Avancées dans les traitements et chimiorésistances du paludisme

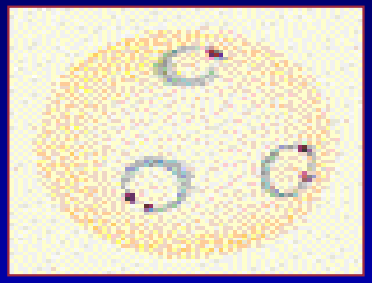
Jacques Le Bras et Martin Danis,

Centre National de Référence du Paludisme,

CHU Bichat-Claude Bernard, CHU Pitié-Salpêtrière,

Paris

Le paludisme à *P. falciparum*

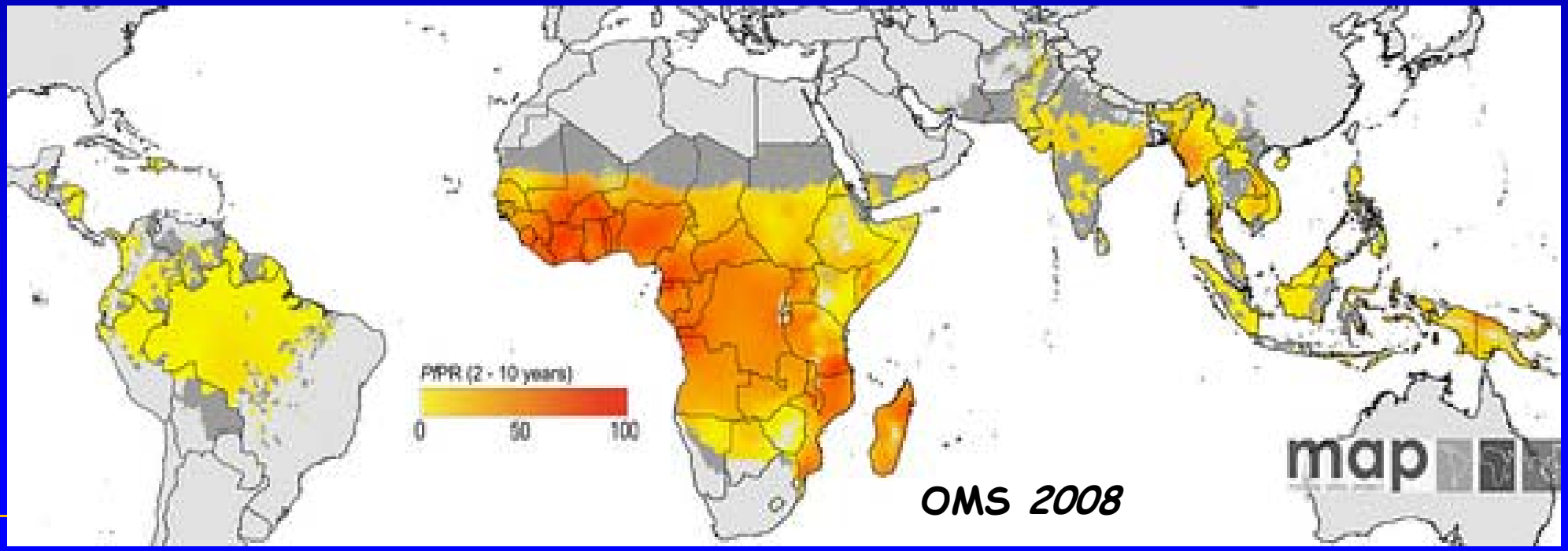


Plasmodies
(Plasmodium falciparum)

Moustique
(Anopheles sp.)

Homme

- **Monde**
  - 250 millions d'accès par an
    ↳ 1 million de morts
- **France**
  - 4000 cas importés par an
    ↳ 16 morts



OMS 2008

Faire reculer le paludisme 1998-2010

- Réduire la morbidité et la mortalité :

→ intensifier l'accès et l'usage de la prévention

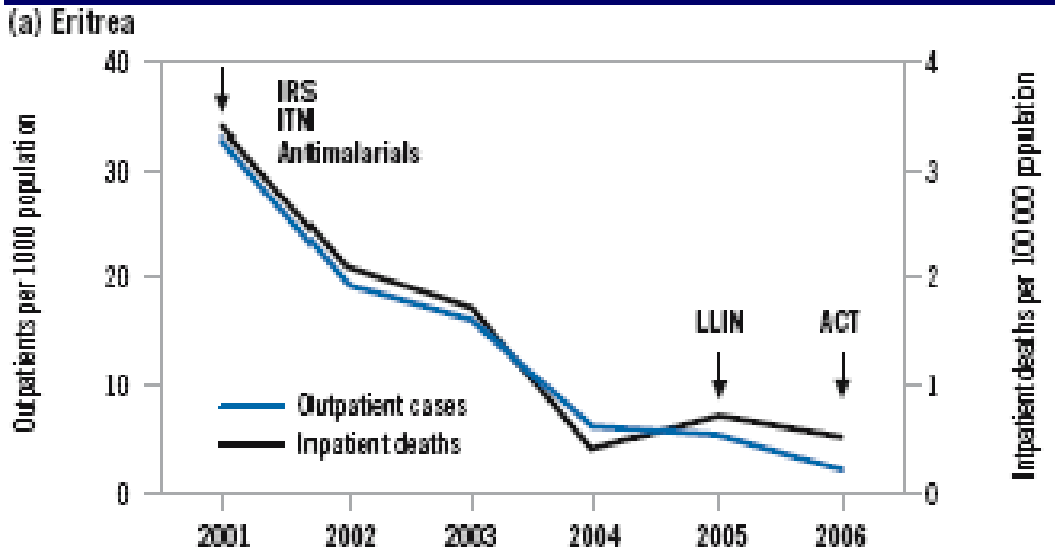
→ favoriser l'accès rapide à un traitement efficace

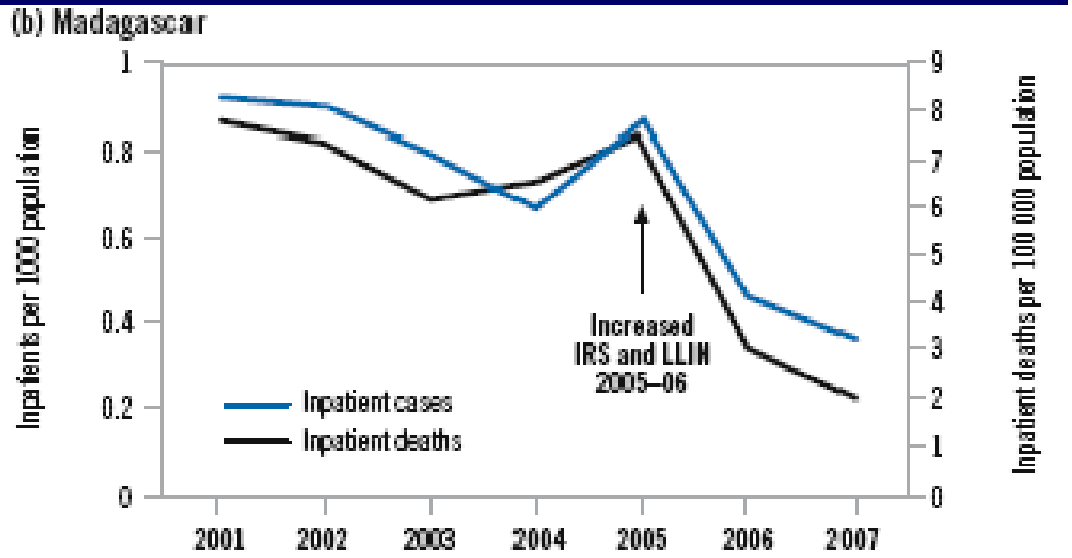
→ renforcer les systèmes de santé

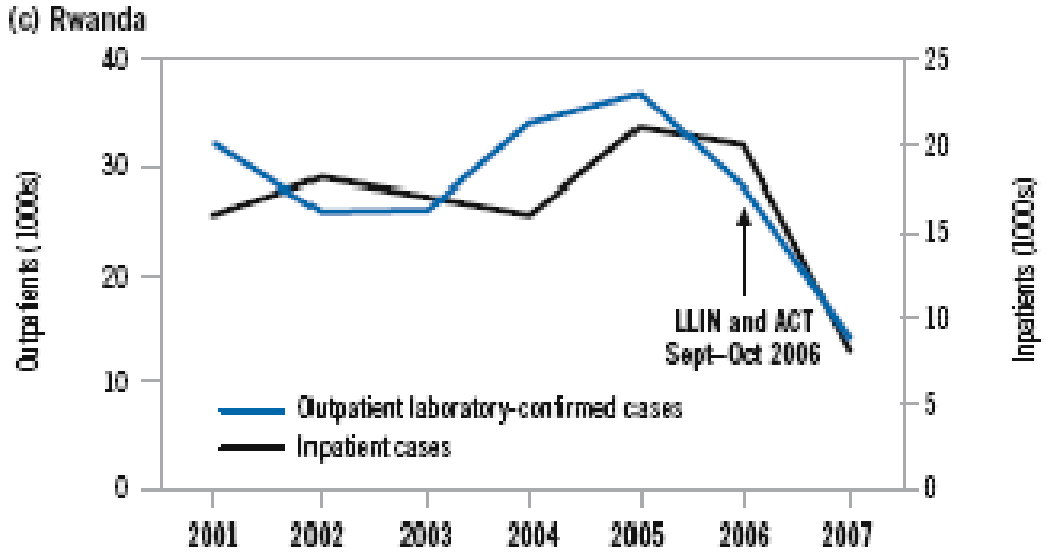
→ soutenir les méthodes nouvelles d'un bon rapport coût/efficacité

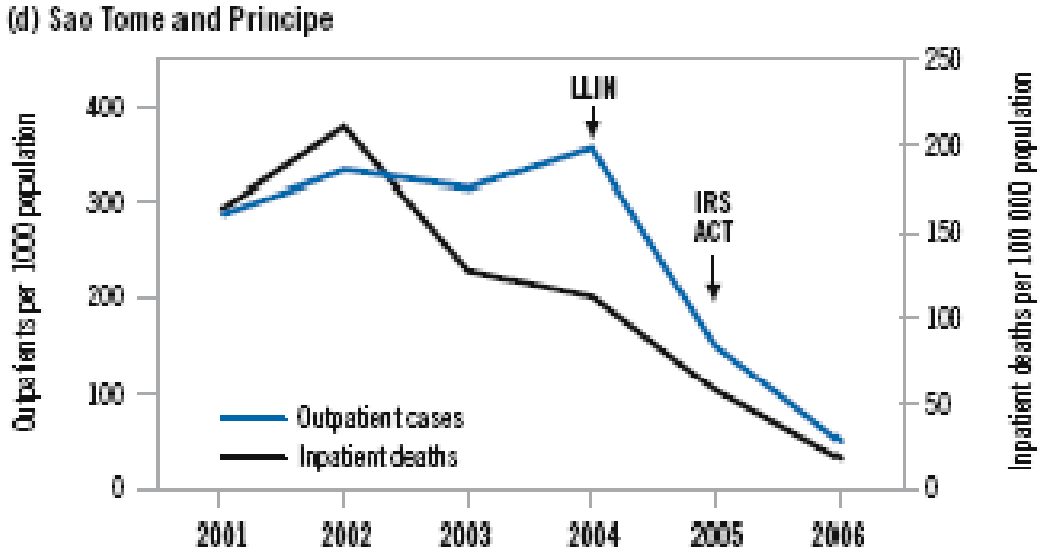
OMS

Premiers résultats (rapport OMS 2008)

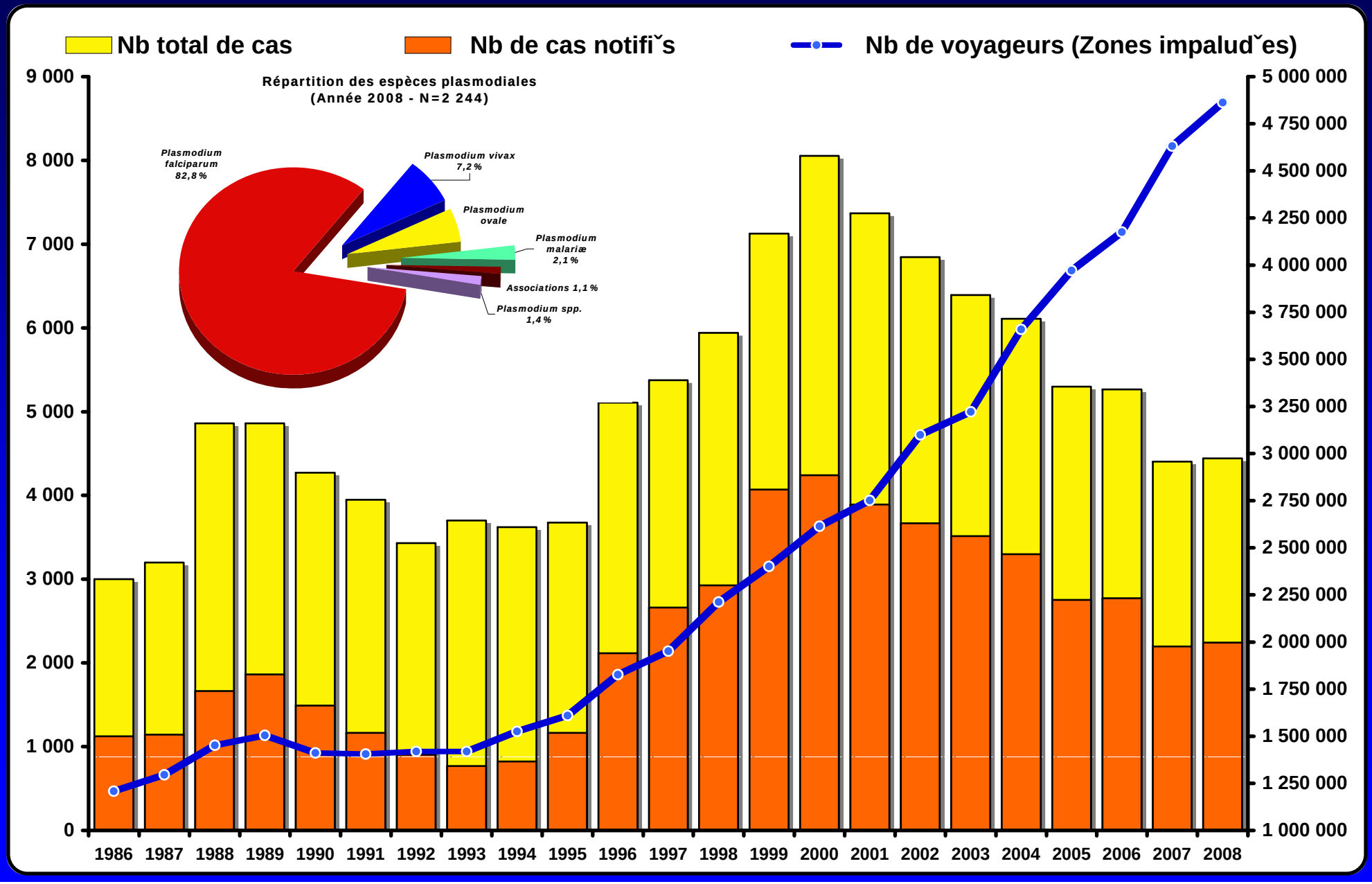




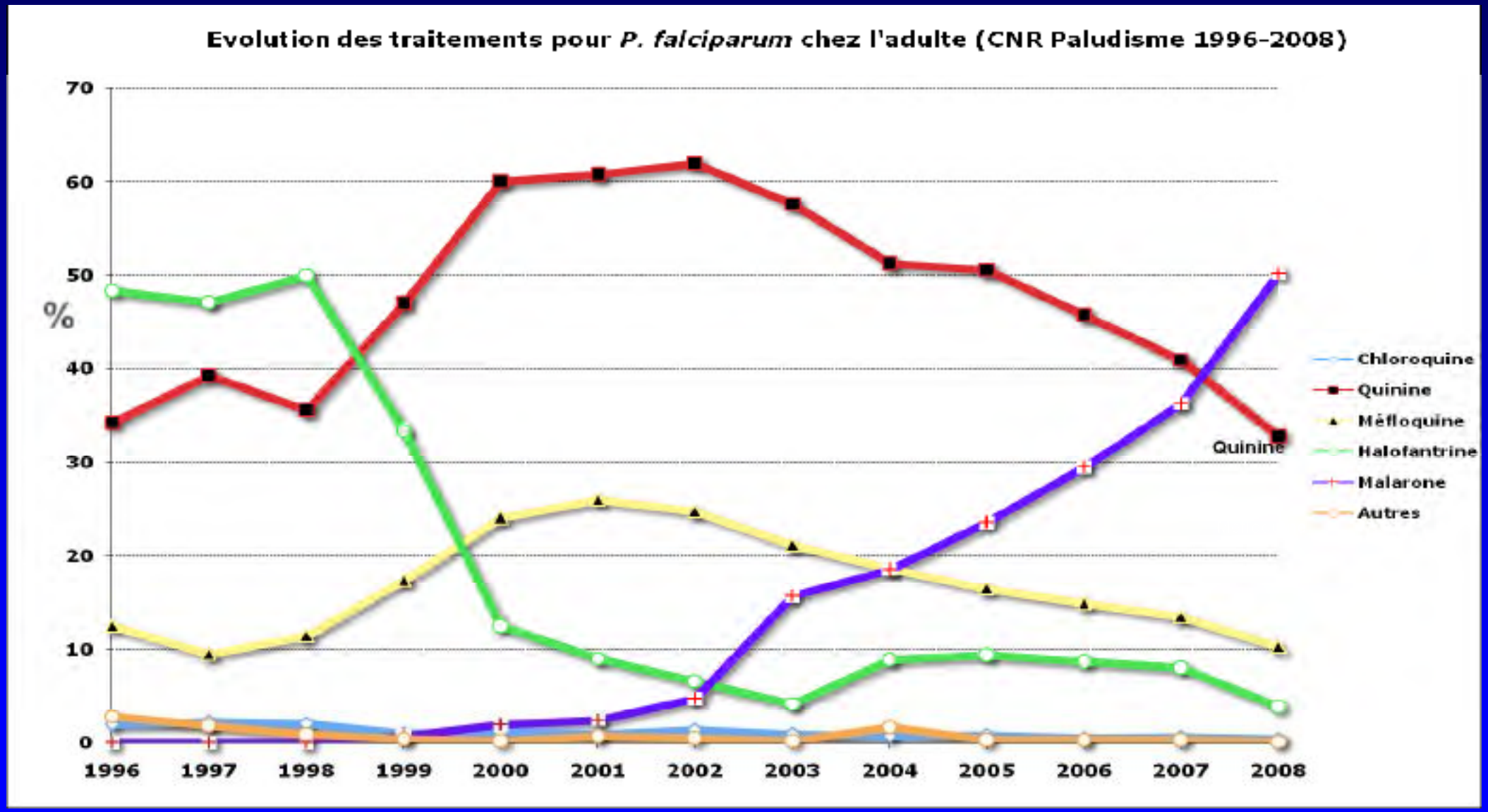




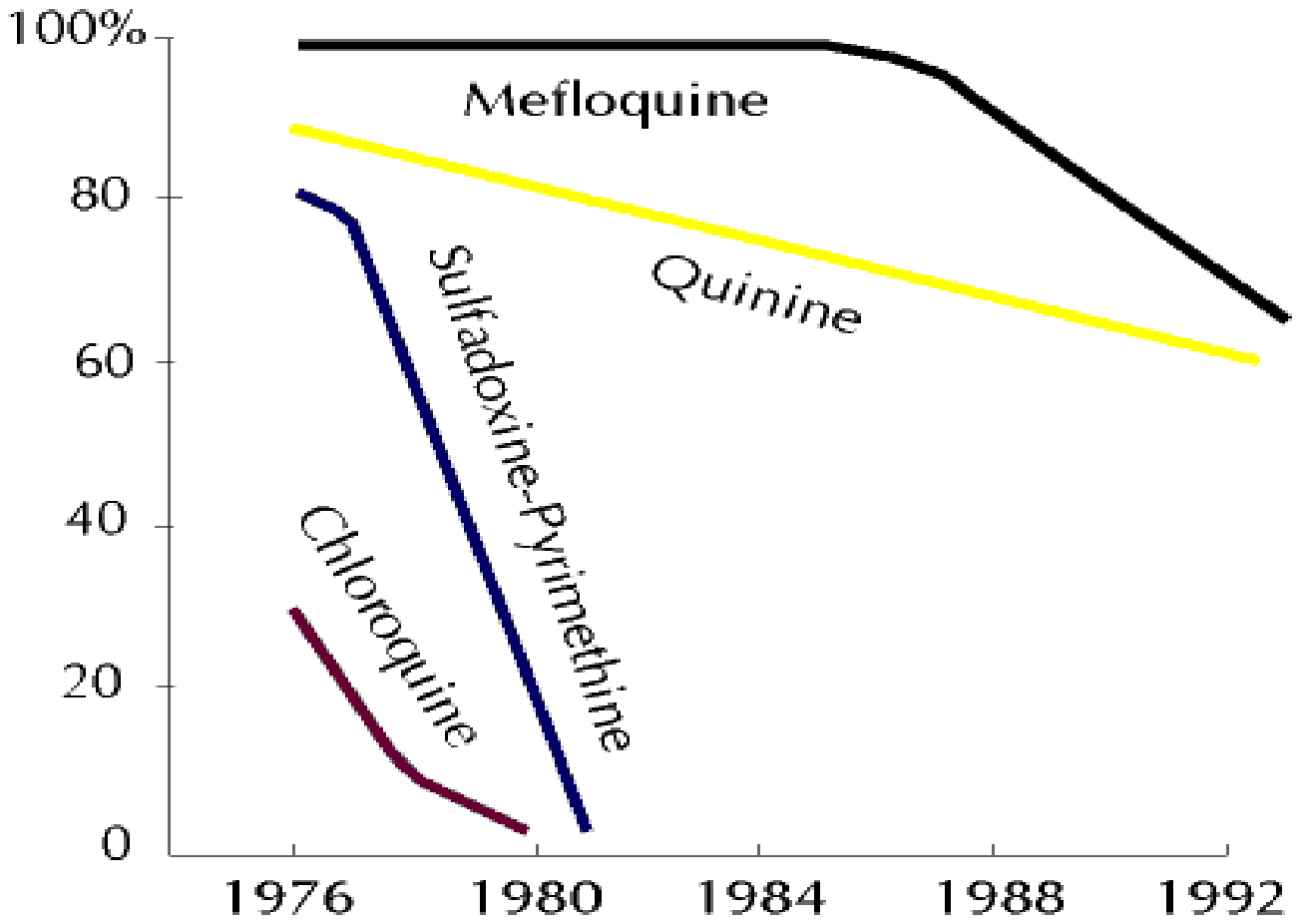
Paludisme importé, France : vers une maladie rare ?



Traitement du paludisme en France métropolitaine

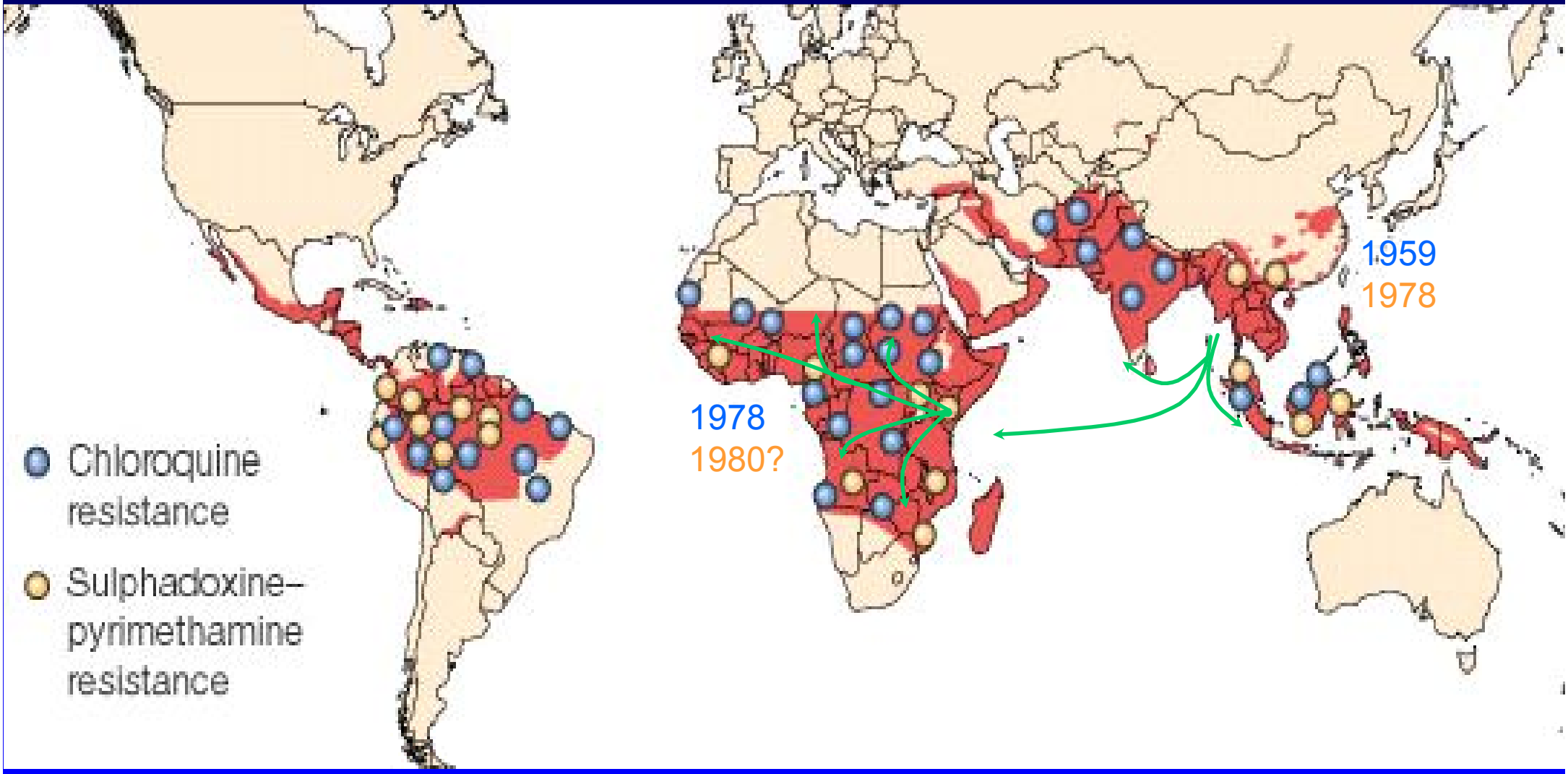


DECLINING RESPONSE TO ANTIMALARIAL DRUGS



The Southeast Journal of Tropical Medicine and Public Health, Mekong Malaria, Volume 30, Supplement 4, p 68, 1999

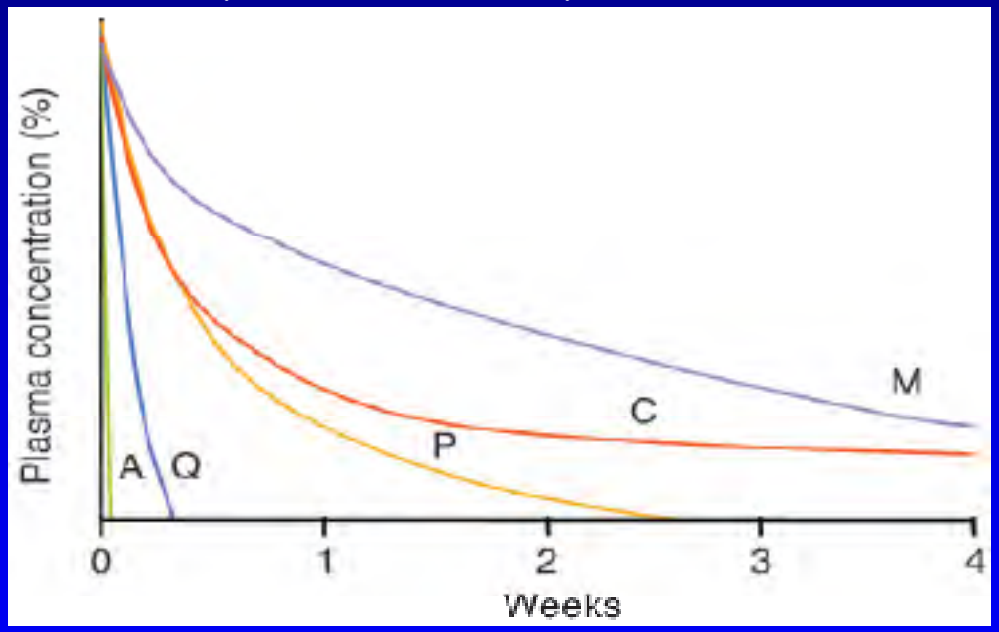
Propagation de la chimiorésistance aux antipaludiques



Origines rares (1 à 3 SNPs) + Migrations + Sélection intense + Transmission

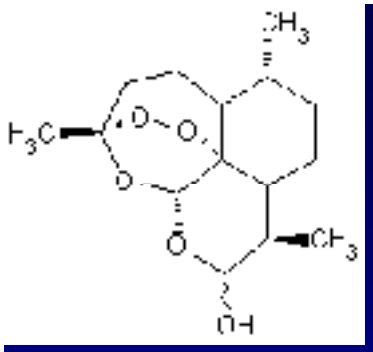
Propriétés des molécules (1)

A: artémisine Q: quinine P: pyriméthamine
C: chloroquine M: méfloquine



- Plus la demi-vie d'une molécule est longue,
- Plus un parasite à une probabilité élevée d'être exposé à des doses infra thérapeutiques,
- ↗ probabilité d'émergence de résistance

White NJ. (2004) JCI:113,8

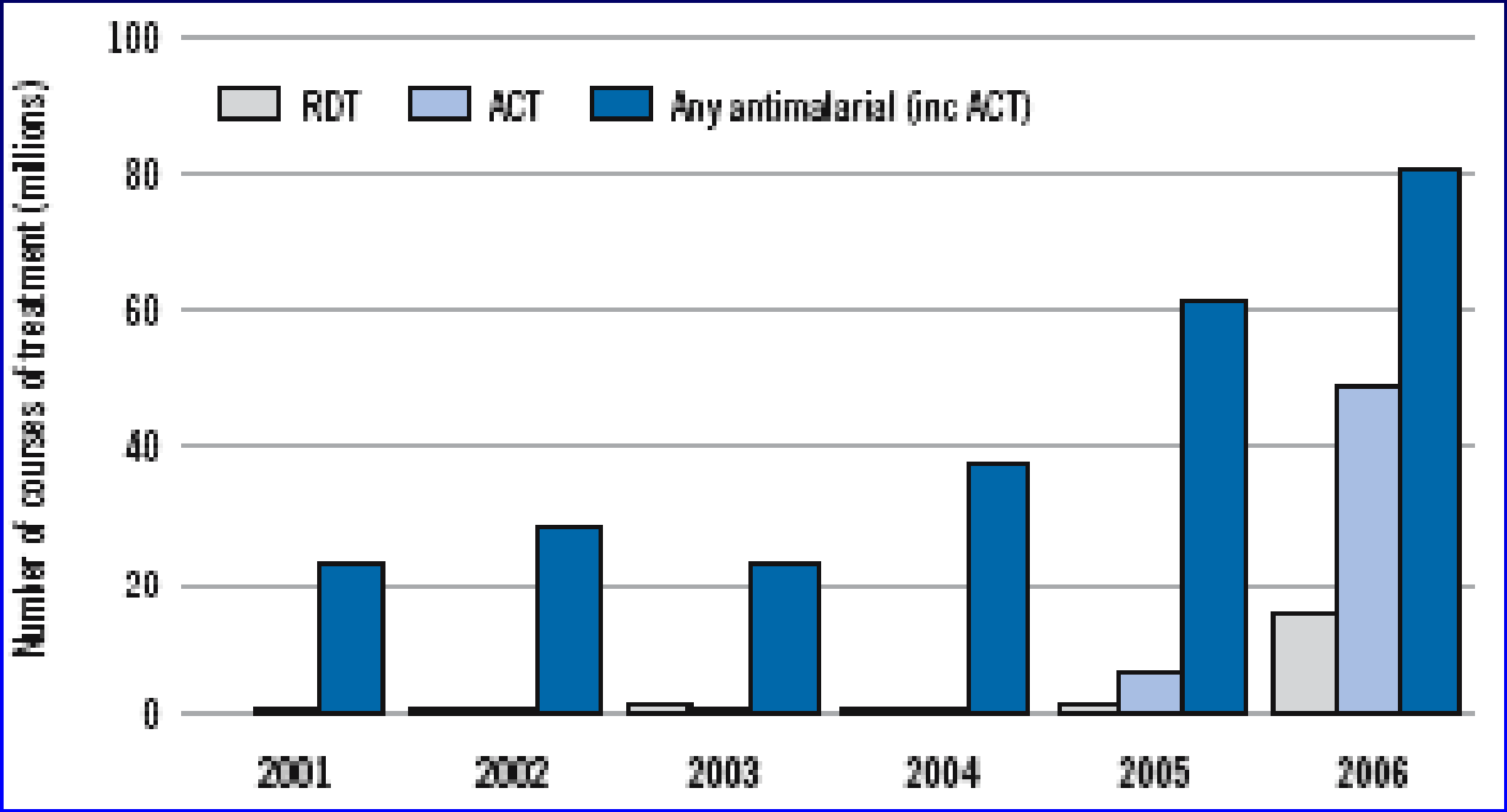


Nouveaux dérivés à base d'artémisinine

- Associations libres :
  - artésunate + méfloquine (Mepha, Artequin®)
  - artésunate + amodiaquine (Sanofi, Arsucam®)
  - artésunate + sulfadoxine-pyriméthamine (Sanofi, Arsudar®)
  - artésunate + pyronaridine (MMV, Pyramax®)
  - artésunate + atovaquone-proguanil

- Associations fixes :
  - artéméther-luméfantrine (Riamet®, Coartem®)
  - artésunate + amodiaquine (Coarsucam®, ASAQ®)
  - dihydroartémisinine-pipéraquine (Duo-cotecxin®, Artekin®, Eurartesim®)

Adoption et mise en place des ACT et TDR

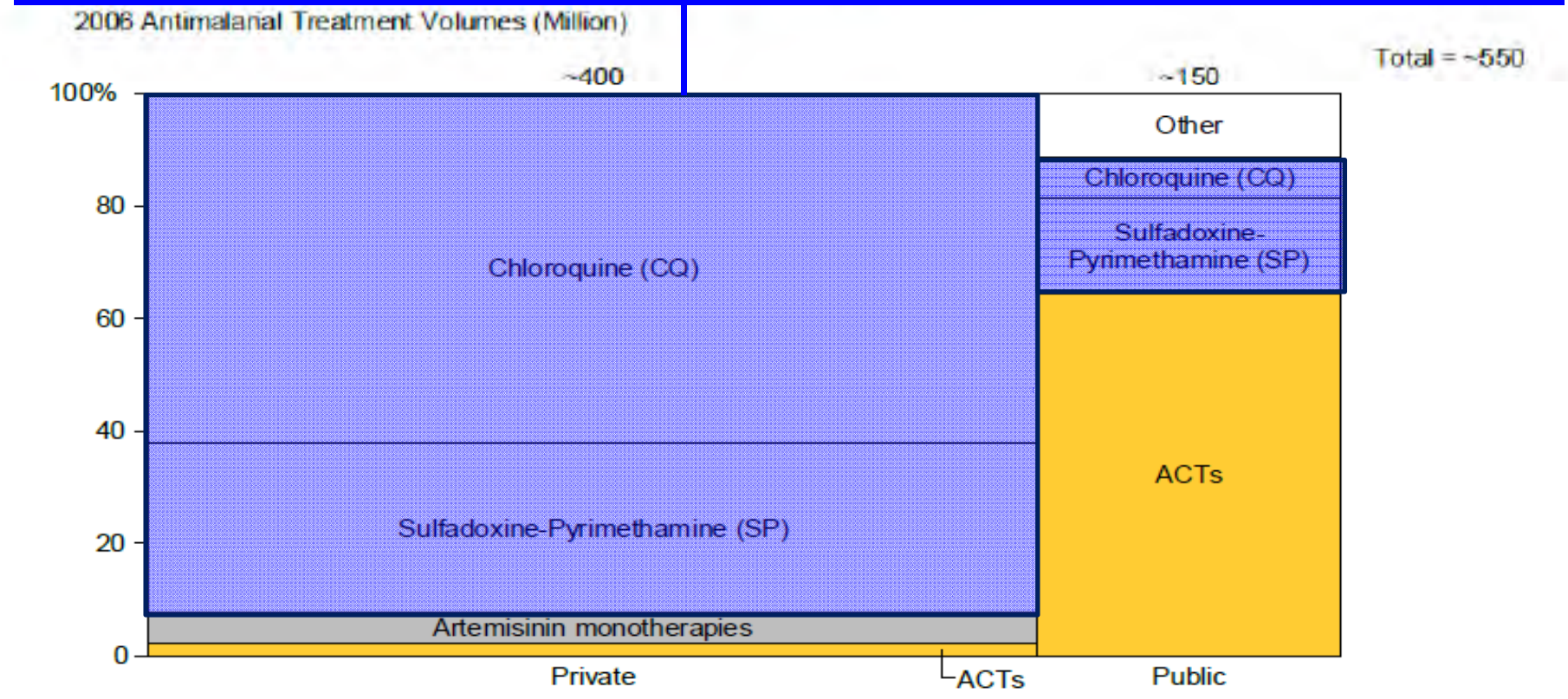


Bosman & Mendis 2008

NMCPs to WHO, 2008

Traitement & Resistance (1)

Inefficace ou partiellement efficace



Note: Other category includes Mefloquine, Amodiaquine and others. ACT data based on WHO estimates and manufacturer interviews.
Source: Biosynthetic Artemisinin Roll-Out Strategy, BCG/Institute for OneWorld Health, WHO, Dalberg.

Dalberg

Traitement & Resistance (2)

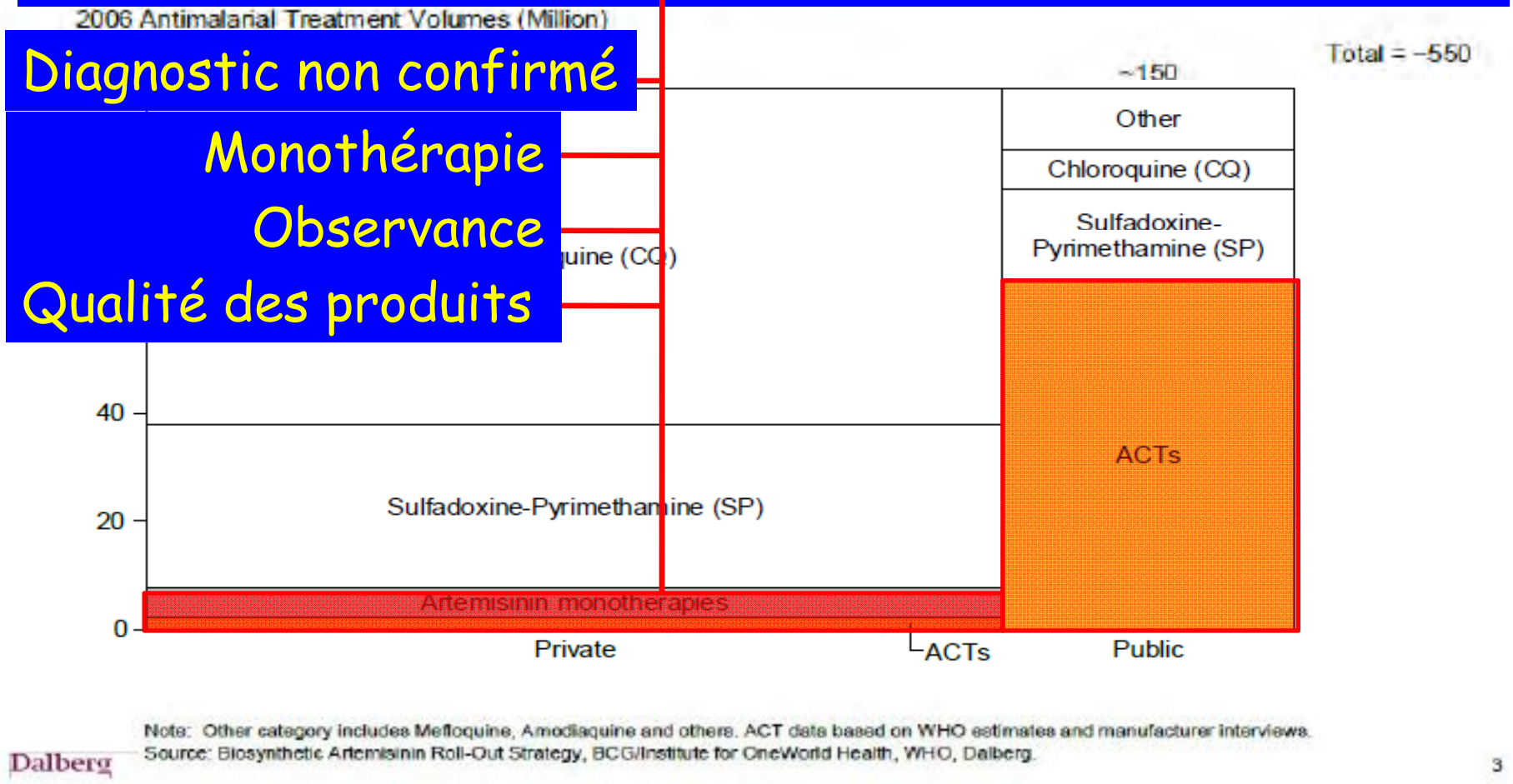
Lit de l'émergence de résistance

Diagnostic non confirmé

Monothérapie

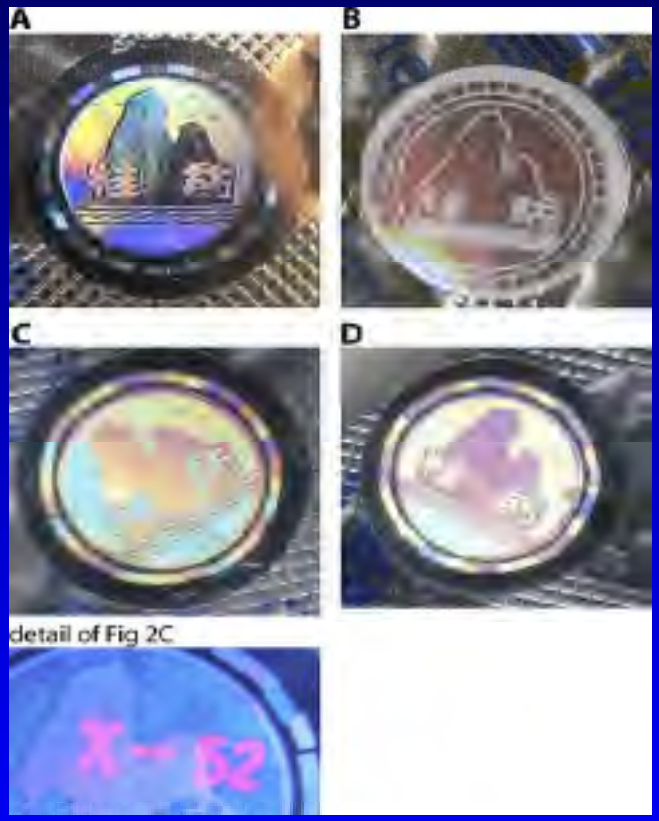
Observance

Qualité des produits



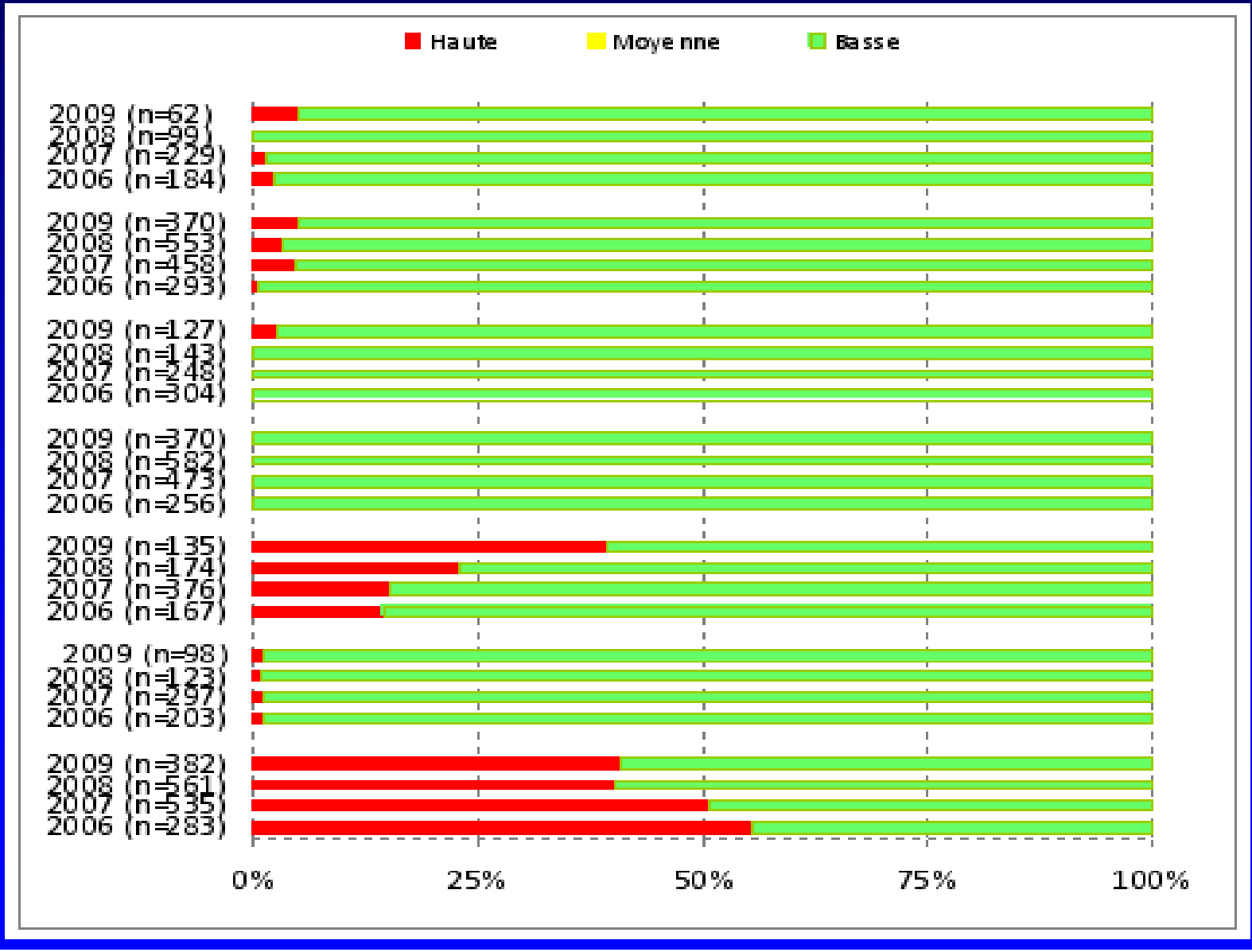
Qualité des médicaments

- Médicaments contrefaits
  - Investigation Asie du Sud Est 2007:
    - 195 produits contrefaits sur 391 échantillons (Laos, Thaïlande, Myanmar, Vietnam, Cambodge)
    - Peu ou pas d'artesunate
      - Beaucoup d'autres produits potentiellement dangereux (produits proscrits [metamizole, safrole, ecstasy])
  - Concentration de médicaments sous optimale



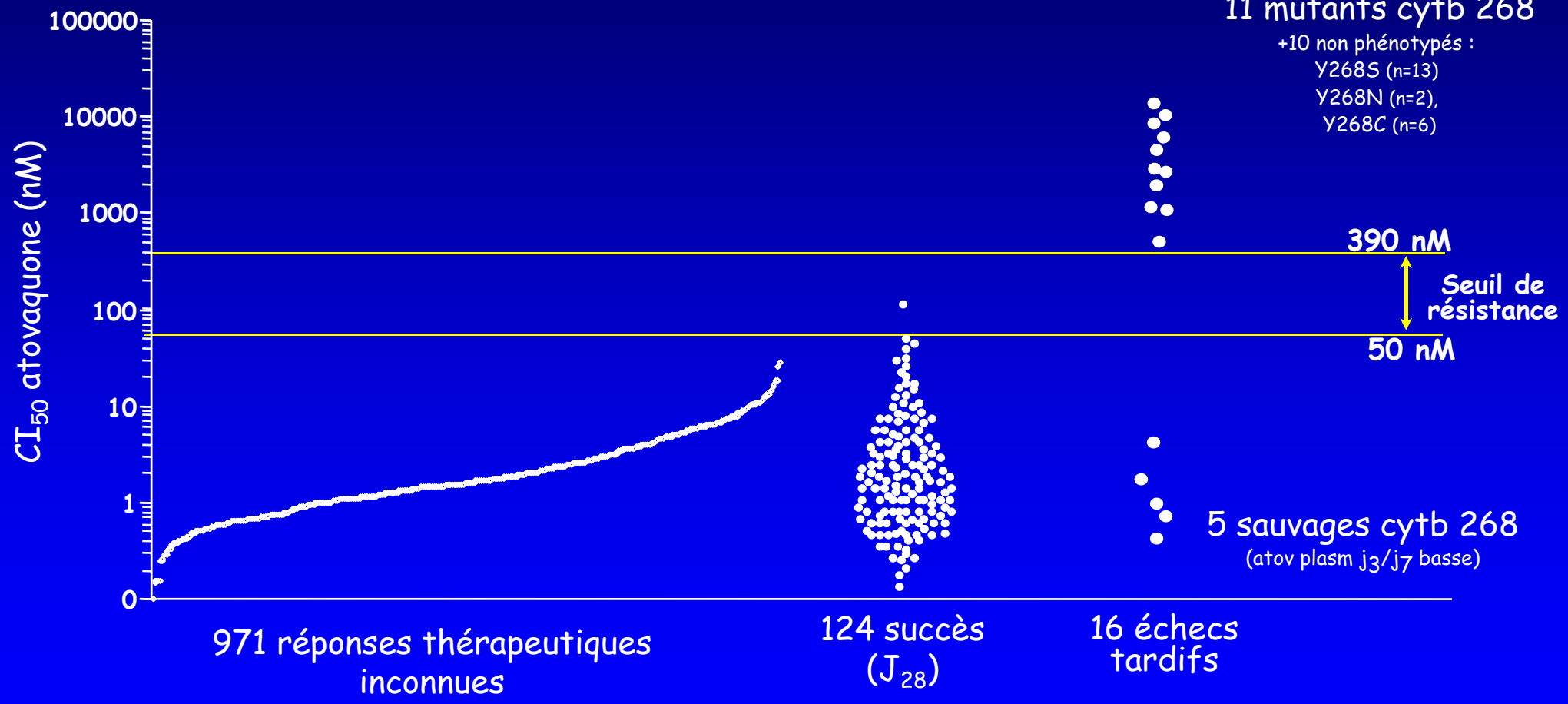
Newton PlosMed 2008;5(2):e32

Résistance in vitro de *P. falciparum* cas importés en France métropolitaine 2006-09



Résistance à l'atovaquone-proguanil

Incidence de la R parasitaire à l'A-P : 0.019-0.14
Incidence de la R clinique à l'A-P : 0.01-0.08



Musset JAntimicr Chemother 2006 ; Musset Micr Infect 2007 ; Pradines Antimicr Ag Chemother 2008 + données CNRPalu 2007-08

De quelles informations disposons nous?

- Absence de données
  - couverture géographique incomplète
- Données de mauvaise qualité
- Absence de standardisation
- Délai important pour accéder aux données
  - Publication des années après la collecte de données
  - Données non publiées
    - Utilisées uniquement pour l'enregistrement des médicaments ou considérées comme non prioritaires

Mission WWARN

- WorldWide Antimalarial Resistance Network (WWARN) produira une information complète, mise a jour, de qualité contrôlée, sur la résistance aux antipaludiques dans l'ensemble des pays endémiques

Usagers de WWARN

- Patients
- Décideurs de politiques de santé
- Programmes Nationaux de lutte contre le paludisme
- OMS
- ONGs
- Communauté scientifique
- Industrie pharmaceutique
- Agences de financements
- …

Objectifs

- site Web, accès libre
- Accès à des outils gratuits pour la mise en ligne de données
  - Protocoles standardisés : harmonisation
  - Procédures standardisées
  - Base de données type
  - Méthodologie Analytique
- Procédures d'assurance qualité
- Outils d'analyse finale
  - Information géographique
  - Donnes harmonisées, comparables
  - Suivi de tendance

WWARN
WorldWide Antimalarial Resistance Network

Moyens

- Priorité aux données prospectives
- Données individuelles par patient
- Assurance qualité
- Quatre modules interactifs
  - Efficacité clinique (Oxford)
  - Pharmacologie (Bangkok, Captown)
  - In vitro (Paris)
  - Marqueurs moléculaires (Baltimore)

WWARN
WorldWide Antimalarial Resistance Network

WWARN
WorldWide Antimalarial Resistance Network

www.wwarn.org

HOME | NETWORK | ABOUT | REFERENCES | NEWS | CONTACT | INTERNAL RESOURCES

WorldWide Antimalarial Resistance Network

WWARN is a global collaboration working to ensure that anyone affected by malaria receives effective and safe drug treatment. WWARN will provide urgently needed, comprehensive, timely and quality-assured intelligence to track the emergence of malarial drug resistance.

More about WWARN

Our modules

Clinical Module

Clinical responses of malaria patients treated with various drugs
Find out more

Pharmacology Module

Precise antimalarial drug concentrations and pharmacokinetic parameters for key target populations
Find out more

In vitro Module

In vitro drug susceptibility results from malaria parasites collected from infected patients
Find out more

Molecular Module

Molecular markers for drug resistance in malaria parasites
Find out more

Our network

WWARN affiliated networks support and enhance capacity in malaria endemic countries. See how your research group could become a contributor to the network.
Find out more

Project focus

News update

26.09.2009
This week there was international excitement over news that researchers had discovered how the malaria parasite resists the killing power of chloroquine, once the key drug in the war against the microbe.
Read the full story

25.09.2009
Resistance observed on the Cambodian-Thai border threatens to overturn decades of progress in the worldwide fight against the disease, doctors from the World Health Organisation (WHO) warned at a regional conference in Hong Kong on Wednesday.
Read the full story

23.09.2009
The leaders of 20 African nations, meeting in New York during the UN General Assembly, have launched ALMA (the African Leaders Malaria Alliance), in order to achieve a united

Clinique : vue de l'étude

- Analyses standardisées
- Mise a disposition d'outils d'analyse
- Stockage de données brutes permettant des analyses multiples et corrélation avec d'autres bases de données

WWARN WorldWide Antimalarial Resistance Network

Resistance spread: chloroquine and SP

WWARN
WorldWide Antimalarial Resistance Network

Dashboard | Countries | Treatments | Geomap | Analysis | Single Study

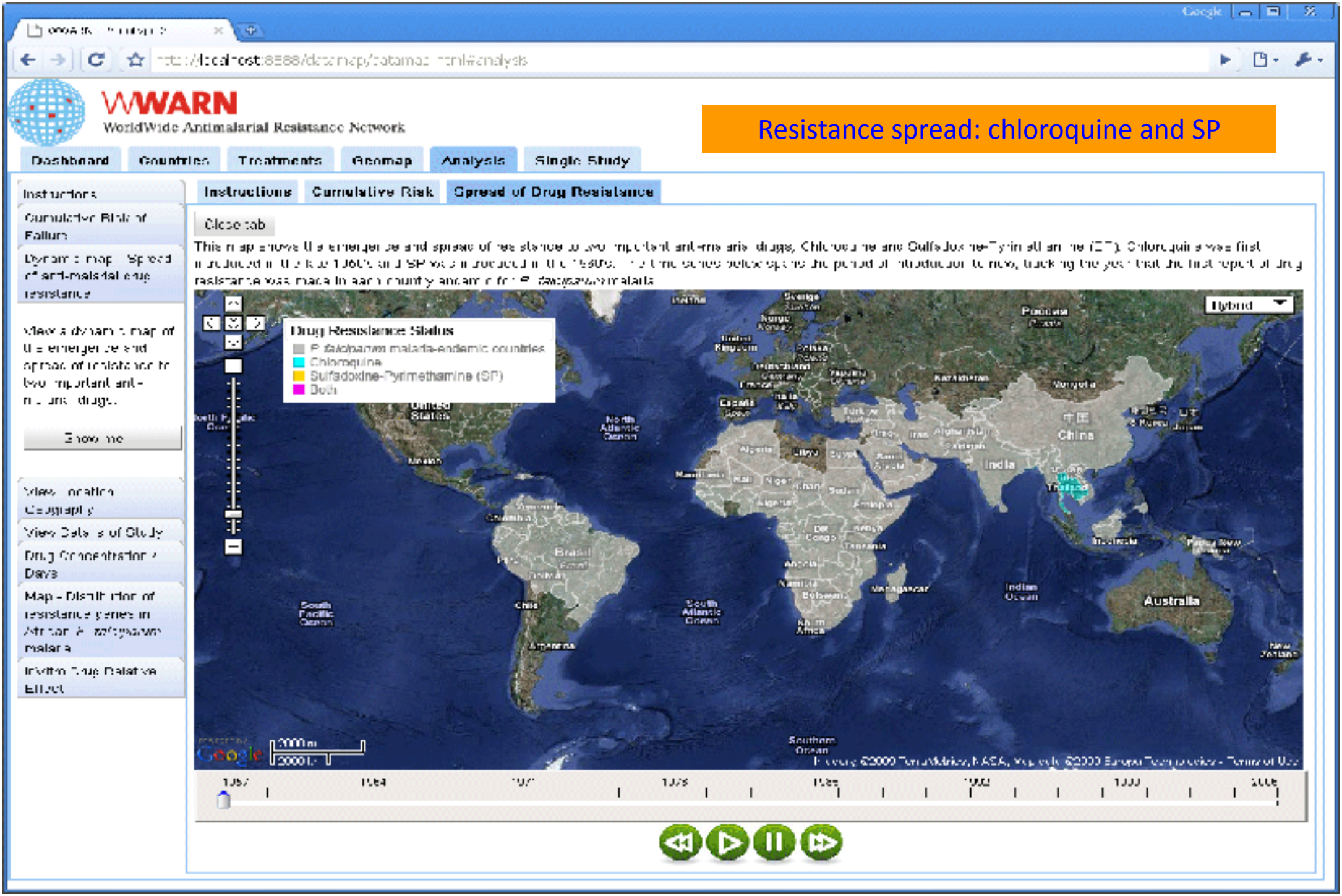
Instructions | Cumulative Risk | Spread of Drug Resistance

Close tab

This map shows the emergence and spread of resistance to two important antimalarial drugs, Chloroquine and Sulfadoxine-Pyrimethamine (SP). Chloroquine was first introduced in the 1940s and SP was introduced in the 1960s. [illegible] the period of introduction to now, tracking the year that the first report of drug resistance was made in each country endemic for P. falciparum malaria.

Instructions
Cumulative Risk of Failure
Dynamic map - Spread of anti-malarial drug resistance
View a dynamic map of the emergence and spread of resistance to two important anti-malarial drugs.
Show me
View Location Geography
View Details of Study
Drug Concentration / Days
Map - Distribution of resistance genes in African P. falciparum malaria
In vitro Drug Relative Effect

Resistance spread: chloroquine and SP



WWARN
WorldWide Antimalarial Resistance Network

www.wwarn.org

Resistant malaria a concern, WHO says

25th September 2009

from Jacob Gold, The Phnon Penh Post:

A drug-resistant strain of malaria observed on the Cambodian-Thai border threatens to overturn decades of progress in the worldwide fight against the disease, doctors from the World Health Organisation (WHO) warned at a regional conference in Hong Kong on Wednesday.

"Artemisinin-based combination therapy, the most effective antimalaria treatment to date, and among the last resources in our arsenal of drugs against the disease, is seriously threatened by evidence of resistance to the treatment in the Cambodian-Thai border," said Shin Young-soo, WHO regional director for the Western Pacific.

"Artemisinin-resistance needs urgent containment to prevent further spread of drug resistance."

Artemisinin is only the latest antimalarial drug to be compromised by resistance developed on the Cambodian-Thai border.

A 2007 WHO report on the phenomenon describes how, beginning in the 1970s, Cambodia reported malaria strains resistant to the drugs chloroquine, sulfadoxine-pyramethamine and mefloquine. Infections treated with artemisinin have already begun taking longer and longer to clear, requiring increasingly elaborate multi-drug treatment courses.

According to government figures, the number of malaria cases and deaths has risen in 2009. The National Centre for Parasitology, Entomology and Malaria Control reported that in the first six months of 2009, 27,105 people caught the disease and 103 died. In comparison, 25,033 were infected during the same period last year, causing just 65 fatalities.

WHO officials at the conference said the spread of malarial drug-resistance in Cambodia is being fuelled by an abundance of cheap counterfeit drugs containing little or no active medicine. Rather than clearing out the infection completely, inadequate treatments kil only the weakest parasites, leaving behind the strongest and most resistant.

Et les résistances aux dérivés de l'artémisinine ?

Aucune de 1990 à 2004

Craintes en 2005 ?

Réalité en 2009 ?

***Artemisia annua L* → Artémisinine**

Lancet 2005; 366: 1960–63 (3 dec)

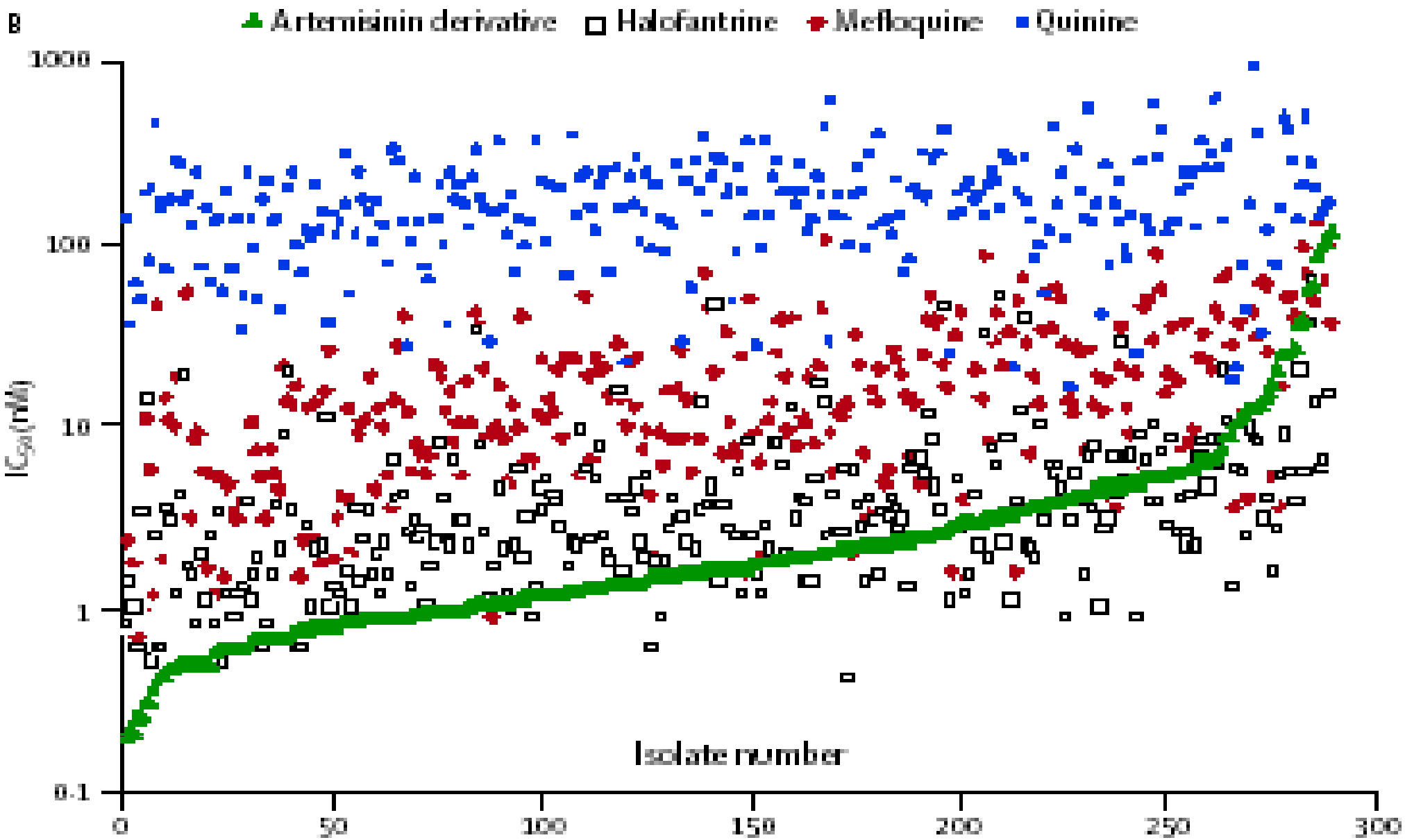
ALERTE !?

Resistance of *Plasmodium falciparum* field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6

***Ronan Jambou, *Eric Legrand**, Makhtar Niang, Nimol Khim, Pharath Lim, Béatrice Volney, Marie Thérèse Ekala, Christiane Bouchier, Philippe Esterre, Thierry Fandeur, Odile Mercereau-Puijalon

Artemisinin derivatives are an essential component of treatment against multidrug-resistant *Plasmodium falciparum* malaria. We aimed to investigate in-vitro resistance to artemisinin derivatives in field isolates. In-vitro susceptibility of 530 *P falciparum* isolates from three countries (Cambodia, French Guiana, and Senegal) with different artemisinin use was assessed with an isotopic microtest. Artemether IC_{50} up to 117 and 45 nmol/L was seen in French Guiana and Senegal, respectively. DNA sequencing in a subsample of 60 isolates lends support to SERCA-PfATPase6 as the target for artemisinins. The S769N PfATPase6 mutation, noted exclusively in French Guiana, was associated with raised (>30 nmol/L) artemether IC_{50}s ($p<0\cdot0001$, Mann-Whitney). All resistant isolates came from areas with uncontrolled use of artemisinin derivatives. This rise in resistance indicates the need for increased vigilance and a coordinated and rapid deployment of drug combinations.

Distribution des IC_{50} de 289 isolats de *P. falciparum* en **Guyane Française** en 2002-03



Interprétation ? Problèmes de méthode ?

- In vitro uniquement
- Dépistage phénotypique par culture d'isolats
- Avec l'artésunate au Cambodge, l'artéméther au Sénégal et en Guyane
- Clones ou isolats utilisés comme contrôle de qualité interne différents selon les pays
- Temps de conservation des plaques de cultures avant usage ? L'artéméther se conserve mal…
- Mais corrélation avec une mutation sur *PfATPase6* en Guyane ? Que personne n'a retrouvé ailleurs…

Fausse alerte ?

Dondorp *AM et al.* Artemisinin-Resistant *Plasmodium falciparum* Malaria

N Engl J Med 2009; 361: 455-67.(july 30)

Nord-Ouest de la Thaïlande

Ouest du Cambodge

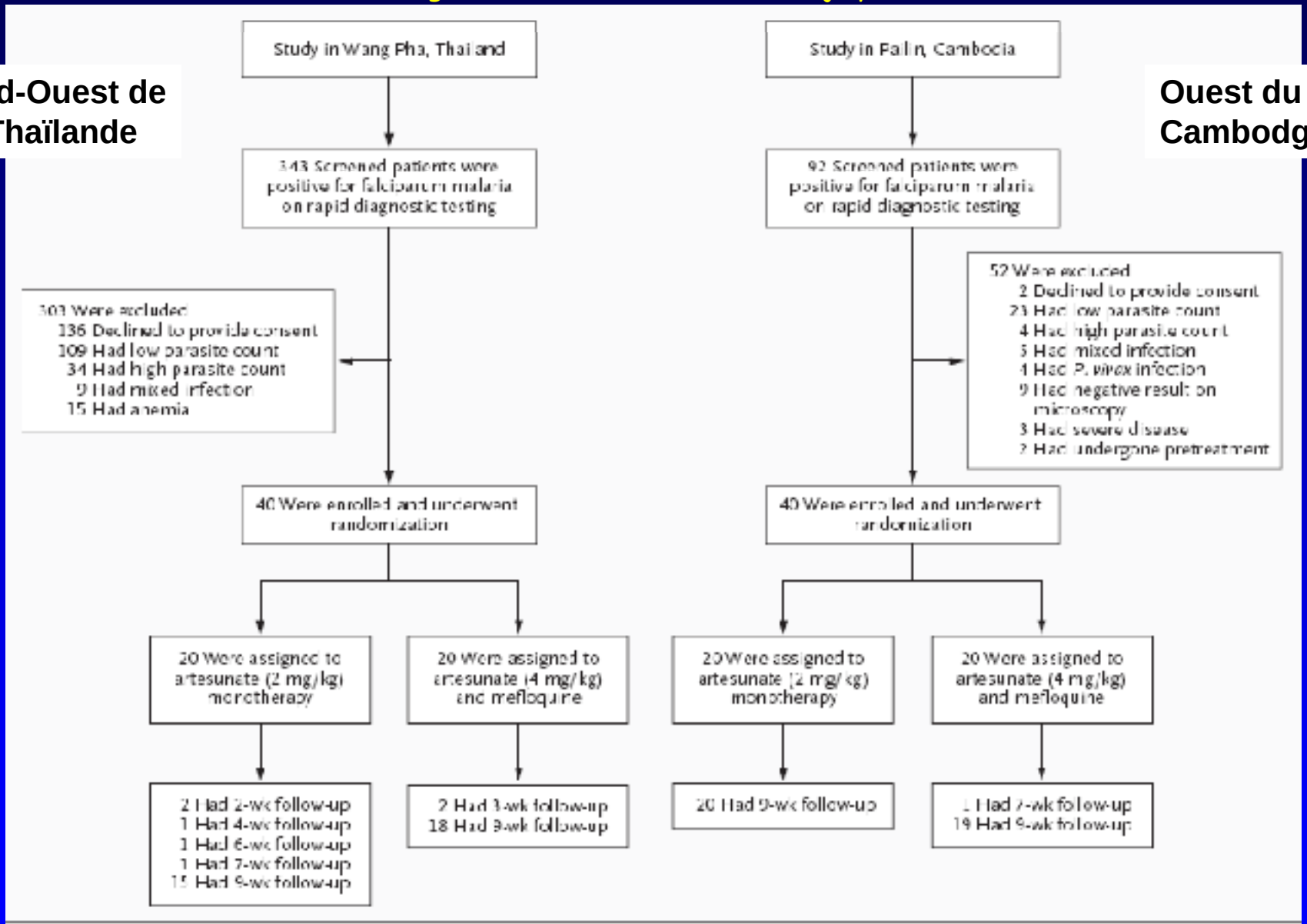
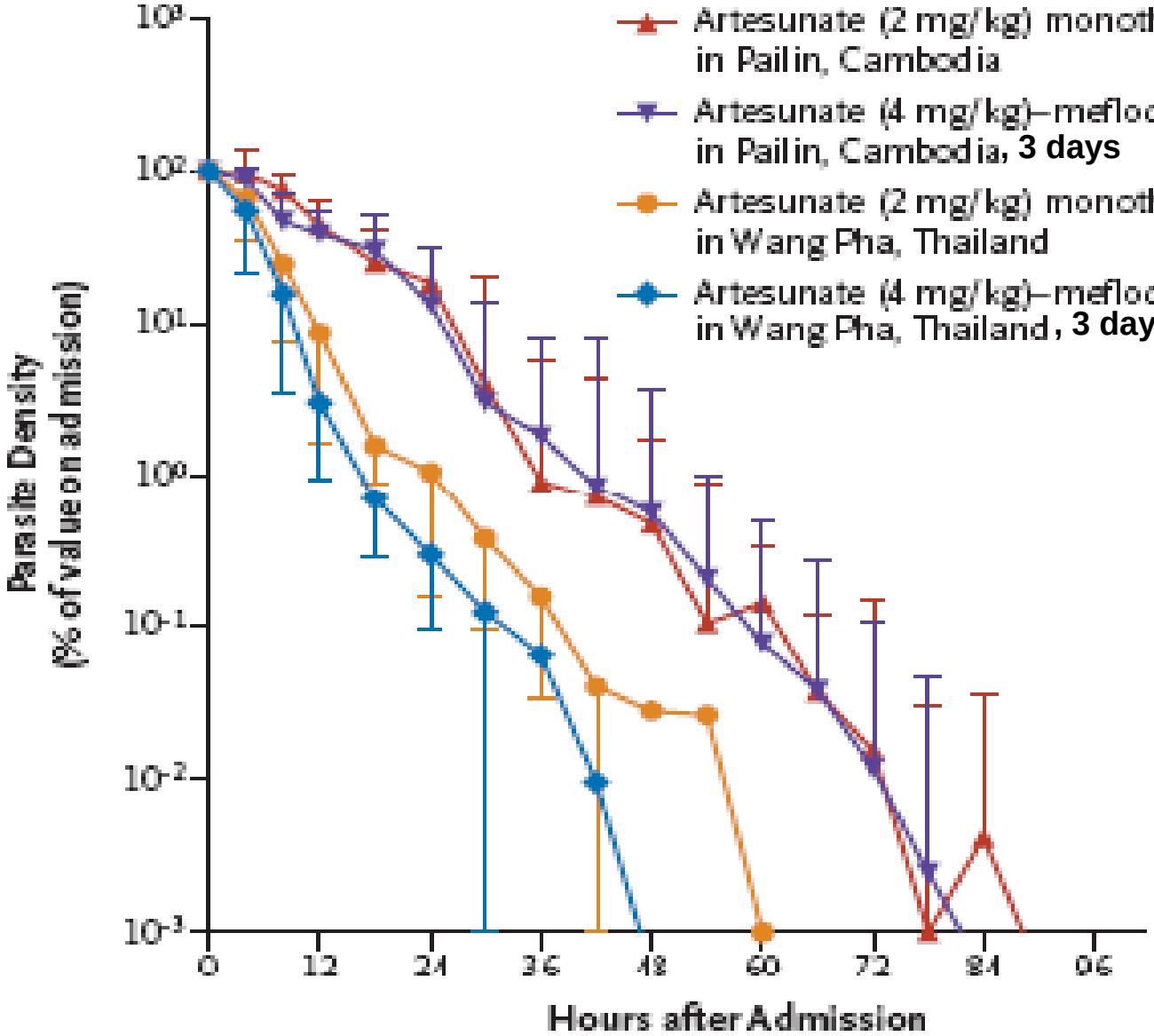


Figure 1. Enrollment, Randomization, and Follow-up of the Patients in the Two Studies.
Mixed infection was infection with *Plasmodium vivax* and *P. falciparum*.

Dondorp *AM et al.* Artemisinin-Resistant *Plasmodium falciparum* Malaria

N Engl J Med 2009; 361: 455-67 (july 30)



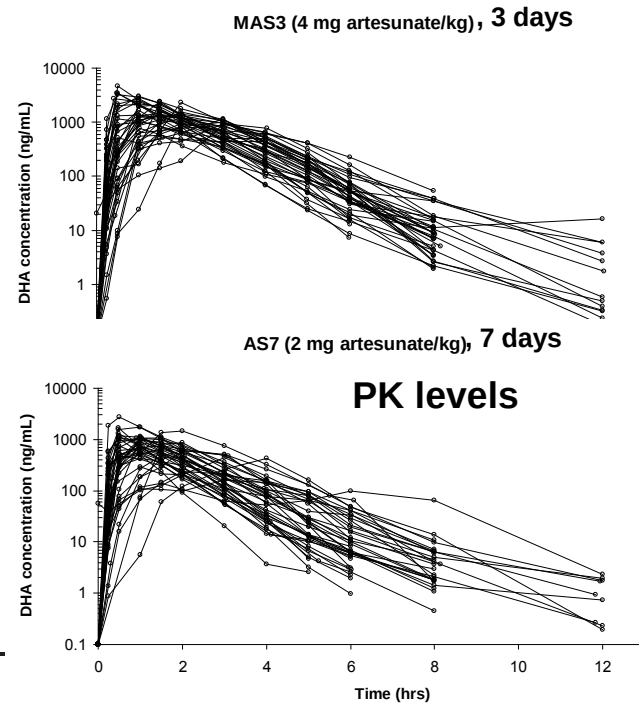


Figure 2. Parasite Clearance Curves.

TESTS in vitro : phénotypage en culture: Concentration inhibitrice 50% à 48 h.

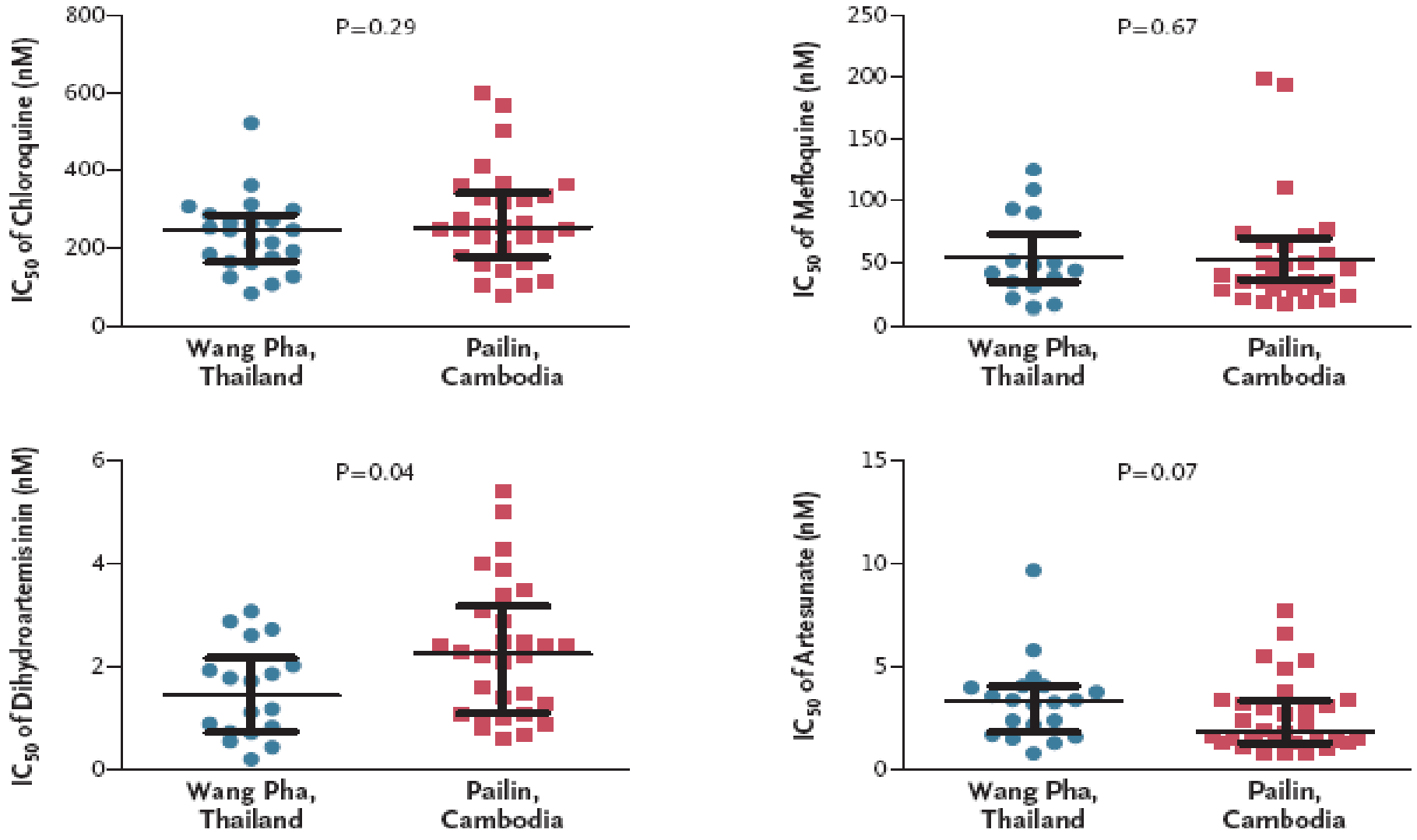


Figure 3. The 50% Inhibitory Concentration (IC_{50}) for *Plasmodium falciparum*, According to Antimalarial Drug.

The panels show the concentrations of chloroquine, mefloquine, dihydroartemisinin, and artesunate resulting in the inhibition of hypoxanthine uptake by 50% after 48 hours of in vitro culture of freshly isolated *P. falciparum* from the study patients. The horizontal lines are the medians; the I bars represent the interquartile ranges.

Artemisinin Resistance in *Plasmodium falciparum* Malaria

CONCLUSIONS

- *P. falciparum* has reduced in vivo susceptibility to artesunate in western Cambodia as compared with northwestern Thailand.
- Resistance is characterized by slow parasite clearance in vivo without corresponding reductions on conventional in vitro susceptibility testing.
- Containment measures are urgently needed.

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S. **N Engl J Med 2009;361:455-67.**

BEH Bulletin épidémiologique hebdomadaire

InVS INSTITUT DE VEILLE SANITAIRE

24 juin 2008 / n° 25-26

Recommandations sanitaires pour les voyageurs 2008

Health recommendations for travellers 2008

p.225 **Éditorial - Préserver sa santé en voyage !**
Editorial - Preserve one's health while travelling!

1. VACCINATIONS ..... p. 227
1.1 Pour tous et quelle que soit la destination
1.2 En fonction de la situation épidémiologique de la zone visitée
1.3 En fonction des conditions et de la durée du séjour

2. PALUDISME ..... p. 228
2.1 Données épidémiologiques
2.2 Chimioprophylaxie
2.2.1 Principes
2.2.2 Les schémas prophylactiques
2.2.3 Chimioprophylaxie selon les zones
2.3 Séjours de longue durée (plus de 3 mois)
2.4 Séjours itératifs de courte durée
2.5 Traitement présomptif

3. RISQUES LIÉS AUX INSECTES ET AUTRES ANIMAUX ..... p. 232
3.1 Moustiques
3.2 Autres insectes piqueurs (phlébotomes, mouches, punaises, poux et puces)
3.3 Autres arthropodes (tiques, araignées, scorpions)
3.4 Animaux venimeux (serpents, poissons, etc.) et plantes vénéneuses
3.5 Contacts avec d'autres animaux

4. DIARRHÉE DU VOYAGEUR ..... p. 233

5. RISQUES ACCIDENTELS (circulation, altitude, baignades...) ..... p. 233

6. PRÉCAUTIONS EN FONCTION DES PERSONNES p. 234
6.1 Les enfants
6.2 Les femmes enceintes
6.3 Les personnes âgées
6.4 Les patients infectés par le VIH
6.5 Les patients atteints d'affections chroniques

7. HYGIÈNE ..... p. 235
7.1 Hygiène alimentaire
7.2 Hygiène corporelle et générale
7.3 Prévention des infections sexuellement transmissibles

8. TROUSSE A PHARMACIE ..... p. 236

9. ASPECTS ADMINISTRATIFS ..... p. 236

Pour en savoir plus ..... p. 236

Note sur les modalités de surveillance du paludisme d'importation en France métropolitaine, 2008 ..... p. 236

nté)

http://invs.sante.fr/beh