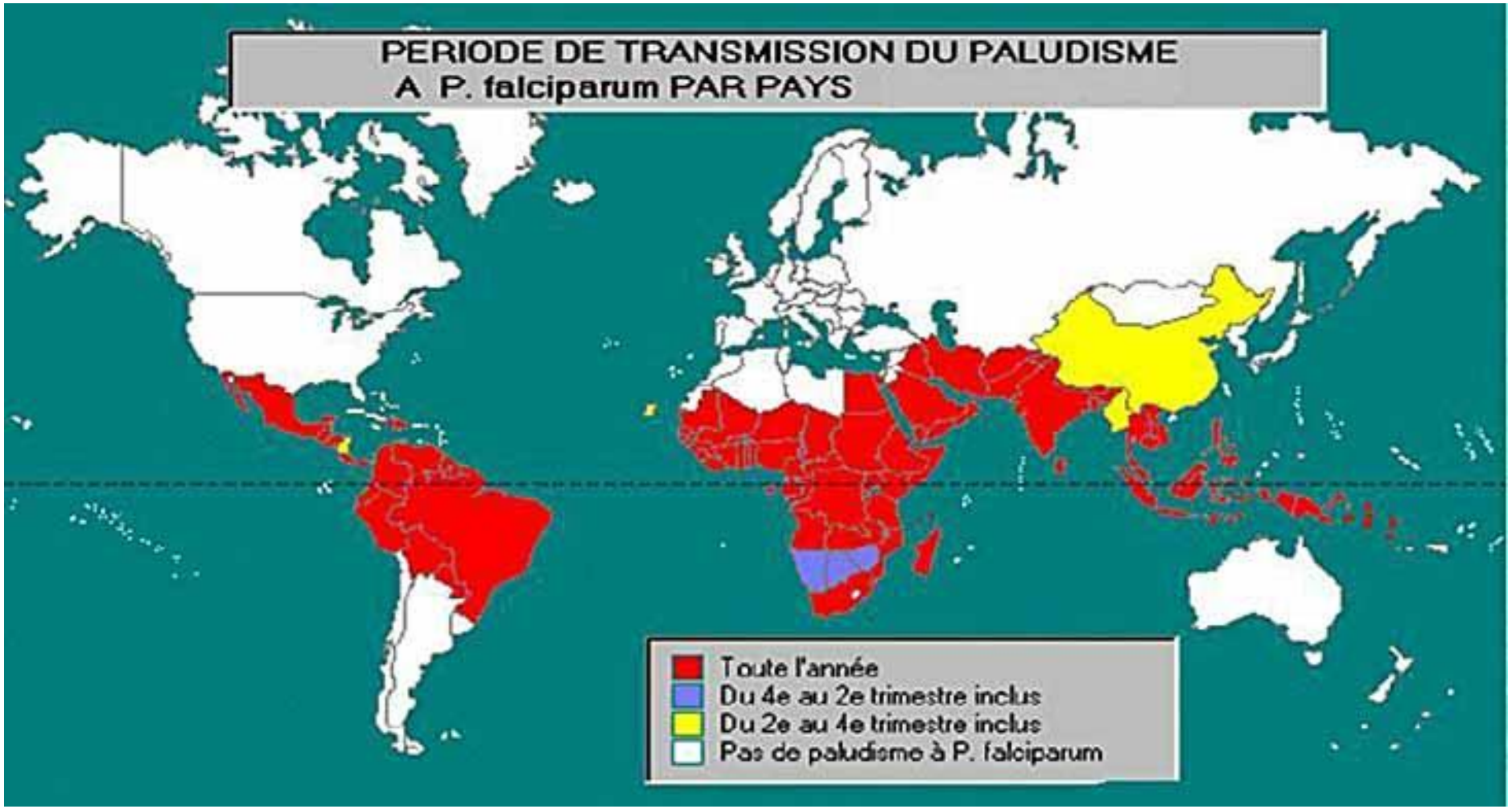
Guidelines

Guidelines for Treatment of Malaria in the United States

(Based on drugs currently available for use in the United States – updated July 1, 2013)


World Health Organization
GUIDELINES FOR THE TREATMENT OF MALARIA
Second edition

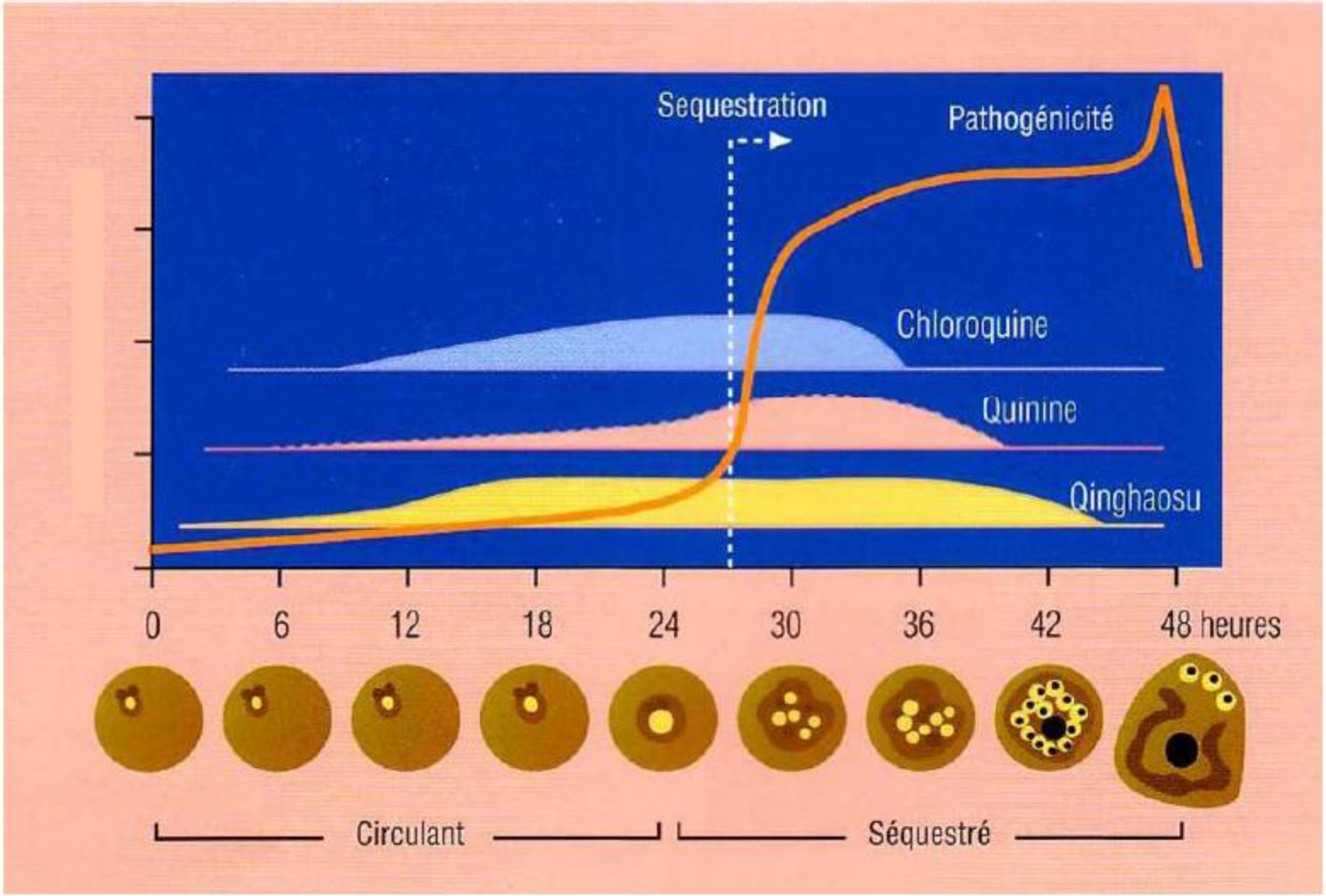
P. falciparum


PERIODE DE TRANSMISSION DU PALUDISME
A P. falciparum PAR PAYS
Toute l'année
Du 4e au 2e trimestre inclus
Du 2e au 4e trimestre inclus
Pas de paludisme à P. falciparum

Historique

- Années 50: élimination du paludisme des pays occidentaux
- 1979: dernier cas autochtone tunisien
- Chloroquinorésistance
- Dérivés du quinghaosu recommandés à partir des années 2003
- « résistance » aux dérivés de l'artémisinine
- Expansion des résistances à sulfadoxine-pyriméthamine
- Associations depuis 2006

Phases auxquelles 3 antipaludiques sont actifs en fonction du cycle érythrocytaire de *P. falciparum (White NJ et al. 1989)*



Mono ou bithérapie, laquelle?

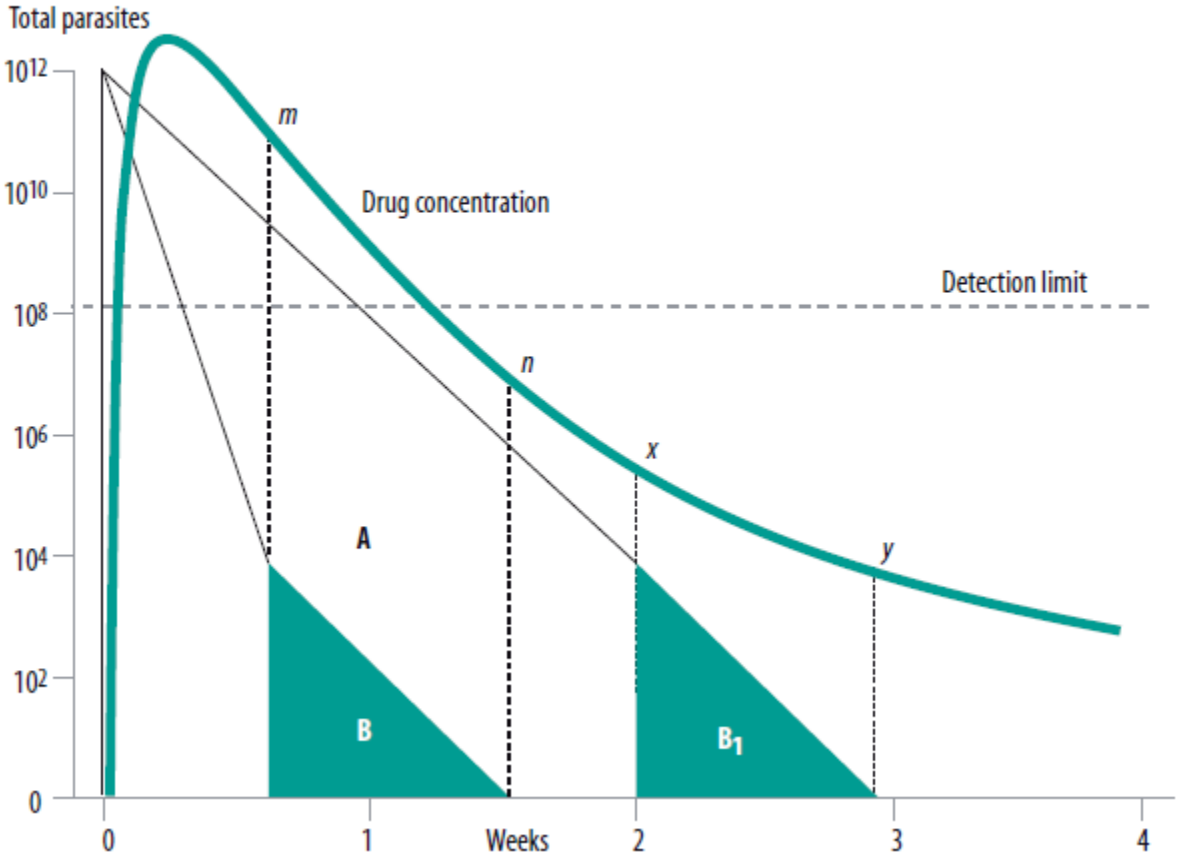
- Bithérapie pour deux raisons
  - Association plus efficace et plus rapide
  - Un mutant de novo à l'un des médicaments, sera tué par le deuxième
- Association recommandée par l'OMS

RECOMMENDATION: *withdrawal of non-ACTs for treatment of uncomplicated falciparum malaria*

Artemisinin-based combination therapies should be used in preference to amodiaquine plus sulfadoxine-pyrimethamine for the treatment of uncomplicated *P. falciparum* malaria.
Strong recommendation, moderate quality evidence

Guidelines for the treatment of malaria – 2nd edition

Figure A6.2 **Effectiveness of artesunate plus mefloquine combination on parasite levels and resistance**



Accès grave

Clinical features:

- impaired consciousness or unrousable coma
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- failure to feed
- multiple convulsions – more than two episodes in 24 h
- deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- haemoglobinuria
- abnormal spontaneous bleeding
- pulmonary oedema (radiological)

Laboratory findings:

- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- haemoglobinuria
- hyperparasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5% or 250 000/µl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 µmol/l).

Accès grave

- Urgence médicale
- Adulte:
  - Artesunate IV ou IM
  - Alternative: arthémeter ou quinine
- Si conditions impropres au ttt
  - Débuter ttt avant transfert par voie rectale ou IM
  - Dérivés d'artémisinine ou quinine
    - Artesunate: 10 mg/kg suppositoire
    - Quinine rectale: 12 mg/kg
    - Artemether: 10-40 mg/kg

Nouvelles recommandations OMS

TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

- Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.

  Strong recommendation, high quality evidence.

Protocole

Adulte

- Aresunate
  - 2,4 mg/kg IM ou IV
  - h0, h12, h24 puis 1x/j
- Artemether
  - 3,2 mg/kg IM à h0
  - puis 1,6 mg/kg/j
- Quinine
  - 16 mg/kg puis 8 mg/kg/8h

Enfant

- Artesunate
  - 2,4 mg/kg IM, IV
  - h0, h12, h24 puis 1x/j
- Artemether
  - 3,2 mg/kg IM à h0
  - puis 1,6 mg/kg/j
- Quinine
  - 16 mg/kg puis 8 mg/kg/8h

Conduite du traitement

- Voie injectable au moins pendant 24 h
- Prise en charge des complications
- En cas d'amélioration, compléter par une cure de
  - ACT (association comprenant de l'artémisinine)
  - Artesunate + clindamycine ou doxycycline
  - Quinine + clindamycine ou doxycycline

Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course of:

- artemether plus lumefantrine,
- artesunate plus amodiaquine,
- dihydroartemisinin plus piperaquine,
- artesunate plus sulfadoxine-pyrimethamine,
- artesunate plus clindamycin or doxycycline,
- quinine plus clindamycin or doxycycline.

Guidelines for the treatment of malaria – 2nd edition

Accès simple

- Accès palustre symptomatique sans signes cliniques ou biologiques de gravité ni atteinte d'organe

Accès simple

- Traitement combiné à base d'artemisinine (ACT): recommandé
- ACT recommandés
  - Artemether-lumefantrine
  - Artesunate-amodiaquine
  - Artesunate-mefloquine
  - Artesunate-sulfadoxine-pyrimethamine
- Artemisinine et ses dérivés ne doivent plus être utilisés en monothérapie

Antipaludéens de deuxième ligne

- ACT connus actifs dans la région
  - Région de résistance: Asie Est
    - Artesunate-mefloquine
    - Artemether-lumefantrine
    - Dihydroartemisinin-piperaquine
  - Autres régions/Afrique
    - ACT même ceux comprenant
      - amodiaquine ou sulfadoxine-pyrimetahmine
- Combinaison de 7 jours
  - Artesunate-tetracycline
  - Artesunate-doxycycline
  - Artesunate-clindamycine

Combinaison de 7 jours

Quinine-tetracycline

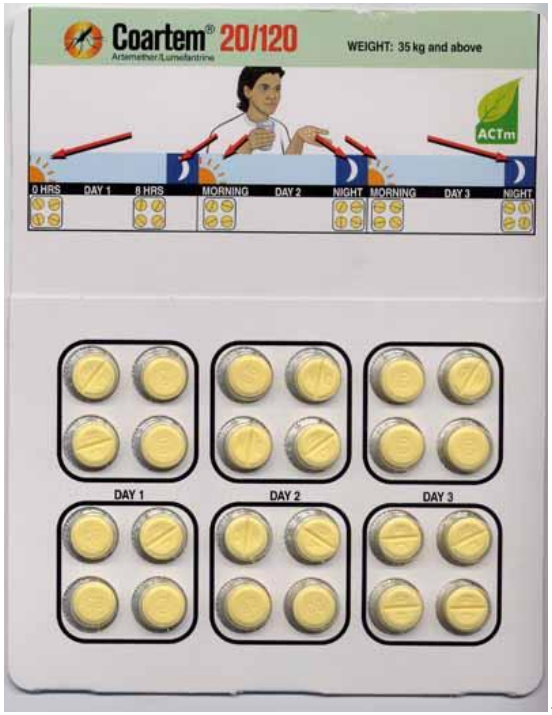
Quinine-doxycycline

Quinine-clindamycine

Protocole

RECOMMENDATION: *duration of artemisinin component in combination treatment of uncomplicated* P. falciparum *malaria*

- **ACTs should include at least 3 days of treatment with an artemisinin derivative.**
  Strong recommendation, high quality evidence



Total

- Les associations actuellement recommandées pour le ttt des accès simples
  - Artemether-lumefantrine
  - Artesunate-amodiaquine
  - Artesunate-mefloquine
  - Artesunate-sulfadoxine/pyrimethamine
  - Dihydroartemisinin-piperaquine

Guidelines for the treatment of malaria – 2nd edition

25 mg/kg/j en trois doses espacées de 8 heures: 3-2-1

Molécule	Dose	Durée
Artemether-lumefantrine (20 mg/120 mg)	1,7/12 mg/kg x 2/jour	6 doses, 3 jours
Artesunate-amodiaquine (25/67,5 mg ou 50/135 ou 100/270 mg)	4/10 mg/kg x 1/jour	3 doses, 3 jours
Artesunate-mefloquine (cp séparés, 50/250 mg)	4/8,3 mg/kg x 1/jour	3 doses, 3 jours
Artesunate-sulfadoxine/pyrimethamine (cp séparés 50/500/25 mg)	4 mg/kg x 1/jour 25/1,25 mg/kg x 1 jour	3 doses, 3 jours 1 dose, 1 jour
Dihydroartemisinin-piperaquine (40/320 mg)	4/18 mg/kg x 1/jour	3 doses, 3 jours

Femme enceinte

- Premier trimestre
  - Quinine-clindamycine x 7 jours
  - Artesunate-clindamycine x 7 jours
  - ACT uniquement
    - Si seul disponible
    - Si échec quinine
    - Si observance incertaine
- Deuxième et troisième trimestre
  - ACT efficace dans la région
  - Artesunate-clindamycine x 7 jours
  - Quinine-clindamycine x 7 jours

Femme allaitante

- ACT standard

- Molécules contre indiquées
  - Dapsone
  - Primaquine
  - Tétracyclines

Nourrissons et Enfants

- ACT
  - en adaptant les doses selon le poid
  - En assurant l'observance

5 - <15 kg: 1 tablet per dose
15 - <25 kg: 2 tablets per dose
25 - <35 kg: 3 tablets per dose
≥35 kg: 4 tablets per dose

RECOMMENDATION: *treatment for infants and young children with uncomplicated falciparum malaria*

- **The acutely ill child requires careful clinical monitoring as she/he may deteriorate rapidly.**
- ACTs should be used as first-line treatment for infants and young children with uncomplicated malaria, and careful attention should be paid to accurate dosing and ensuring the administered dose is retained.
- Referral to a health centre or hospital is indicated for young children who cannot swallow antimalarial medicines reliably. If referral is expected to take more than six hours, pre-referral treatment with rectal artesunate is indicated.

Voyageurs revenant vers des zones non endémiques

- Atovaquone-proguanil: Malarone®
  - 4 cp/j x 3 jours au milieu d'un repas
- Artemeter-lumefantrine: Coartem®
- Quinine-doxycycline
- Quinine-clindamycine
  - Quinine cp à 500 mg: 8 mg/kg x 3/j

Gestion de l'échec

- Artesunate/tétracycline ou doxycycline ou clindamycine
  - Terrain particulier/Femme enceinte
  - Artesunate : 2 mg/kg/j
  - Tétracycline : 4 mg/kg x 4/j
  - Doxycycline : 3,5 mg/kg/j
  - Clindamycine : 10 mg/kg x 2/j
  - Durée : 7 jours

Primaquine et *P. falciparum*

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- Artemisinin-based combination therapies should be used in preference to sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) for the treatment of uncomplicated *P. falciparum* malaria.

  Strong recommendation, moderate quality evidence.

- ACTs should include at least 3 days of treatment with an artemisinin derivative.

  Strong recommendation, high quality evidence.

- Dihydroartemisinin plus piperaquine (DHA+PPQ) is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.

  Strong recommendation, high quality evidence.

- Addition of a single dose primaquine (0.75 mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme.

Guidelines for the treatment of malaria – 2nd edition

Primaquine et *P. falciparum*

Gametocytemia levels according to treatment groups and day of follow-up.

Treatment	% Of gametocyte carriers (*n*)		
	Day 1	Day 4	Day 8
A. Gametocyte prevalence			
AQ–SP	15.0 (3)	35.0 (7)	55.0 (11)
AQ–SP–PQ	30.0 (6)	40.0 (8)	35.0 (7)
MQ–AS	34.8 (8)	30.4 (7)	13.0 (3)
MQ–AS–PQ	31.6 (6)	15.8 (3)	5.3 (1)
p^b	0.501	0.394	0.001

E.M. Arango et al. / Acta Tropica 122 (2012) 177–182

Zones à transmission limitée: éviter la contamination du vecteur

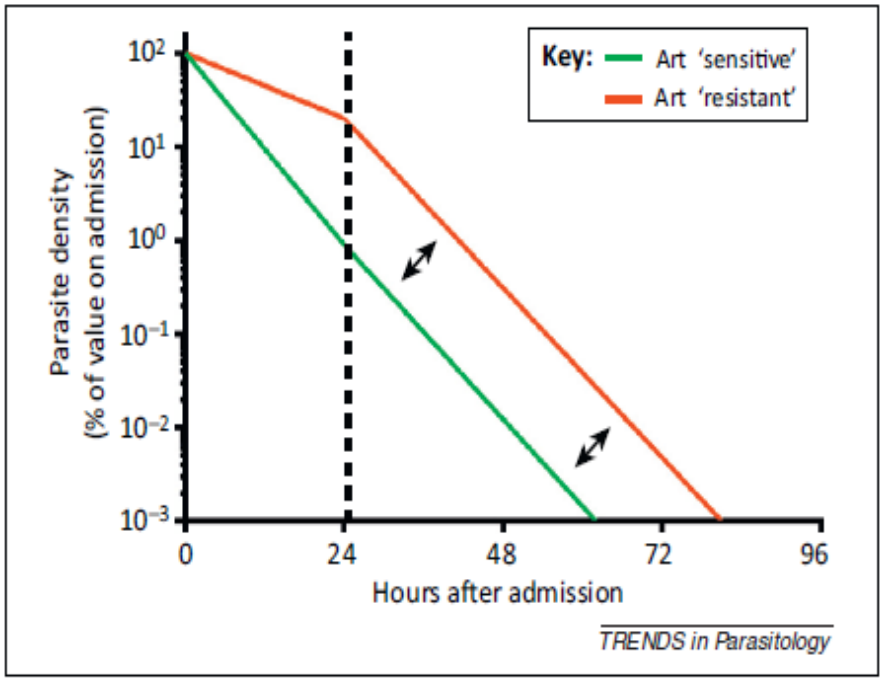
Primaquine: seule active contre gamétocytes matures

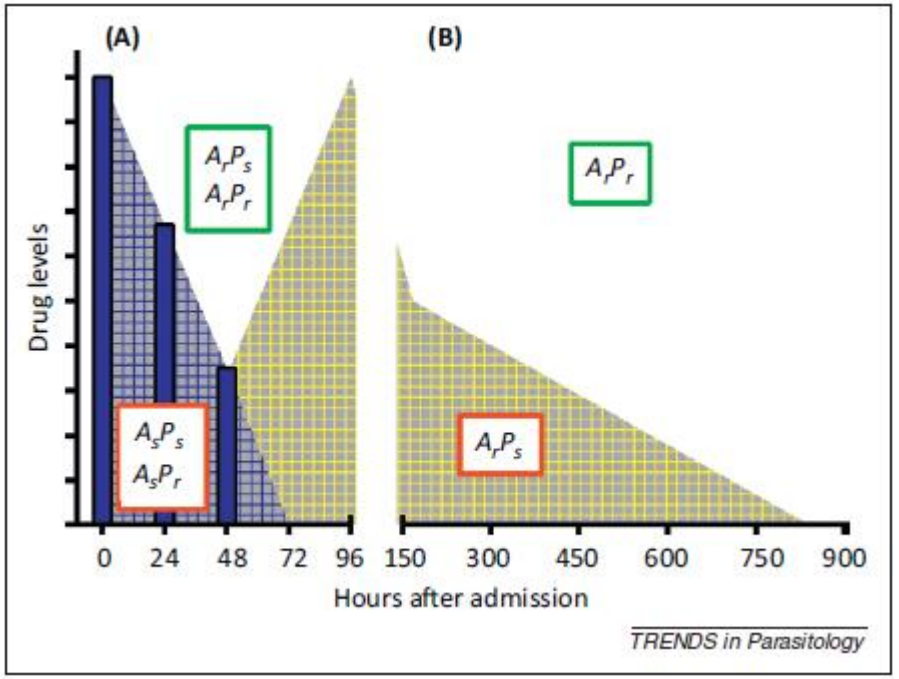
Dérivés d'artémésinine: actifs contre formes jeunes, séquestrées

Primaquine: 0,75 mg/kg x 1 dose, J2 d'ACT

J4: prolonge la durée des gamétocytes

Résistance à l'artémisinine





Liée à la densité parasitaire initiale

Trends in Parasitology July 2013, Vol. 29, No. 7

alternatives

126

Asian Pacific Journal of Tropical Medicine (2012)126-129

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

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

Document heading doi:

Antimalarial potency of the leaf extract of *Aspilia africana* (Pers.) C.D. Adams

Akuodor Godwin Christian[1*], Amos Grace Mfon[2], Essien Augustine Dick[1], Essien David-Oku[3], Akpan Joseph Linus[4], Ezeokpo Basil Chukwuma[4]

[1]*Department Pharmacology, College of Medical Sciences, University of Calabar, Nigeria*
[2]*Department of Pharmacology and Toxicology, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria*
[3]*Department of Biochemistry, College of Medical Sciences, University of Calabar, Nigeria*
[4]*Department of Pharmacology and Therapeutics, Faculty of Clinical Medicine, Ebonyi State University, Abakaliki, Nigeria*

Alternatives

Asian Pacific Journal of Tropical Disease (2012)S809-S814

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

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

Document heading doi:

Preliminary studies on the antiplasmodial potential of aqueous and methanol extracts of *eucalyptus camadulensis* leaf

Kabiru, Y. A[1]., Okolie, N. L[2]., Muhammad, H. L [2] and Ogbadoyi, E. O.[1, 2, 3]

[1] *1Trypanosomiasis and Malaria Research Unit, Department of Biochemistry, Federal University of Technology, Minna, Nigeria.*
[2] *Department of Biochemistry, Federal University of Technology, Minna, Nigeria.*
[3] *Global Initiatives for Bio – Exploration (GIBEX), Federal University of Technology, Minna, Nigeria.*

Alternatives

Openion

Cell PRESS

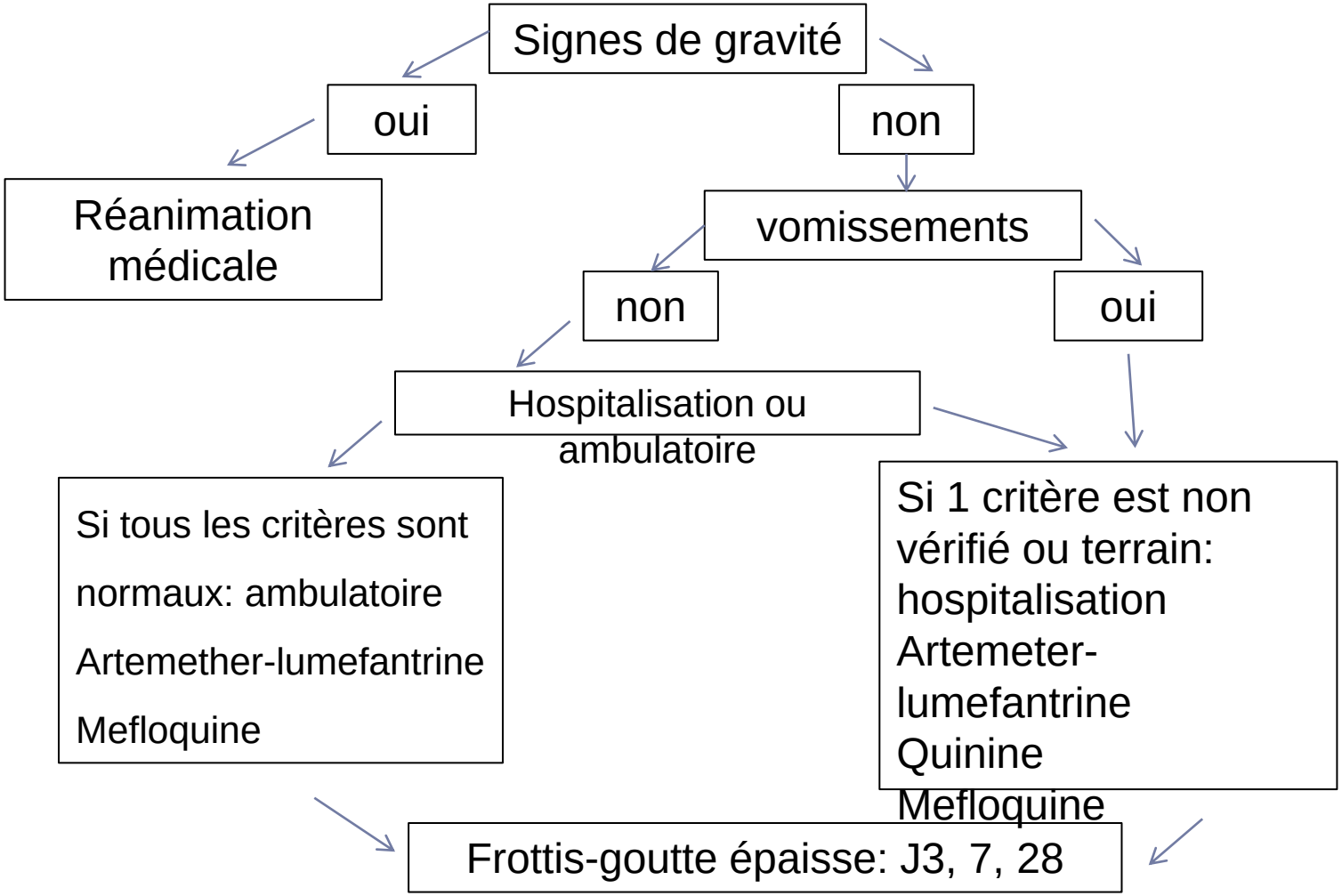
Anticancer agents against malaria: time to revisit?

Alexis Nzila[1,2], John Okombo[1], Ruy Perez Becker[3], Roma Chilengi[1,2], Trudie Lang[1,2] and Tim Niehues[3]

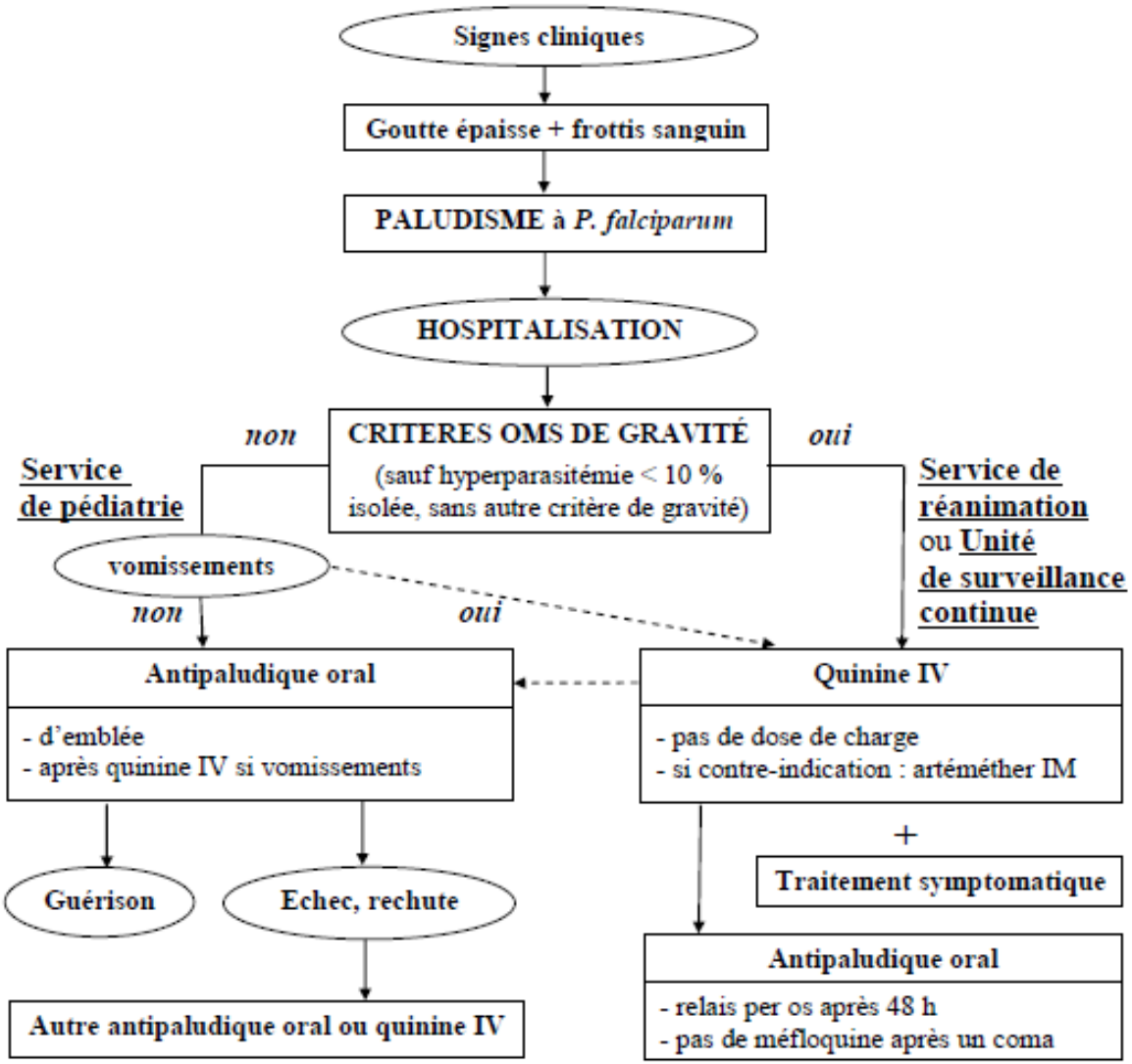
[1] Kenya Medical Research Institute (KEMRI)/Wellcome Trust Collaborative Research Programme, PO Box 230, 80108, Kilifi, Kenya
[2] University of Oxford, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK
[3] Helios Klinikum Krefeld Academic Hospital, Lutherplatz 40, 47805 Krefeld, Germany

Methotrexate: 2,5 mg/j x 3-5 jours: *P. falciparum et malariae*
Trimetrexate < 10-20 mg

Conduite à tenir devant un paludisme à *P. falciparum* de l'adulte en Tunisie

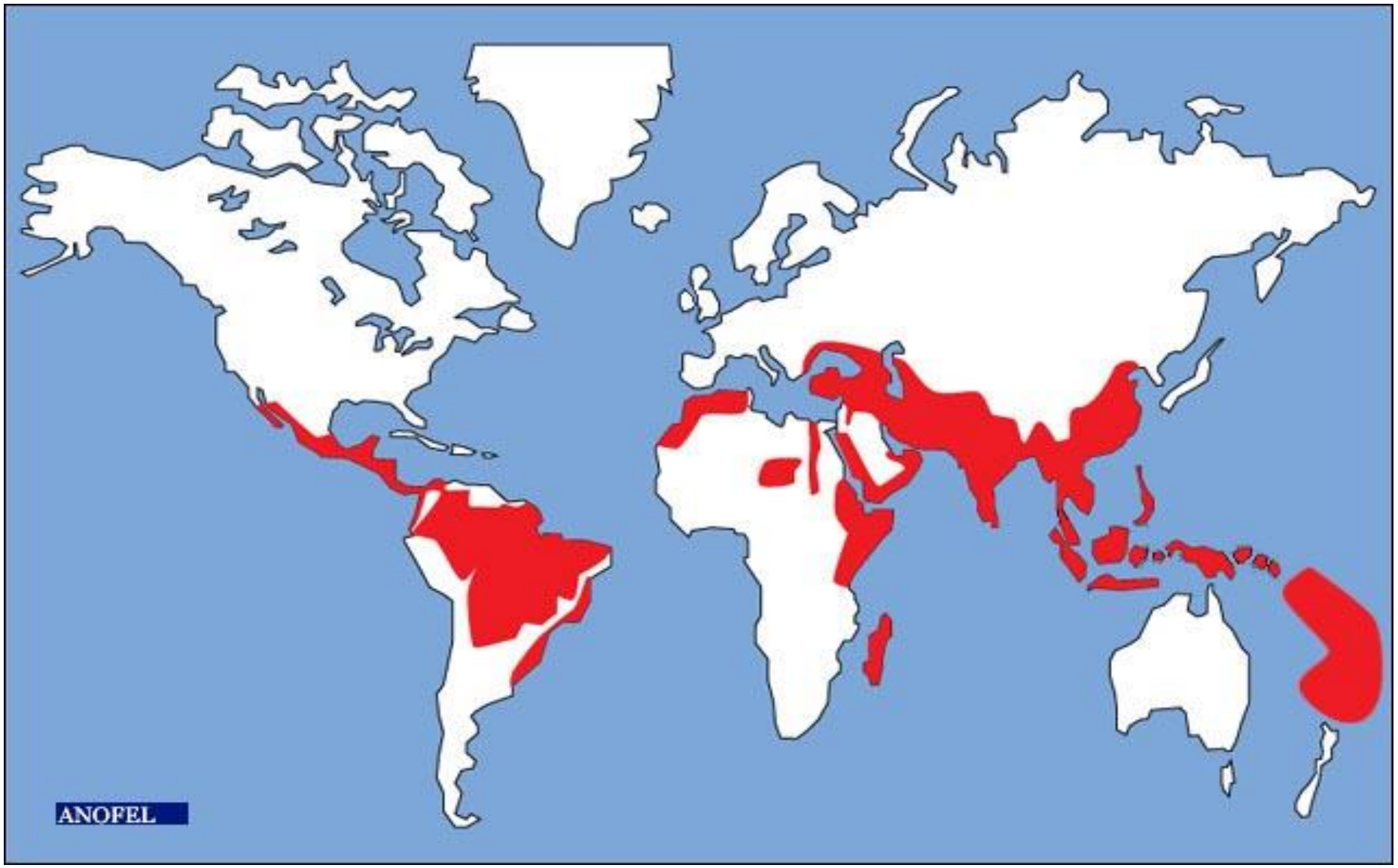


Modalités du traitement du paludisme à *P. falciparum* chez l'enfant en France



Antipaludique oral : 1e intention : méfloquine, atovaquone-proguanil, artéméther-luméfantrine
2e intention : halofantrine, quinine

P. vivax


ANOFEL

Etat des résistances

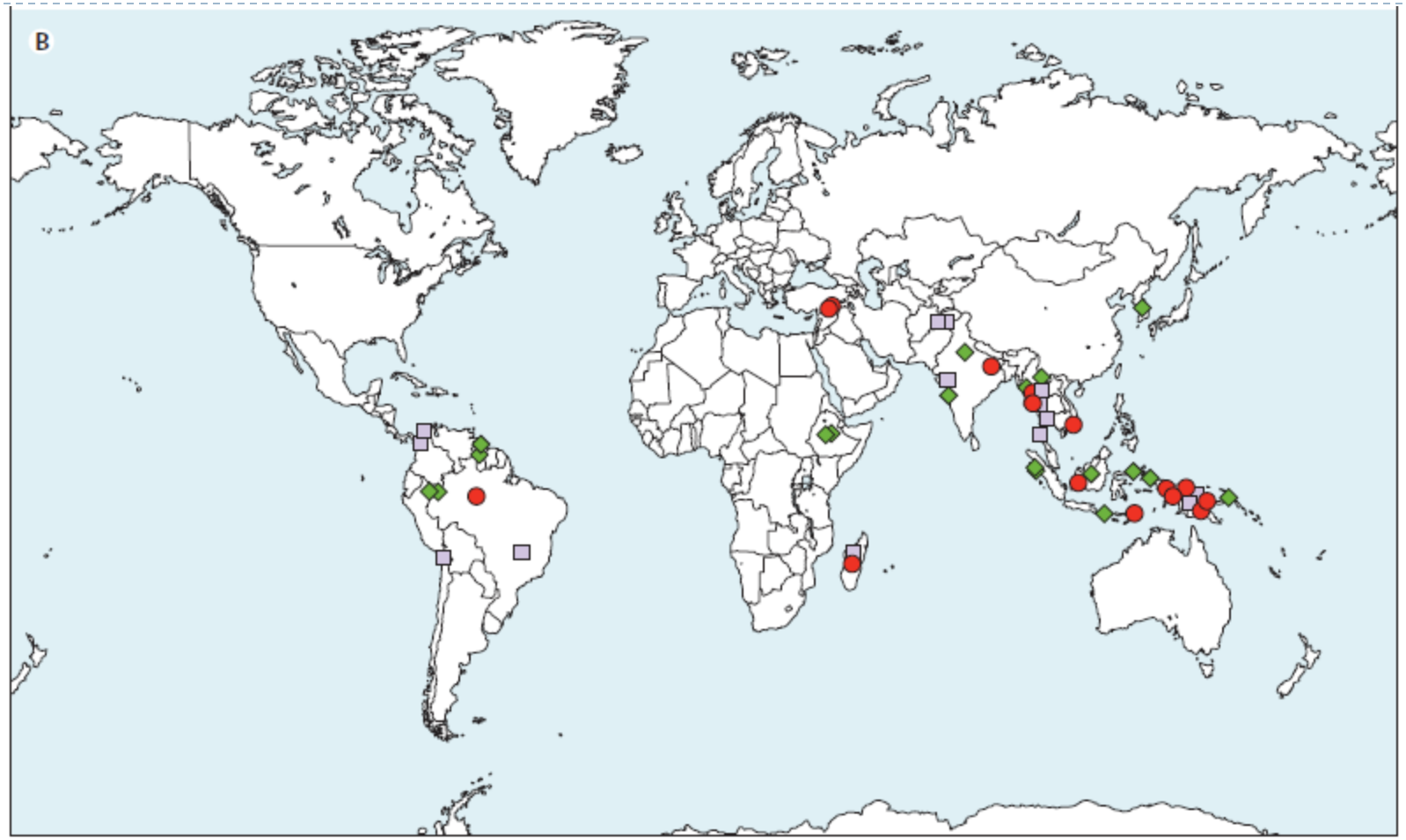


Figure: **Reports of chloroquine-resistant *Plasmodium vivax* by 1999 (A) and 2009 (B)**
Red circles represent greater than 10% recurrence (and more than five absolute failures) by day 28 with or without measurement of chloroquine concentrations. Green diamonds represent less than 10% recurrence (or fewer than five absolute failures) by day 28, with measurement of chloroquine concentrations. Purple squares represent less than 10% recurrence (or fewer than five absolute failures) by day 28, without measurement of chloroquine concentrations.

	Location; study design	Drug (treatment duration)	Number of patients	Parasite clearance time	Fever clearance time	Proportion of patients free of recurrence
Li et al[77]*	China; efficacy study, not otherwise specified	Higher dose: artemether (3 days) plus lumefantrine (3 days)	36	33·5 h	22·3 h	..
		Lower dose: artemether (3 days) plus lumefantrine (3 days)	41	30·5 h	23·2 h	..
		Chloroquine plus piperaquine†	55	44·9 h	25·0 h	..
LeYuan et al[78]*	Eritrea; efficacy study, not otherwise specified	Dihydroartemisinin† plus pyronaridine†	..	24·0 h	..	..
		Pyronaridine†	..	32·0 h	..	..
Tjitra et al[79]	Papua, Indonesia; non-randomised, pilot efficacy study	Artesunate (3 days) plus sulfadoxine and pyrimethamine (1 day)	22	1·1 days	1·4 days	100% (day 14), 89·5% (day 28)
		Chloroquine (3 days) plus sulfadoxine and pyrimethamine (1 day)	6	..	..	67% (day 28)
		Chloroquine (3 days)	9	..	..	11% (day 28)
Hung et al[67] and Karunajeewa et al[80]	Cambodia; non-randomised, population pharmacokinetics and safety evaluation	Dihydroartemisinin (2 days) plus piperaquine (2 days)	10	12 h	9·0 h	100% (day 28)
Hasugian et al[81]	Papua, Indonesia; open-label, randomised controlled trial	Dihydroartemisinin (3 days) plus piperaquine (3 days) plus primaquine (14 days)	74	..	..	84% (day 42)
		Artesunate (3 days) plus amodiaquine (3 days) plus primaquine (14 days)	75	..	..	52% (day 42)
Kolaczinski et al[82]	Afghanistan; open-label, randomised controlled non-inferiority trial	Artesunate (3 days) plus sulfadoxine and pyrimethamine (1 day)	94	..	..	99% (day 28), 76% (day 42)
		Chloroquine (3 days)	96	..	..	96% (day 28), 54% (day 42)
Krudsood et al[83]	Bangkok, Thailand; open-label, randomised controlled trial	Artemether (3 days) plus lumefantrine (3 days) plus primaquine (14 days)	47	41·6 h	21·8 h	97·4% (day 28)
		Chloroquine (3 days) plus primaquine (14 days)	51	55·8 h	25·3 h	100% (day 28)
Ratcliff et al[41]	Papua, Indonesia; open-label, randomised controlled trial	Dihydroartemisinin (3 days) plus piperaquine (3 days) plus primaquine (14 days)‡	147	..	..	86% (day 42)
		Artemether (3 days) plus lumefantrine (3 days) plus primaquine (14 days)‡	141	..	..	43% (day 42)
Karunajeewa et al[84]	Papua New Guinea; open-label, randomised population pharmacokinetics and efficacy trial	Dihydroartemisinin (3 days) plus piperaquine (3 days)	3	..	..	66·7% (day 42)
		Chloroquine (3 days) plus sulfadoxine and pyrimethamine (3 days)	1§	..	..	..
Karunajeewa et al[42]	Papua New Guinea; open-label, randomised controlled trial	Artemether (3 days) plus lumefantrine (3 days)	39	1·4 days	2·1 days	48·5% (day 28), 30·3% (day 42)
		Dihydroartemisinin (3 days) plus piperaquine (3 days)	44	1·2 days	1·9 days	84·2% (day 28), 69·4% (day 42)
		Artesunate (3 days) plus sulfadoxine and pyrimethamine (1 day)	51	1·1 days	2·1 days	51·3% (day 28), 33·3% (day 42)
		Chloroquine (3 days) plus sulfadoxine and pyrimethamine (1 day)	61	3·1 days	2·3 days	51·0% (day 28), 13·0% (day 42)
Awab et al[51]	Afghanistan; open-label, randomised controlled trial	Chloroquine (3 days)	268	..	..	100% (day 28), 91·1% (day 56)
		Dihydroartemisinin (3 days) plus piperaquine (3 days)	268	..	..	100% (day 28), 97·2% (day 56)

Excludes studies of artemisinin plus primaquine since the latter has no activity against asexual *P falciparum* parasites and is therefore not an option as the sole partner drug for widespread use against both species. Studies by Ratcliff,[41] Hasugian,[81] and Karunajeewa[42,84] included patients with *P vivax* and mixed *P vivax*/*P falciparum* infections in their analyses of *P vivax* recurrence. *Assessment based on abstract alone. †Unknown duration. ‡Primaquine delayed until day 2. §Lost to follow-up.

Table 1: **Studies of the effectiveness of an artemisinin derivative combined with a blood schizonticide for the treatment of *Plasmodium vivax* malaria**

Protocoles

- Chloroquine:
  - Traitement de choix pour les souches sensibles
  - Chloroquine 25 mg/kg en trois jours
  - Deux protocoles
    - J1 et 2: 10 mg/kg/j
    - J3: 5 mg/kg/j

ou

H0: 10 mg/kg

H6, h24, h48: 5 mg/kg

- ACT sauf artesunate-sulfadoxine-pyrimethamine
  - Dans le zones de chloroquinorésistance
  - En association à la primaquine x 14 jours

Primaquine

- Nécessaire pour éviter les récurrences et assurer l'éradication du parasite
- Comprimés 7,5 et 15 mg
- 15 mg/j x 14 jours(durée optimale) (0,25 mg/kg/j)
- Pays de l'Asie du Sud Est, Indonésie, Océanie: 0,5 mg/kg/j
- Déficit en G6PD
  - Sévère: contre indiquée
  - Modérée: 0,75 mg/kg/semaine x 8 semaines

P. malariae, ovale

- Quelques résistances à la chloroquine en Indonésie chez *P. malariae*
- Chloroquine 25 mg/kg en trois jours
- Deux protocoles

- J1 et 2: 10 mg/kg/j
- J3 : 5 mg/kg/j

ou

H0: 10 mg/kg

H6, 24, 48: 5 mg/kg

- Primaquine uniquement pour *vivax*

Prophylaxie

Zone	Molécule	Durée
Pays du groupe 1	Chloroquine 100 mg/j (Nivaquine®)	Séjour + 4 semaines
Pays du groupe 2	Chloroquine 100 mg + Proguanil 200 mg « Nivaquine®+Paludrine® » ou Savarine® 1prise par jour Ou Atovaquone 250 + Proguanil 100 mg (Malarone®) une prise par jour	Séjour + 4 semaines Séjour + 1 semaine
Pays du groupe 3	Atovaquone 250 + Proguanil 100 mg (Malarone®) une prise par jour Ou Mefloquine 250 mg (Lariam®) une prise par semaine Ou monohydrate de doxycycline 100 mg (Doxypalu®) une prise par jour	Séjour + 1 semaine 10 jours avant séjour et 3 semaines Séjour + 4 semaines

Conclusion

- Maladie grave potentiellement mortelle
- Prise en charge dépend de la gravité clinique et du terrain
- ACT constituent le ttt de référence mondial
- Primaquine indiquée pour éradiquer les gamétocytes
  - *P. vivax*
  - *P. falciparum*