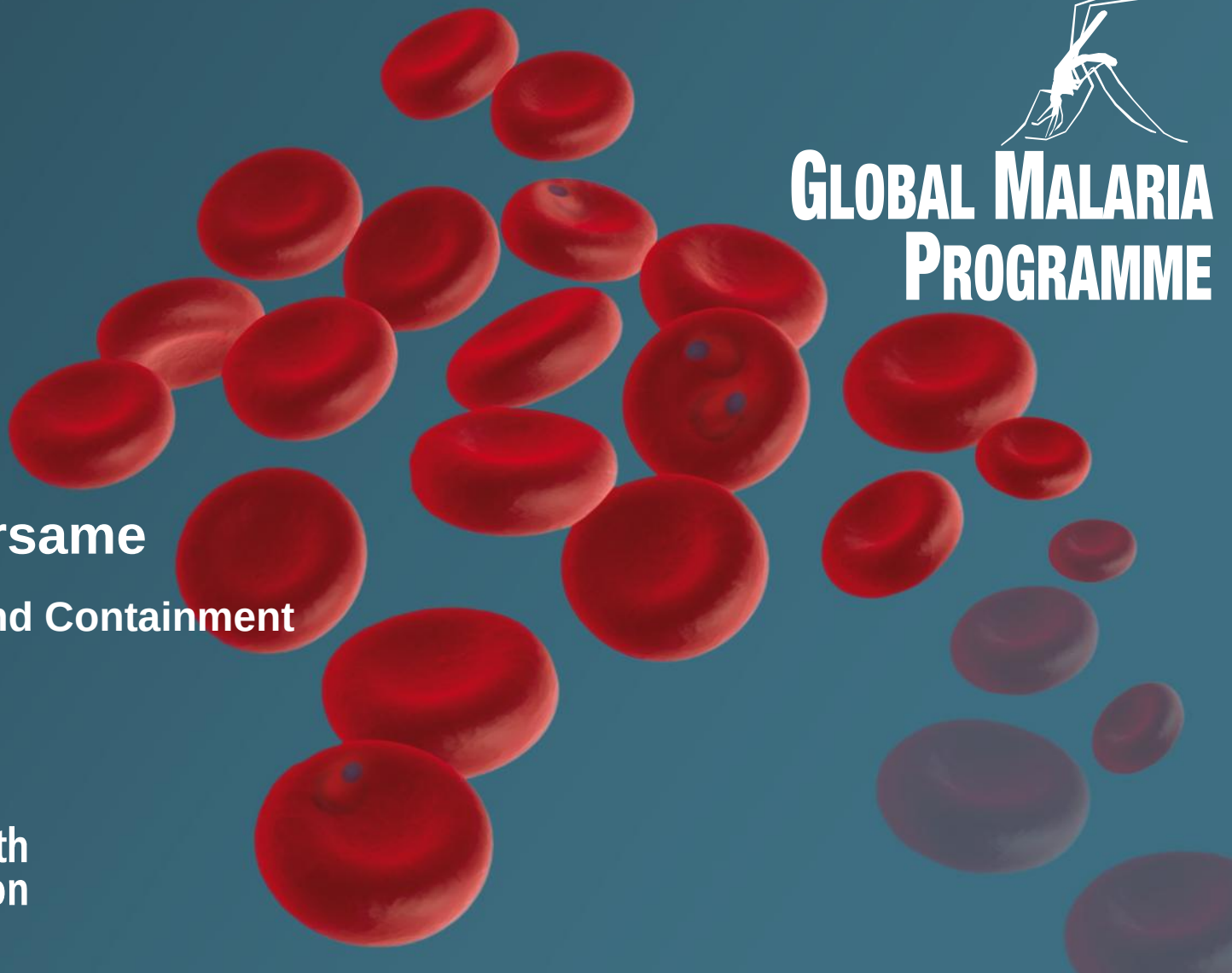
Global situation and strategies for artemisinin resistance



GLOBAL MALARIA PROGRAMME

Dr Marian Warsame

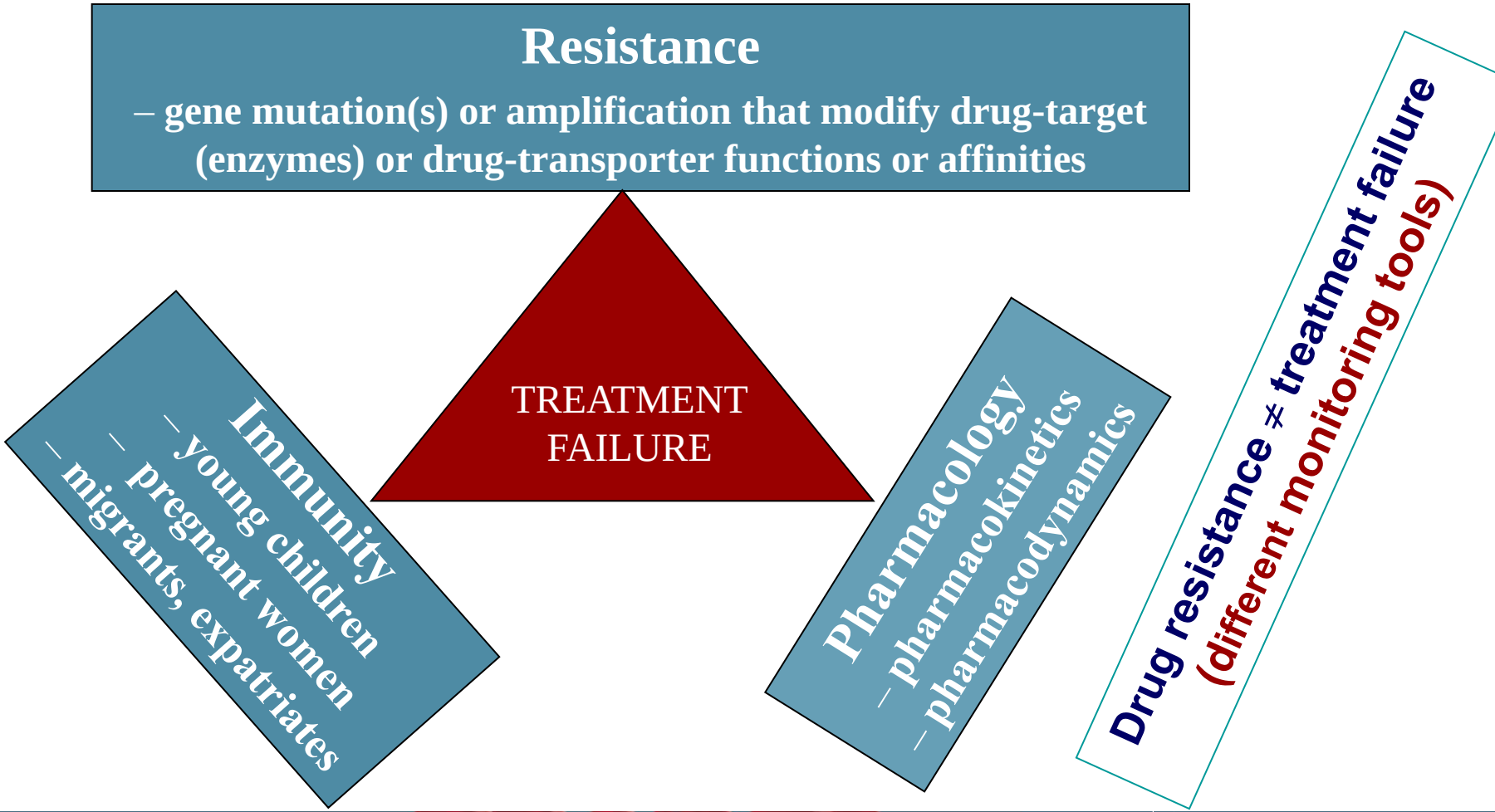
Drug Resistance and Containment

World Health Organization

What is antimalarial drug resistance?

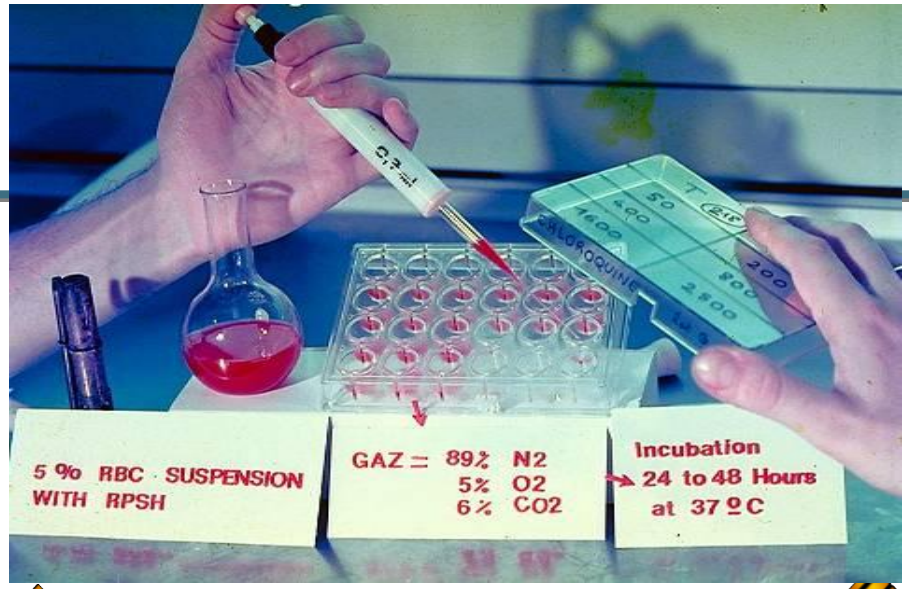
- Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject (WHO, 1973).
- The drug must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action (Bruce-Chwatt et al., 1986).

Factors influencing treatment outcome

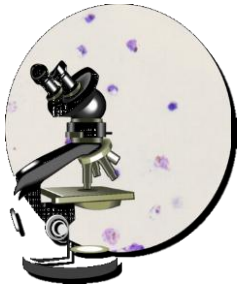


Tools for assessing drug resistance

In vitro tests

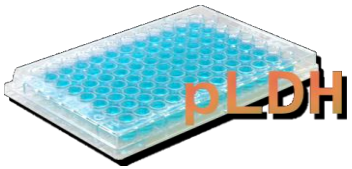


SCHIZONT MATURATION

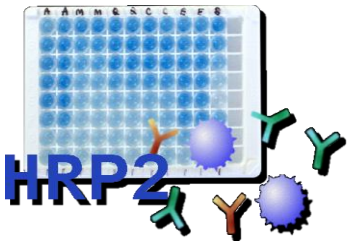


ISOTOPIC ASSAY

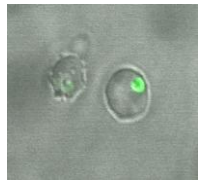
pLDH ASSAY



HRP2 ASSAY

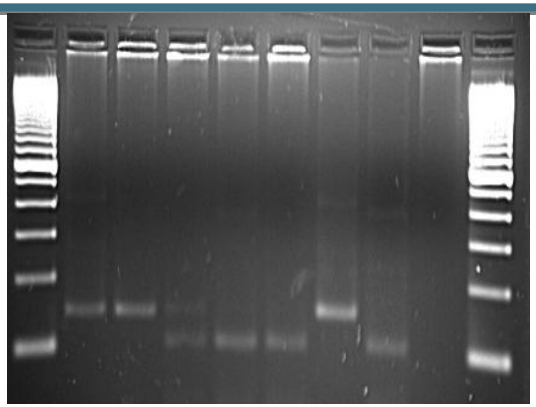


SYBR Green ASSAY

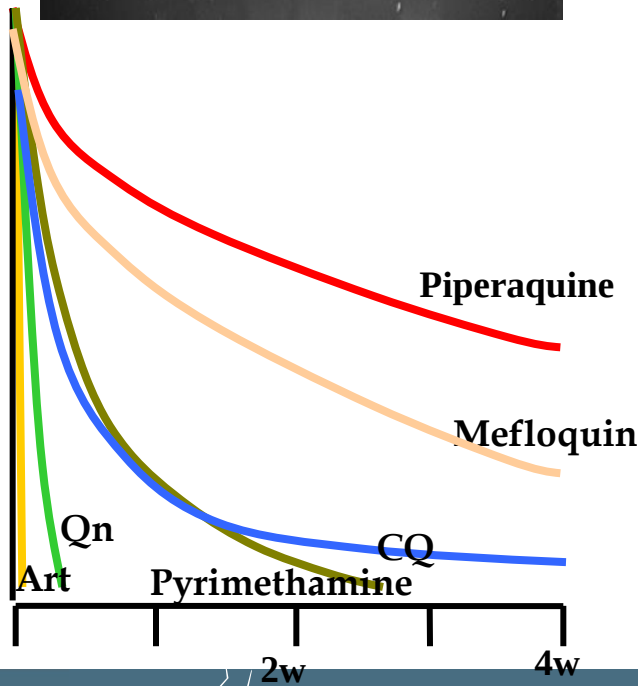


Measure the intrinsic susceptibility of parasites to antimalarial drugs

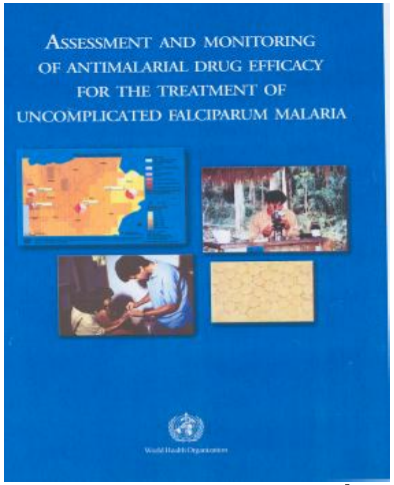
- **Molecular markers:** identify genetic mutations related to antimalarial drug resistance in the parasite genome.



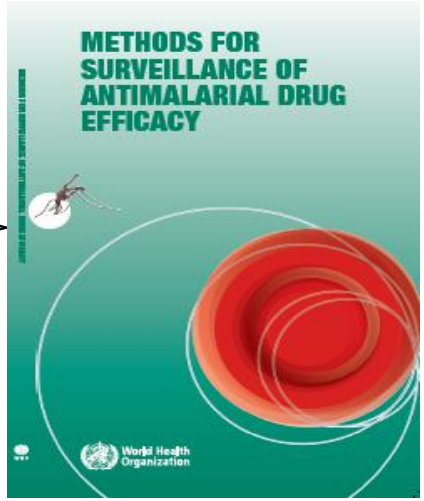
- **Pharmacokinetic studies:** characterize antimalarial drug absorption, distribution, metabolism and elimination in the body.



Monitoring antimalarial drug efficacy: updated WHO Protocol



WHO Protocol 2003



WHO Protocol 2009

- Overview of the updates
- Template for TET

Technical Expert Group on Malaria Chemotherapy, which met in 2005 and 2008 recommended changes and adjustments of the WHO 2003 protocol

The updates to the 2009 protocol

- Same definitions of treatment responses across all levels of malaria transmission applied (inclusion criteria slightly adjusted).
- Rescue treatment to patients with parasitological treatment failures at all levels of malaria transmission.
- Duration of follow-up
  - **28-day or 42-day follow-up**
  - ***Day 3 marker for artesunate tolerance* but cannot replace full 28-day follow-up**
- PCR genotyping to distinguish between recrudescence & reinfection is mandatory.

Updates to the 2009 protocol *continue*

- **From high transmission → low-to-moderate transmission**
  - History of fever in the past 24 hours.
  - Parasitemia ranges:
    - Reduce lower limit to 1,000/µl.
      - **asymptomatic carriers: underestimation of failure, reliability of microscopy.**
    - Increase upper limit to 250,000/µl.
  - Age groups: up to 10 years, adults.

Updates to the 2009 protocol *continue*

- **Low-to-moderate transmission→ low transmission**
  - Parasitemia range:
    - Reduce lower limit to 500-250/ µl (*reliability of microscopy*).
    - History of fever over last 48 or 72 hours.

Updates to the 2009 protocol *continue*

- **Low to very low transmission**
  - Multicentre approach of a one arm study.
  - Molecular markers, if known and validated (chloroquine, mefloquine, SP).
  - Monitoring every 3 years.
  - In between trends measured using molecular markers.
  - If TET unfeasible, use only early warning tools (molecular markers or in vitro tests).

Updates to the 2009 protocol *continue*

- **Countries targeting elimination**
  - All patients need to be followed-up (28 days).
  - No loss to follow-up.
  - Hospitalise all *P. falciparum* patients .
  - Routine in vivo monitoring of therapeutic efficacy regardless of parasitaemia or age criteria.
  - Use in vitro and molecular markers as additional tools.

- **Template for therapeutic efficacy test**

- Background
- Objectives
- Methods
- Treatments
- Evaluation procedures
- Study assessments

- Data management
- Statistical methods
- Ethical consideration
- Budget
- Data collection tools

Template for assessing therapeutic efficacy

SUMMARY

Title: Efficacy and safety of (name of antimalarial drug(s) or drug combination) for the treatment of uncomplicated *Plasmodium falciparum* malaria in (name of the sentinel site(s)), (department/province/country).

Background: (Paragraph describing current first-line and second-line treatment for *P. falciparum* in the country, drug resistance and the rationale for conducting the study).

Objective: To assess the efficacy and safety of (name of the antimalarial drug(s) or drug combination) for the treatment of uncomplicated *P. falciparum* infections in (name of the sentinel site(s)), (department/province/country)

Methods: An antimalarial drug efficacy trial will be conducted in (name of the sentinel site(s)), (country). The participants will be febrile people (specify age range) with confirmed uncomplicated *P. falciparum* infection. Patients will be treated with (name of the antimalarial drug(s) or drug combination(s), dosage and treatment regimen). Clinical and parasitological parameters will be monitored over a (28/42)-day follow-up period to evaluate drug efficacy. The study will be conducted from (month) to (month), (yyyy). The results of this study will be used to assist the Ministry of Health of (country) in assessing the current national treatment guidelines for uncomplicated *P. falciparum* malaria.

1. BACKGROUND

Paragraph describing currently recommended first- and second-line treatment in the country.

Paragraph describing results of previous efficacy studies in the area, recent trends in drug resistance in the country and the rationale for conducting the study.

Paragraph describing the known efficacy and side-effects of the antimalarial drug(s) or drug combination to be tested.

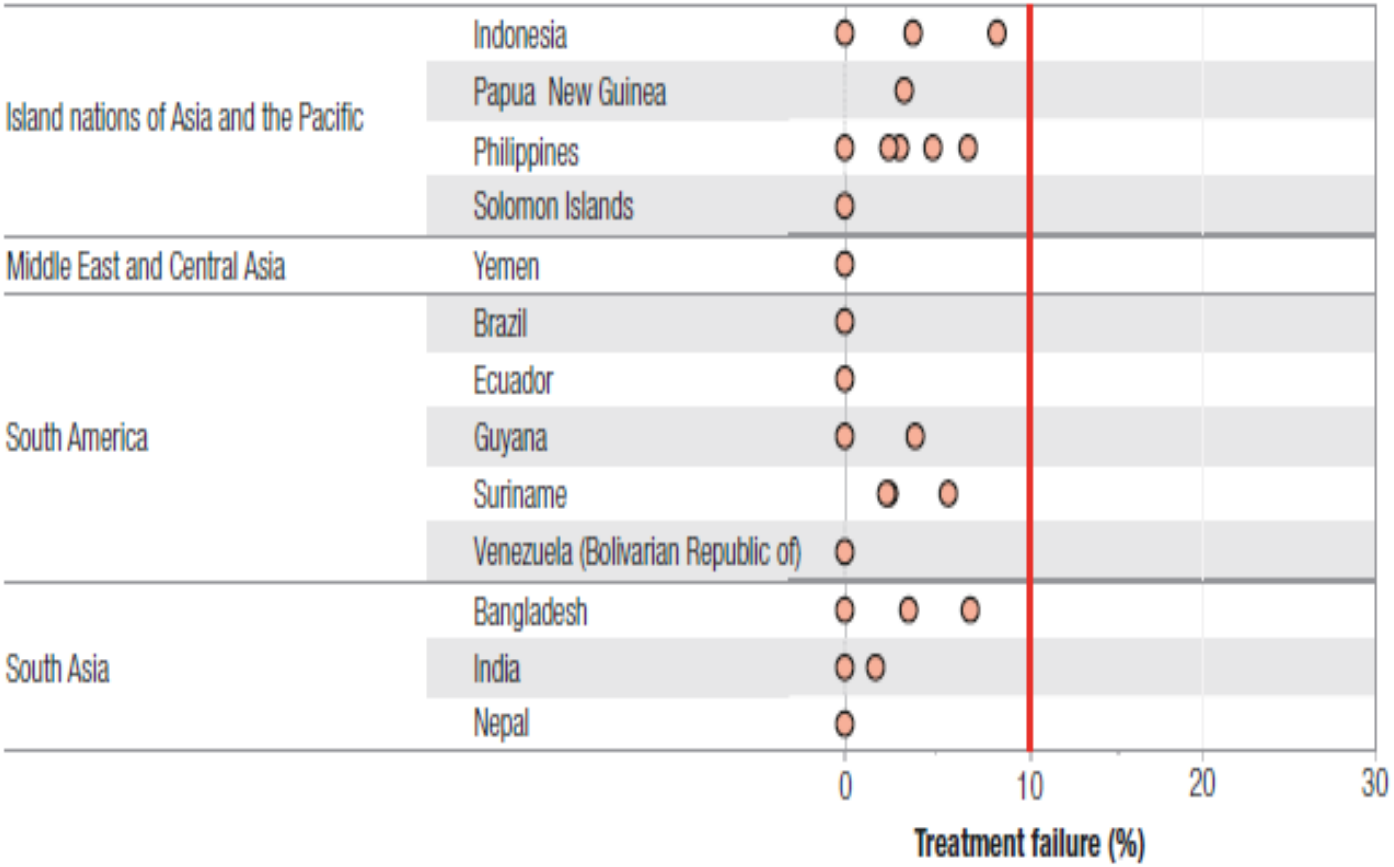
2. OBJECTIVES

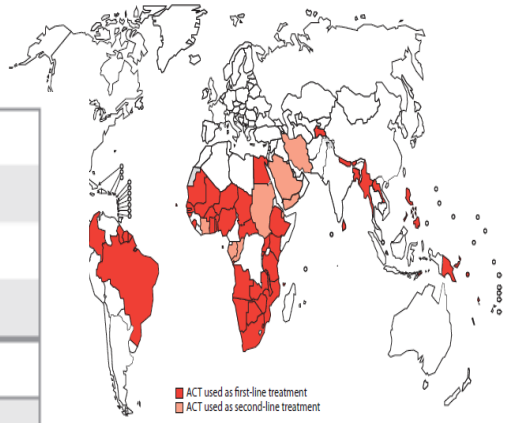
The general objective of this study is to assess the therapeutic efficacy and safety of (name of the antimalarial drug(s) or drug combination(s)) for the

Global report on antimalarial drug efficacy and resistance: 2000–2010

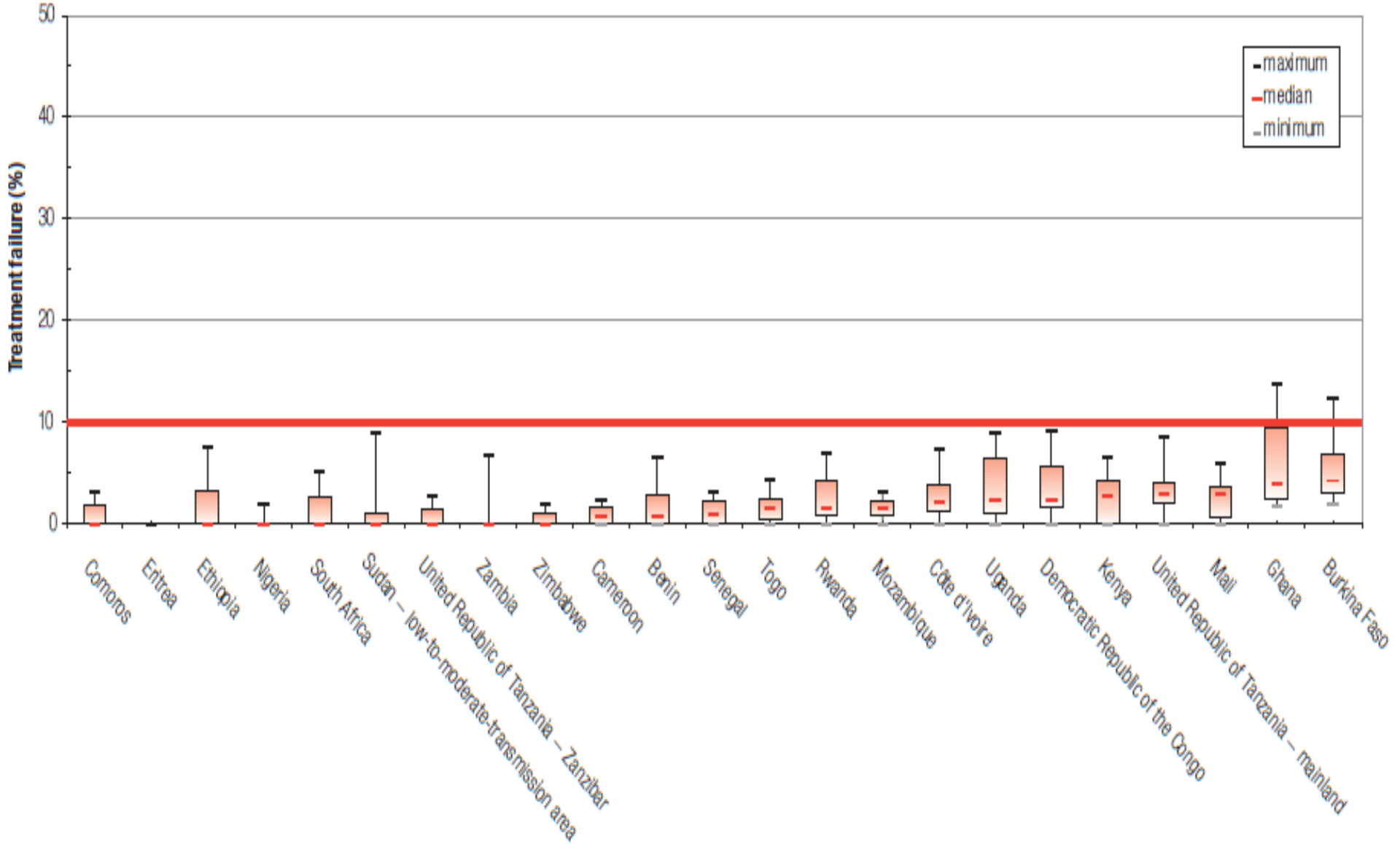
- **WHO database developed since 2000.**
- **Contains 4000 studies**
  - **1120 studies representing 81 848 patients**
  - **ACTs and monotherapies**
- **Latest report on antimalarial drug resistance published in November 2010.**

Artemether–lumefantrine treatment failure rates by subregion (2003–2009)

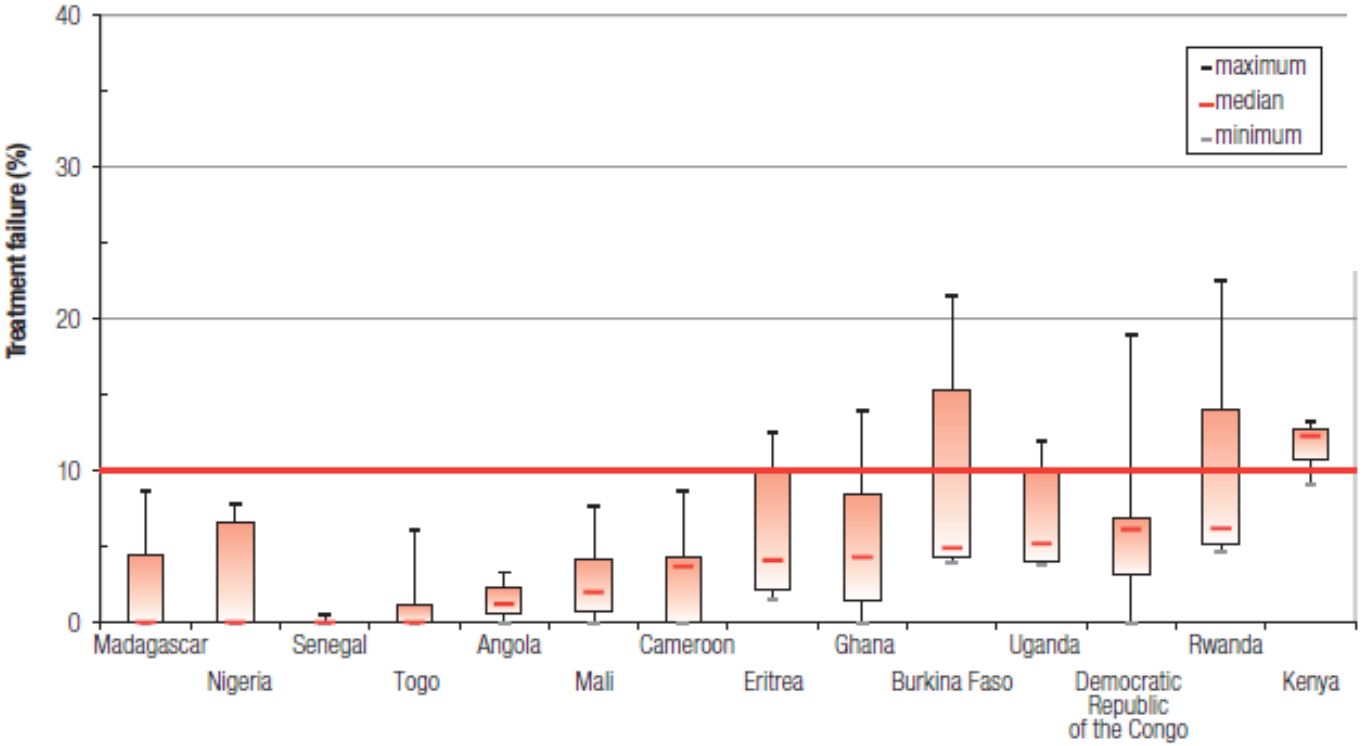


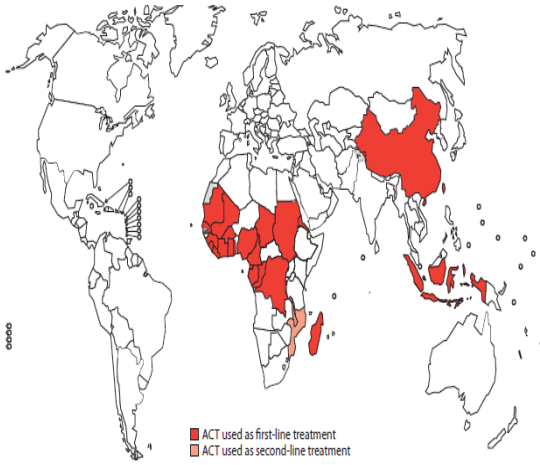


Artemether–lumefantrine treatment failure rates in Africa (2002–2009)

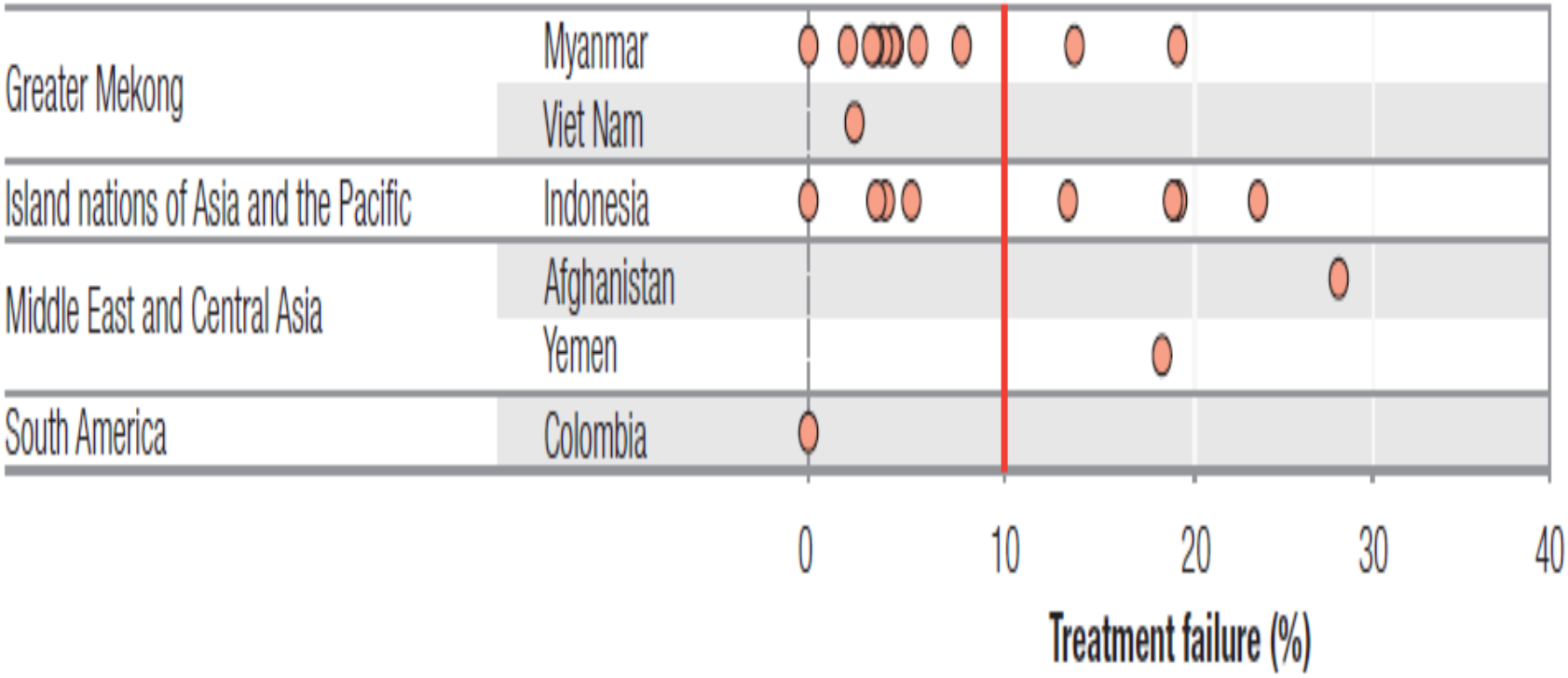


Artesunate-amodiaquine treatment failure rates in Africa (2002–2009)

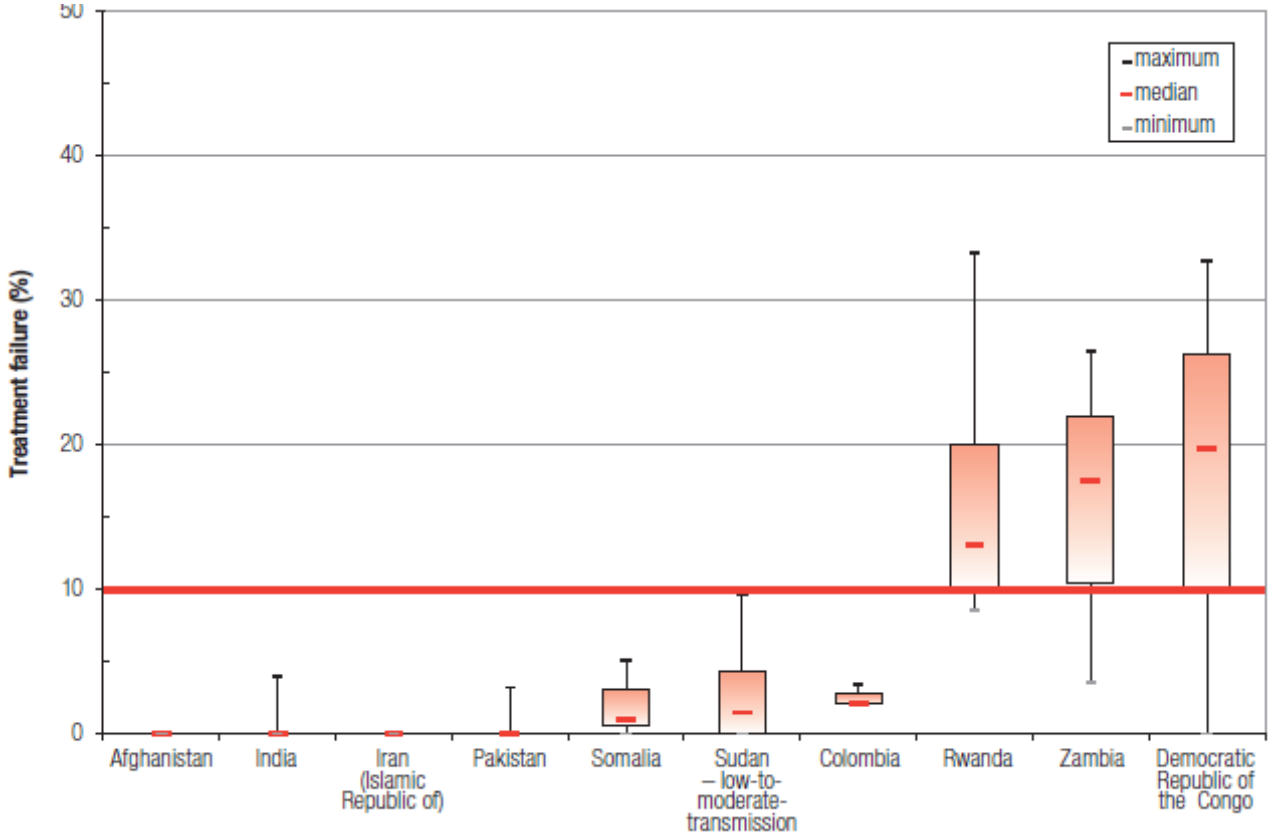


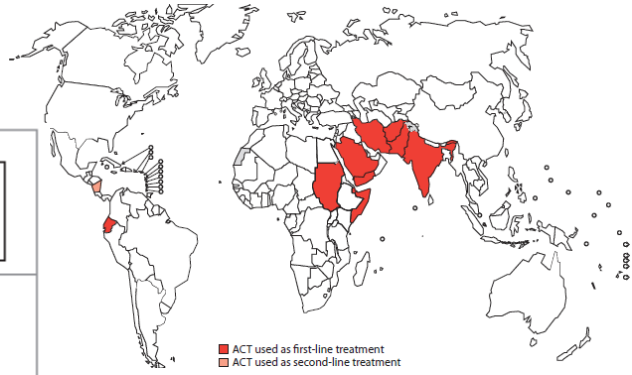


Artesunate-amodiaquine treatment failure rates by subregion (2002–2009)

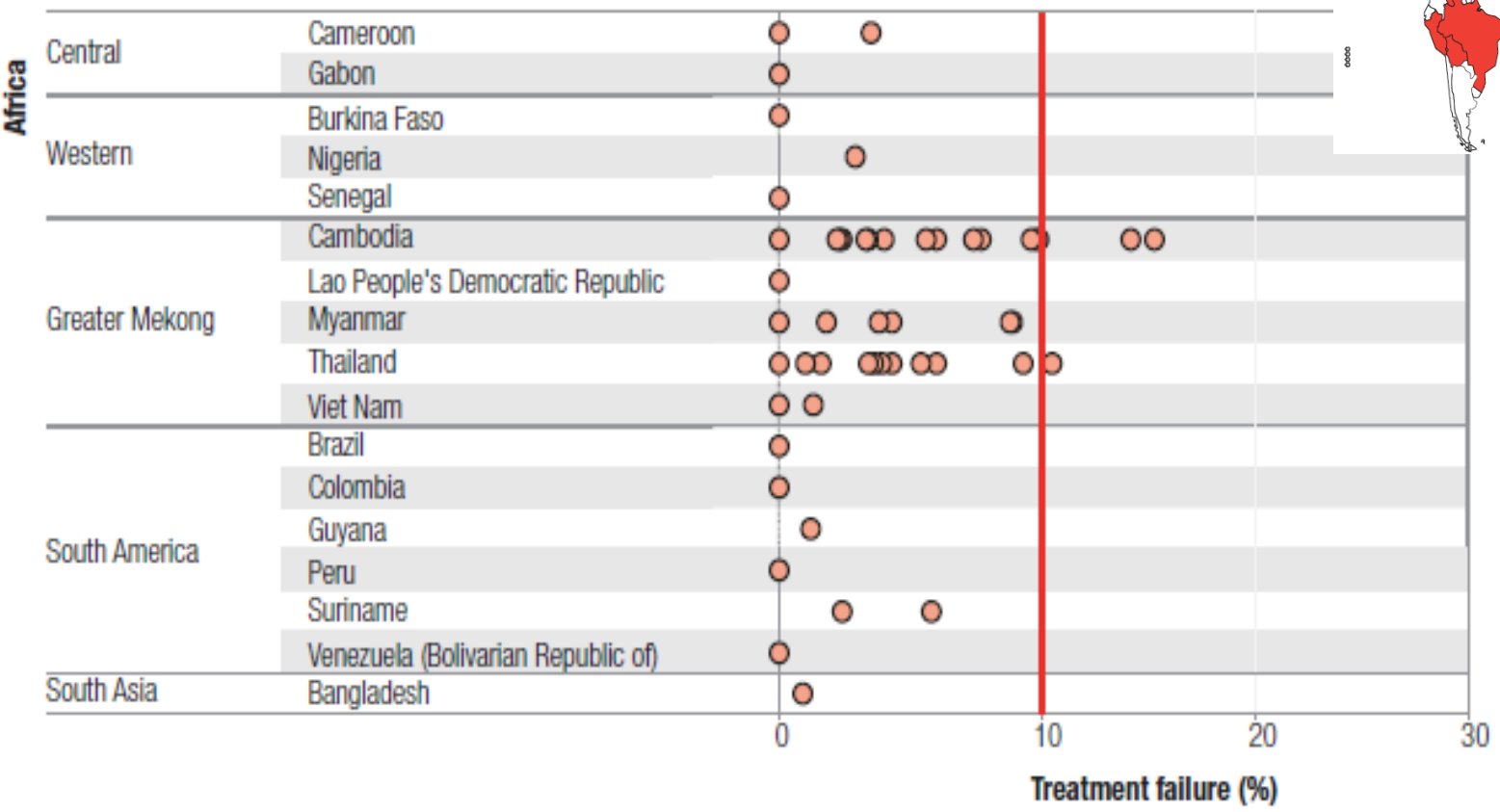


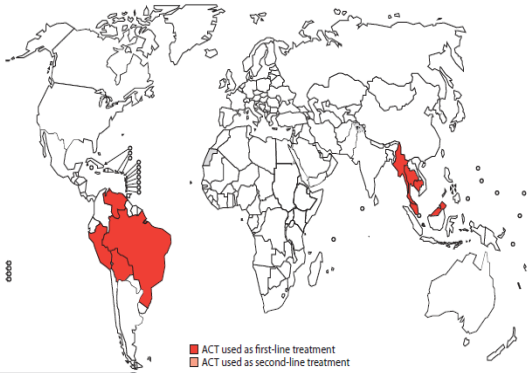
Artesunate–sulfadoxine/pyrimethamine treatment failure rates by subregion (2000–2010)



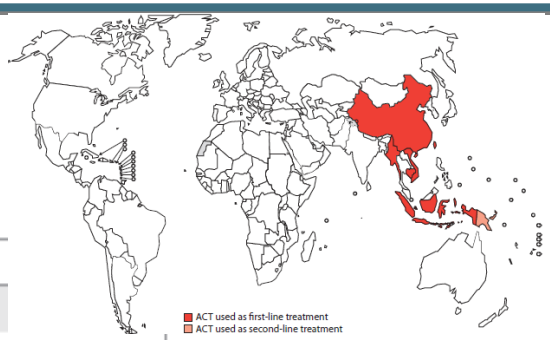


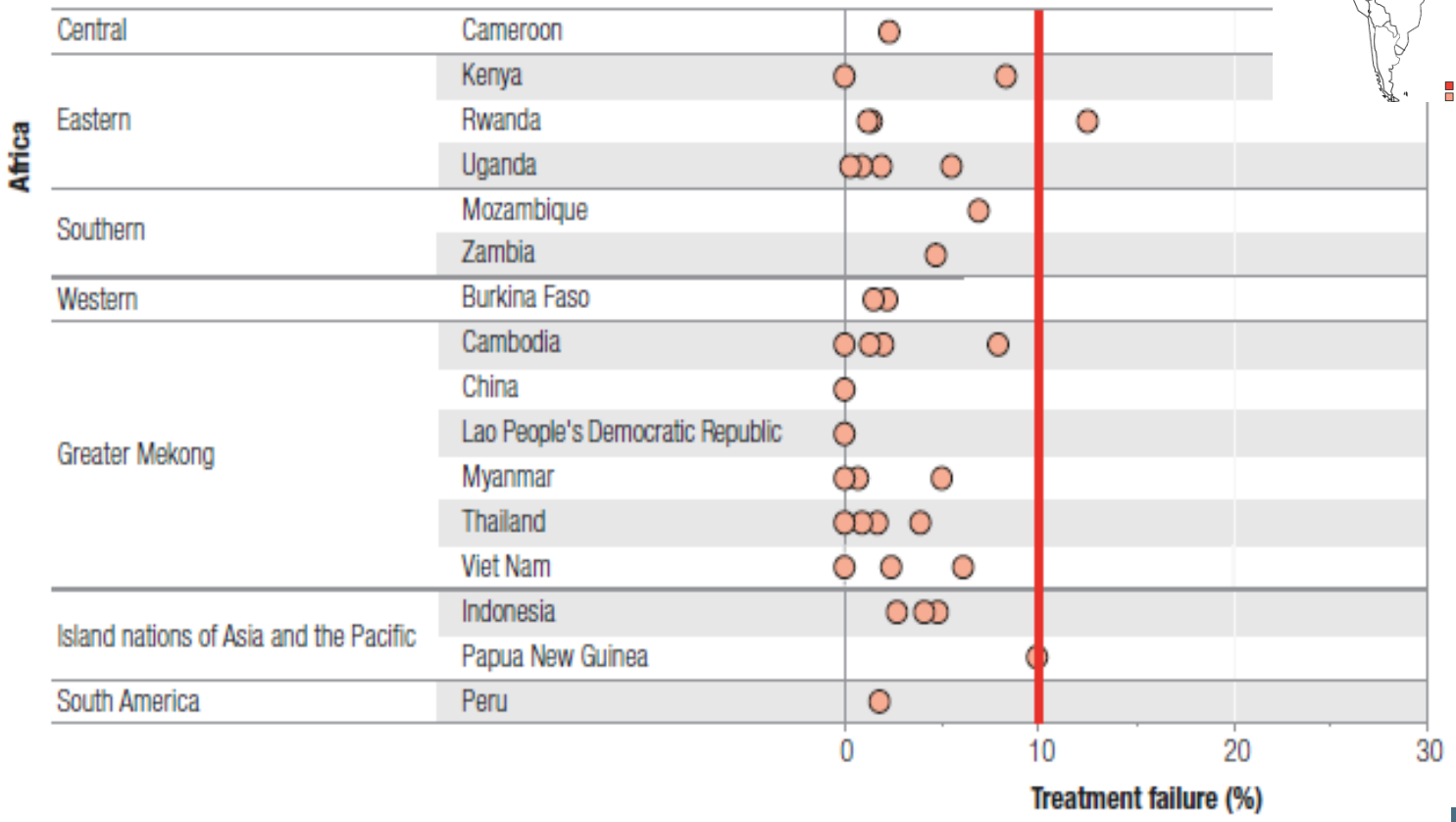
Artesunate–mefloquine treatment failure rates by subregion (2000–2010)





Dihydroartemisinin–piperaquine treatment failure rates with by subregion(2001–2009)



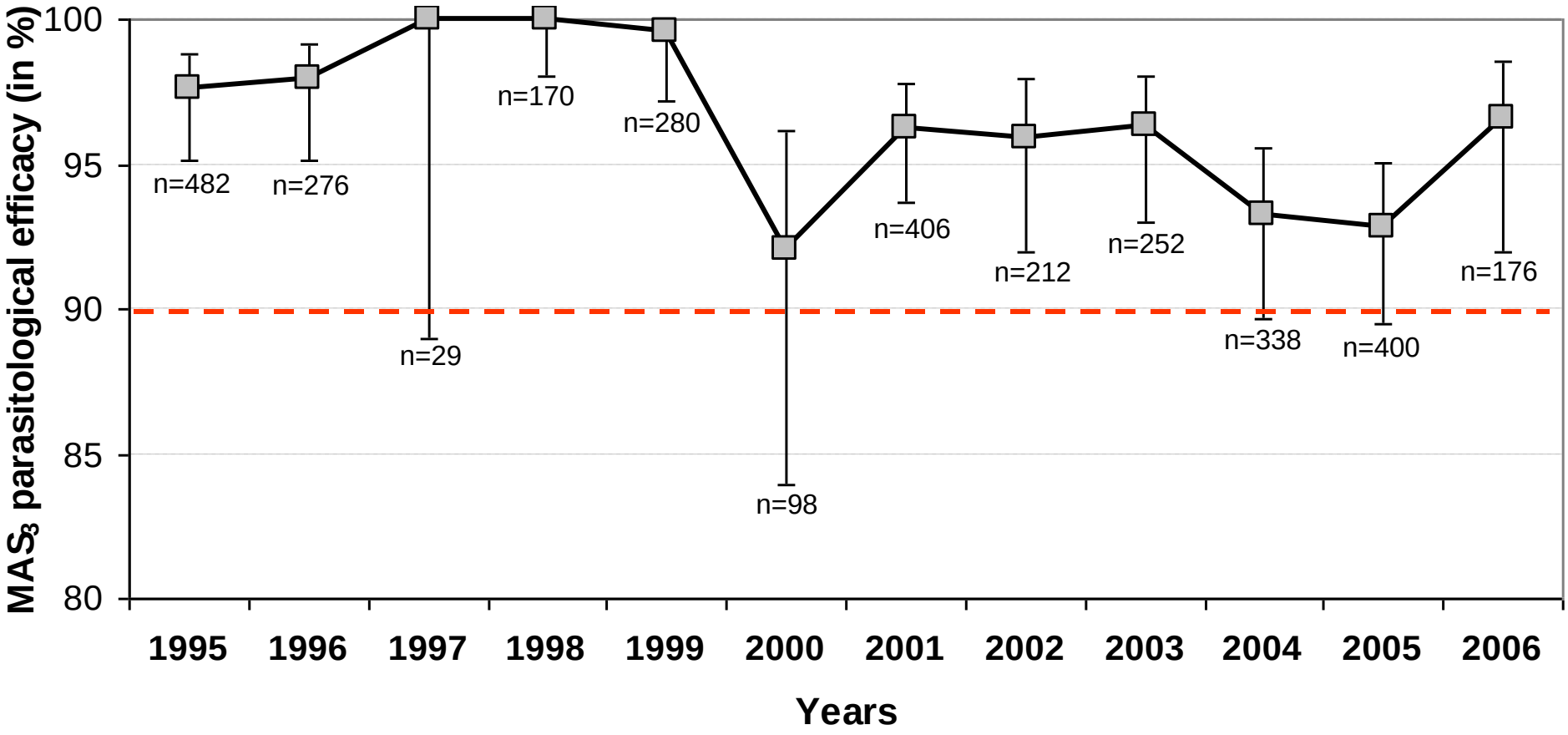


Summary on the global antimalarial drug efficacy

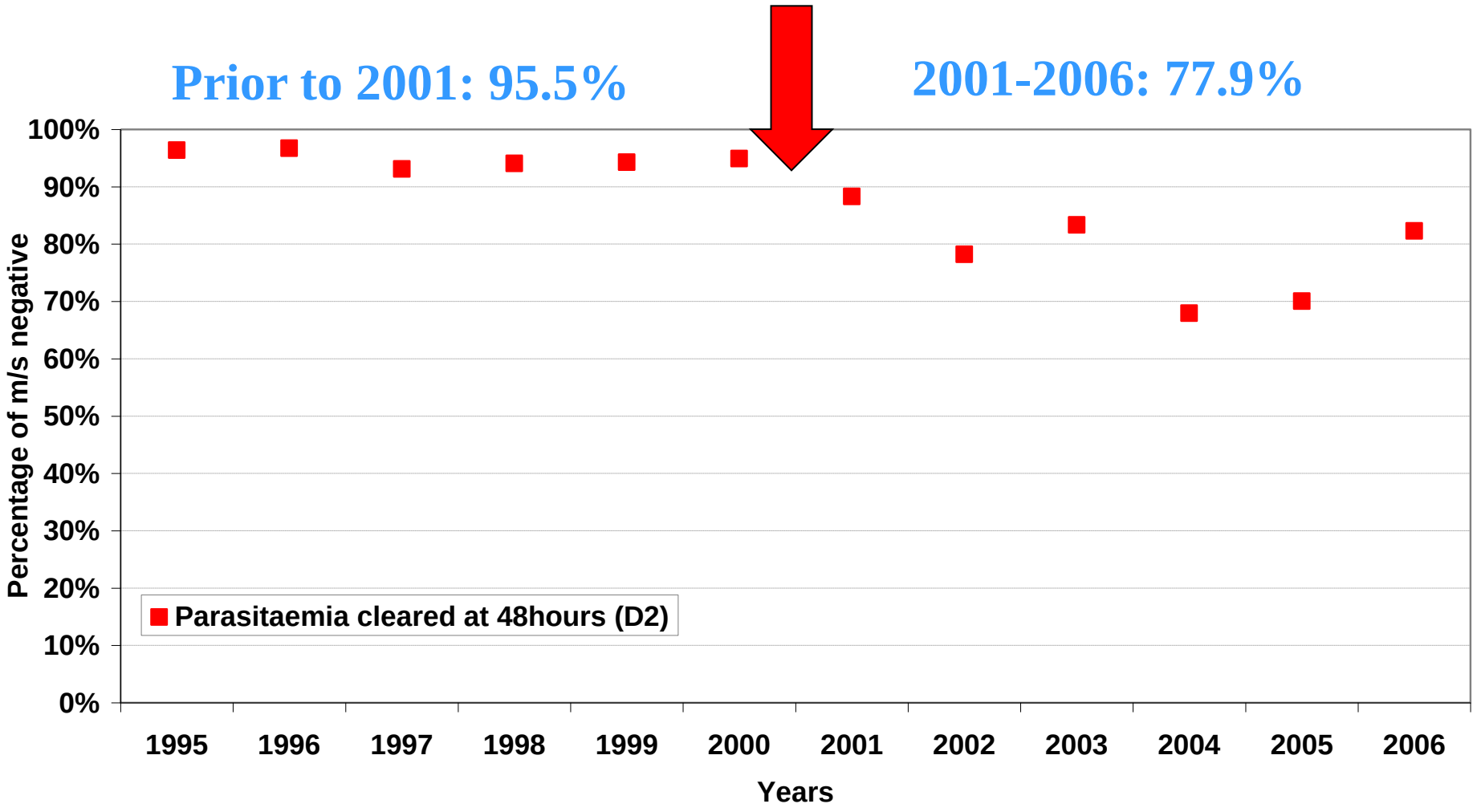
- Artemether–lumefantrine: highly effective except Cambodia.
- Artesunate–amodiaquine: high treatment failure rate in Africa and Indonesia.
- Artesunate–mefloquine: high treatment failure rate in areas where mefloquine resistance is prevalent (Greater Mekong subregion). Highly effective in Africa and the Americas.
- Artesunate–sulfadoxine/ pyrimethamine: high treatment failure rates in regions where resistance to SP is high. Remains effective in countries in which it is used as first-line treatment.
- Dihydroartemisinin–piperaquine: high efficacy (few studies).

Emergence of artemisinin resistance?

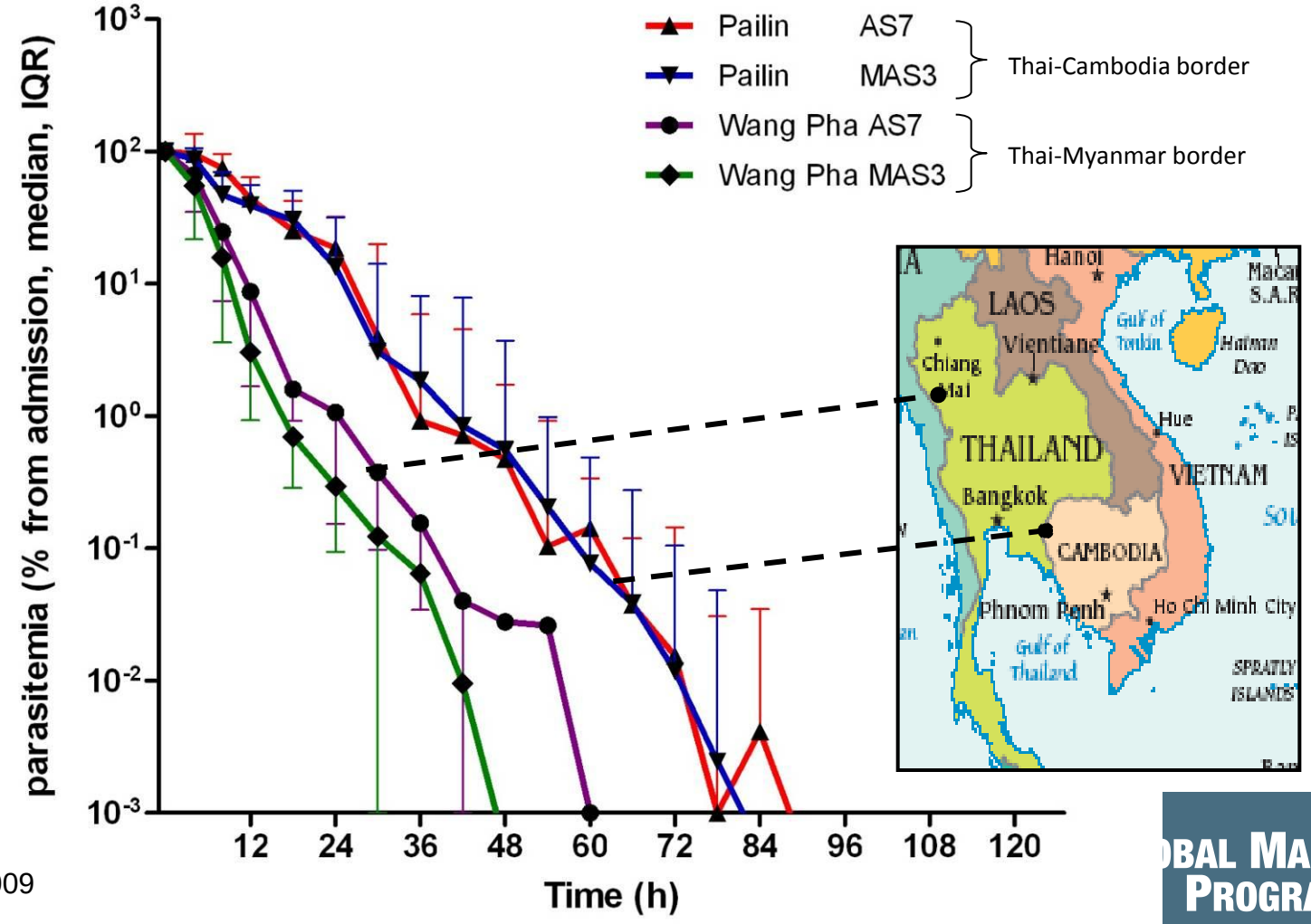
PCR-adjusted parasitological efficacy of MAS3 at Day 42



Parasite clearance

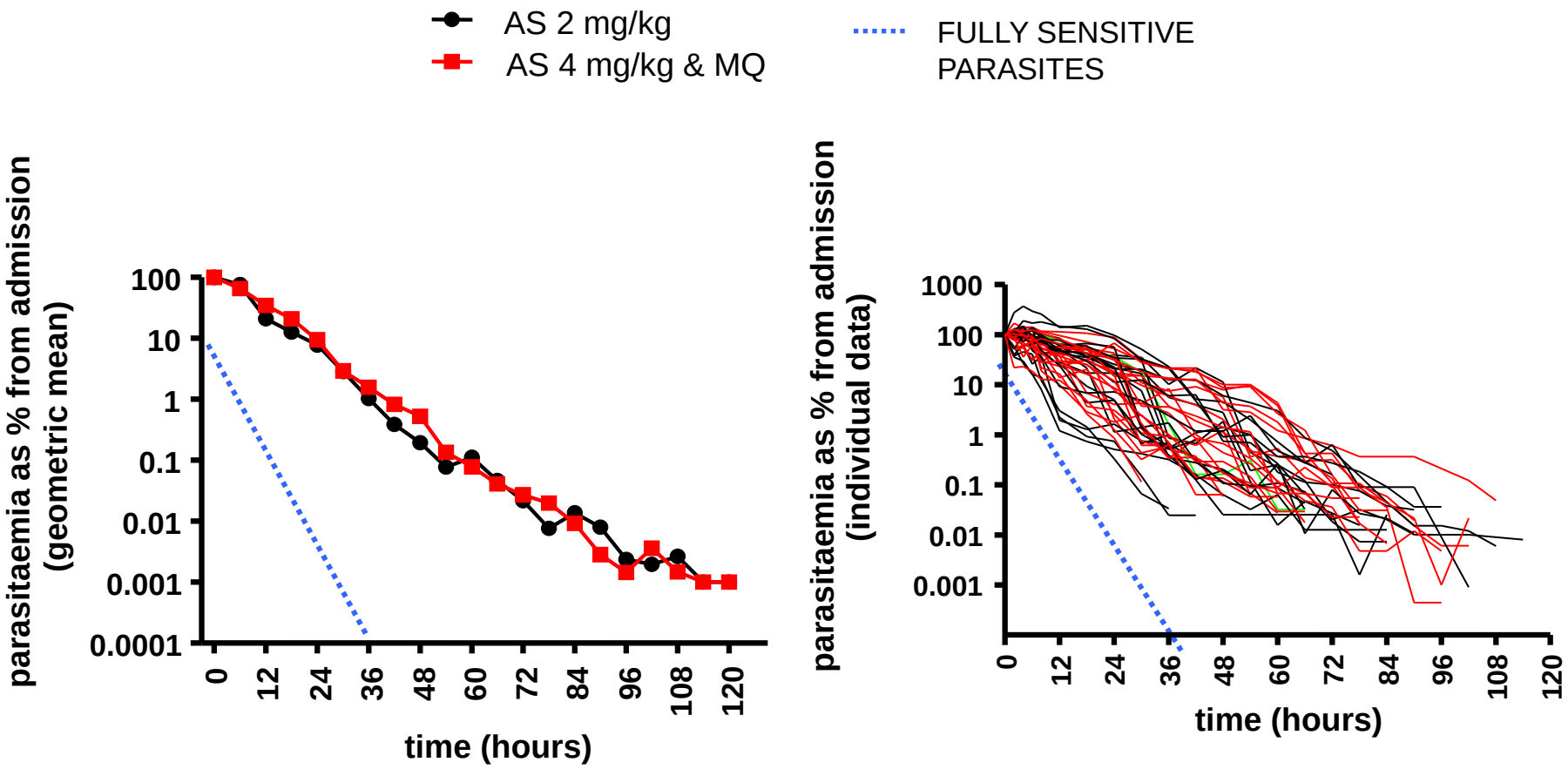


Confirmatory study: parasite Clearance



Dondorp, NEJM, 2009

Parasite Clearance Time in Pailin (2007-08)



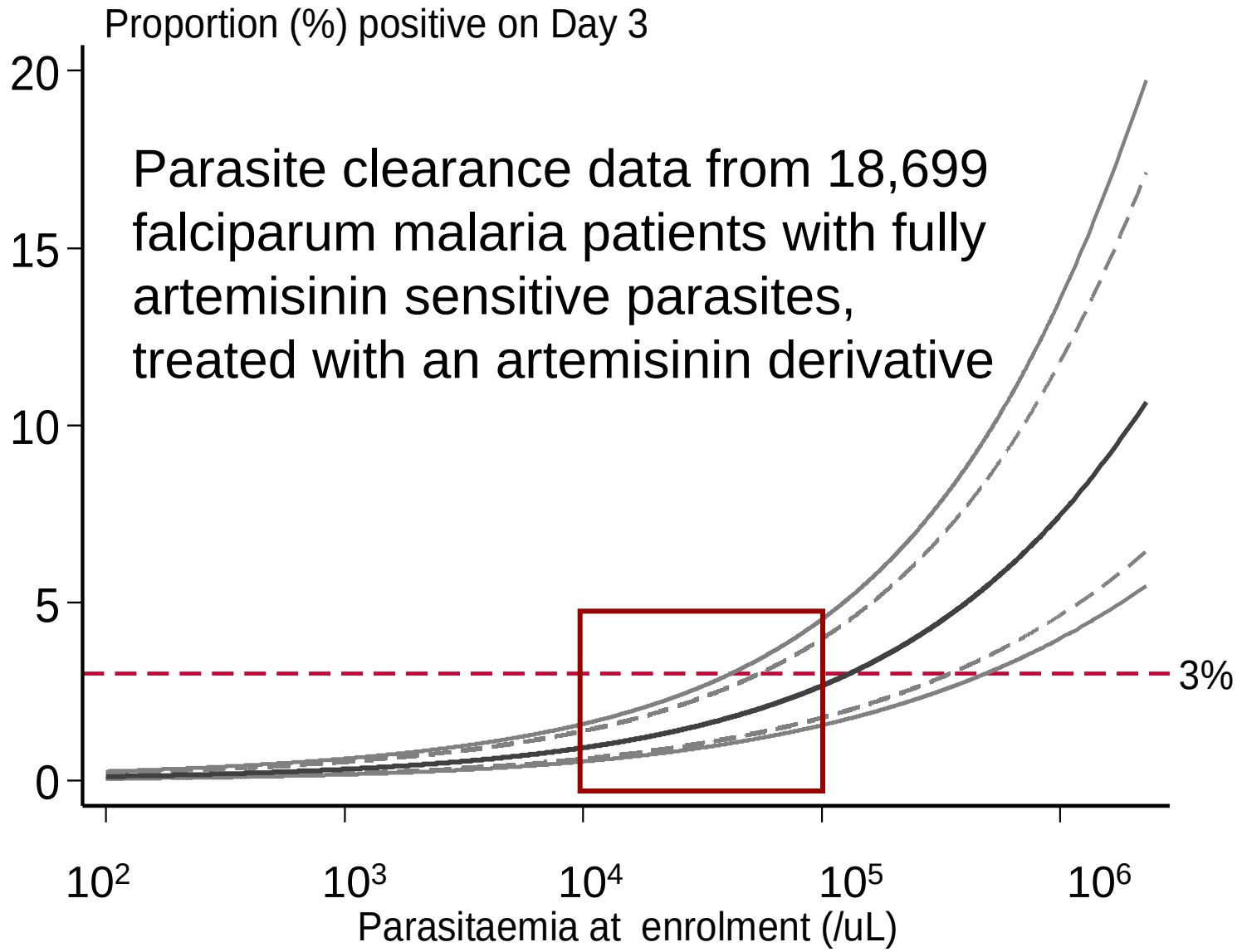
Dondorp, NEJM, 2009

Artemisinin resistance?

- **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, it is possible to confirm resistance to the partner drug but not to artemisinin.**

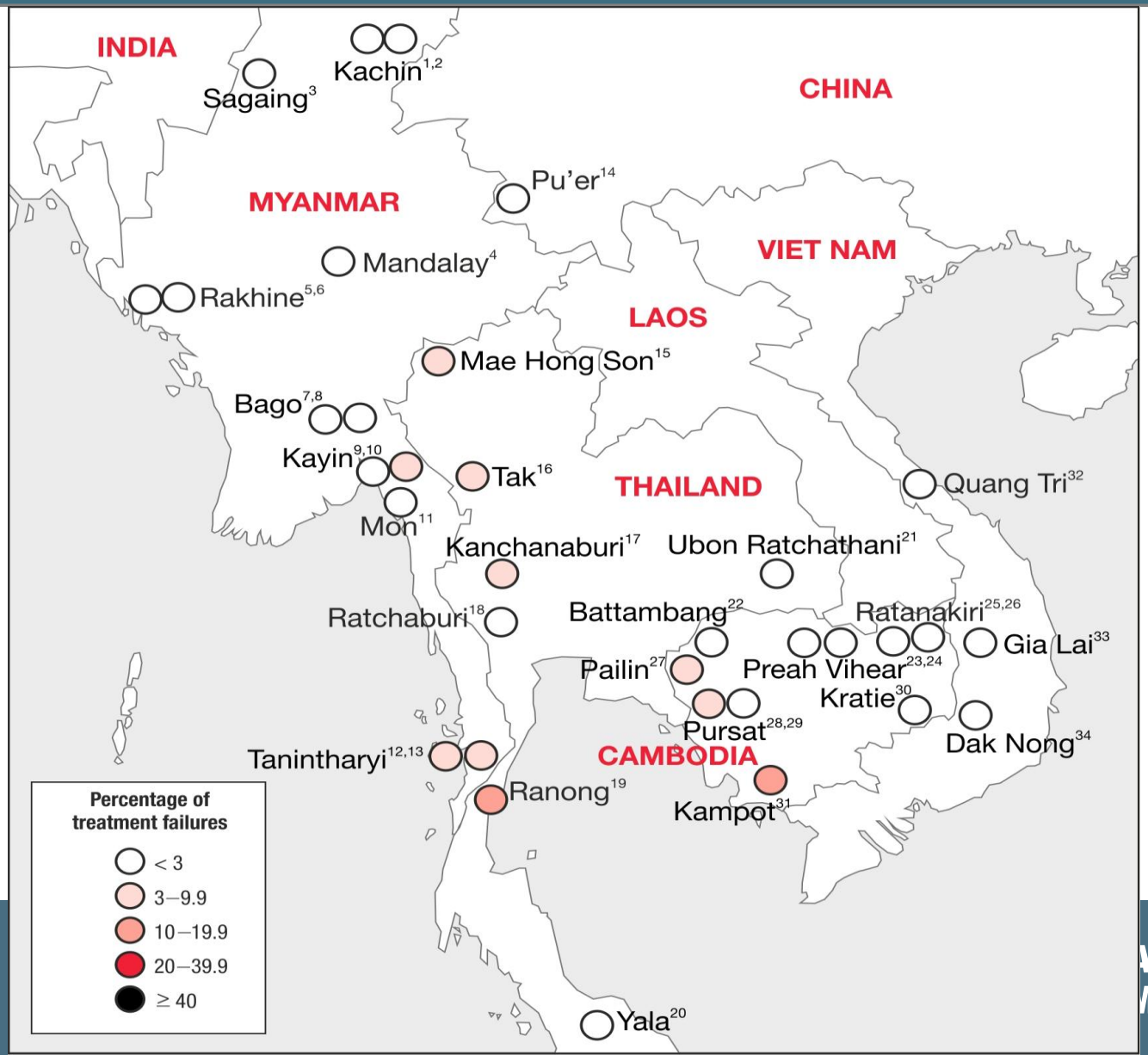

Proportion (%) positive on Day 3
20
15
10
5
0
Parasite clearance data from 18,699 falciparum malaria patients with fully artemisinin sensitive parasites, treated with an artemisinin derivative
3%
10^2
10^3
10^4
10^5
10^6
Parasitaemia at enrolment (/uL)

Recommendation on monitoring artemisinine resistance

- **A standard in vivo efficacy study with ACT;**
  - If >10% positive after 72 hours: proceed with confirmation and further investigations (as below).

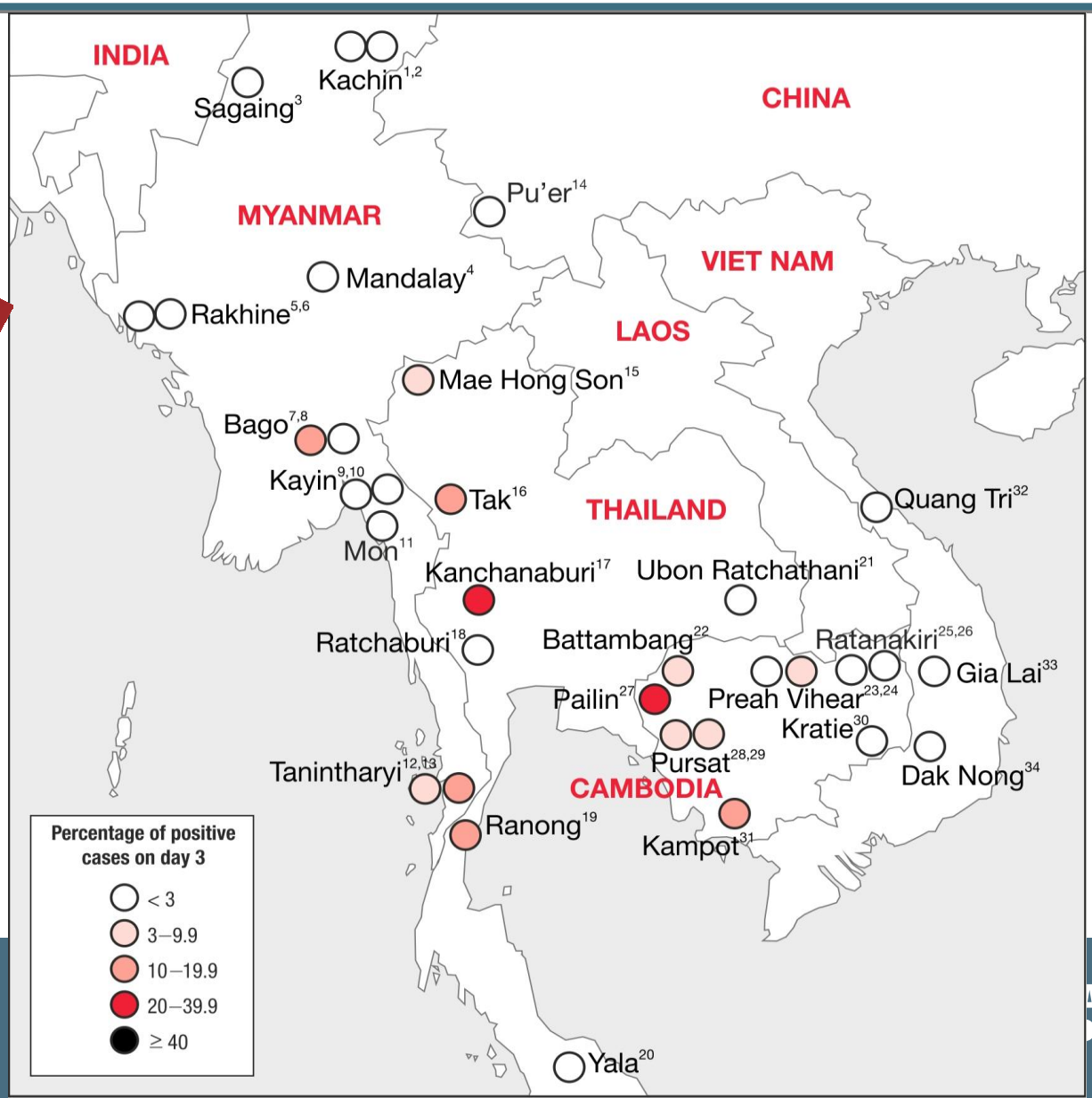
- **Monitoring efficacy of artemisinin monotherapy to assess:**
  - treatment failure;
  - parasite positivity at D3;
  - PK measurements;
  - PCT;
  - PRR at 48 hours;
  - slope of the linear parasite clearance curve.

% treatment failure (28 days) after ACT in Greater Mekong subregion (2006-2010)



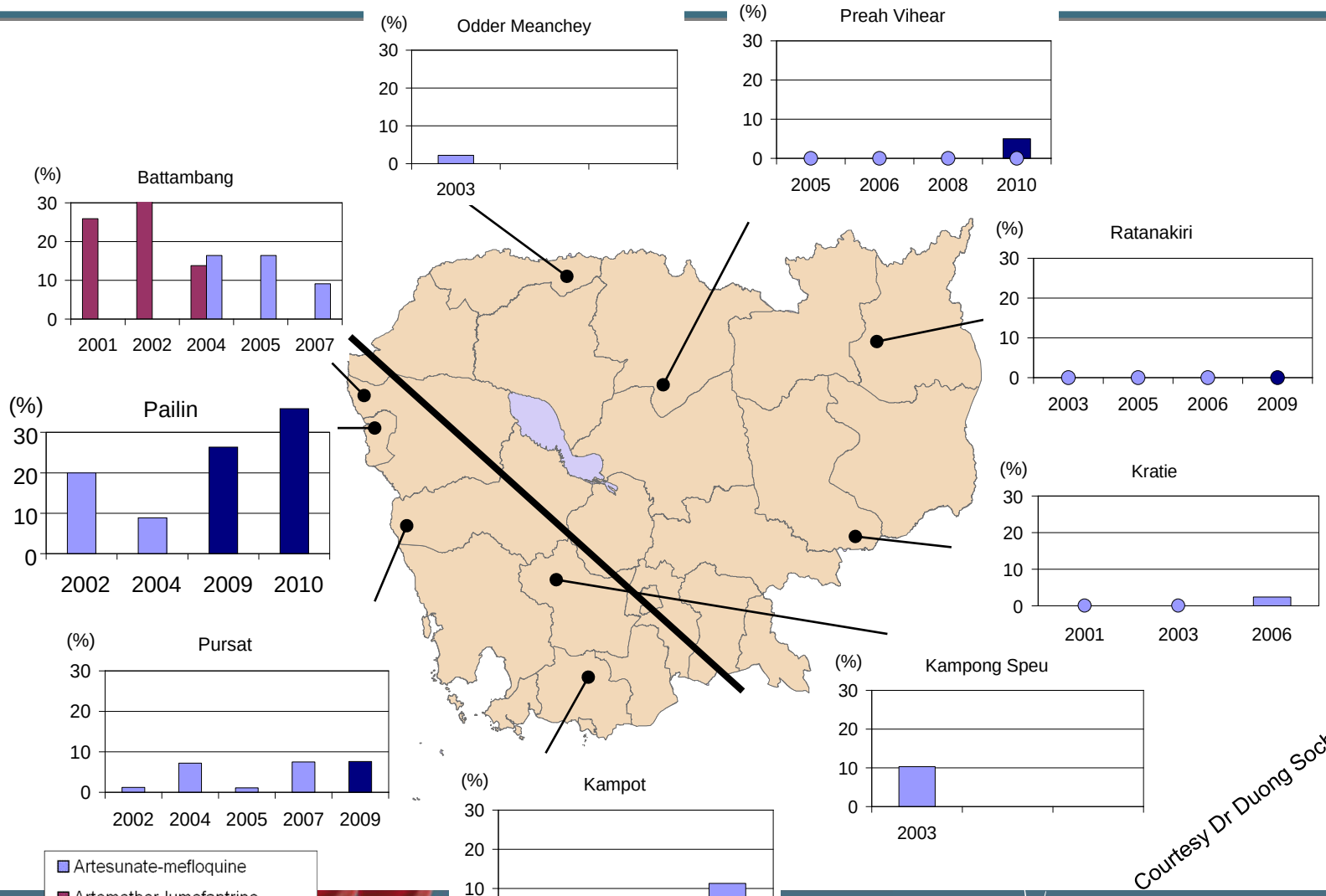
World Health Organization

Day 3 parasite positivity rate after ACT in Greater Mekong subregion (2006-2010)



Proportion of positive cases on day 3 (2001-2010).

Cambodia



Courtesy Dr Duong Socheat

Strategy for containing artemisinin resistance (1)

- 08 with
- .
- ssure
- ant

Strategy for containing artemisinin resistance (2)

- **WHO Global Malaria Programme launched the *Global Plan for Artemisinin Resistance Containment (GPARC)*, with the goal of protecting ACTs as an effective treatment for *P. falciparum* malaria.**
- **Collaboration with >100 partners.**

GPARC goals and recommendations

Contain or eliminate artemisinin resistance where it already exists
Prevent artemisinin resistance where it has not yet appeared

1. Stop the spread of resistant parasites
2. Increase monitoring and surveillance to evaluate the artemisinin resistance threat
3. Improve access to diagnostics and rational treatment with ACTs
4. Invest in artemisinin resistance-related research

5. Motivate action and mobilize resources

1. Stop the spread of resistant parasites

- In areas with confirmed artemisinin resistance:
  - **immediate, comprehensive response with a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites.**

- In areas without known resistance:
  - **effective malaria control can reduce transmission.**
  - **increased coverage with preventive measures, especially vector control, is a priority.**

2. Increase monitoring and surveillance to evaluate the threat of artemisinin resistance

- Regular monitoring and surveillance are critical to identify new foci rapidly and to provide information for containment and prevention activities.
- WHO recommends that countries endemic for malaria perform routine monitoring of antimalarial drugs at sentinel sites every 24 months in order to detect changes in their therapeutic efficacy (WHO, 2009).
- An immediate priority is to assess ACT therapeutic efficacy in countries where no studies have been performed in the past 2 years.

3. Improve access to diagnostics and rational treatment with ACTs

- Increase access to affordable, quality-assured diagnostics and treatment with ACTs.
- Remove oral artemisinin-based monotherapies and substandard and counterfeit drugs.
- Implement effective education and communication strategies focused on diagnosis and treatment.

4. Invest in artemisinin resistance-related research

- Research to improve understanding of resistance and the ability to manage it.
  - laboratory research (e.g. to identify a molecular marker for artemisinin resistance),
  - Research and development (e.g. of novel non-artemisinin-based antimalarial combinations),
  - Applied and field research (e.g. pilot studies of transmission reduction tools, such as mass screening and treatment or mass drug administration),
  - Operational research (e.g. scalable programmes for mobile populations).

5. Motivate action and mobilize resources.

Motivate stakeholders at global, regional and national levels to support or conduct the recommended activities.

What can countries do to prevent the emergence of resistance?

- Due to regional differences and varying levels of artemisinin resistance, each endemic country is expected to evaluate its level of risk, and then apply the GPARC recommendations accordingly.

- Three areas of risk have been identified:
  - **Tier I** (areas for which there is credible evidence of AR);
  - **Tier II** (areas with significant inflows of people from Tier I, including those immediately bordering Tier I);
  - **Tier III** (areas with no evidence of artemisinin resistance and which have limited contact with Tier I).

Example of GPARC Implementation: ARCE project on Thai-Cambodia border

- **Ambitious cross-border strategy to eliminate artemisinin resistant parasites**
- **Coordinated by WHO working closely with Cambodian and Thailand Ministries of Health; largely funded by BMGF, GFATM, and USAID**

Target areas

<u>Zone 1</u>: areas where artemisinin tolerance detected

- Cambodia: ~ 270K people in 4 provinces
- Thailand: ~110K people

<u>Zone 2</u>: areas without evidence of tolerance, but high risk (close to zone 1)

- Cambodia: 9 provinces / ~4M people
- Thailand: 7 provinces / ~7M people

Program combines proven malaria prevention & treatment strategies

Activities designed for specific cultural, social, scientific context

- Large-scale distribution of LLINs
- Free early diagnosis and treatment of malaria at the village level
- 24-hour health facilities to diagnose and treat malaria
- Intensive surveillance of positive cases
- Education programs
- Innovative approaches to reach mobile populations
- Efforts to stop the sale of fake and substandard drugs
- Stringent measures to stop the sale and use of monotherapies
- Pilot intensive screening in most malaria-affected border villages
- Basic and operational research

GPARC to avoid emergence and spread

World Health Organization

GLOBAL MALARIA PROGRAMME