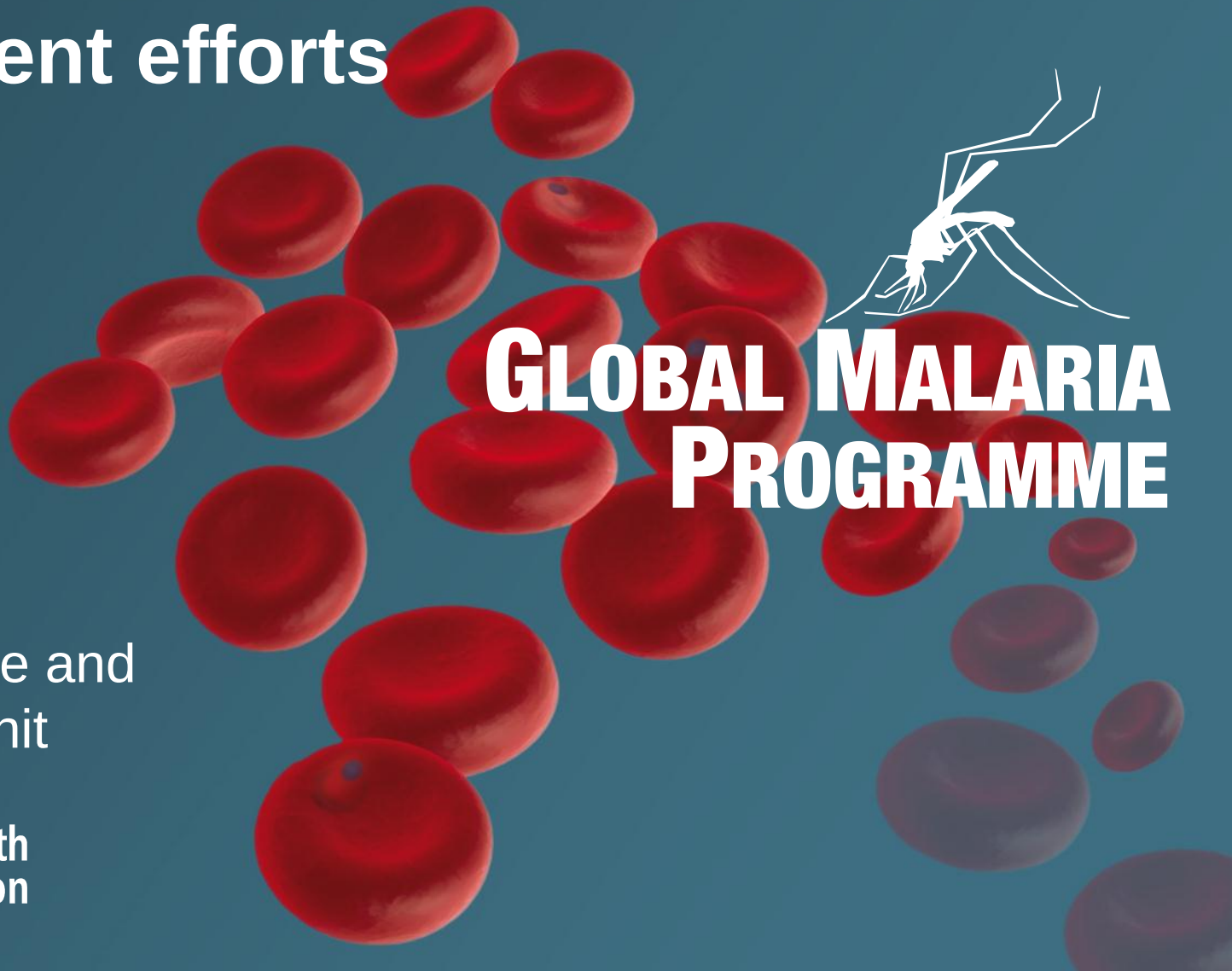
An update of antimalarial resistance and its containment efforts

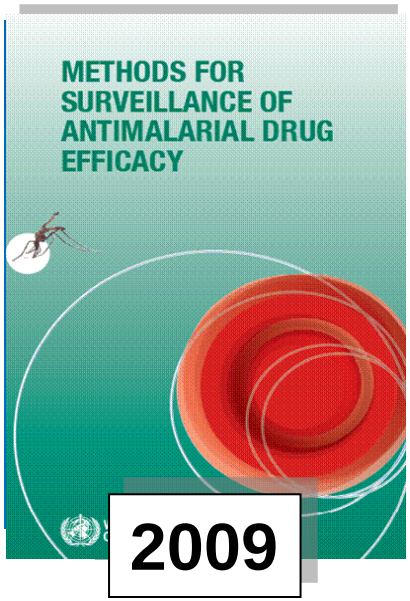


GLOBAL MALARIA PROGRAMME

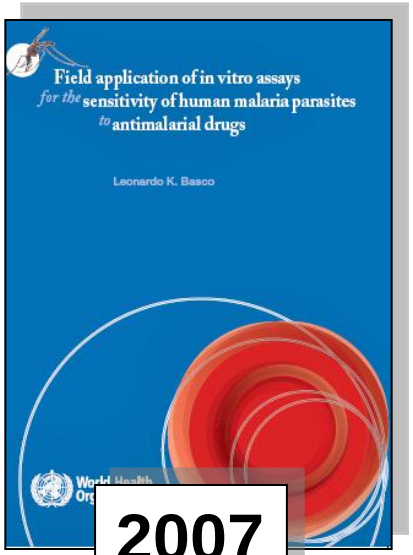
P. Ringwald
Drug Resistance and Containment Unit

World Health Organization

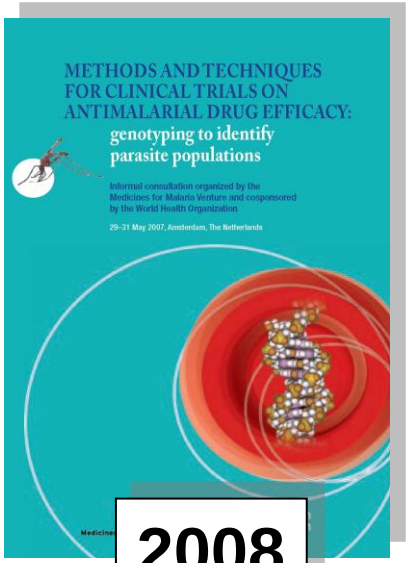
WHO/GMP Guidelines



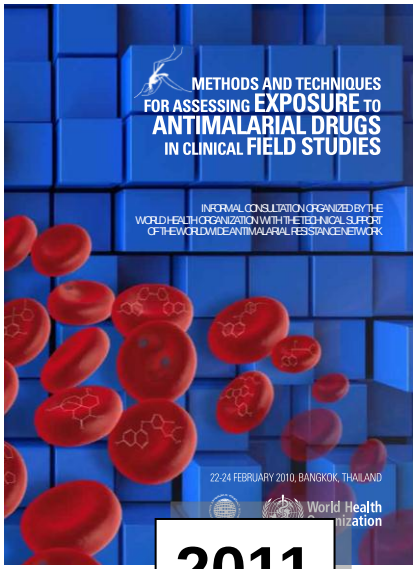
2009



2007



2008



2011

Role of WHO in monitoring antimalarial drug efficacy

- **Technical and financial support to NMCP/research institutes**
- **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
- **Training**
  - Protocol and microscopy (+++)
- **Report and publication**
- **Mapping**

WHO database

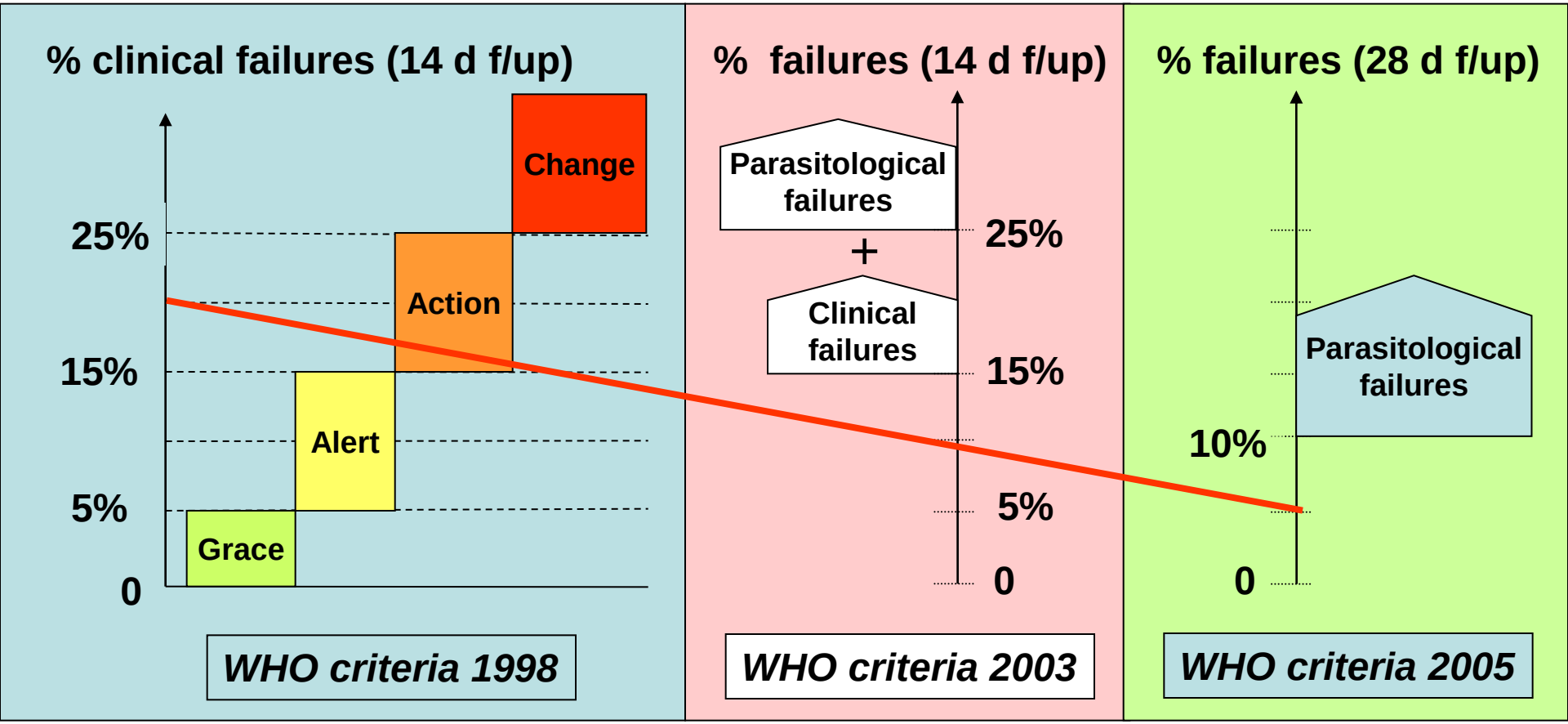
- **The data in the database come from three main sources:**
  - published data, obtained by searching journal articles
  - unpublished data from reports by ministries of health, national malaria control programmes, nongovernmental organizations, research institutes and partners involved in the development of new antimalarial medicines; and
  - raw data from regular surveillance studies conducted
- **The database contains 3932 studies representing 267 841 patients**

TABLE A1.2. Efficacy of antimalarial drugs against *P. falciparum* by WHO region and country, expressed as percentage of treatment failure, after a minimum 28-day follow-up*

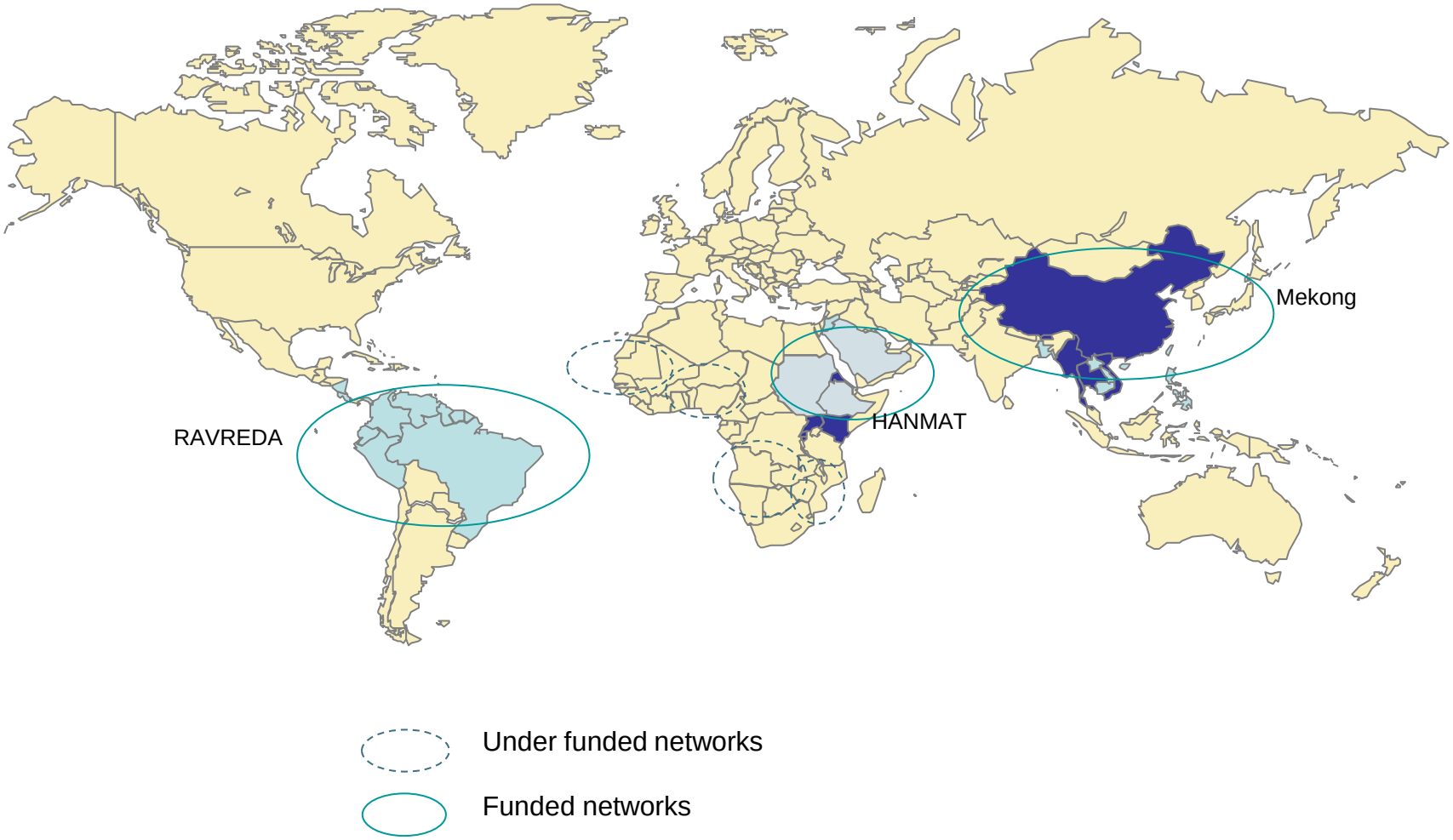
	STUDY YEARS	NUMBER OF STUDIES	MEDIAN	MINIMUM	MAXIMUM
WHO AFRICAN REGION					
Angola					
Amodiaquine	2002–2003	2	20.4	19.1	21.6
Artemether–lumefantrine	2003–2004	2	1.2	0.0	2.3
Artesunate–amodiaquine	2003–2004		1.2	0.0	3.3
Artesunate–sulfadoxine–pyrimethamine	2003–2003	1	1.2	1.2	1.2
Chloroquine	2002–2002	1	85.7	85.7	85.7
Sulfadoxine–pyrimethamine	2002–2003	2	33.0	27.1	38.8
Benin					
Artemether–lumefantrine	2005–2007	4	0.8	0.0	6.5
Artesunate–amodiaquine	2007–2007	1	0.0	0.0	0.0
Artesunate–sulfadoxine–pyrimethamine	2003–2005	1	5.6	5.6	5.6
Chloroquine	2002–2005	6	35.5	15.0	73.9
Mefloquine	2005–2005	1	2.6	2.6	2.6
Sulfadoxine–pyrimethamine	2002–2007	8	35.7	3.3	71.7
Botswana					
Sulfadoxine–pyrimethamine	2006–2006	3	24.6	12.2	30.1

Instrument of policy change

Threshold levels for changing malaria treatment policy



Regional networks



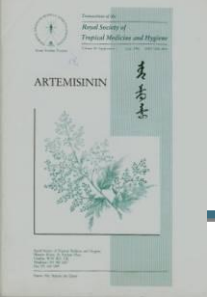
WHO report on monitoring antimalarial drug efficacy

- Latest report on antimalarial drug resistance published in November 2010
- Calls for enhanced monitoring of therapeutic efficacy of antimalarial medicines in order to update drug policy where needed and to detect artemisinin resistance

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 dose equal to or higher than those usually recommended but within tolerance of the subject" (WHO, 1973)**
- **Therapeutic efficacy is used as an 'alert' to detect resistance but not <u>all treatment failures are due to resistance</u>. Treatment failure can be due to:**
  - pharmacokinetic (low absorption, increased metabolism, etc…)
  - immunity (HIV, pregnancy, etc…)
  - confirmed resistance
- **Therefore other tools are needed to confirm resistance**
  - pharmocokinetics
  - in vitro efficacy
  - molecular markers

This definition could need some adaptation for artemisinin



Clinical trials of artemisinin and its derivatives in the treatment of malaria in China

Guo-Qiao Li, Xing-Bo Guo, Lin-Chun Fu, Hua-Xiang Jian and Xin-Hua Wang *Sanya Tropical Medicine Institute, Guangzhou College of Traditional Chinese Medicine, Guangzhou, People's Republic of China*

Introduction

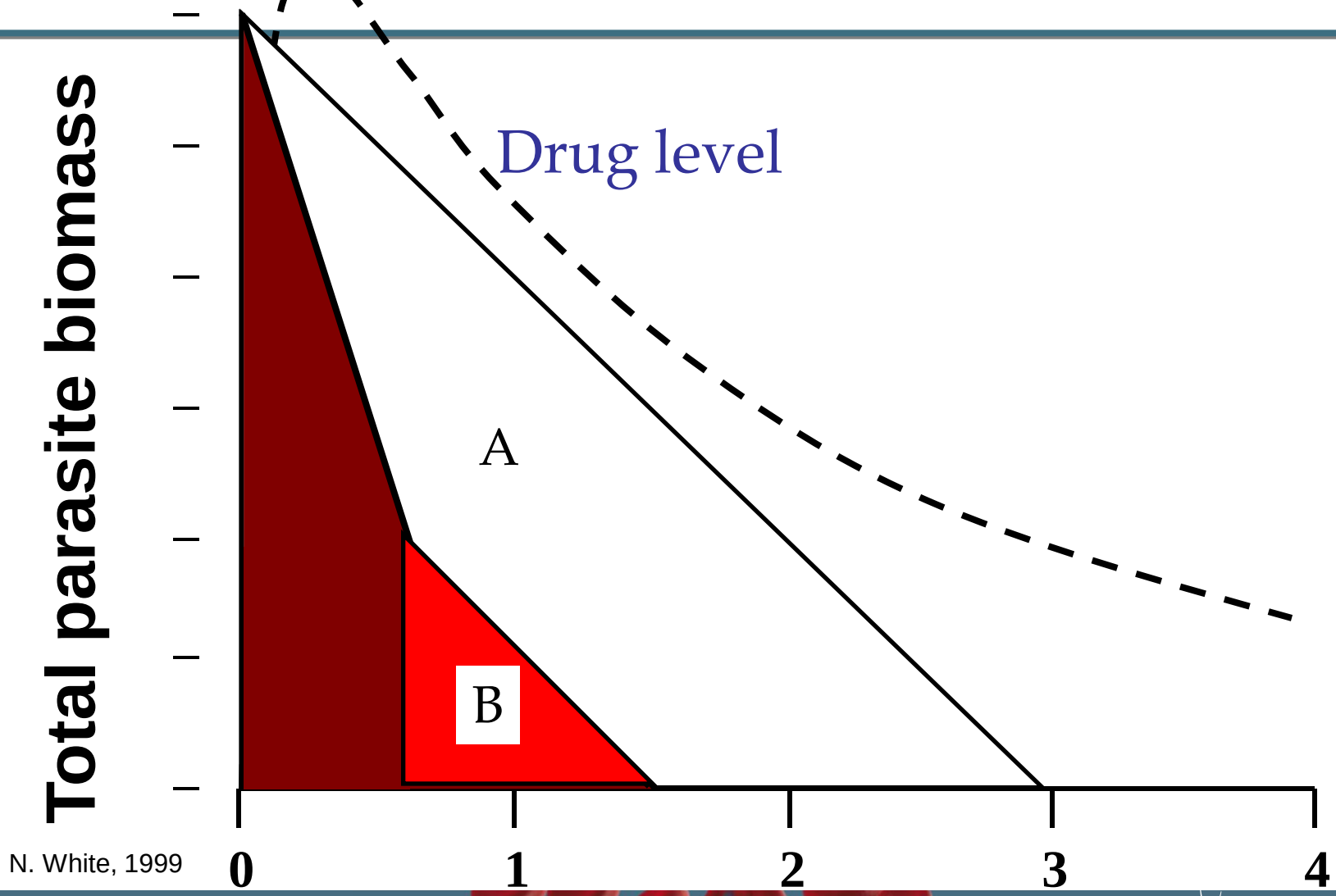
Since 1979, several different formulations of artemis-

Table. The relation between course of treatment and recrudescence of malaria

Drug	Treatment course[a] 3 d		5 d		7 d	
Artemisinin suppositories	50/113	(44%)				
Artesunate						
Tablets	30/56	(54%)	7/144	(5%)		
Intramuscular	13/25	(52%)	9/82	(10%)	1/40	(2·5%)
Intravenous	44/89	(49%)			2/36	(6%)
Artemether tablets	14/30	(47%)	5/97	(5%)	2/41	(5%)
Dihydroartemisinin tablets	12/25	(48%)	3/50	(6%)	4/205	(2%)
Total	163/338	(48%)	24/373	(6%)	9/322	(3%)

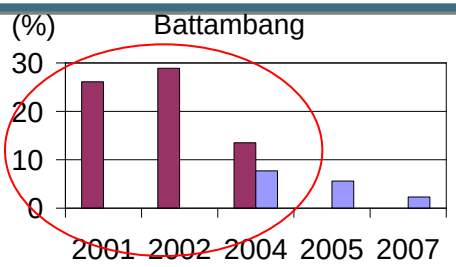
[a]Recrudescence rates are shown as no. of recrudescences/no. treated (with percentages in parentheses).

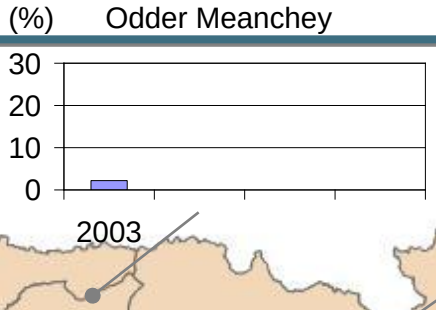
ACT: a different type of combination

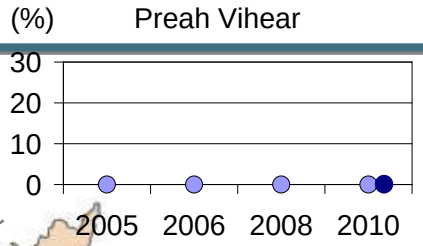


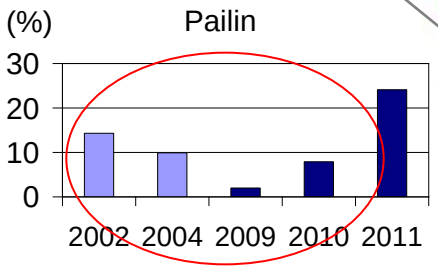
N. White, 1999

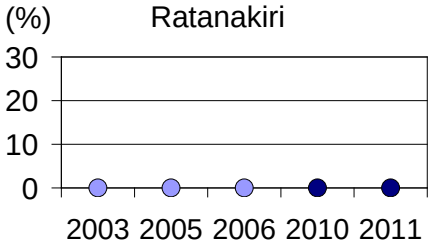
Failure rates after treatment with an artemisinin-based combination therapy, Cambodia (2001–2011)

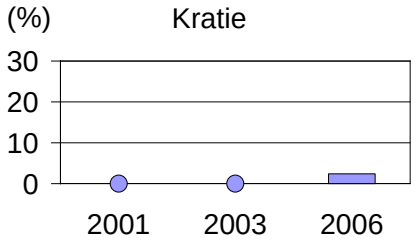


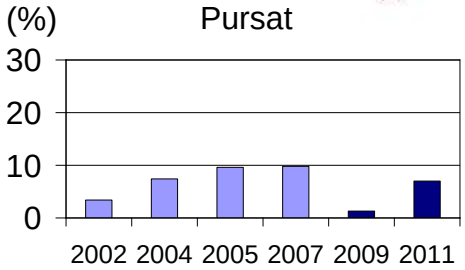


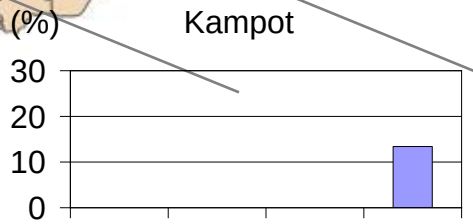


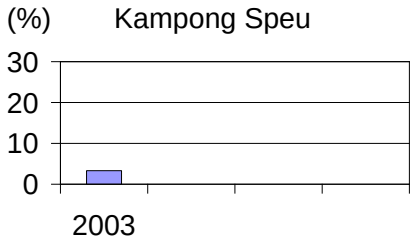


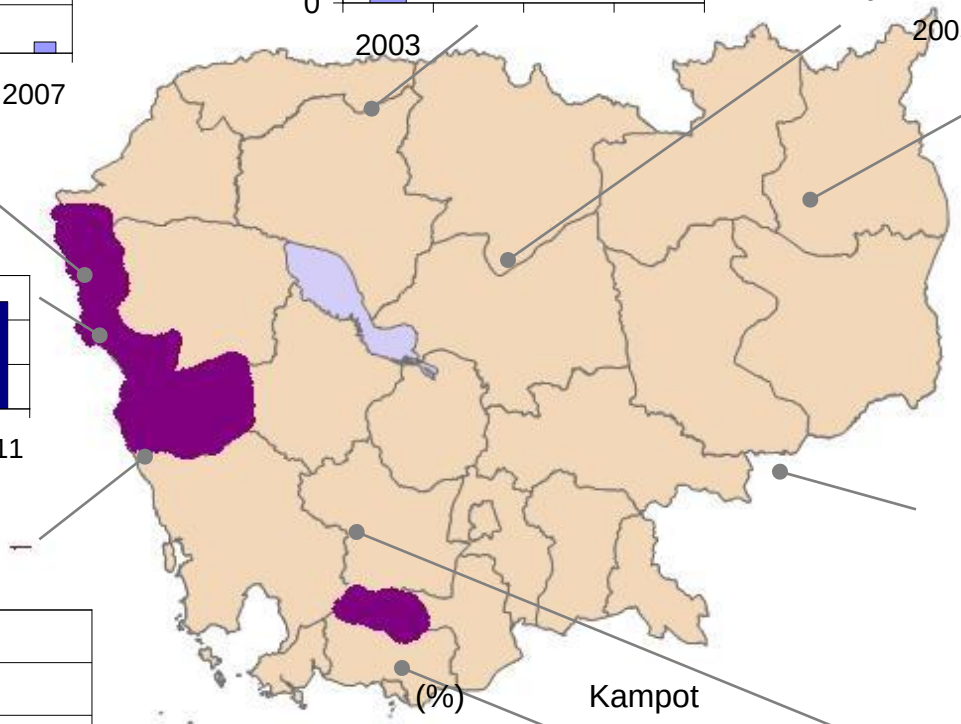








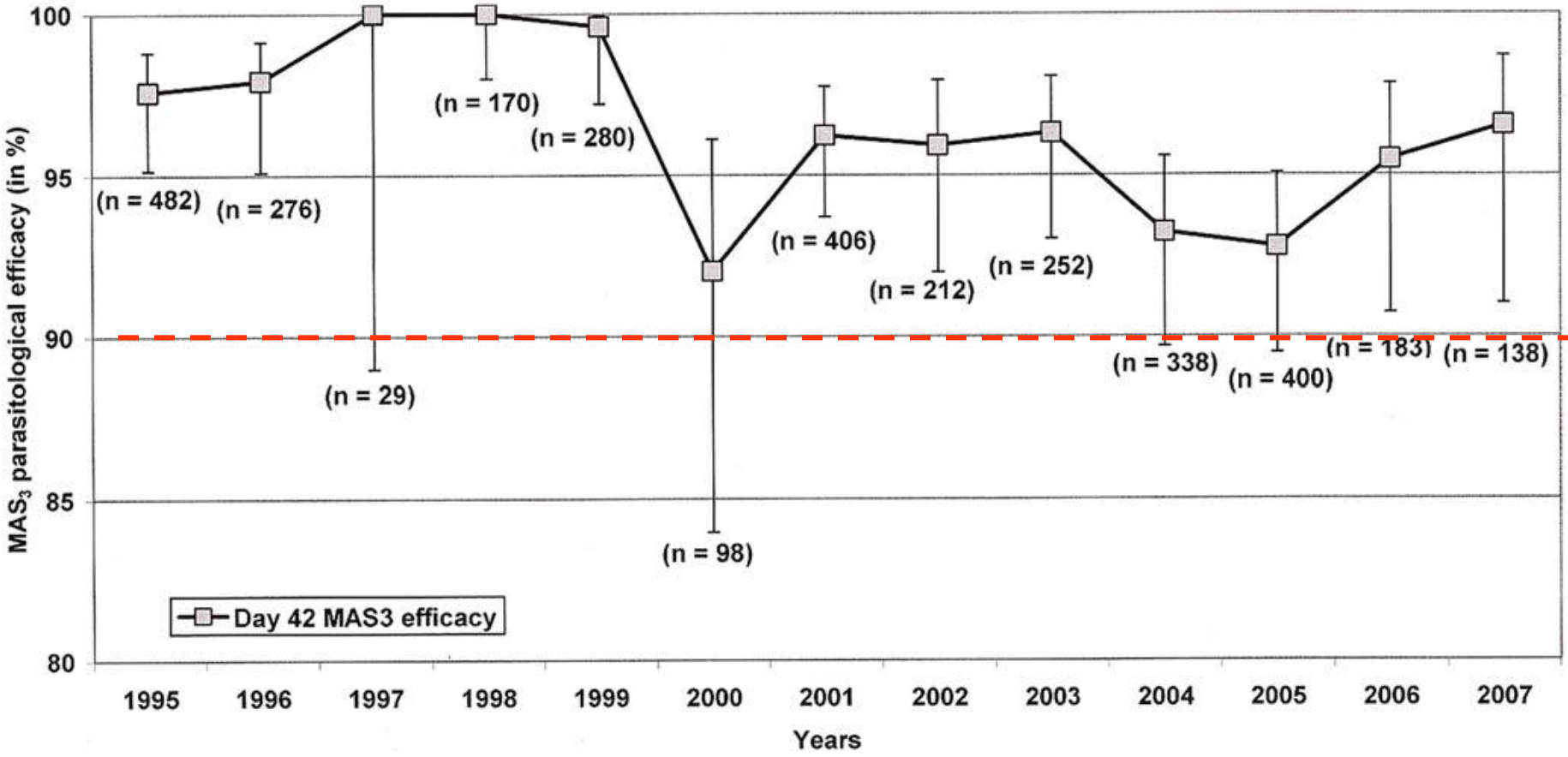




Artemether-lumefantrine
Artesunate-mefloquine
Dihydroartemisinin-piperaquine

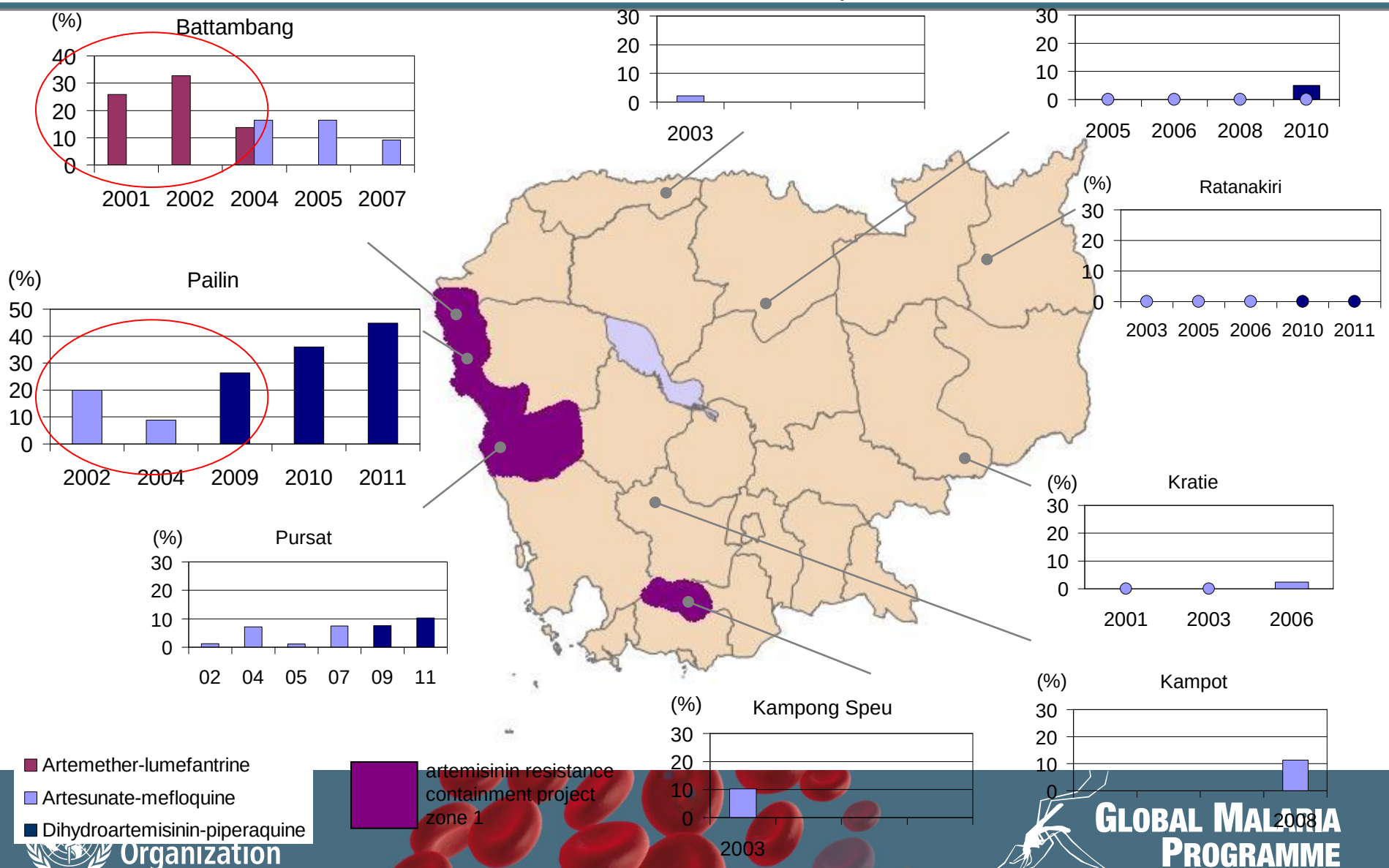
artemisinin resistance containment project zone 1

PCR-adjusted efficacy of MAS3 in Mae Sot



Carrara, PLoS One, 2009

Day 3 positivity rate after treatment with an artemisinin-based combination therapy, Cambodia (2001–2011)



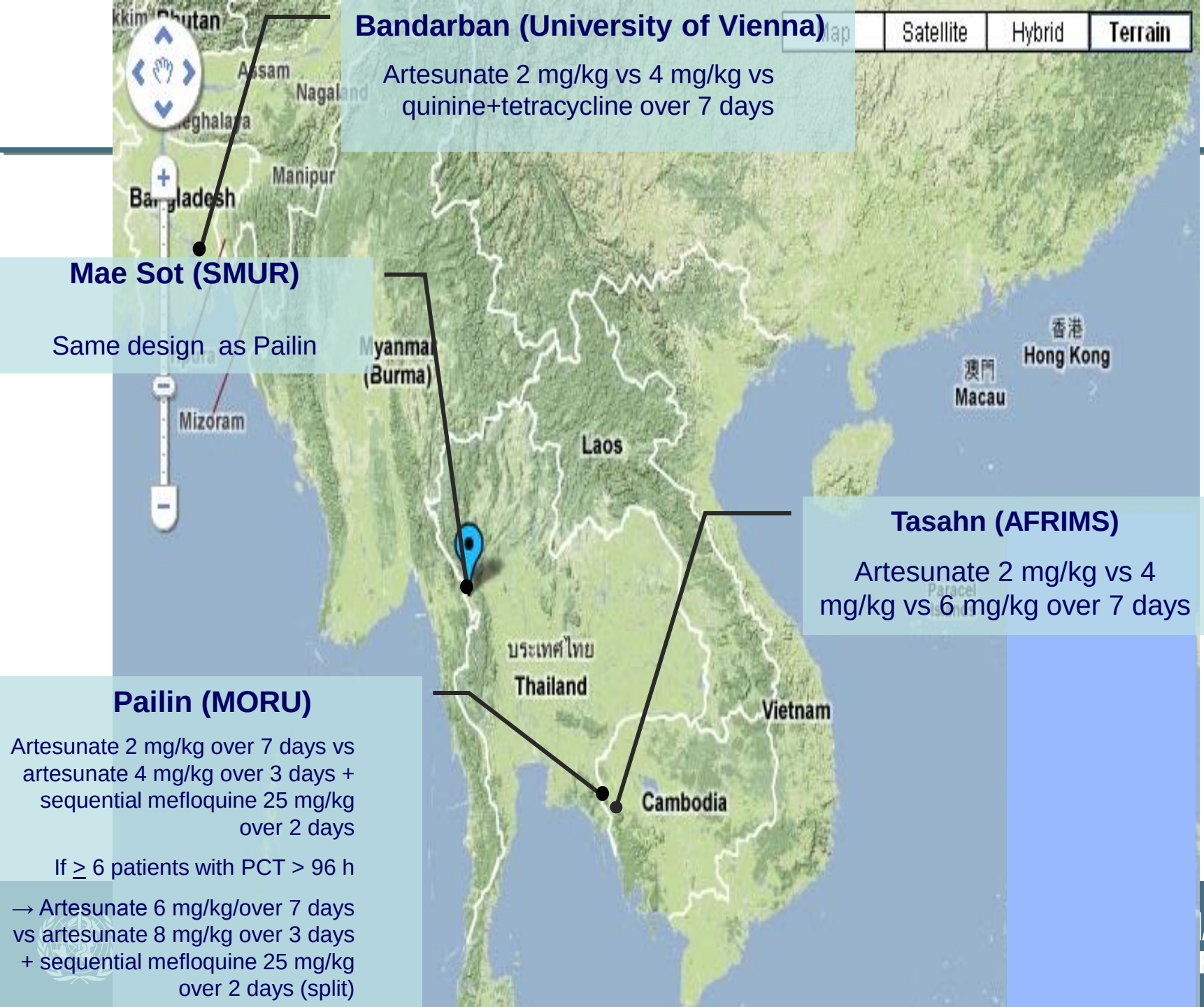
Parasite clearance time with AS+MQ in Trat province

			No of *P. falciparum* positives cases			
Province	Year	N	D2	D3	D7	PCT (days)
Trat	2003	44	14 (31%)	7 (15.9%)	2 (4.5%)	2.0
Trat	2004	15	2 (13.3%)	2 (13.3%)	0	2.1
Trat	2005	22	7 (31.8%)	2 (9%)	1 (4.5%)	2.3
Trat	2006	32	10 (31.2%)	7 (21.8%)	0	3.3
Trat	2007	31	14 (45.1%)	5 (16.1%)	0	3.7

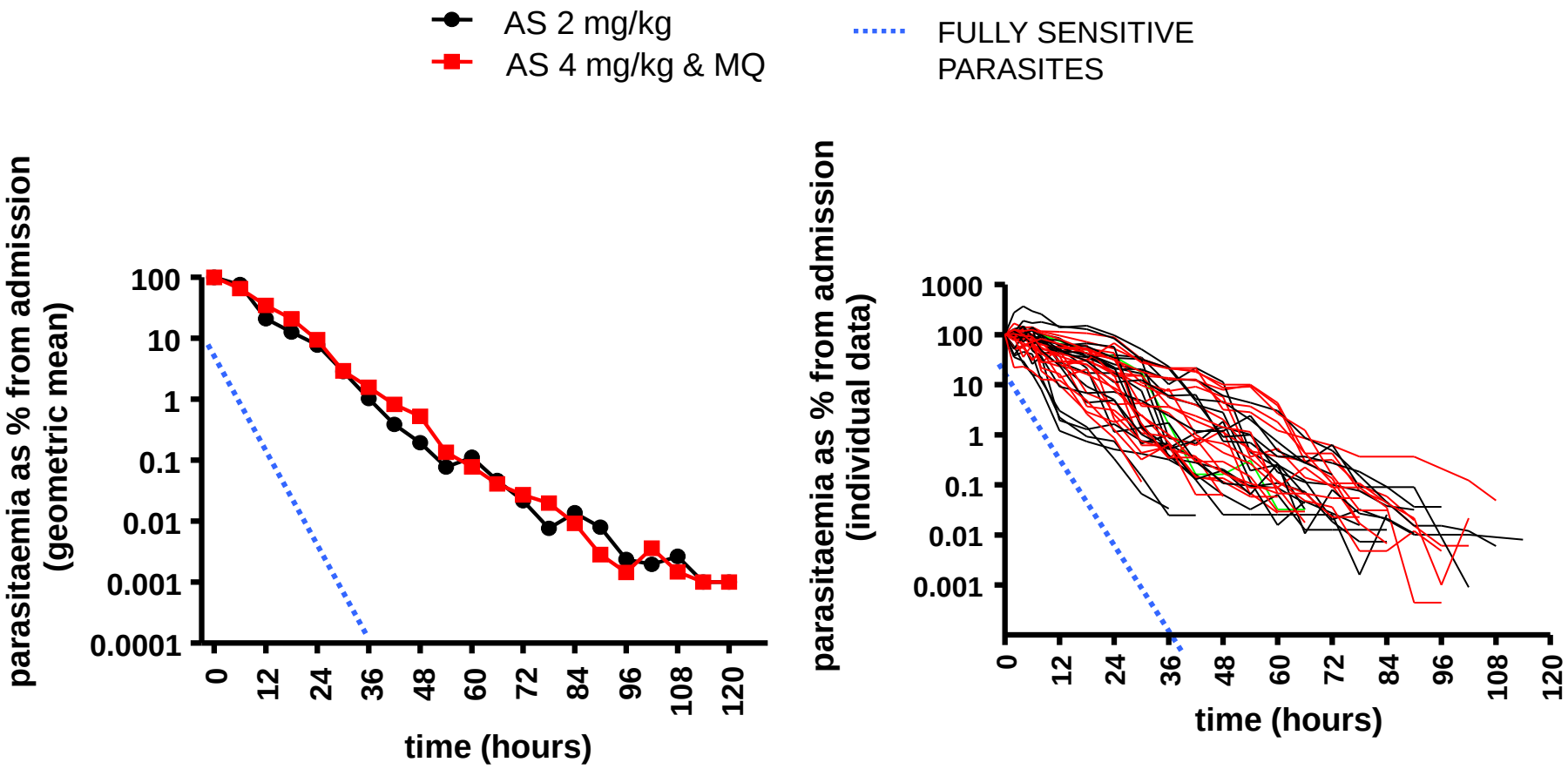
Courtesy Wichai Satimai & Saowanit Vijaykadga, 2008

ARC3 project

- **Funded by BMGF 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


Bandarban (University of Vienna)
Artesunate 2 mg/kg vs 4 mg/kg vs quinine+tetracycline over 7 days
Mae Sot (SMUR)
Same design as Pailin
Tasahn (AFRIMS)
Artesunate 2 mg/kg vs 4 mg/kg vs 6 mg/kg over 7 days
Pailin (MORU)
Artesunate 2 mg/kg over 7 days vs artesunate 4 mg/kg over 3 days + sequential mefloquine 25 mg/kg over 2 days
If ≥ 6 patients with PCT > 96 h
→ Artesunate 6 mg/kg/over 7 days vs artesunate 8 mg/kg over 3 days + sequential mefloquine 25 mg/kg over 2 days (split)
Satellite
Hybrid
Terrain
Bhutan
Assam
Manipur
Bangladesh
Mizoram
Myanmar (Burma)
Laos
Thailand
Vietnam
Cambodia
Hong Kong
Macau

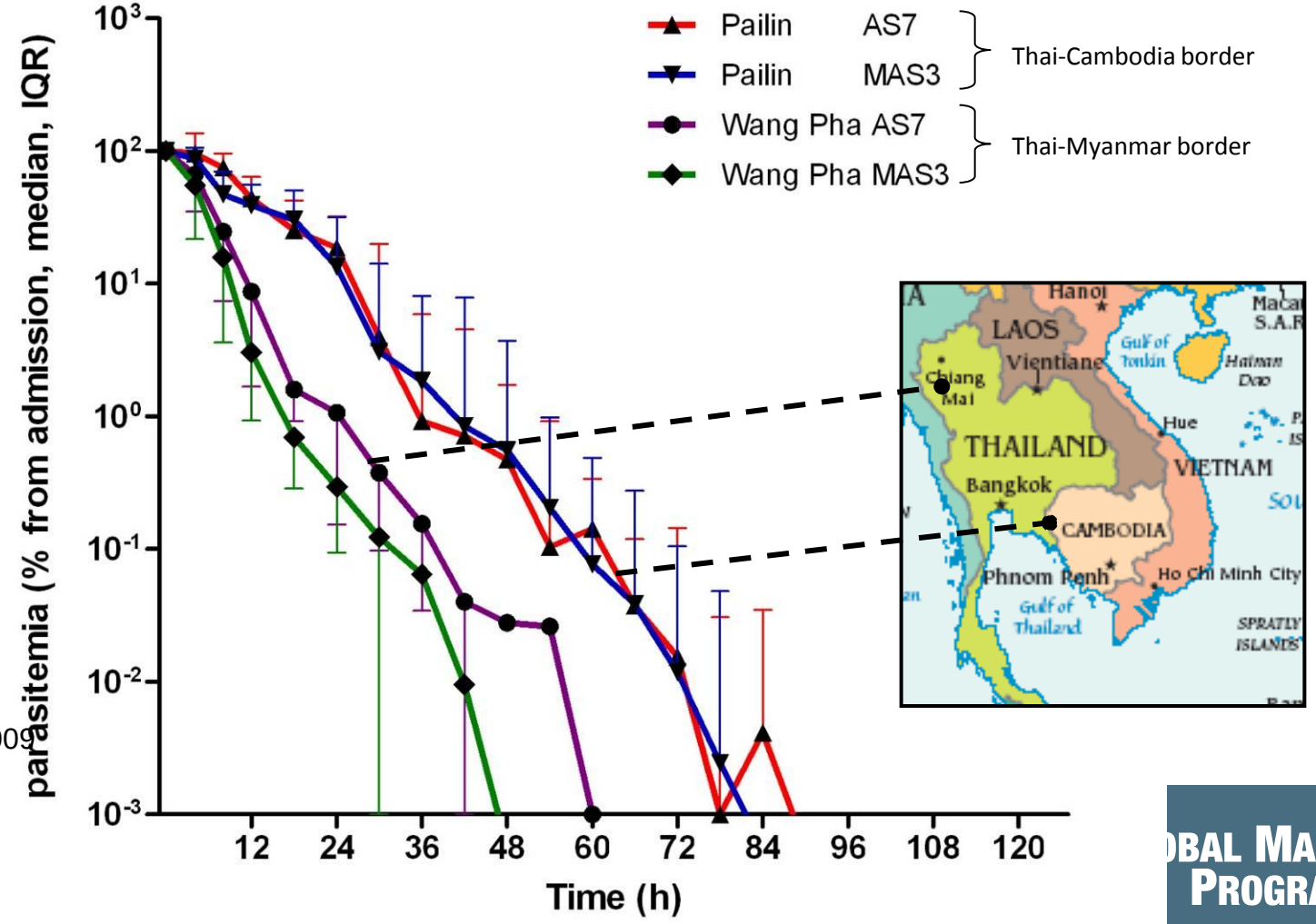
PCT in Pailin study 2007



Dondorp, NEJM, 2009

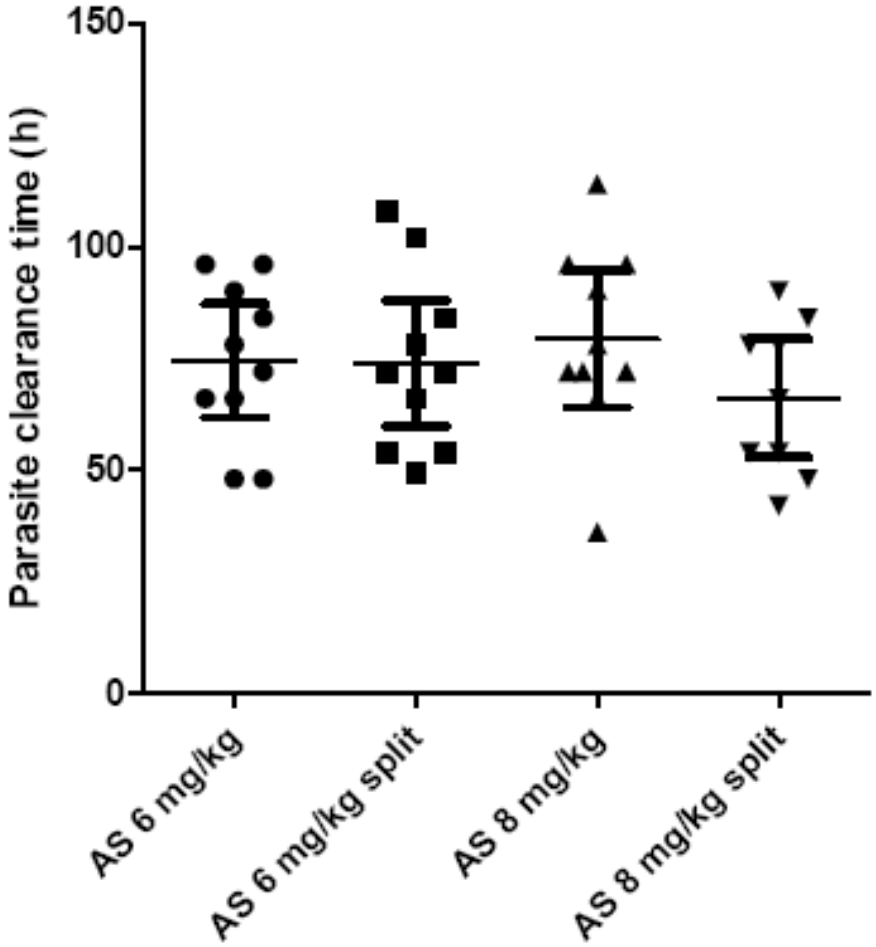
Parasite Clearance

(p=0.0001 for Δ slopes between sites)



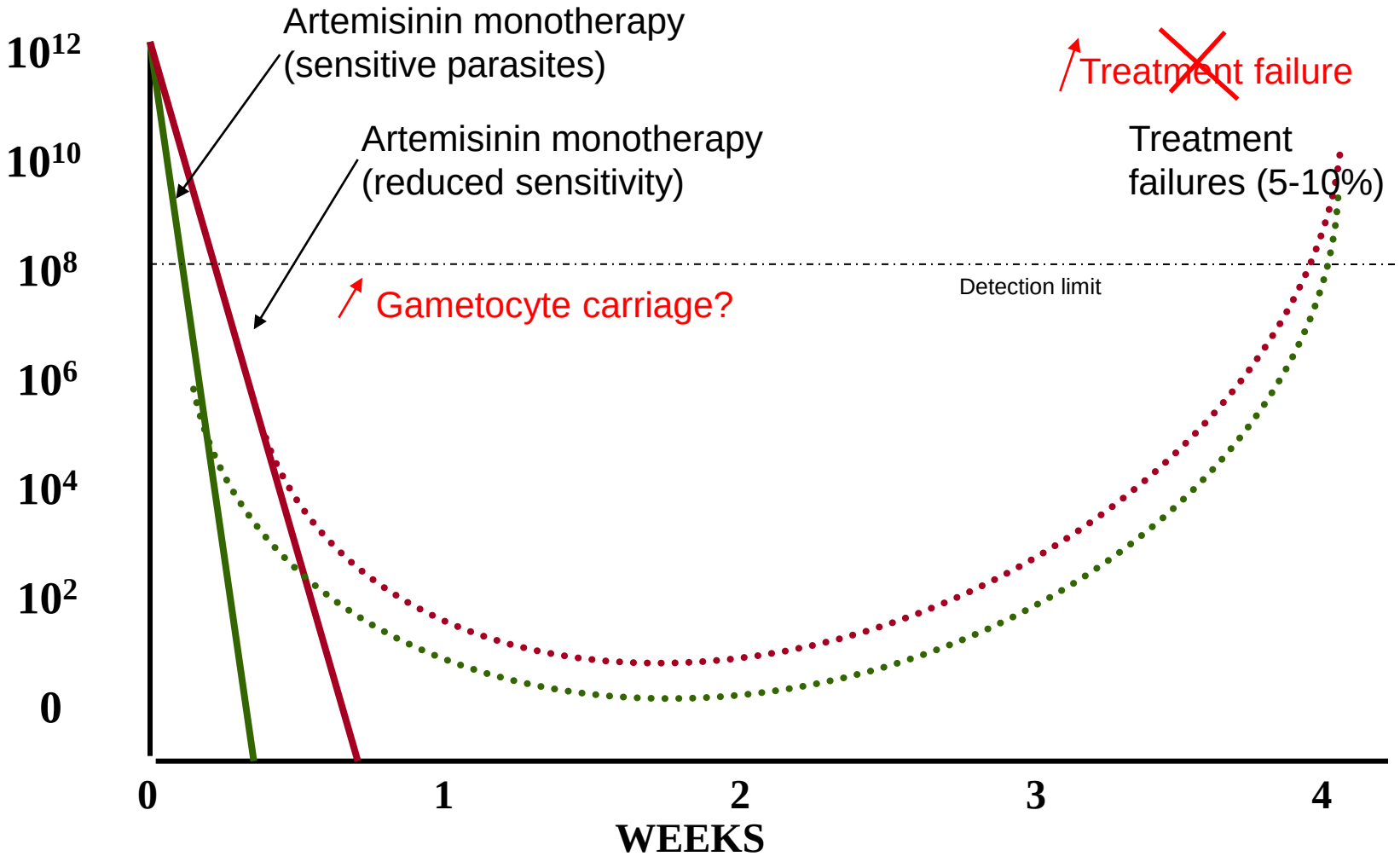
Dondorp, NEJM, 2009

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



N=40

PCT and treatment failure with artemsinin



Definition of artemisinin resistance

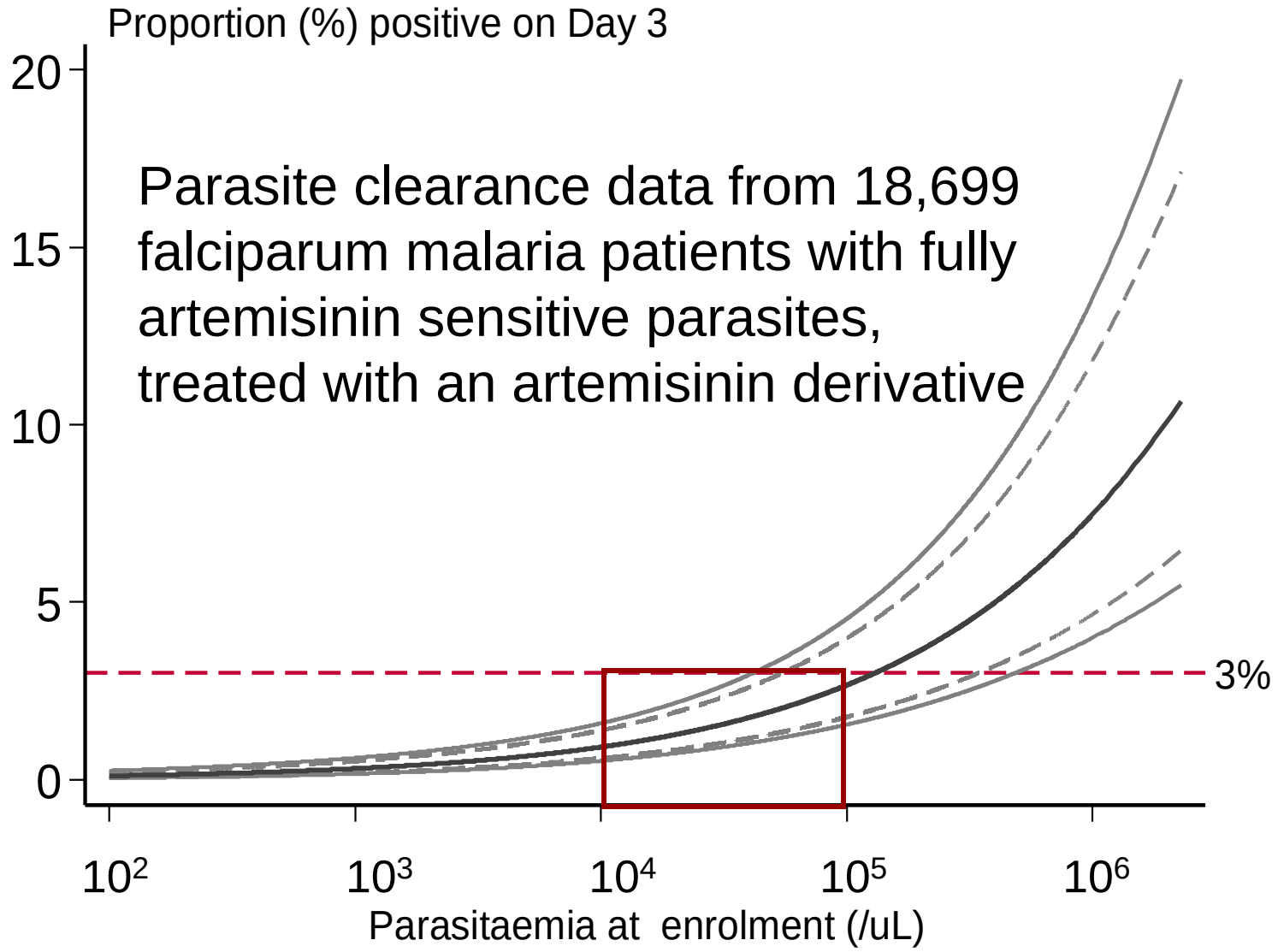
- WHO is using **working definition** as below**:**
  - an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
  - a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance)

Limits of this definition

- The parasite clearance time is prone to be affected by confounding factors (known and unknown) such as splenectomy, haemoglobin abnormalities and reduced immunity.
- The proportion of patients who are parasitaemic after 3 days of treatment has been found to be a suitable though imperfect tool for screening for artemisinin resistance but is highly dependent on:
  - **the initial parasitemia**
  - **immunity of the patients**
  - **the skills of the microscopists**
  - **D3 ≠ 72 hours**
  - **Artemisinin monotherapies ≠ ACTs ≠ among ACTs**

Relation between Day 3 positivity rate and initial parasitemia

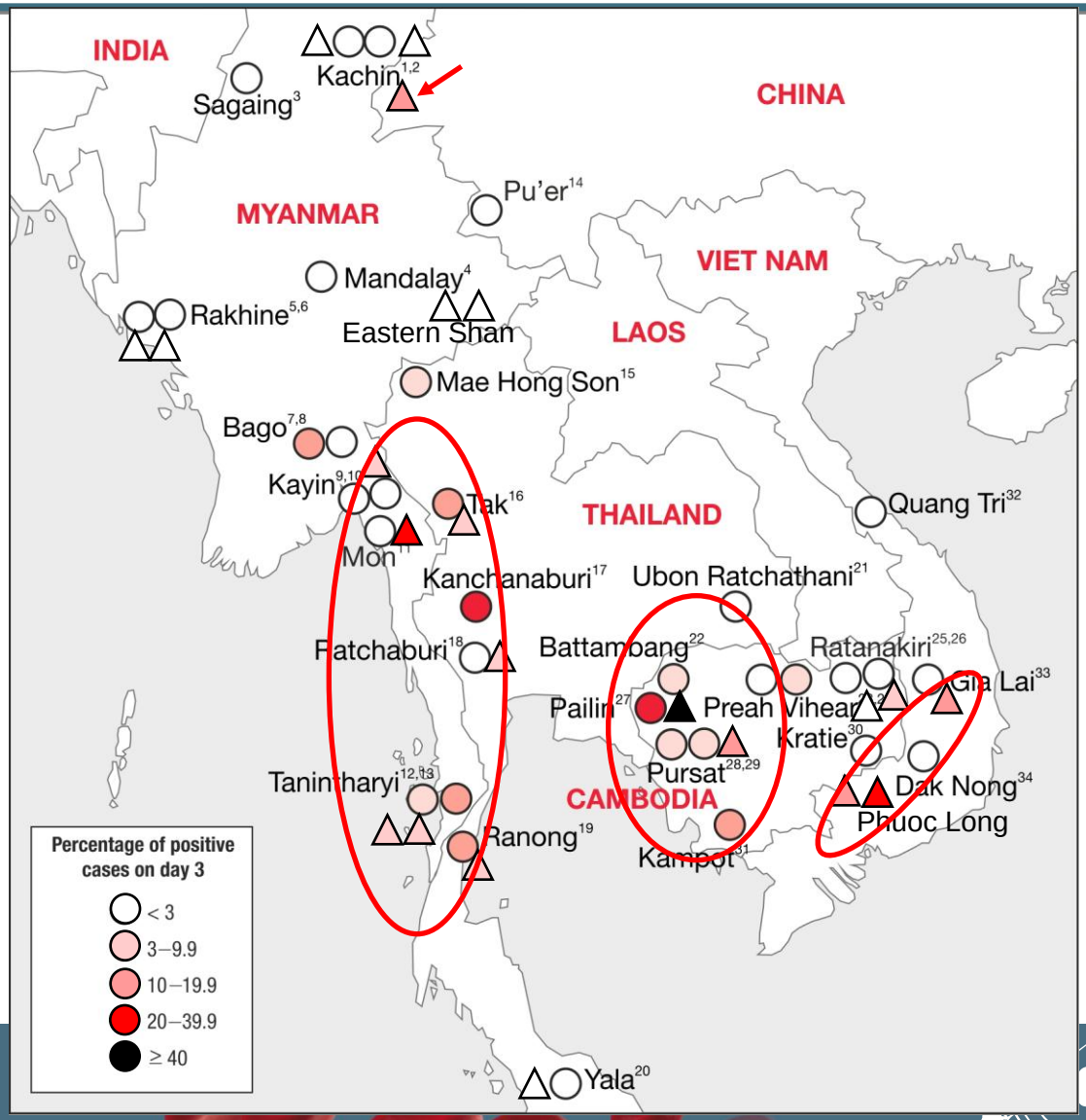
Stepniewska K, J Infect Dis 2010

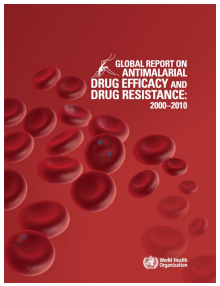


WHO recommendations

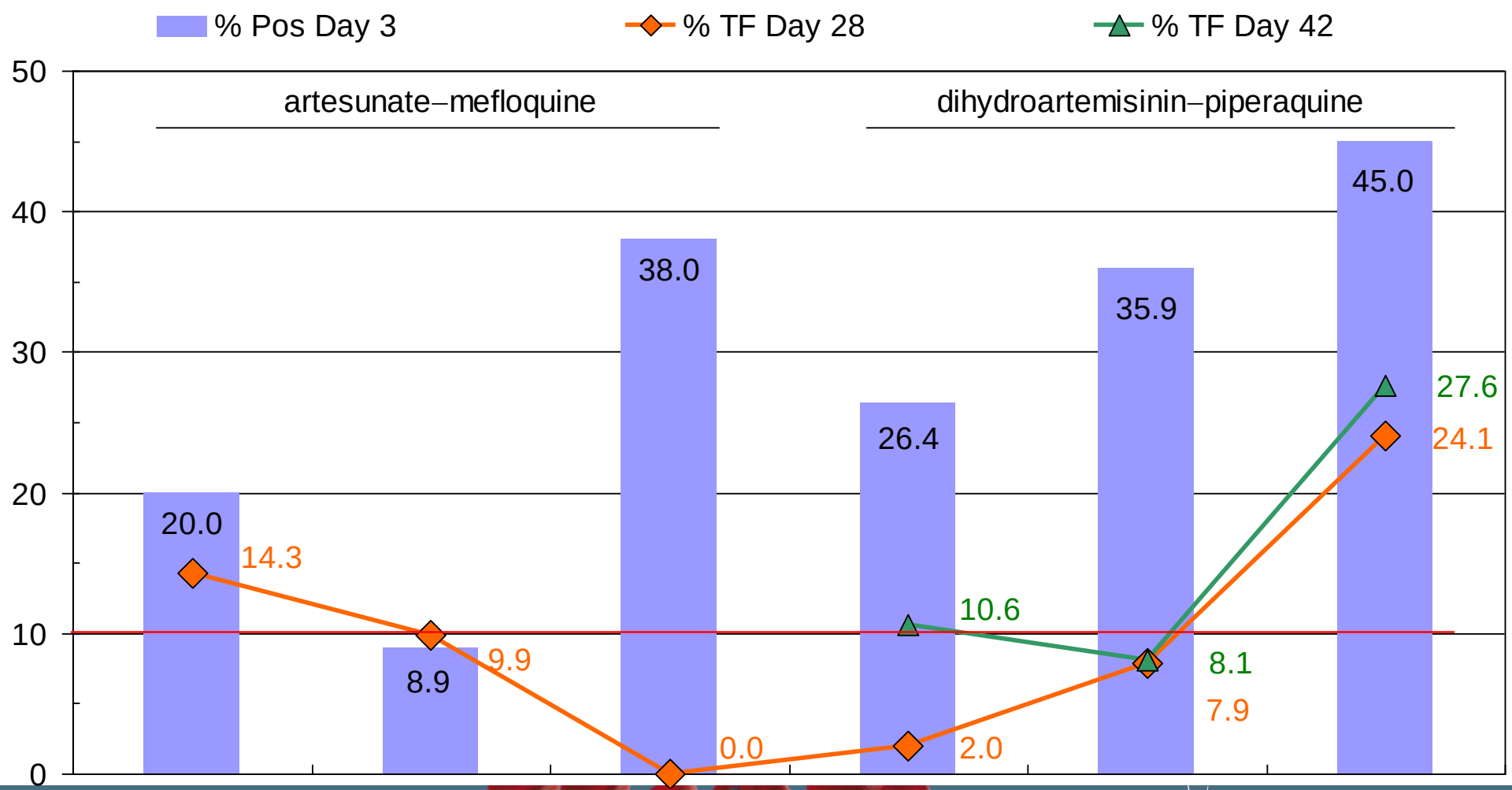
- Monitoring of ACTs is not only essential for timely changes to treatment policy and allows evaluation of the proportion of patients who still have parasites on day 3
- Each country should monitor first- and second-line drugs every 2 years
- Therefore, based on the results of the routine monitoring of ACT efficacy two different recommendations can be made:
  - Policy change of ACTs should be initiated when the treatment failure rate exceeds 10% at the end of follow-up (28 or 42 days, depending on the half life of the medicines), independently to the proportion of patients positive at day 3.
  - If therapeutic efficacy studies find that the threshold of 10% of patient parasitemic at day 3 is reached, studies using oral artesunate monotherapy should be initiated to confirm artemisinin resistance in the area.

Percentage of positive cases on day 3 after ACT

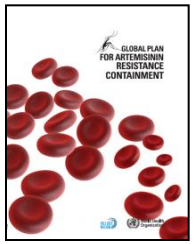




ACT efficacy in Pailin Province, Cambodia (2002-2011)



GPARC action pillars



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 & surveillance to evaluate the AR threat**
3. **Improve access to diagnostics & rational treatment with ACTs**
4. **Invest in artemisinin resistance-related research**

5. **Motivate action and mobilize resources**

Malaria containment/elimination zoning overview: Thailand - Cambodia

Note: The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations
Source: FAO GAUL – Release January 2007; Department of Geography; Royal Government of Cambodia; Global Containment Project, WHO

Example of GPARC Implementation in Tier 1: ARCE project on Cambodia-Thailand 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

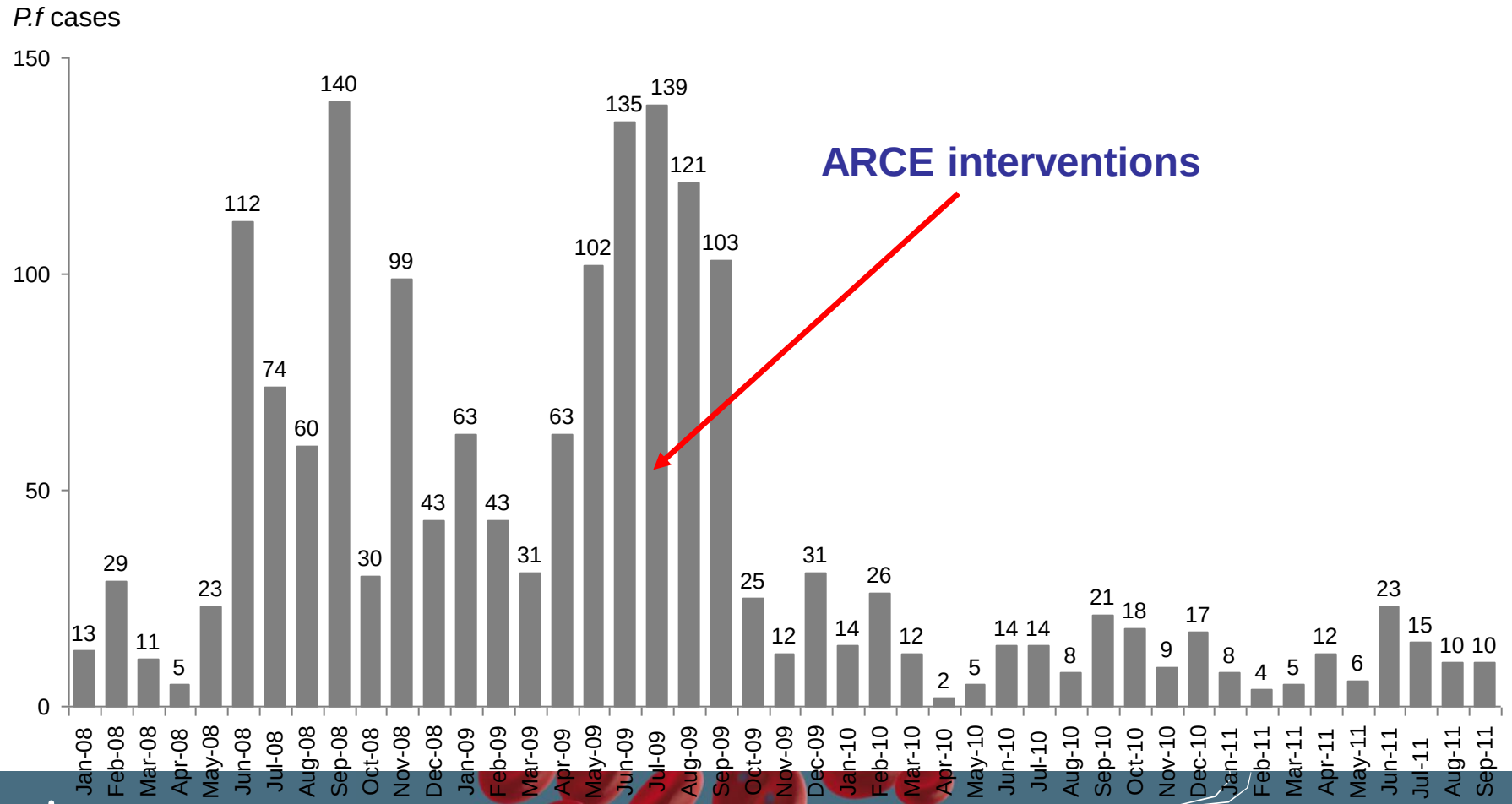
Program combines proven malaria prevention & treatment strategies

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

Cases diagnosed in Pailin province

_P.f_ cases diagnosed by microscopy and RDT at health facilities in Pailin province (Z1), Jan 2008-Jun 2011

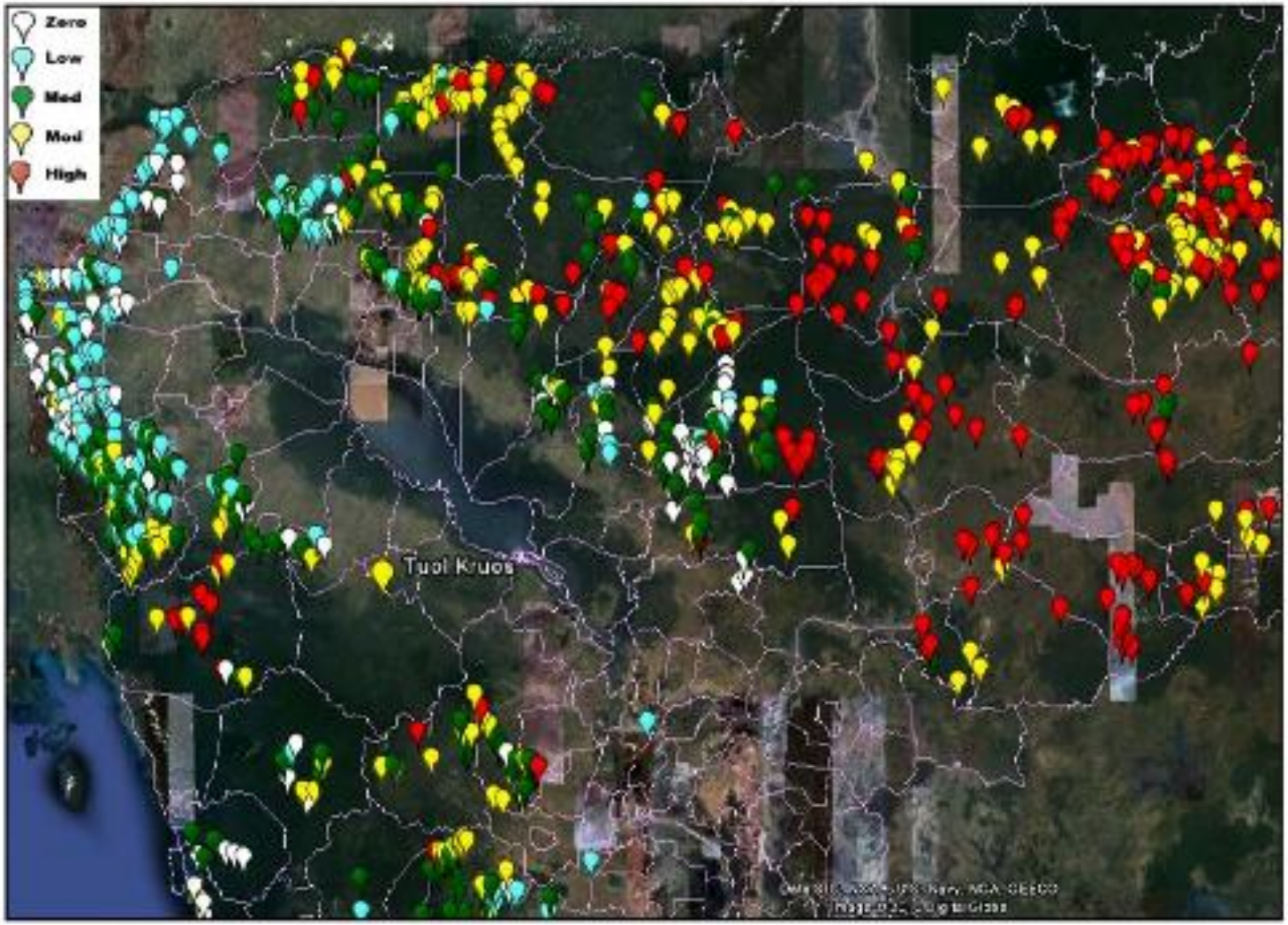


Village and mobile malaria workers.

3,000 village malaria workers (VMWs) and mobile malaria workers (MMWs) have been recruited and trained in Cambodia

VMW: diagnosis and treatment

Map of malaria incidence from MIS (Cambodia)

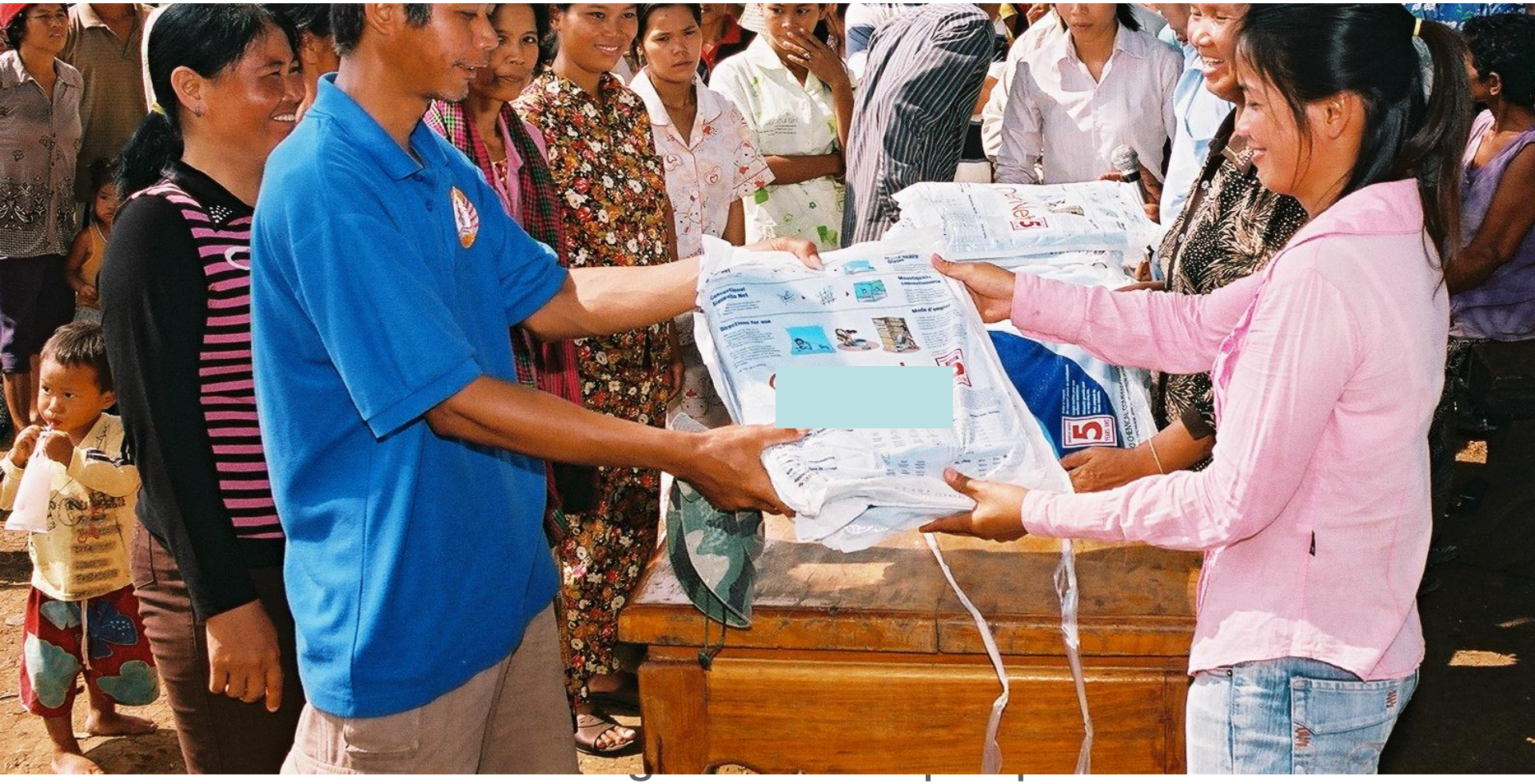


Map of D3+ cases which occurred after DOT with an ACT, zone 2, Thailand (2009-2011)

Encourage community engagement

Cambodian villagers in Kampot province receive insecticide treated nets.

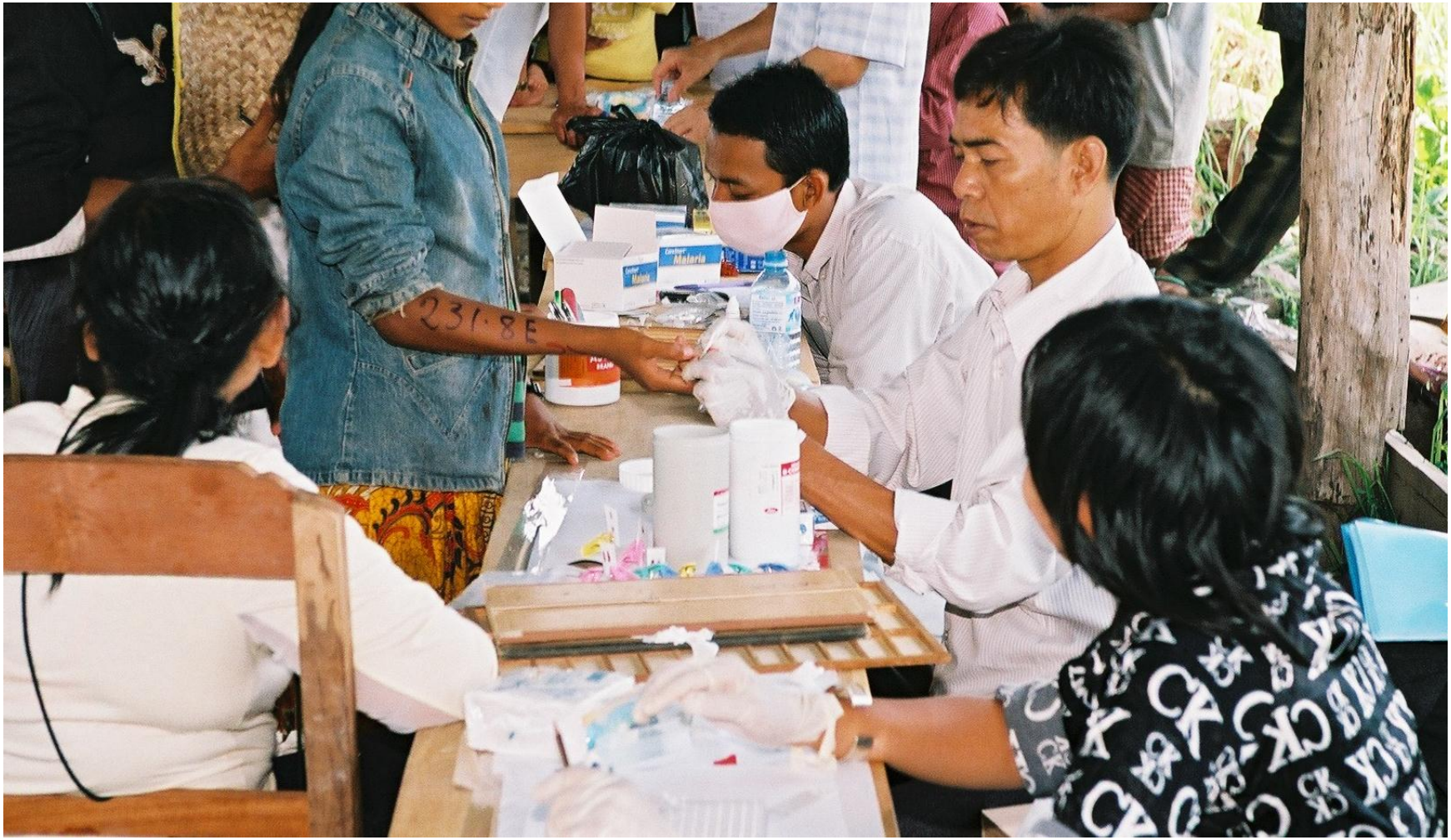
Long lasting insecticide treated nets distribution



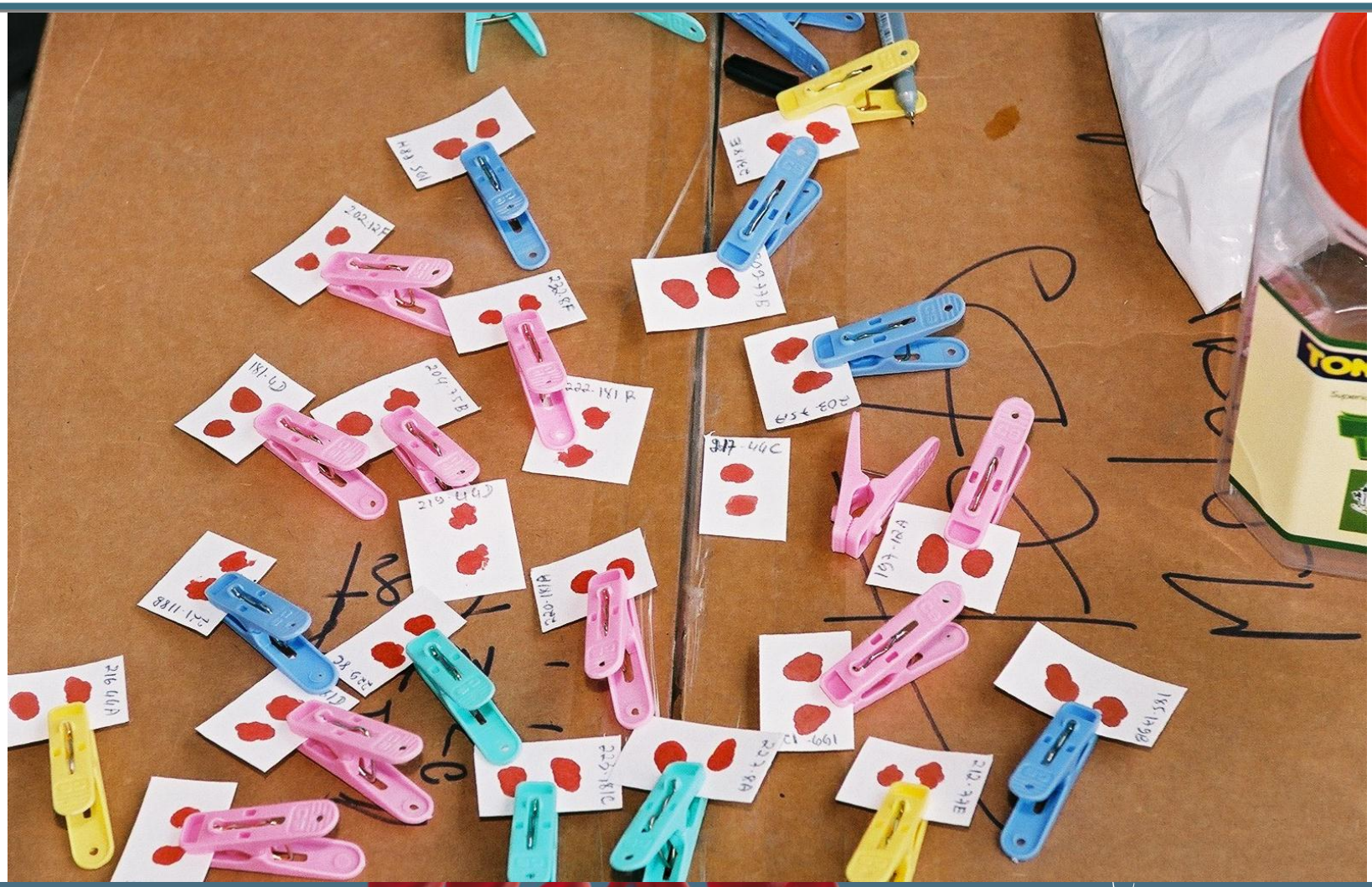
Enforce the ban on artemisinin monotherapy

Focused screening and treatment

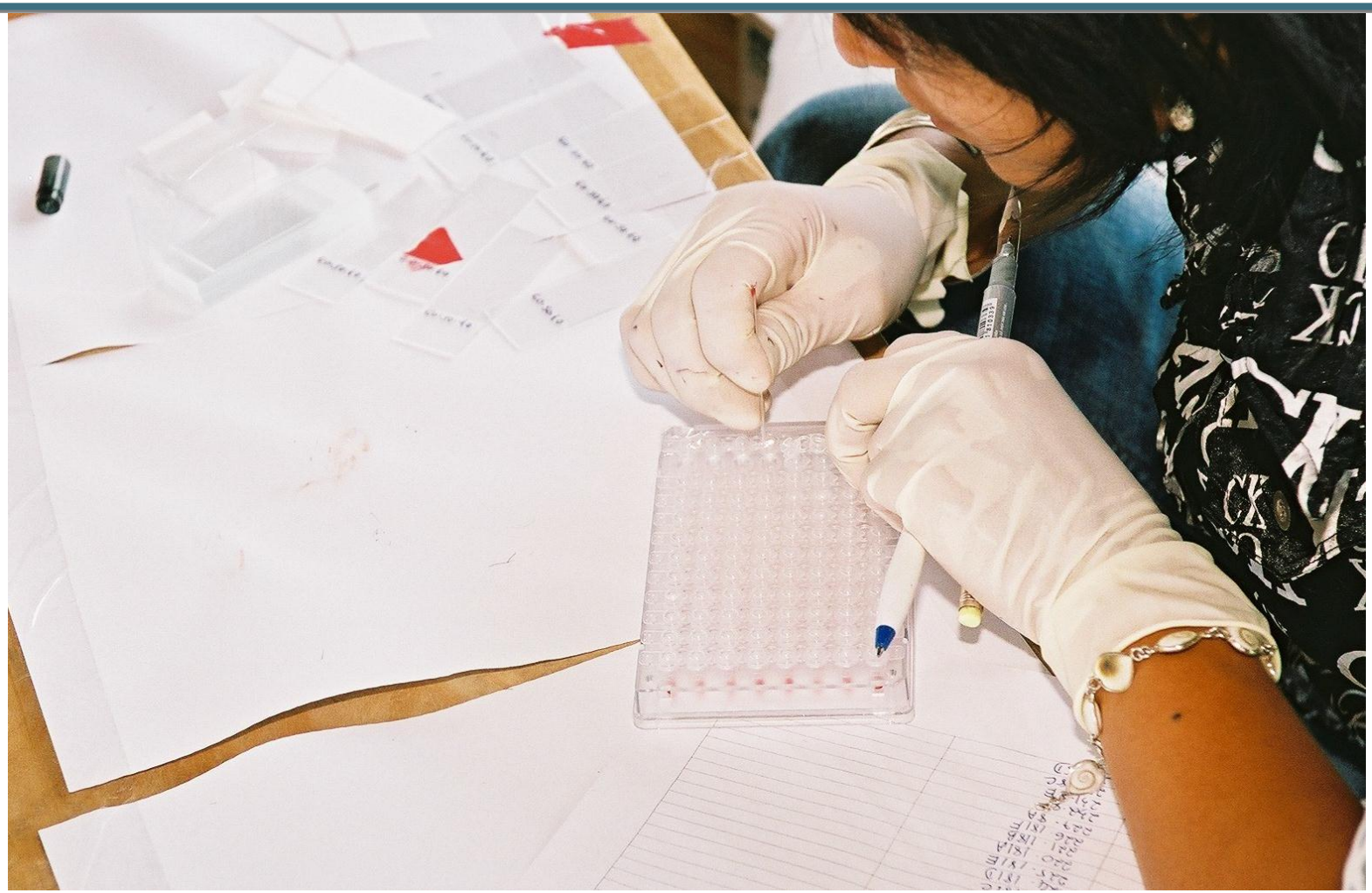
Focused screening and treatment



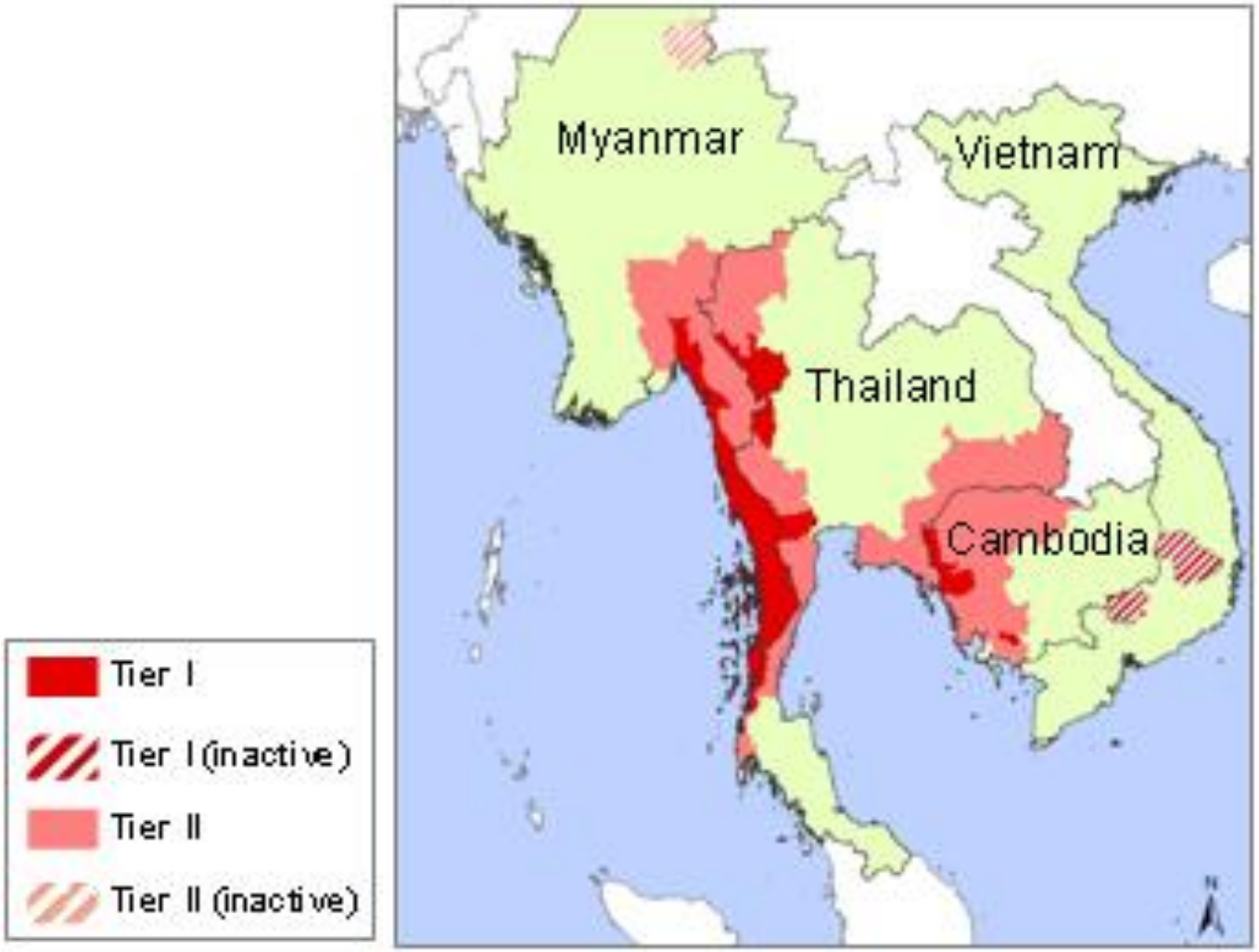
Focused screening and treatment



Focused screening and treatment



Areas of artemisinin resistance and containment



GPARC in Tier III

- **South and Central America are in Tier III**
- **Countries should increase monitoring and surveillance to evaluate threat of artemisinin resistance**
  - All sentinel sites every 2 years
- **Improve access to diagnostics and rational treatments with ACTs**
  - Ban of artemisinin-based monotherapy for uncomplicated falciparum malaria
  - Substandard and counterfeit
- **Preventive measures**
  - Vector control
  - Control malaria in mobile and migrant populations

Update to the protocol

- Low-to-moderate transmission area → very low
  - 4-5 patients/week over 6 months
  - Reduce lower parasitemia to 250/μl (reliability of microscopy)
  - 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)
- Countries targeting elimination/eradication
  - 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

Consequences of artemisinin resistance

FACTS	IMPLICATIONS
(ACPR) Clinical and parasitological cure of ACTs - not compromised	➢ Change in parasite sensitivity 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 – ***Needs more data***	➢ Increased risk of transmission of less sensitive parasites – ***Needs more research***
Infectivity to mosquitoes – data not available	➢ ***Needs more research***
Total parasite biomass over period of infection increased	➢ More parasites exposed to partner medicine alone ➢ Likely to increased propensity for parasite de novo mutations – which favour parasite survival