Parasite Resistance to Artemisinins

AMAZON MALARIA INITIATIVE (AMI) / RAVREDA
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Dr Peter Olumese
Global Malaria Programme

World Health Organization

What is antimalarial drug resistance?

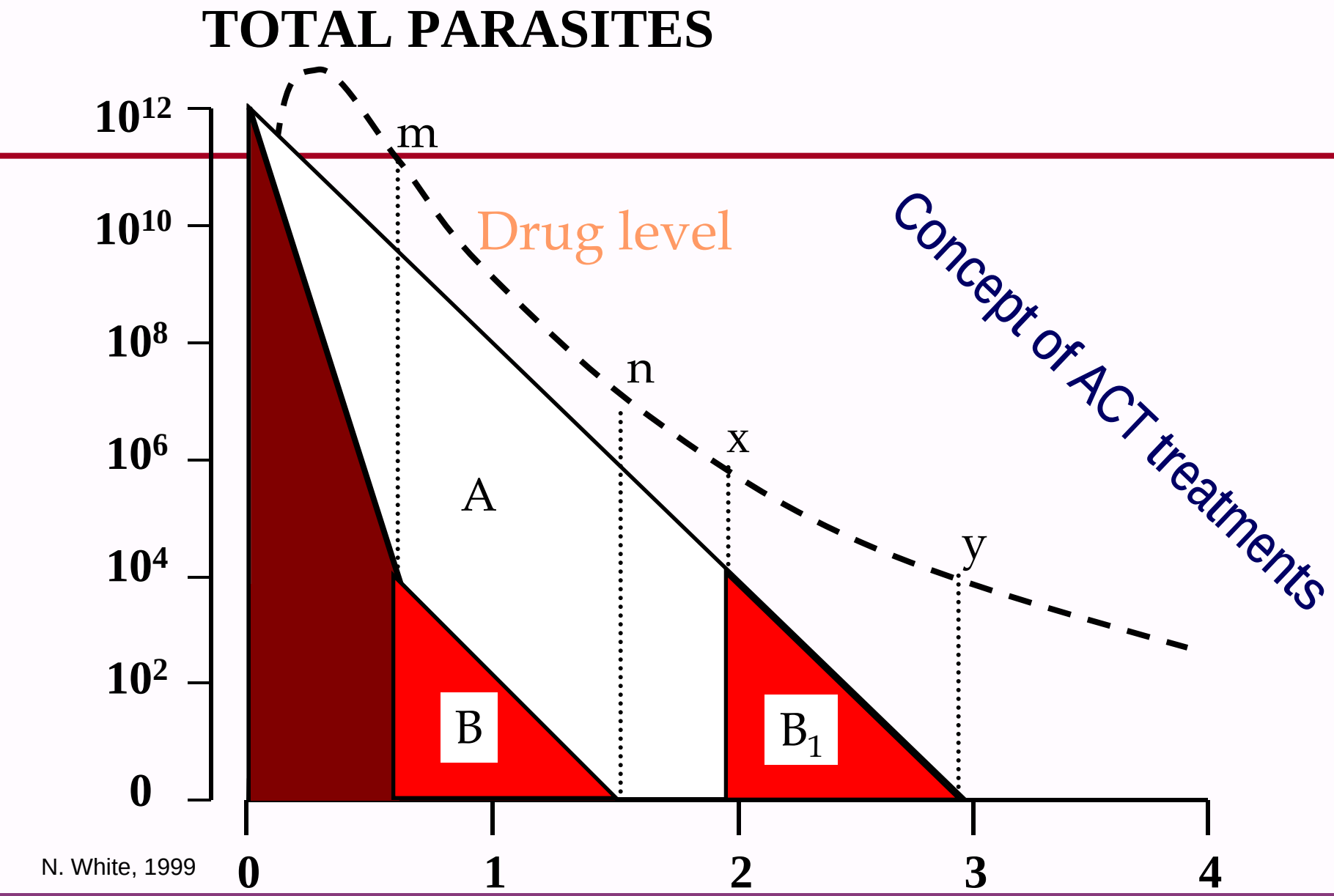
- Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject" (WHO, 1973)

- Therapeutic efficacy is used as an 'alert' to drug resistance but not all treatment failures are due to resistance. Treatment failure can be due to host or parasite factors:
  - Pharmacokinetic (low absorption, increased metabolism, etc…)
  - Immunity (HIV, pregnancy, etc…)
  - Parasite resistance

- Therefore other tools are needed to confirm resistance
  - pharmocokinetics
  - in vitro efficacy
  - molecular markers

Rationale of ACT

- The potential value of drug combinations, notably those including an artemisinin derivative (ACT)
  - to improve efficacy,
  - delay development of drug-resistance and prolong the useful therapeutic life of antimalarial drugs
- The concept of an ACT is based on
  - the artemisinin component to reduce parasite bio-mass (and not to achieve full clearance) and
  - The partner drug to clear residual parasites



N. White, 1999

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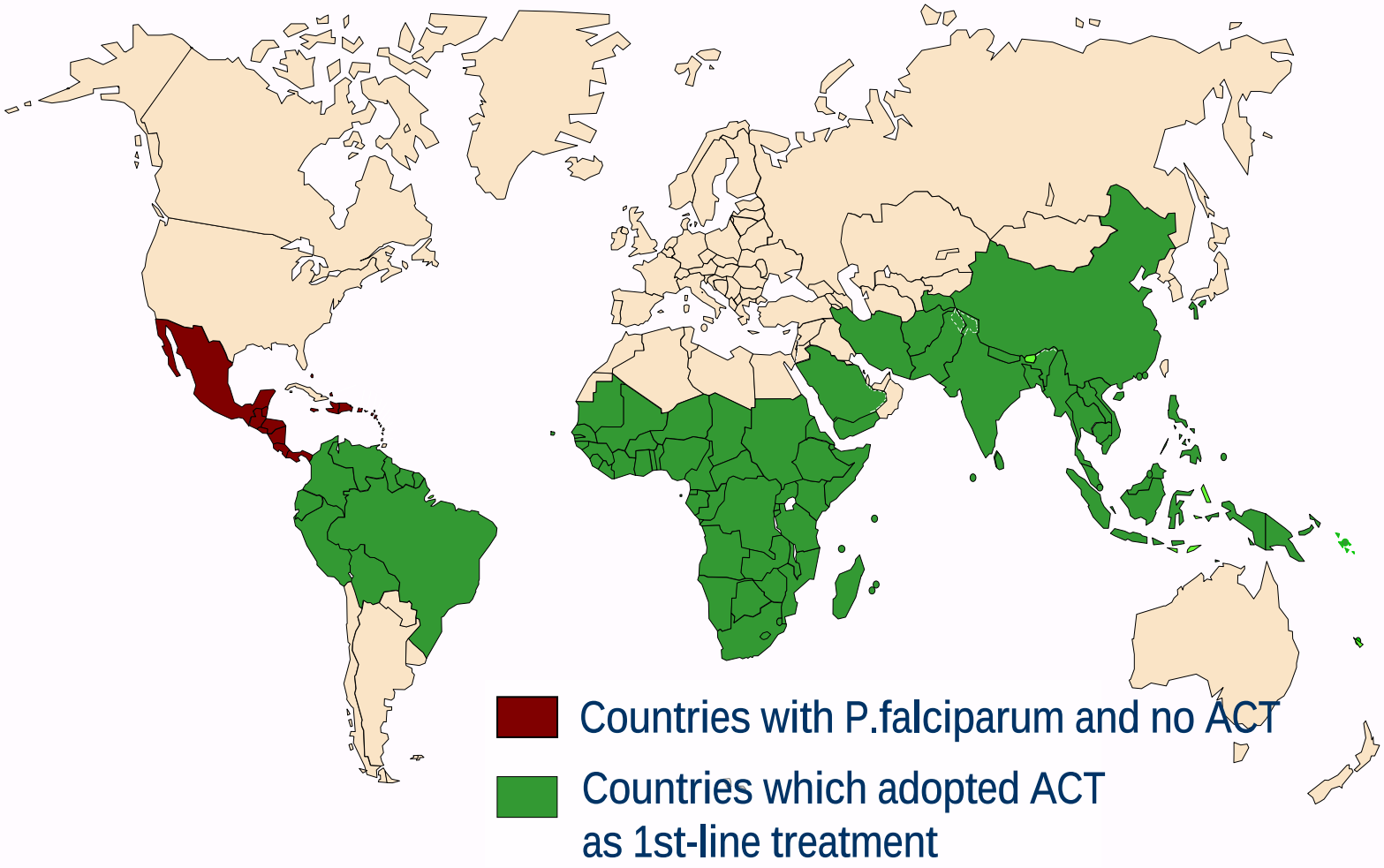
80 countries are using ACTs as first-line malaria treatment



Artemisinin RESISTANCE or TOLERANCE? (1)

- The concept of an ACT is based on
  - the artemisinin component to reduce parasite bio-mass (and not to achieve full clearance) and
  - The partner drug to clear residual parasites

- Therefore, therapeutic failure with an ACT can only be taken to reflect failure of the partner medicine (treatment failure to artemisinin requires evaluation after 7 days of therapy)

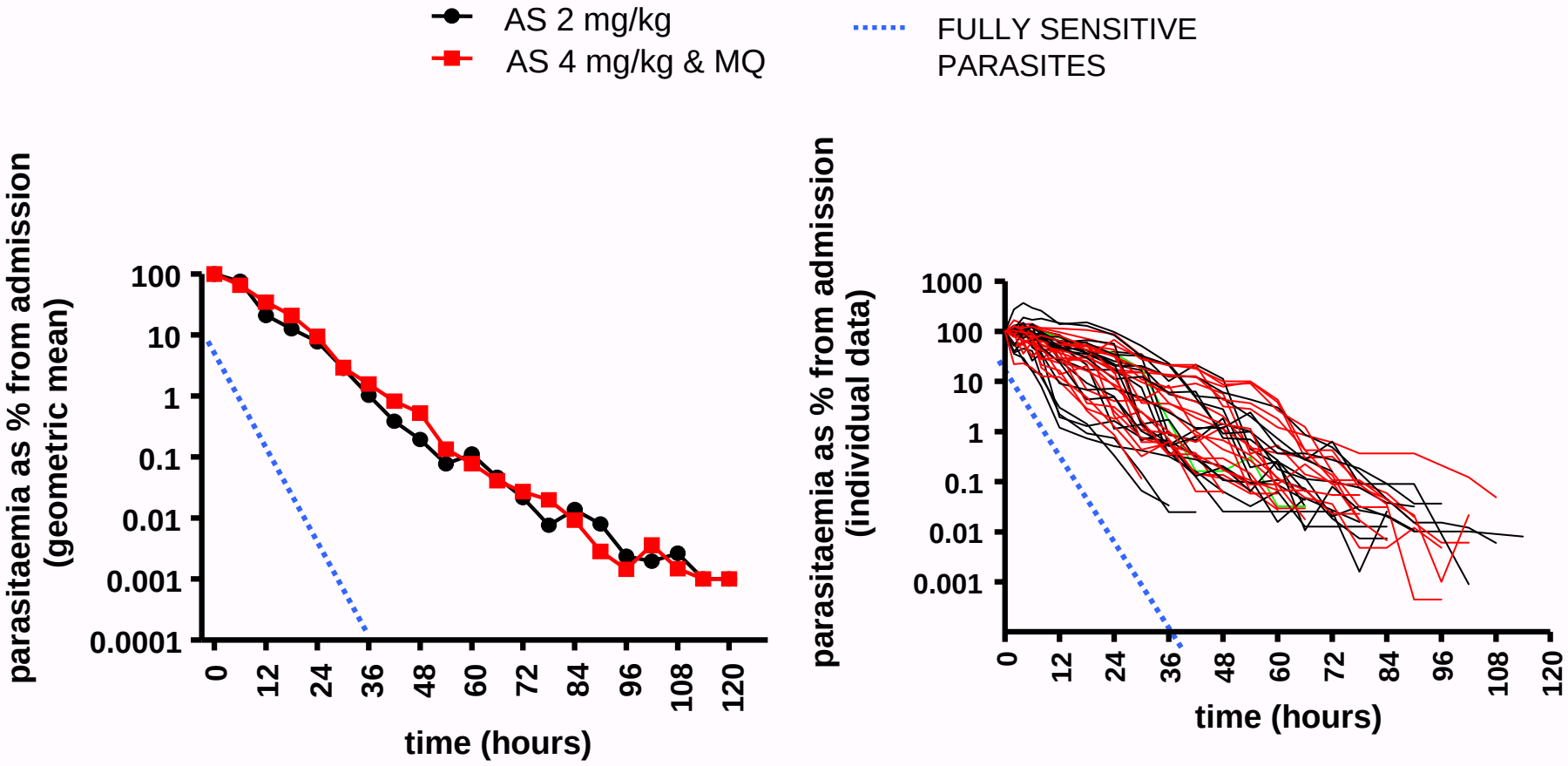
- During a trial with ACT (3 days), it is only possible to confirm resistance to the partner drug but not to artemisinin.

- <u>The term "ACT resistance" should not be based on treatment failure with an ACT</u>

Artemisinin resistance or tolerance? (2)

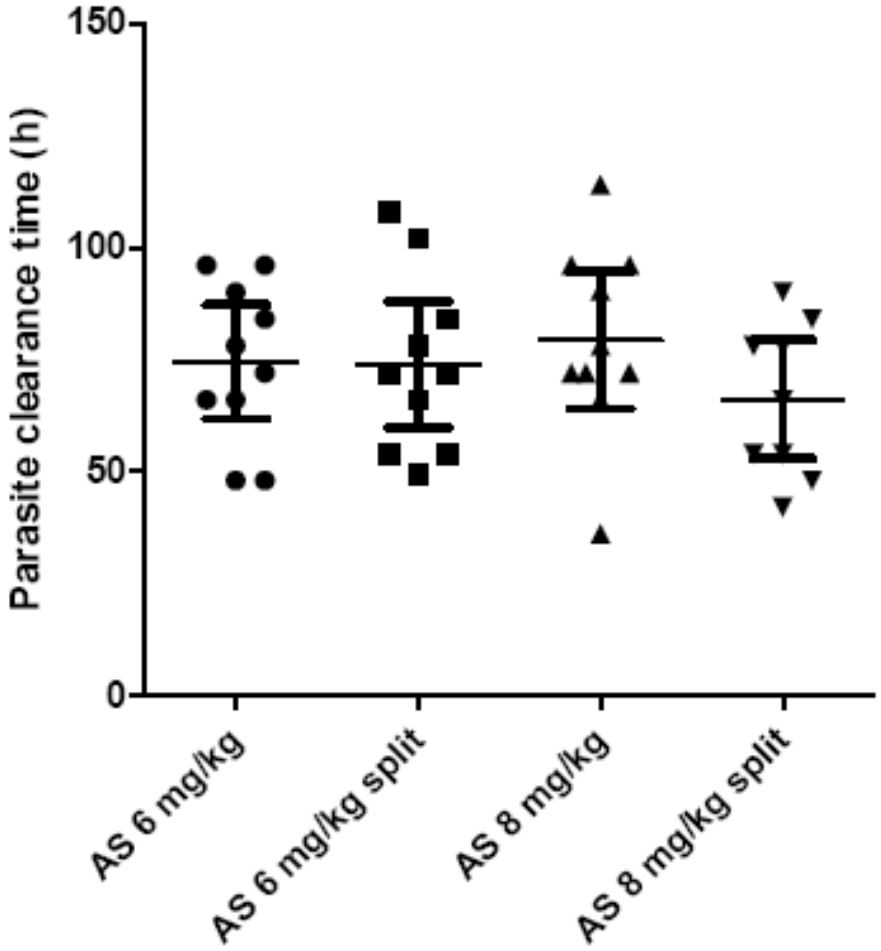
- Routine surveillance in several sites in SEA reported increasing trend of patients presenting with parasites at Day 3 after ACT (Day-3 positivity rate should be < 3%).
- When these parasite populations were subject to 7 day-artesunate monotherapy treatment they were rarely associated with treatment failure to artesunate.
  - does this evidence make it <u>early artemisinin resistance or artemsinin tolerance?</u>
- Nevertheless ,in a very few cases, artesunate resistance has been confirmed in Cambodia with a combination of
  - presence of parasite at Day 3 associated with
  - late treatment failure and
  - high level of artesunate and dihydroartemisinin in patient blood

PCT in Pailin study 2007



Dondorp, NEJM, 2009

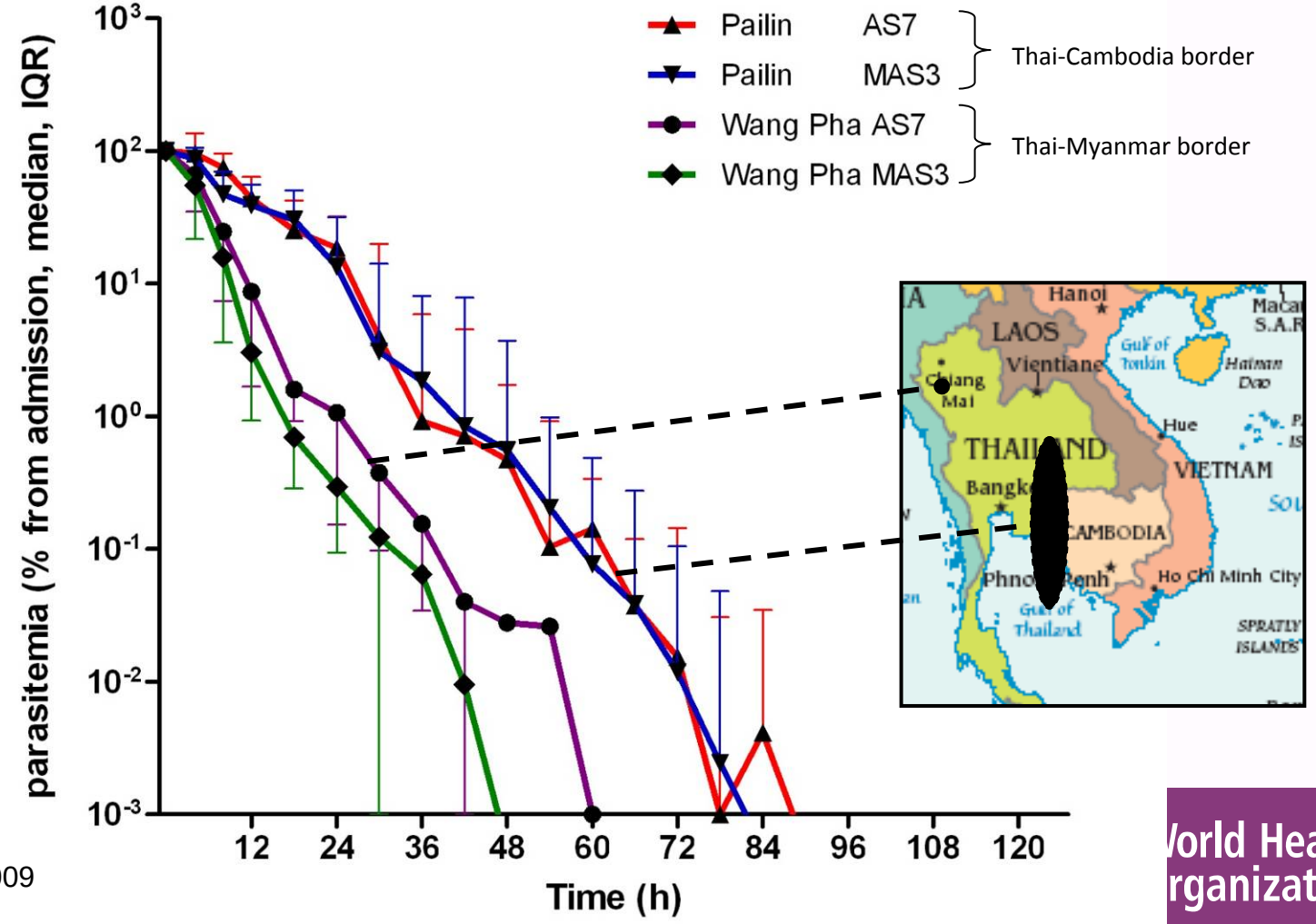
PCT in Pailin with artesunate 6/8 mg/kg/d



N=40

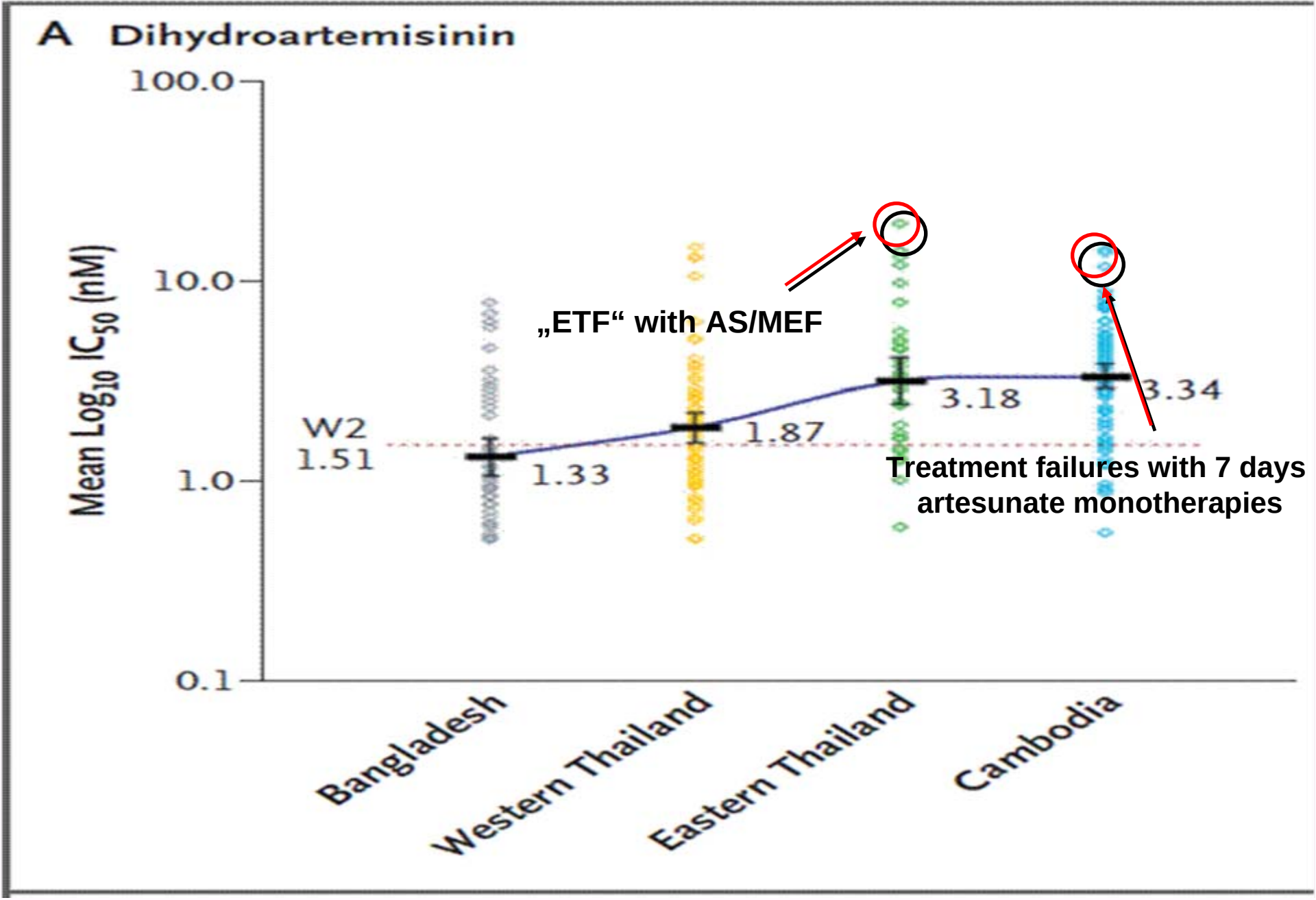
Parasite Clearance

(p=0.0001 for Δ slopes between sites)



Dondorp NEJM, 2009

World Health Organization



Noedl. et al. New England Journal of Medicine, 2009, 361: 540-1.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

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Artemisinin resistance

Artemisinin resistance

Major efforts underway to better understand artemisinin resistance and to prevent it's further spread

Artemisinin Resistance Characterisation, Confirmation, & Containment – ARC3 Project

Artemisinin Containment Project - ARCE Project

To eliminate AS-resistant P.falciparum from the area

ARC3 project

- Funded by BMGF (3.2 M)
- Coordinated by GMP/HQ
- Major partners:
  - Wellcome Trust-Mahidol University, Oxford Tropical Medicine Research Programme, Bangkok, THAILAND
  - US Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, THAILAND
  - Réseau des Instituts Pasteur, Cambodge, Phnom Penh, CAMBODIA
  - University of Vienna, Vienna, AUSTRIA
  - University of Maryland School of Medicine, Baltimore, Maryland, USA
  - University of South Florida, Tampa, Florida, USA
  - USP, Rockville, Madison, USA
  - National Malaria Control Programme, Phnom Penh, CAMBODIA
  - National Malaria Control Programme, Bangkok, THAILAND
  - WHO Mekong project, Bangkok, THAILAND
  - Western Pacific Regional Office, Manila, PHILIPPINES

Objectives of the ARC3 project

- Confirm clinically relevant artemisinin resistance
  - Characterize clinically relevant artemisinin resistance in-vivo by conducting clinical and pharmacokinetic-pharmacodynamic assessments of artesunate, at sites where artemisinin resistance has been reported, where parasite clearance is prolonged but treatment failure not yet manifest, and where artesunate efficacy is preserved;
  - Establish a reference repository of parasite isolates from clinically validated cases of resistance.
- If clinical resistance is confirmed, further characterize this resistance to define resistant in vitro phenotypes and genotypes for use in global surveillance for artemisinin resistance
- To establish the prevalence on substandard and fake drugs on the Thai-Cambodia border
- Develop strategies to combat the spread of artemisinin resistant malaria within Southeast Asia and internationally

Preliminary conclusions of ARC3

- The proportion of patients who are parasitaemic on Day 3 (D3+) is the most appropriate measure of slow parasite clearance from available clinical trial data which could reveal artemisinin resistance/tolerance

- This in vivo phenotype (D3+) does not correlate to standard in vitro assays:
  - There is no correlation between artesunate IC50s and PRR 48 h, proportions of patient still parasitemic day 3 or PCT;
  - The lack of in vitro correlation may be because we are using the wrong tool, therefore there is a need to develop novel in vitro studies

- There was no correlation between a number of different mutations (*pfSERCA* or mtDNA mutations -*coxIII* gene) or pfmdr1 copy number and in vivo phenotype (Day 3+)

Recommendations of ARC3

- A standard in vivo efficacy study with ACT;
- If >10% positive after 72 hours: proceed with confirmation and further investigations (as below)
- Monitoring efficacy of artemisinin monotherapy to assess:
  - treatment failure;
  - parasite positivity at D3;
  - PK measurements;
  - PCT;
  - PRR at 48 hours;
  - slope of the linear parasite clearance curve.

Objectives of containment project

- To eliminate artemisinin tolerant parasites by detecting all malaria cases in target areas and ensuring effective treatment and gametocyte clearance
- To decrease drug pressure for selection of artemisinin resistant malaria parasites (including monotherapy ban)
- To prevent transmission of artemisinin tolerant malaria parasites by mosquito control and personal protection
- To limit the spread of artemisinin tolerant malaria parasites by mobile/migrant populations
- To support containment/elimination of artemisinin resistant parasites through comprehensive behavior change communication (BCC), community mobilization and advocacy
- To undertake basic and operational research to fill knowledge gaps and ensure that strategies applied are evidence-based
- To provide effective management, surveillance and coordination to enable rapid and high quality implementation of the strategy

Factors that drive development and spread of resistance

Mechanism of resistance development

The selection of resistance can be considered in two parts

a) The de-novo selection of a genetic change which confers resistance

b) The preferential transmission of acquired resistant organisms

Mechanism of resistance development

SELECTIVE PRESSURE

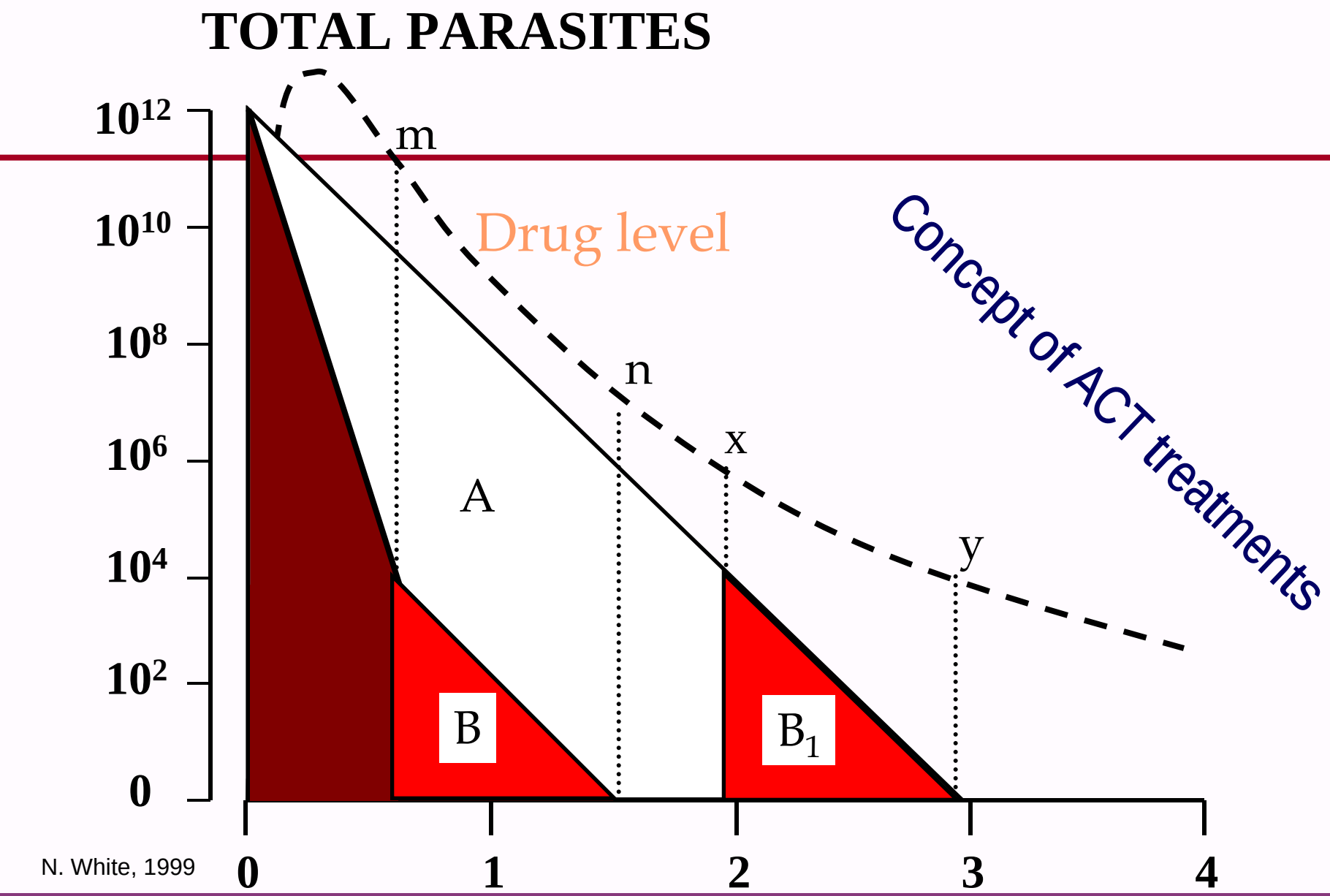
When a parasite population containing resistant organisms is exposed to a concentration of antimalarial drug sufficient to kill the susceptible, but *not* the resistant parasites, these will be selected and transmitted preferentially

Monotherapy….

- Current packaging of ACTs
  - Fixed dose formulation available only for 3 of the currently recommended options
  - Co-packed blisters treatment course - provides a challenge of ensuring that both components of the ACT is used, and not just using 3 days artesunate
- Use of ACTs whose the partner medicines is not efficacious = to artemisinin monotherapy used for only 3 days….
- High costs and heterogeneous quality of ACTs
- Large use as monotherapies especially in the private sector, with limited information and regulation over efficacy, safety and quality
- Counterfeits and substandard medicines

Inappropriate "ACTs"

- ACTs should include at least 3 days of treatment with an artemisinin derivative
  - To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is required to cover up to three post-treatment asexual cycles of the parasite.
  - This ensures that only about 10% of the parasitamia is present for clearance by the partner medicine, thus reducing the potential for development of resistance.
- Shorter courses of 1–2 days of the artemisinin component of the ACTs
  - would lead to a larger proportion of parasitaemia for clearance by the partner medicine;
- this is not recommended for the following additional reasons:
  - they are less efficacious (except when the partner drug is highly effective),
  - they have less of an effect on gametocyte carriage,
  - they provide less protection of the slowly eliminated partner antimalarial.



N. White, 1999

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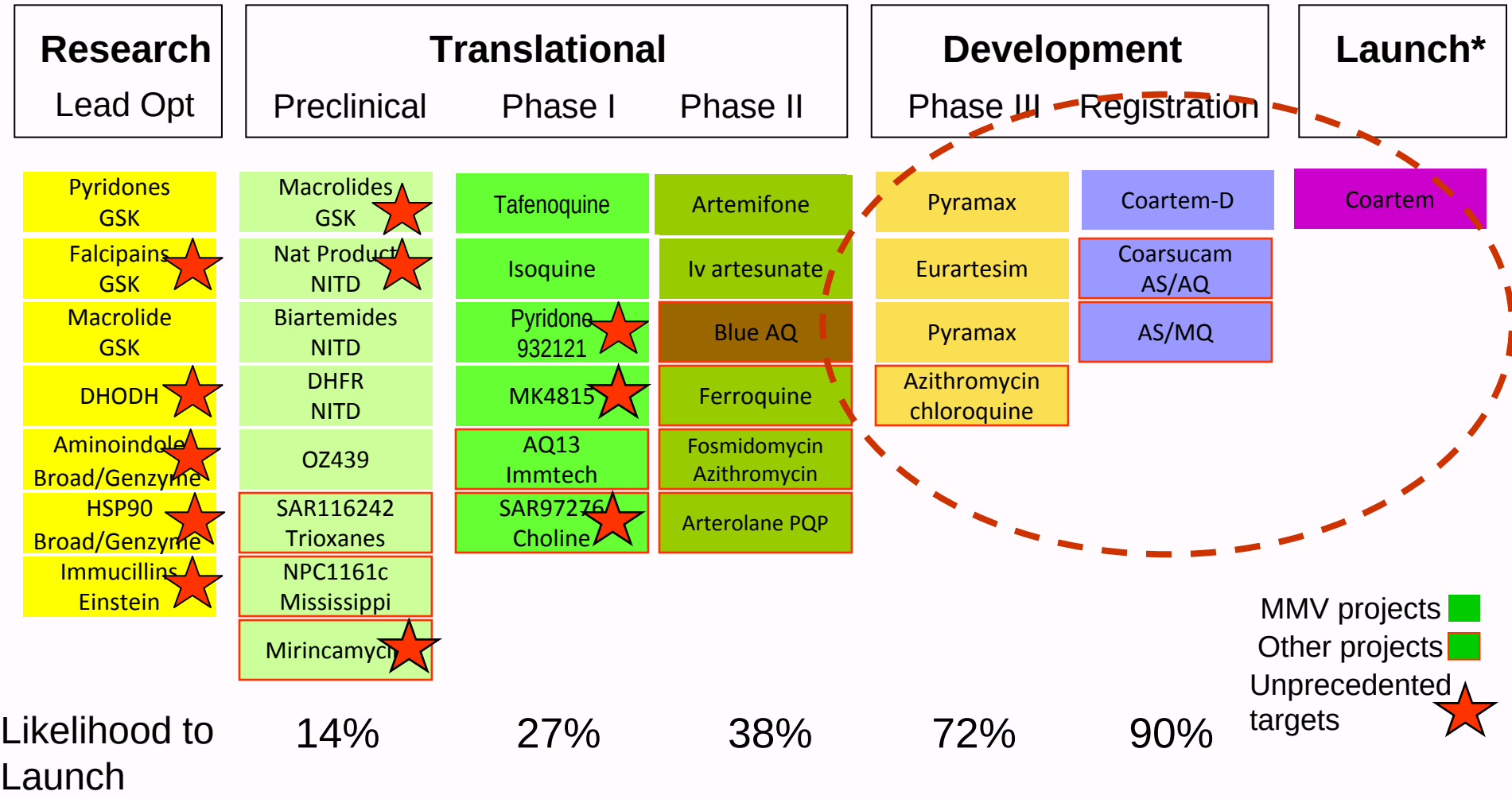
Dealing with the threat of parasite resistance

WHO strategies to prevent and contain parasite resistance

To deal with the threat of drug resistance

1. Develop new medicines
2. Monitor drug efficacy
3. Avoid emergence of drug resistance
4. Contain the spread of drug resistance

1. Global Malaria Portfolio - August 08

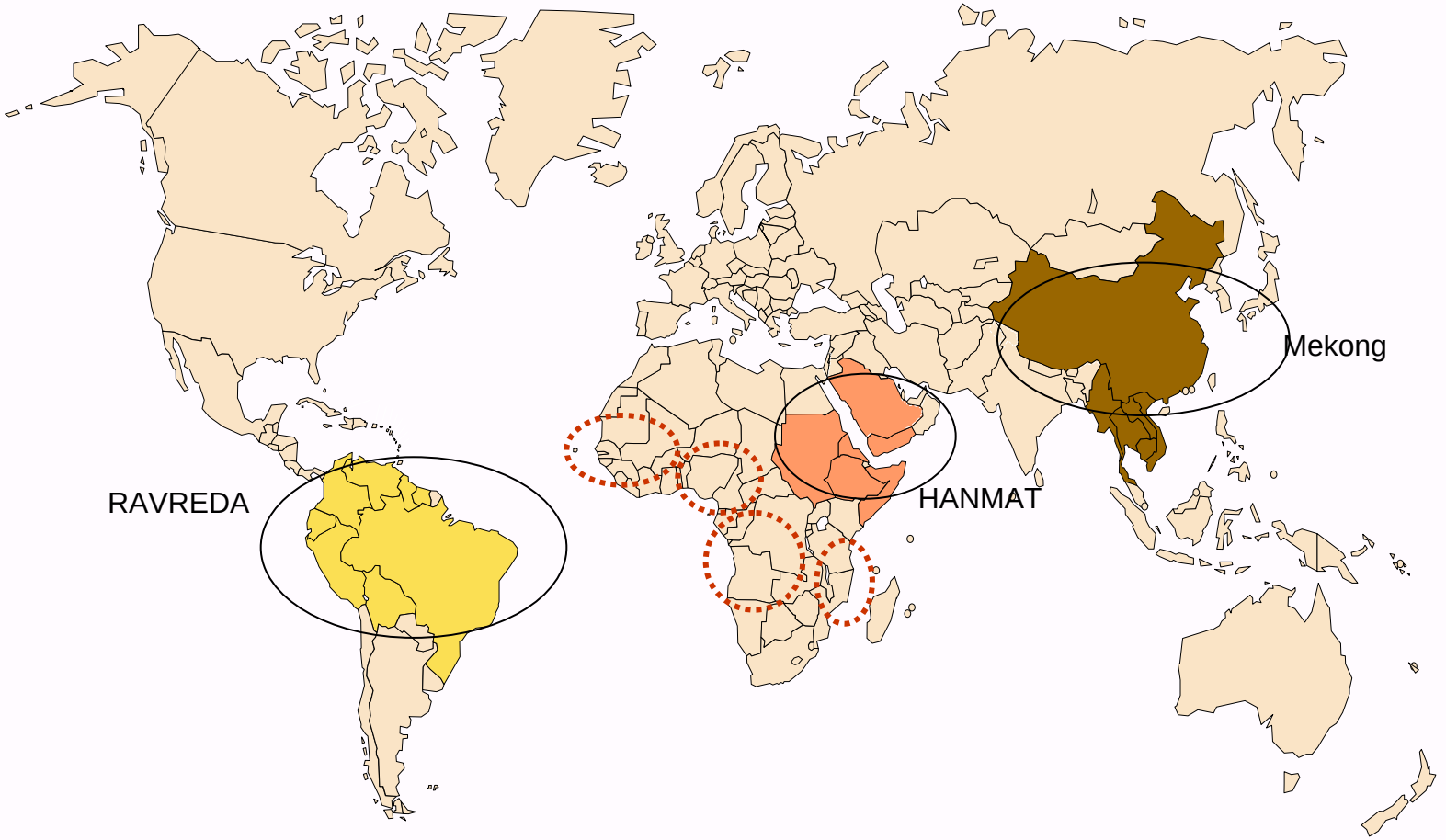


*Note 1: Lead Optimisation projects only includes MMV 2: Launch following registration by stringent authority or WHO-PQ

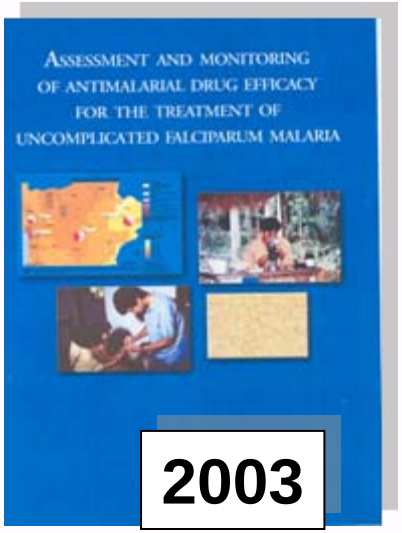
2. Monitoring drug efficacy

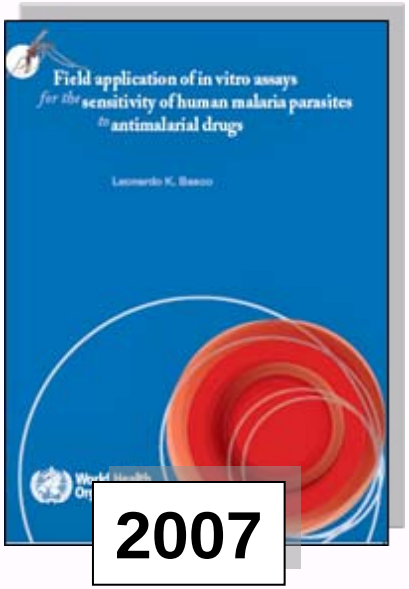
- Countries must closely monitor the efficacy of antimalarial medicines recommended in their treatment guidelines to detect resistance early, and rapidly change drug policy when no longer effective, to avoid the further selection and spread of multidrug-resistance.
  - Routinely monitor therapeutic efficacy of ACTs
  - *In vivo* studies on ACTs
- WHO supported routine surveillance of drug resistance
  - Standardized methodologies, tools and technical assistance
  - To countries and regional and sub-regional networks

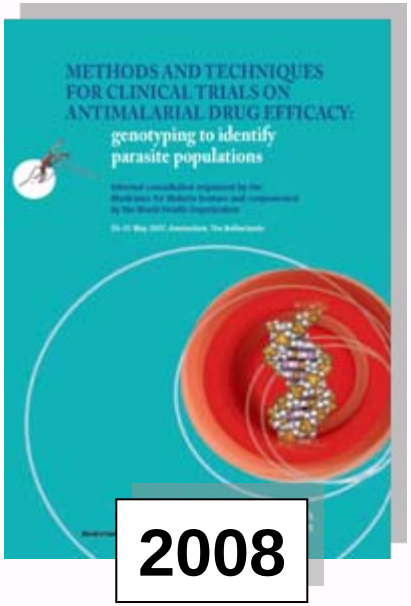
Regional and sub-regional networks on monitoring drug efficacy

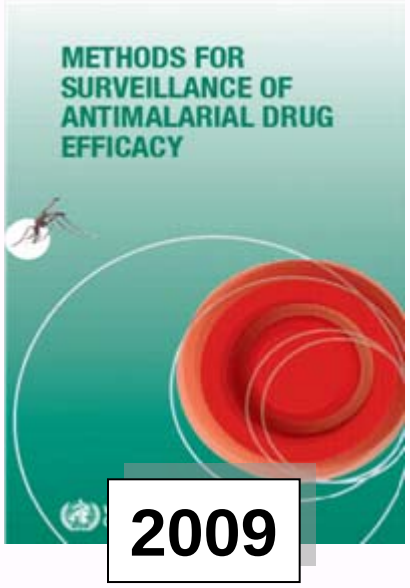


WHO/GMP Guidelines









Planned: guidelines on pharmacokinetic and molecular markers for drug resistance

WHO's role

- Template protocol
  - English, French
  - According to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and cleared by ERC
  - Inclusion, exclusion criteria, sampling methodology, CRF, informed consent, SAE reporting…
- Standardized data entry and data analysis methodology
  - Excel programme + SOP (English, French, Spanish)
  - Improves quality of the data by double entry, cross check, automatic analysis of the data
- Funding
  - USAID, WWARN/WHO, GF
- Antimalarial medicines for monitoring efficacy free of charge
- Training
  - Protocol and microscopy
- Report and publication

WWARN
WorldWide Antimalarial Resistance Network

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WorldWide Antimalarial Resistance Network

WWARN Chair of the Board honored as 2009 sanofi-aventis ICAAC Award Laureate.

Prof Nicholas J. White has spearheaded a "major paradigm shift in policy and practice [that] ha been one of the major drivers of th marked decrease in malaria morbidity seen in over a dozen countries this decade."

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

News update

25.08.2009
Nicholas J. White, Professor, University of Oxford, United Kingdom and Mahid University, Bangkok, and Chair, Wellcome Trust South East Asian Research Units, Bangkok, is honored with the 2009 sanofi-aventis ICAAC Award for his work on the pharmacological aspects of antimalari drugs.
Read the full story

Network of scientists to strengthen the scientific underpinnings of drug resistance & improve its detection and management

GLOBAL MALARIA PROGRAMME
World Health Organization

3. Strategies to avoid drug resistance

- Use of combination therapy
- Effective ACTs of good quality
  - widely accessible
  - correctly used, particularly in the private sector, which includes:
    - education of the practitioners
    - increase compliance by use of co-formulated ACTs.
    - supervised drug administration can help to back up adherence (similar to DOT)
    - Better diagnosis of the disease to avoid misuse of the medicines
    - Fight against drugs of poor quality
- Transmission control to reduce the burden and the use of antimalarial drugs (less drug pressure)
  - vector control and bed-nets (South Africa)
  - reduction of reservoir of infection (responsible for the spread of drug resistance) in improving therapeutic practice, in particular early diagnosis, effective treatment, and use of gametocytocidal drugs.
  - vaccine

4. Contain spread of drug resistance:

Recommendations to countries and partners

- Monitoring antimalarial drug efficacy
  - partners to invest in monitoring antimalarial drug efficacy
- Support and improve access to early and effective treatment
  - increase use of diagnosis
  - increase use of quality ACTs
- Remove the sale and use of monotherapies and sub-standard medicines
  - support surveys on drug quality
- Increase efforts to reduce transmission
- Ensure a steady and robust pipeline of new antimalarial combination medicines

Artemisinin Resistance? or Tolerance? Call it what you may…..

FACTS	IMPLICATIONS
(ACPR) Clinical and parasitological cure of ACTs - not compromised	➢ Change in parasite sensitivity - may not reflected in routine therapeutic efficacy results
Clinical resolution (fever clearance time – prolonged slightly)	➢ May lead to dissatisfied patients and incorrect treatment practices
Parasite clearance time – prolonged	➢ Could potentially increased risk of mortality associated with severe and complicated malaria (which is treated with AS monotherapy)
Incidence of infections with patent gametocytaemia – increased	➢ Increased risk of transmission of less sensitive parasites
Infectivity to mosquitoes – data not available	➢ *Likely to increase*
Total parasite biomass over period of infection increased – data not available	➢ More parasites exposed to partner medicine alone ➢ *Likely to increase propensity for parasite de novo mutations – which favour parasite survival in the presence of the (partner) medicine*

Parasite Resistance to Artemisinins

- Could reverse the malaria control achievements of the past decade…….
- But not inevitable, if the correct course of action is taken

Learning Spanish!!

Muchas Gracias