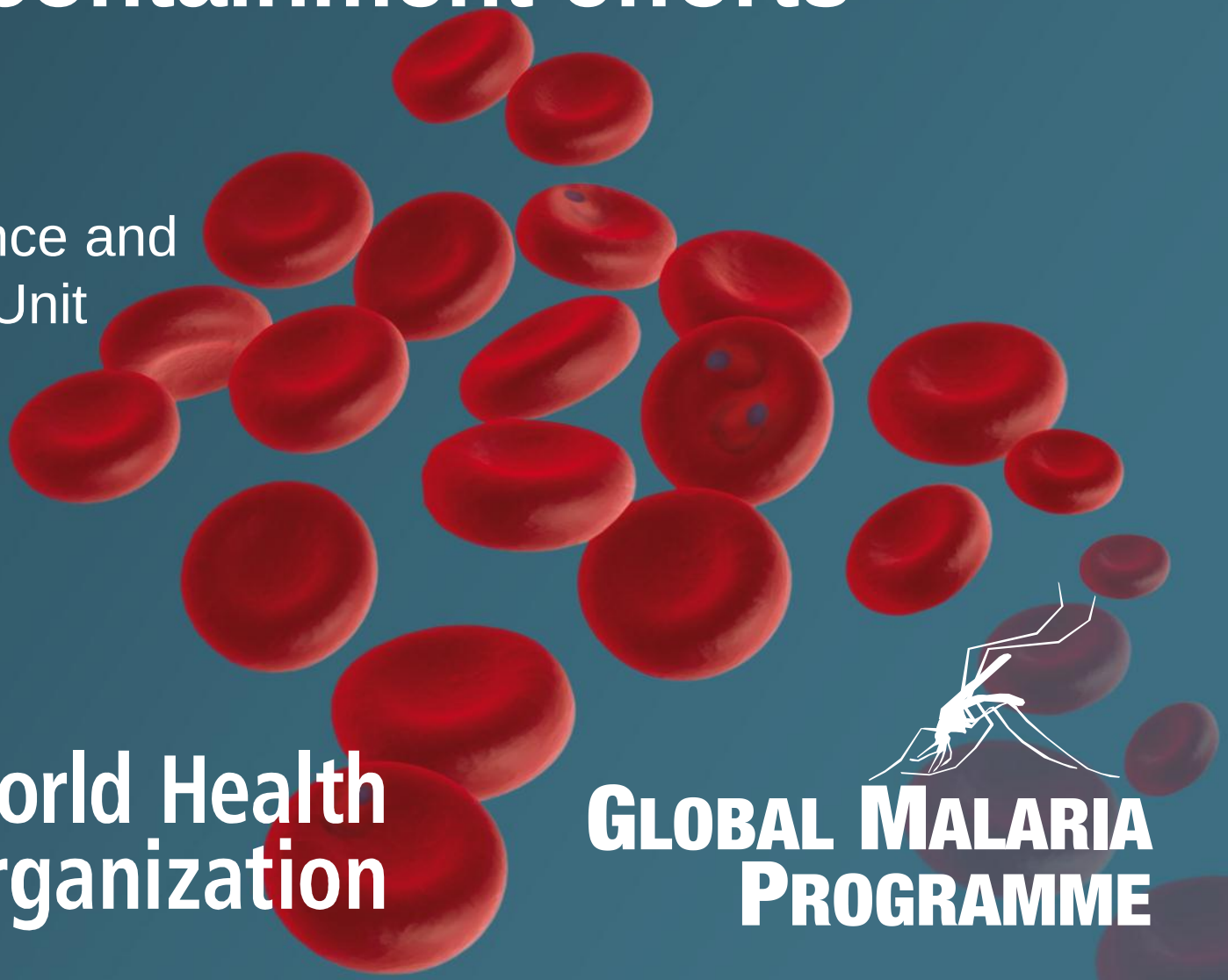
Update of artemisinin resistance and its containment efforts

P. Ringwald
Drug Resistance and Containment Unit



World Health Organization

GLOBAL MALARIA PROGRAMME

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

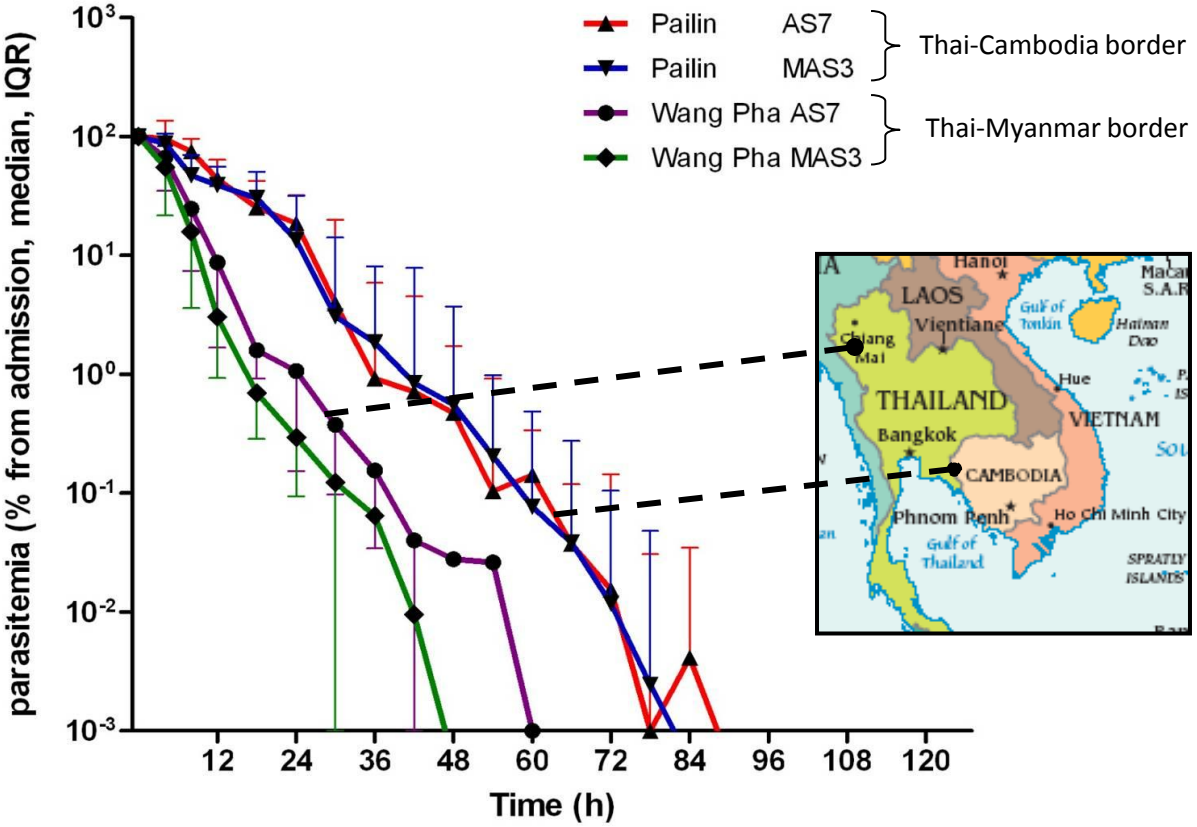
Artemisinin Resistance in *Plasmodium falciparum* Malaria

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 361;5 NEJM.ORG JULY 30, 2009

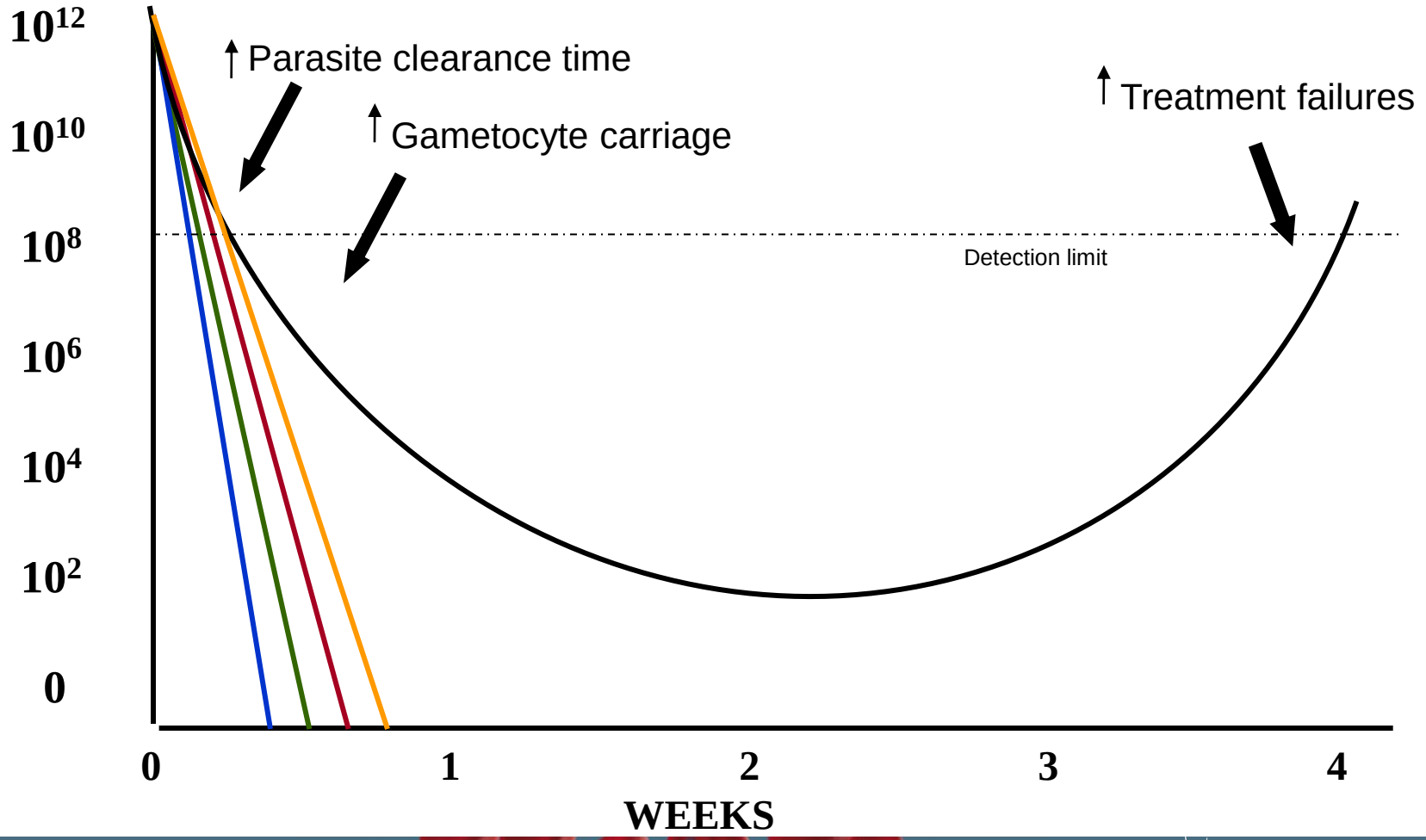
Parasite Clearance

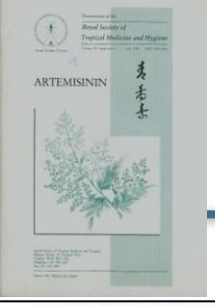
(p=0.0001 for Δ slopes between sites)



Dondorp, NEJM, 2009

Treatment failures with monotherapies





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

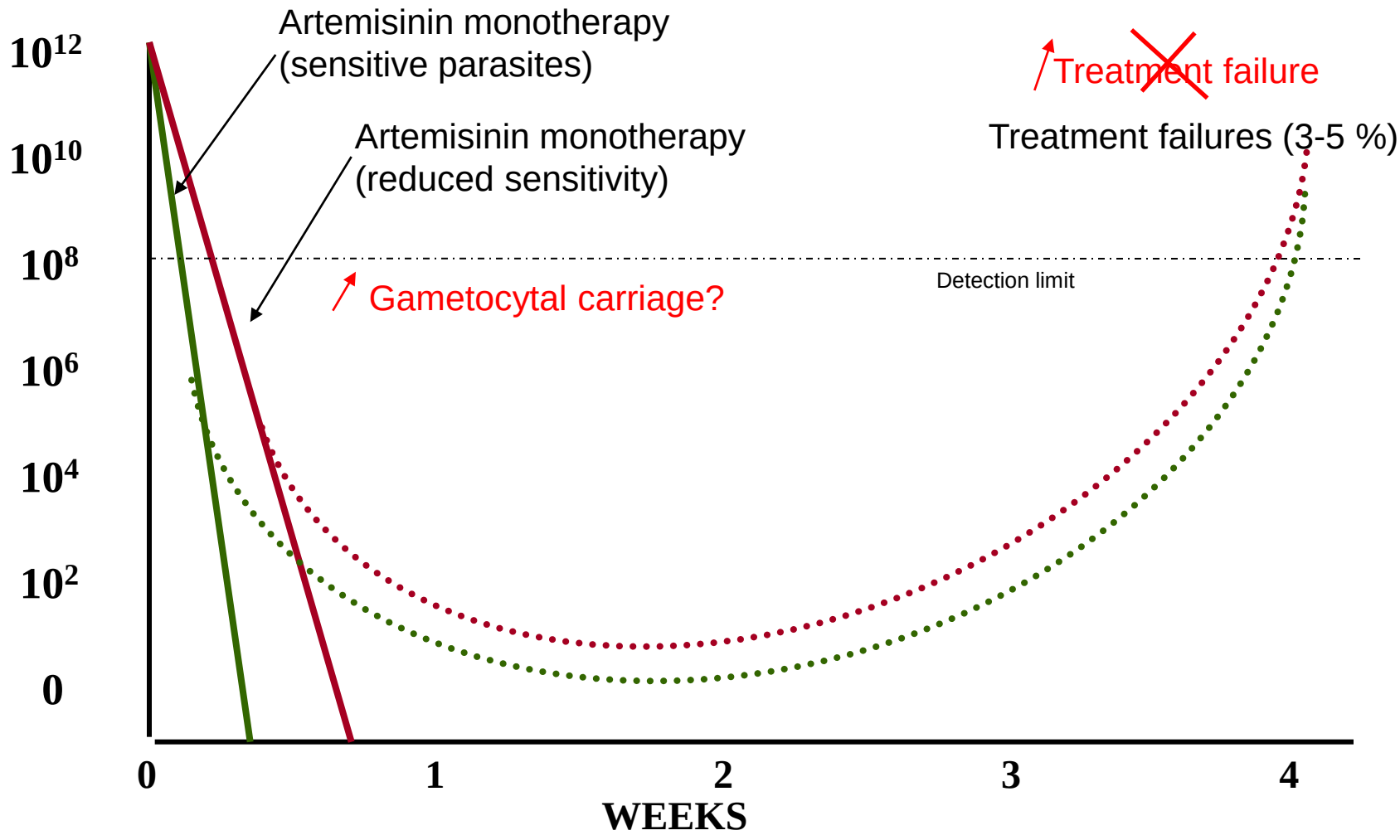
Since 1979, several different formulations of artemis-

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

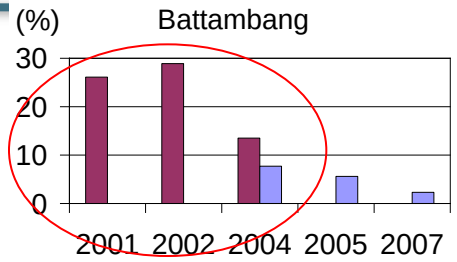
Drug	Treatment course[a] 3 d		5 d		7 d	
Artemisinin suppositories	50/113	(44%)				
Artesunate						
Tablets	30/56	(54%)	7/144	(5%)		
Intramuscular	13/25	(52%)	9/82	(10%)	1/40	(2·5%)
Intravenous	44/89	(49%)			2/36	(6%)
Artemether tablets	14/30	(47%)	5/97	(5%)	2/41	(5%)
Dihydroartemisinin tablets	12/25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

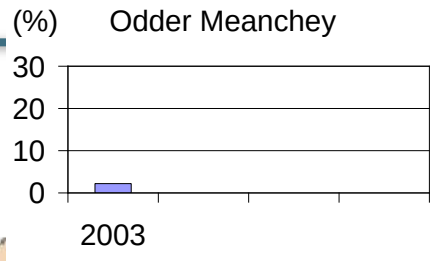
[a]Recrudescence rates are shown as no. of recrudescences/no. treated (with percentages in parentheses).

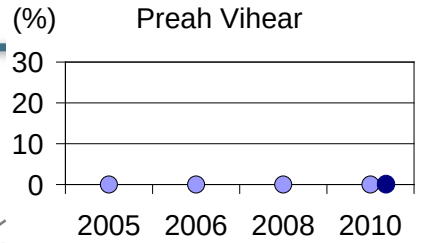
PCT and treatment failure with artemisinin

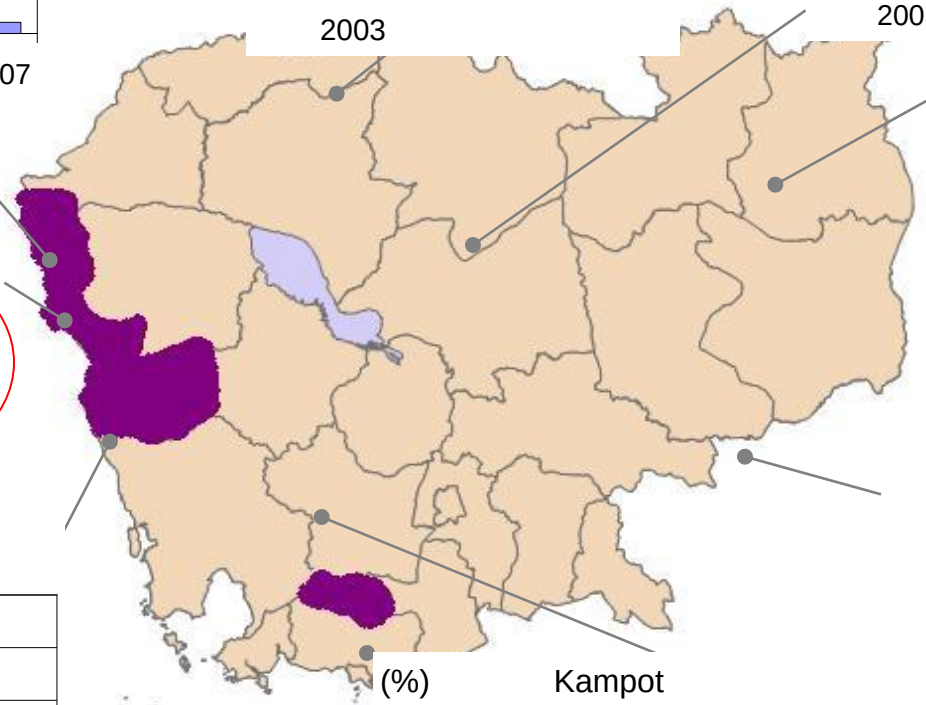


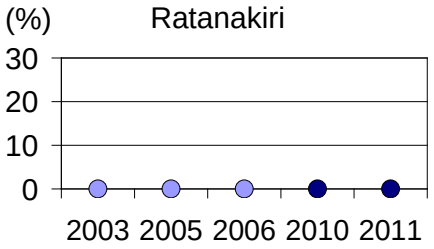
ACT treatment failures, Cambodia (2001–2011)

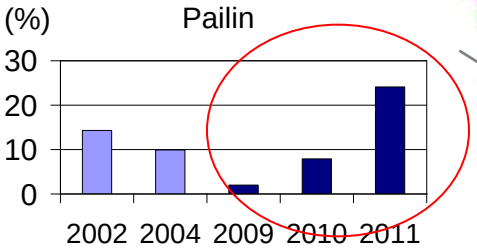


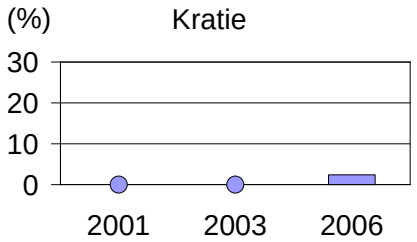


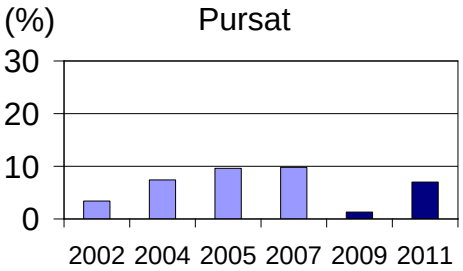


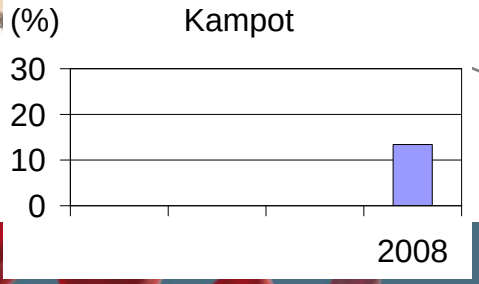


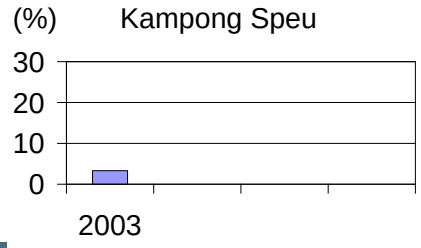












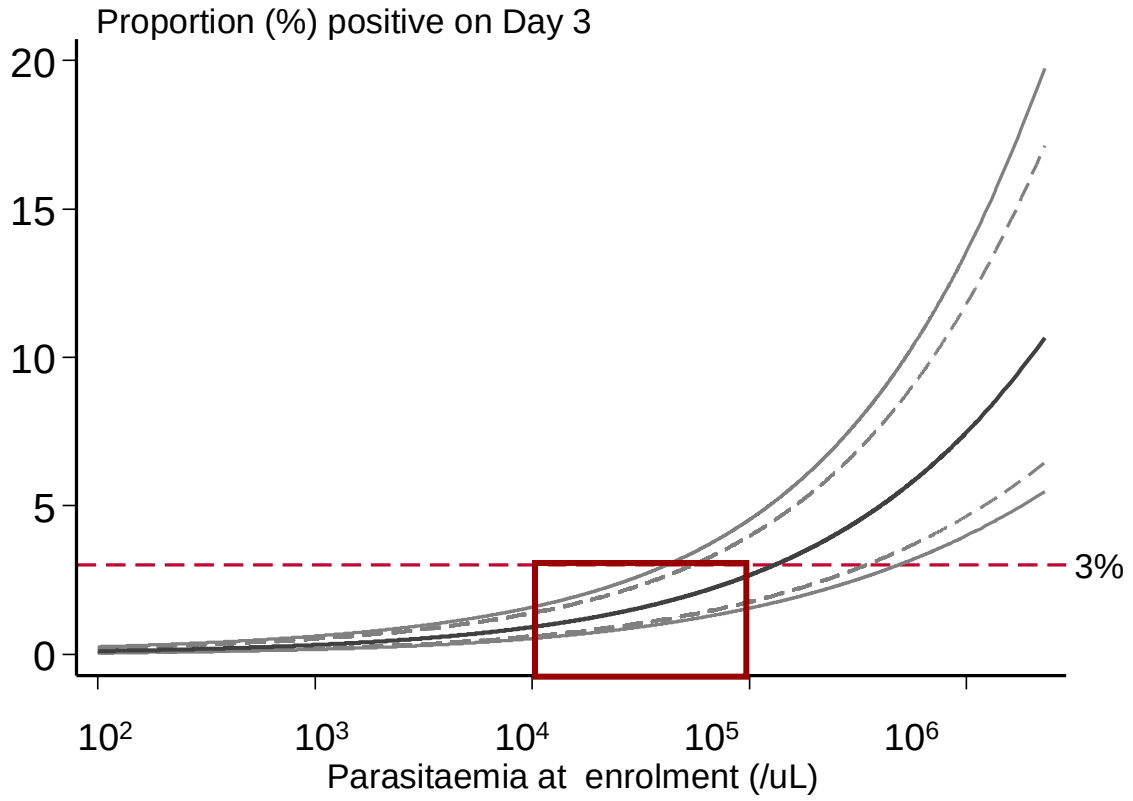
Artemether-lumefantrine
Artesunate-mefloquine
Dihydroartemisinin-piperaquine

artemisinin resistance containment project zone 1

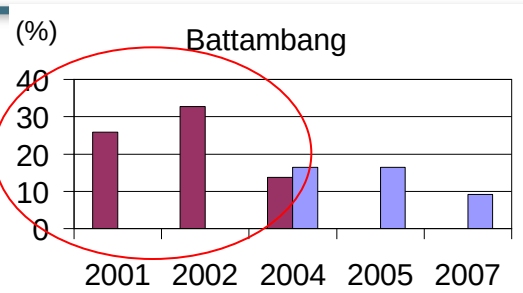
Relation between Day 3 positivity rate and initial parasitemia

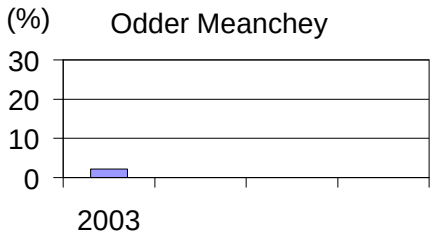
Stepniewska K, J Infect Dis 2010

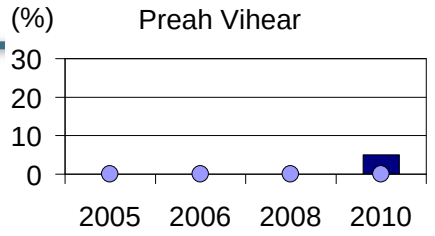
Parasite clearance data from 18,699 falciparum malaria patients with fully artemisinin sensitive parasites, treated with an artemisinin derivative

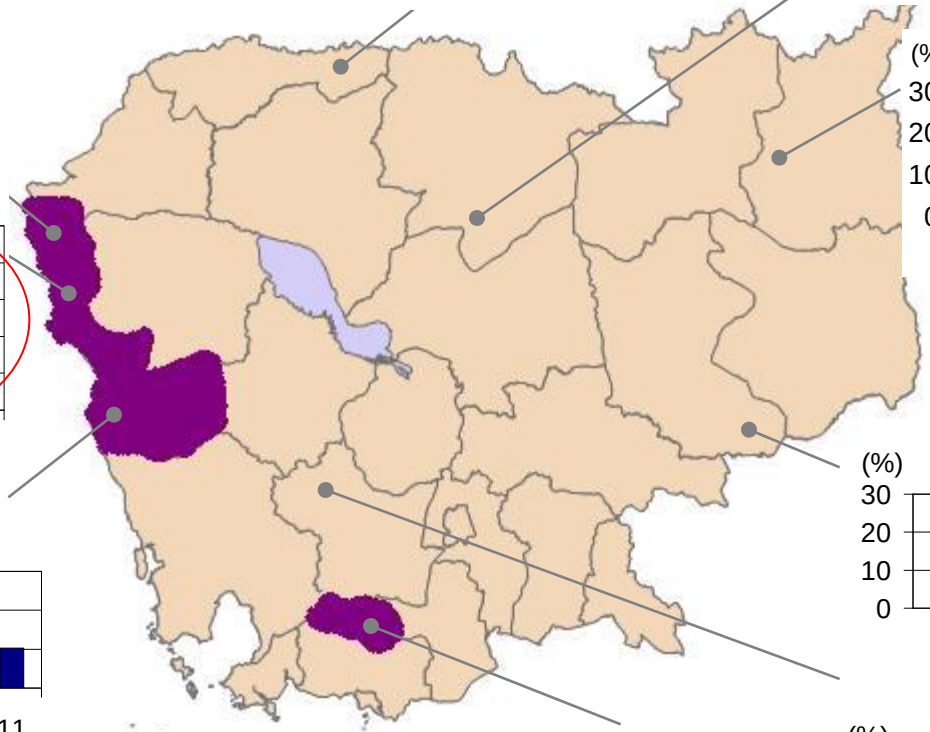


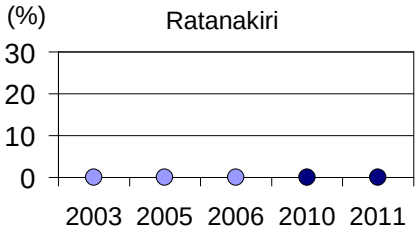
Day 3 positivity rate after ACT treatment, Cambodia (2001–2011)

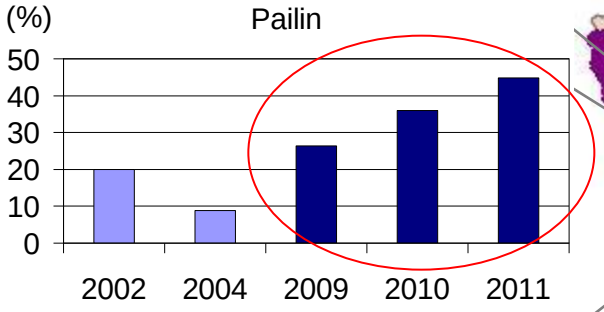


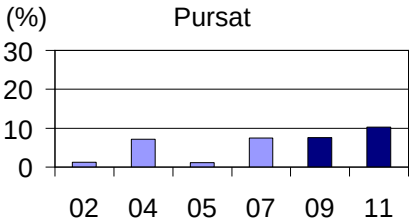


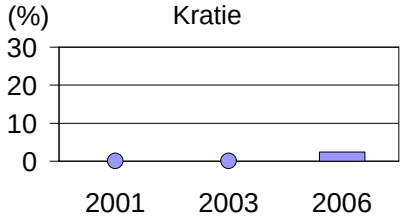


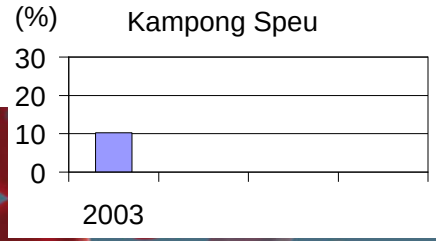


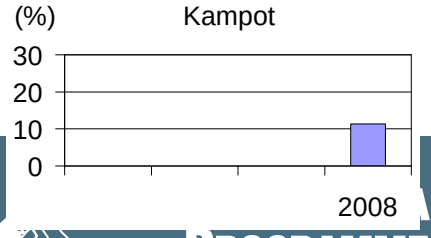












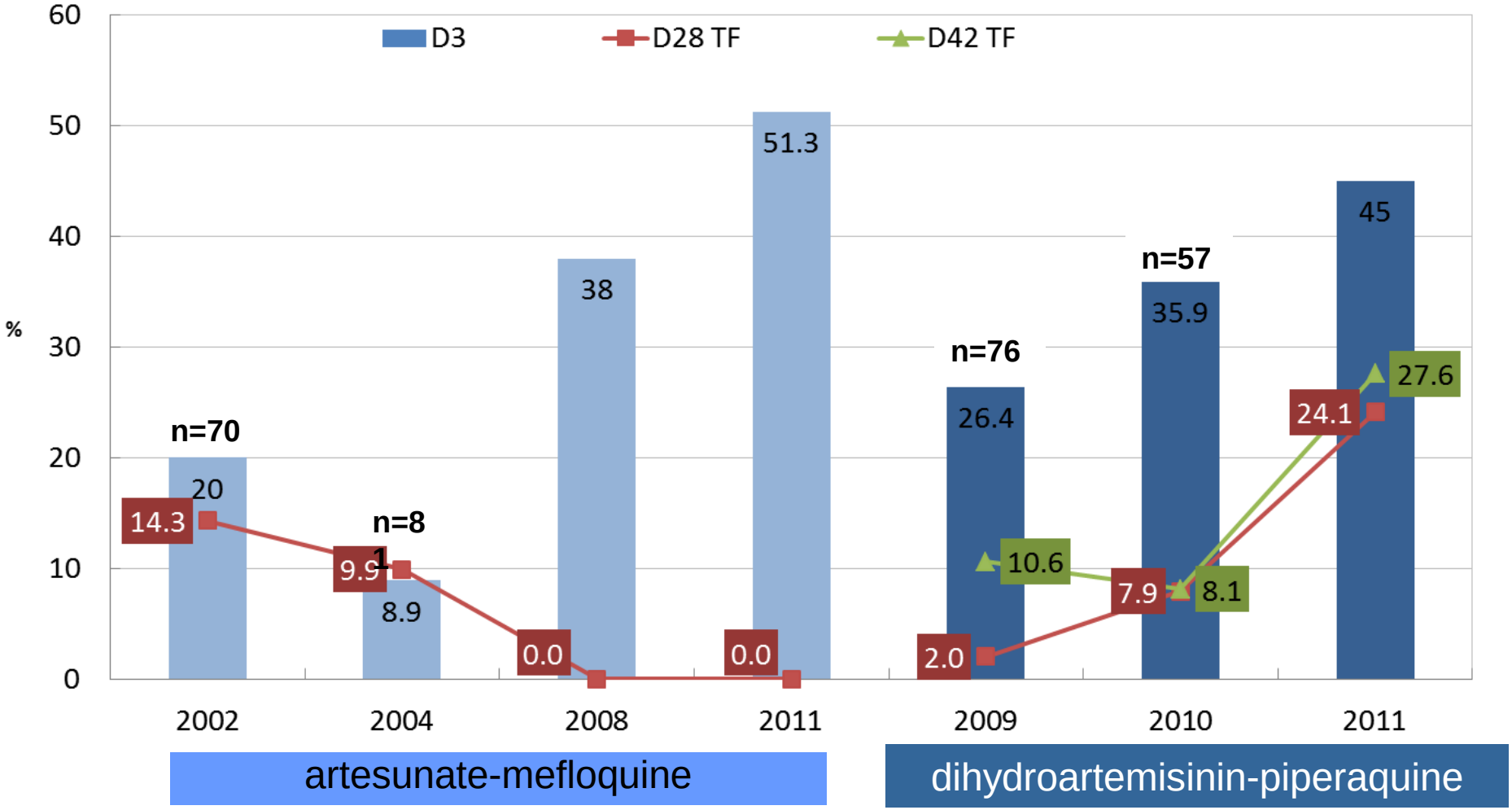
Artemether-lumefantrine
Artesunate-mefloquine
Dihydroartemisinin-piperaquine

artemisinin resistance containment project zone 1

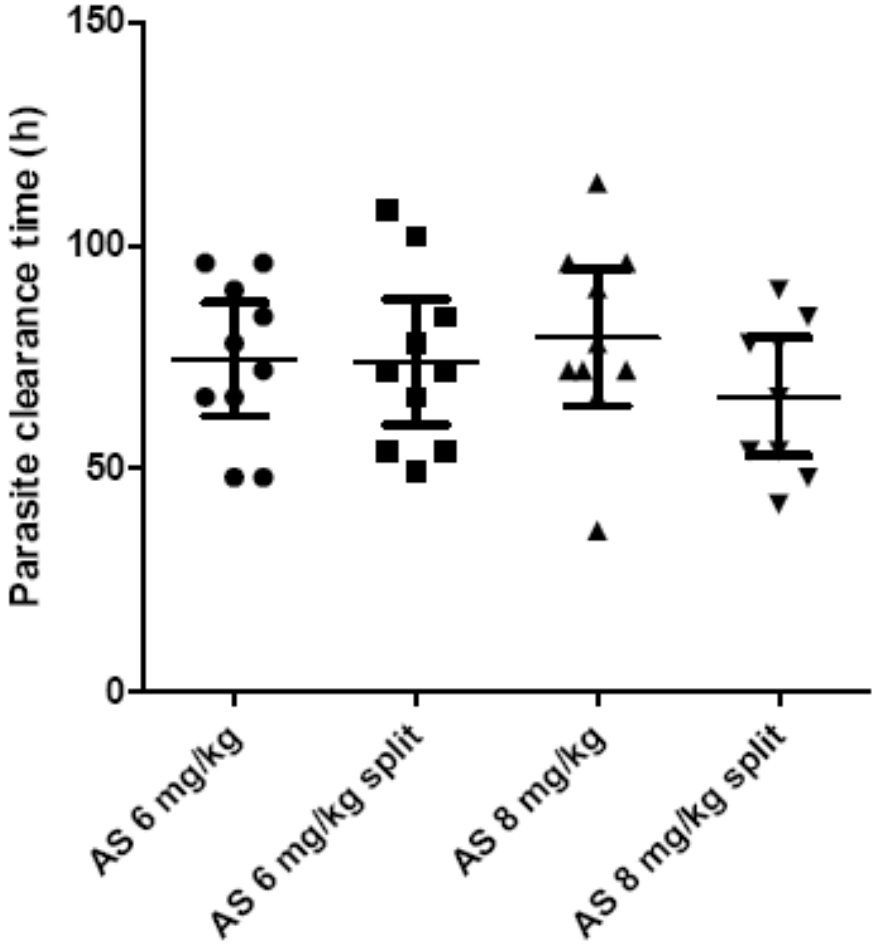
Organization

PROGRAMME

ACT efficacy in Pailin, Cambodia (2002-2011)



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



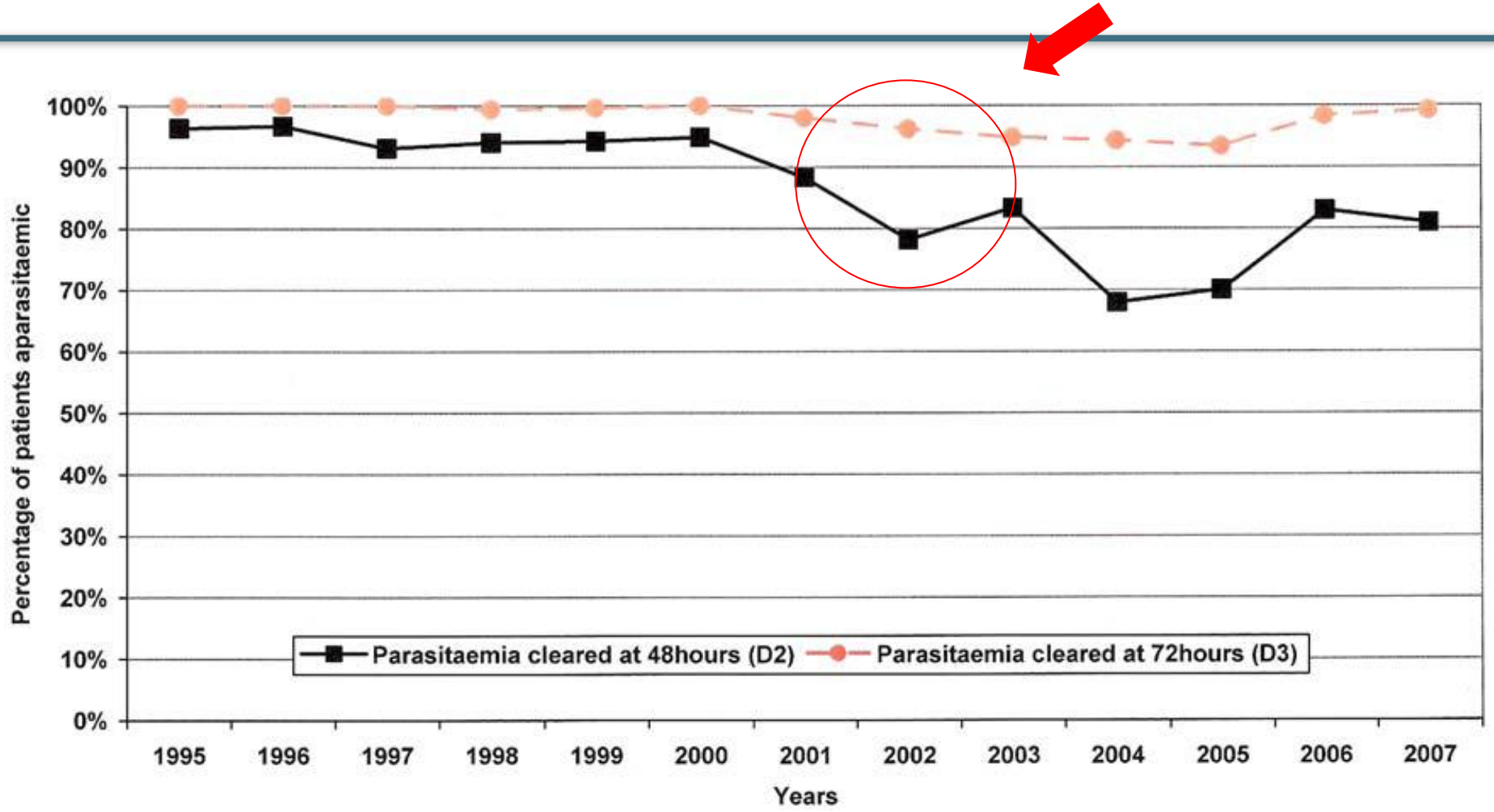
N=40

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

Parasite clearance with AS+MQ in Mae Sot



Carrara, PLoS One, 2009

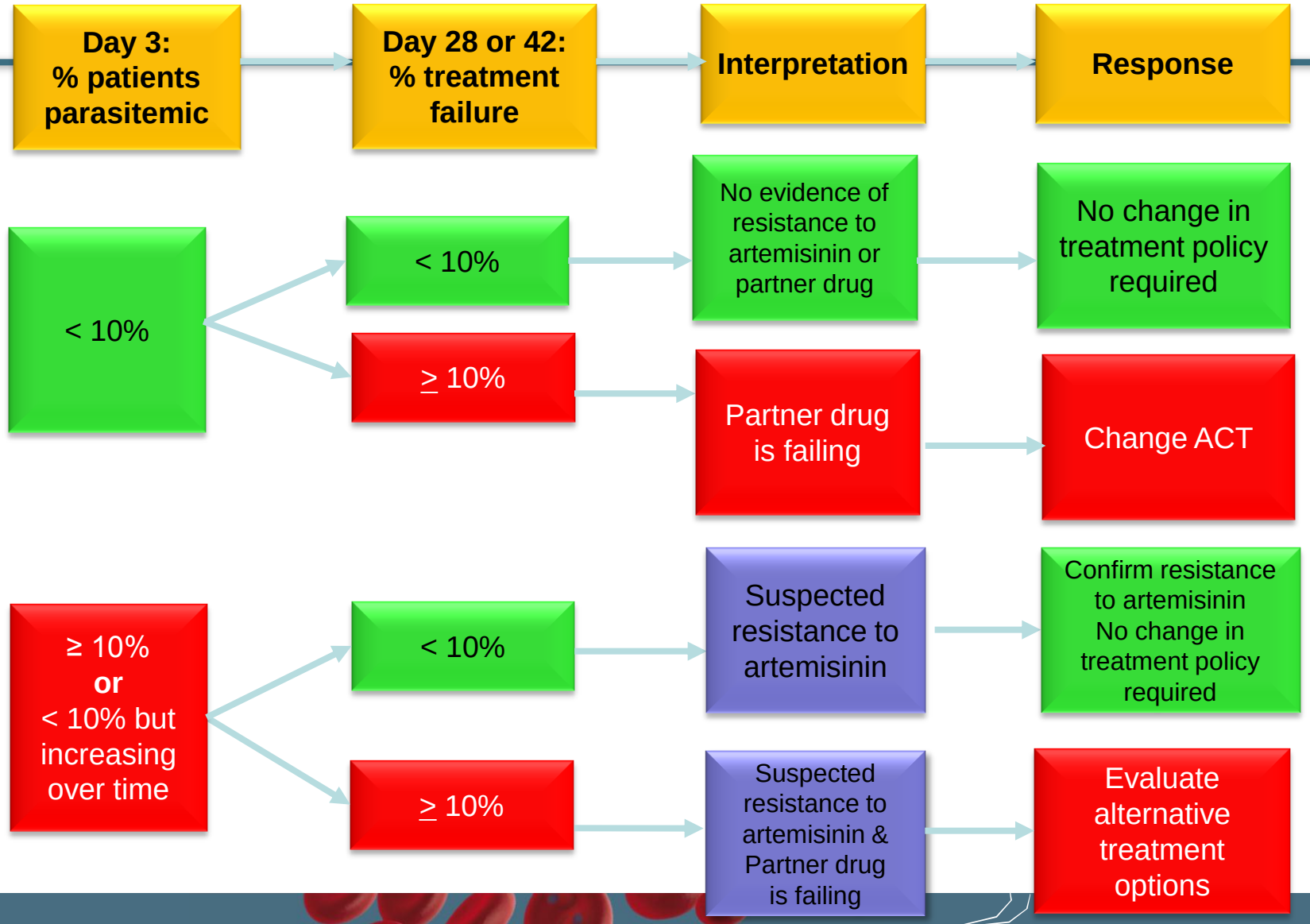
Definition of artemisinin resistance

- 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)

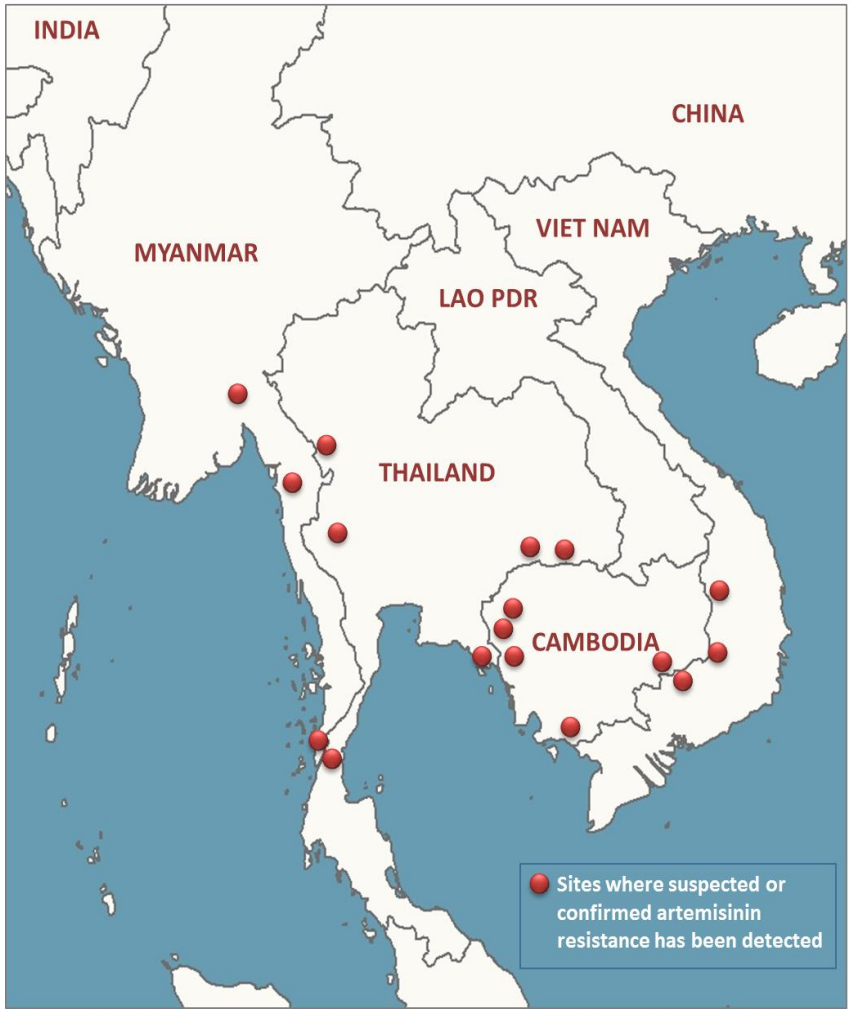
Limits of current definitions

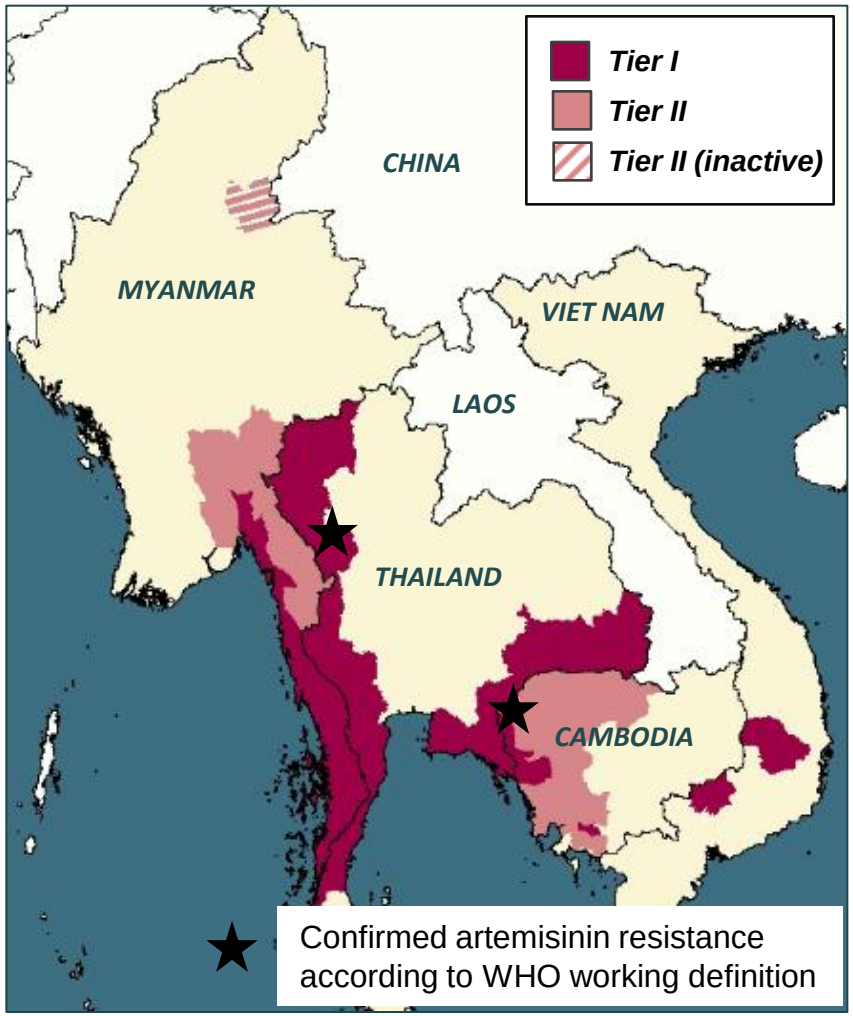
- The parasite clearance time is prone to be affected by several confounding factors (known and unknown) such as splenectomy, haemoglobin abnormalities and reduced immunity.
- The proportion of patients who are parasitaemic after 3 days of treatment is a suitable though imperfect tool to detect suspected 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

Evaluation of therapeutic efficacy study results



Artemisinin resistance containment areas





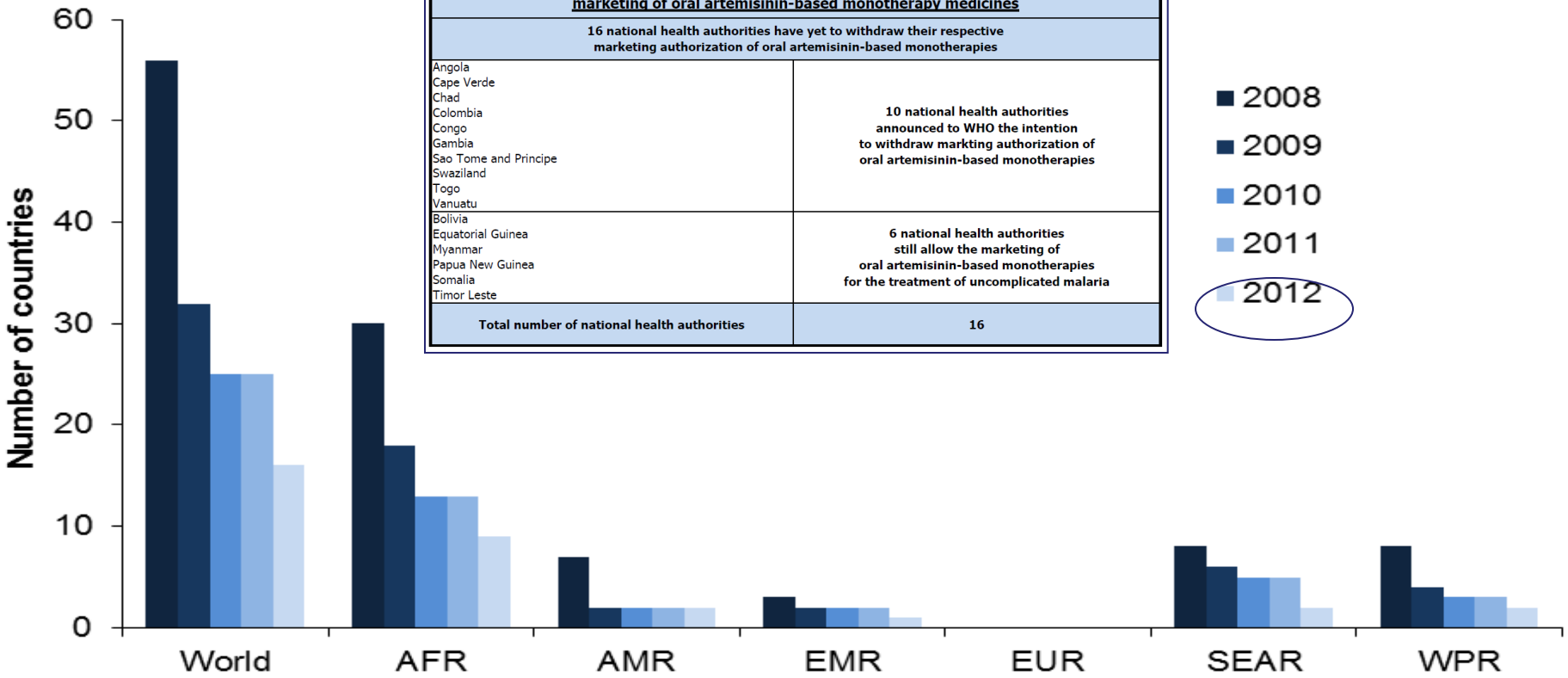
GPARC recommended action by tier

Tier III	*Tier II*	*Tier I*
Good Control	Intensified and accelerated control	Intensified and accelerated control to universal coverage
More routine monitoring	Intensified monitoring, especially around foci	Intensified monitoring, especially around foci
Eliminate mono-therapies and poor-quality drugs	Actively eliminate mono-therapies and poor-quality drugs	Aggressively eliminate monotherapies and poor-quality drugs
	Lower transmission; focus on mobile and migrant populations	Lower transmission; focus on mobile and migrant populations
		Consider ACD, MSAT, FSAT or MDA

Oral artemisinin-based monotherapies

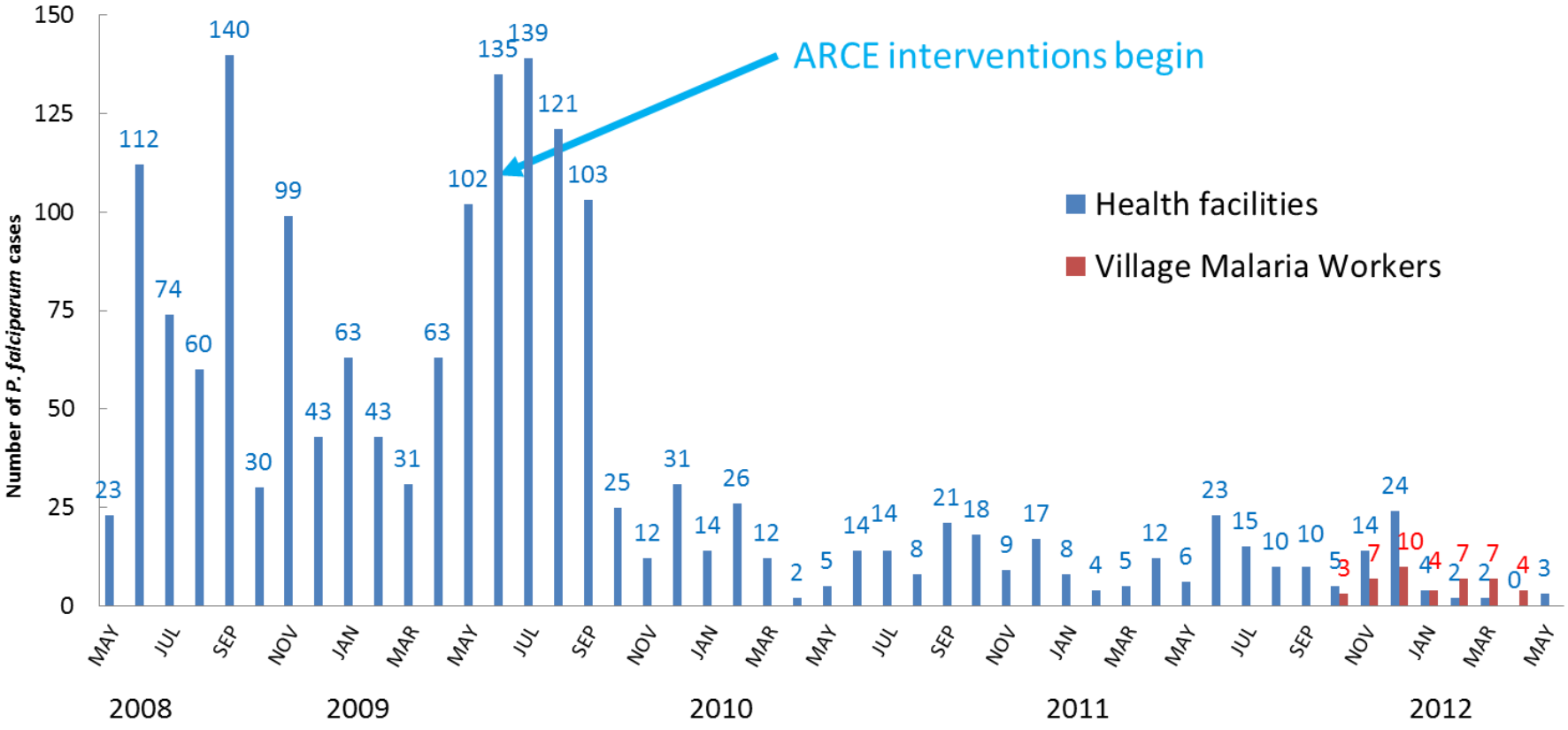
Figure 6.15 Number of countries allowing marketing of oral artemisinin-based monotherapies by WHO Region, 2008-2012

National health authorities which still allow marketing of oral artemisinin-based monotherapy medicines	
16 national health authorities have yet to withdraw their respective marketing authorization of oral artemisinin-based monotherapies	
Angola Cape Verde Chad Colombia Congo Gambia Sao Tome and Principe Swaziland Togo Vanuatu	10 national health authorities announced to WHO the intention to withdraw markting authorization of oral artemisinin-based monotherapies
Bolivia Equatorial Guinea Myanmar Papua New Guinea Somalia Timor Leste	6 national health authorities still allow the marketing of oral artemisinin-based monotherapies for the treatment of uncomplicated malaria
Total number of national health authorities	16



Cases diagnosed in Pailin province

Number of *P. falciparum* cases diagnosed by microscopy and RDT at health facilities in Pailin province, Cambodia, May 2008 – May 2012



Consequences of artemisinin resistance

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

Thank you
for your attention

World Health Organization

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