Best Science for the Most Neglected

DNDi's
3rd Partners' Meeting
in collaboration with ICMR

New Delhi, India,
December 3, 2010

Indian Council of Medical Research

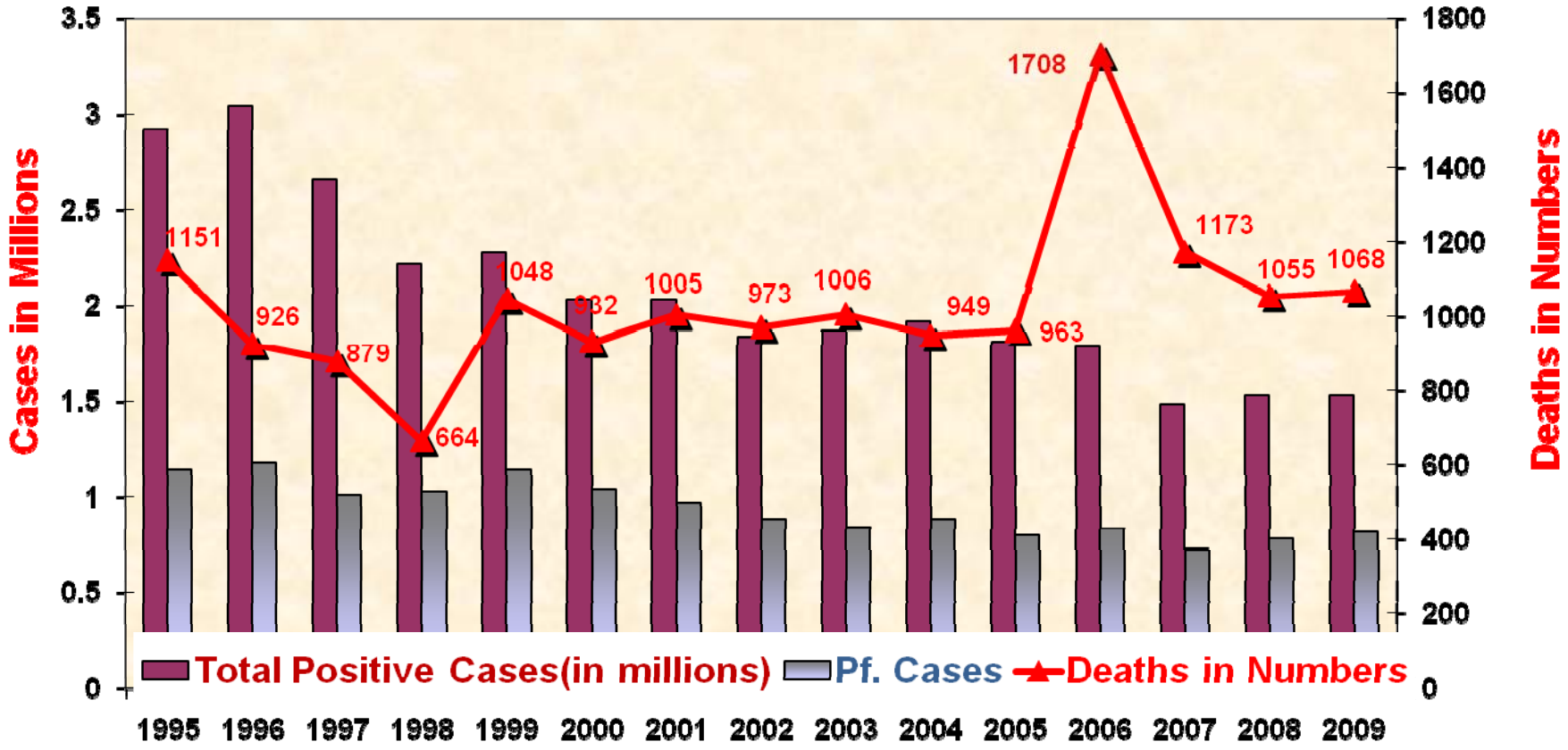
From patient needs to implementation of new treatments

Fixed Dose ACTs for Malaria in India

Dr Neena Valecha
National Institute of Malaria Research

DNDi Drugs for Neglected Diseases initiative

Reported Malaria Cases & Deaths in India (1995-2009)



Source: NVBDCP

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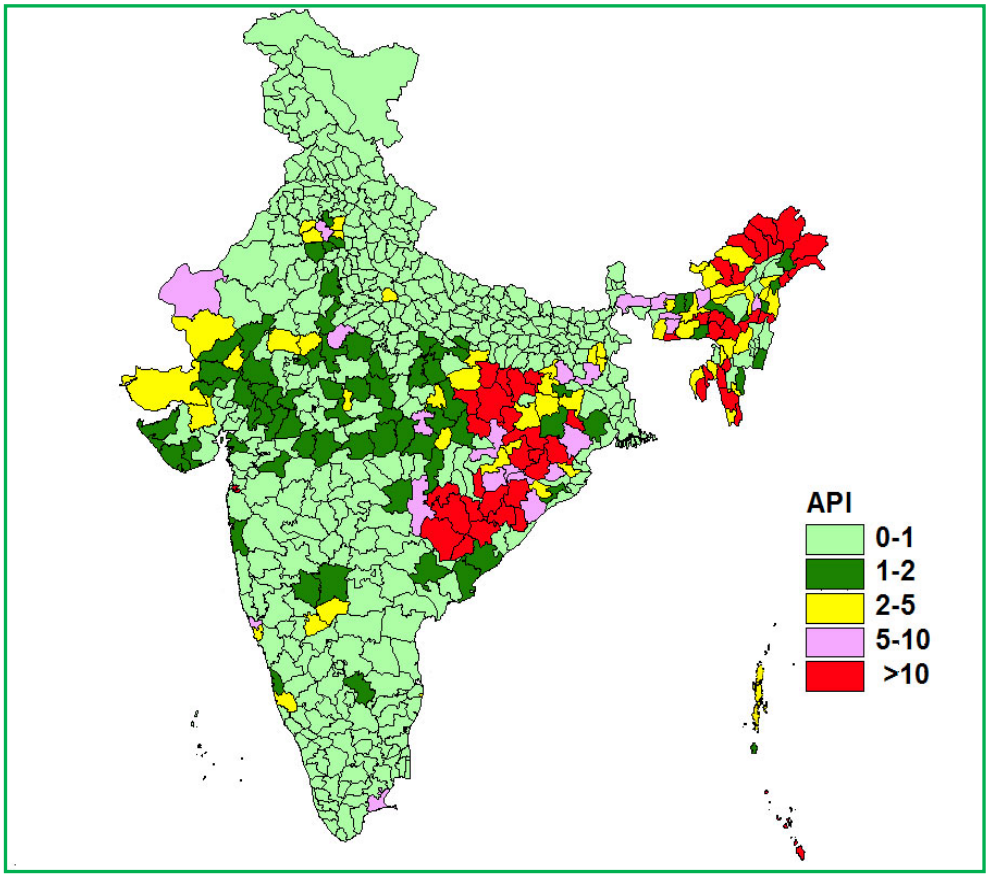
Malaria Endemic Areas



Percentage Contribution of Population, Malaria Cases, Pf Cases and Deaths in 2009 (Compared to the country total)				
States	% Population	% Malaria cases	% Pf cases	% Death
N.E. States	4	13	17	46
Other high endemic states*	42	67	77	43
Other	54	20	6	11

*Andhra, Chhattisgarh, Gujarat, Jharkhand, MP, Maharashtra, Orissa, Rajasthan

Source: NVBDCP

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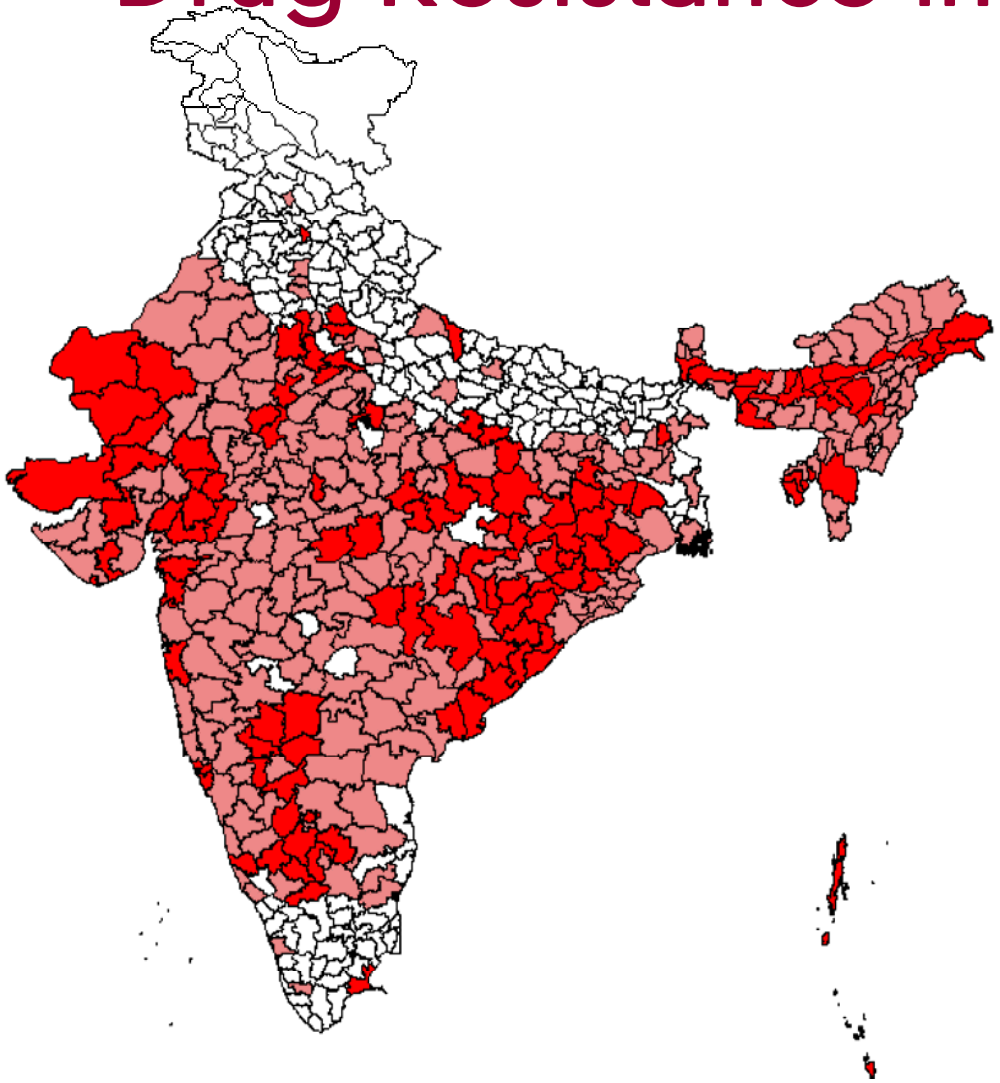
Drug Resistance in India



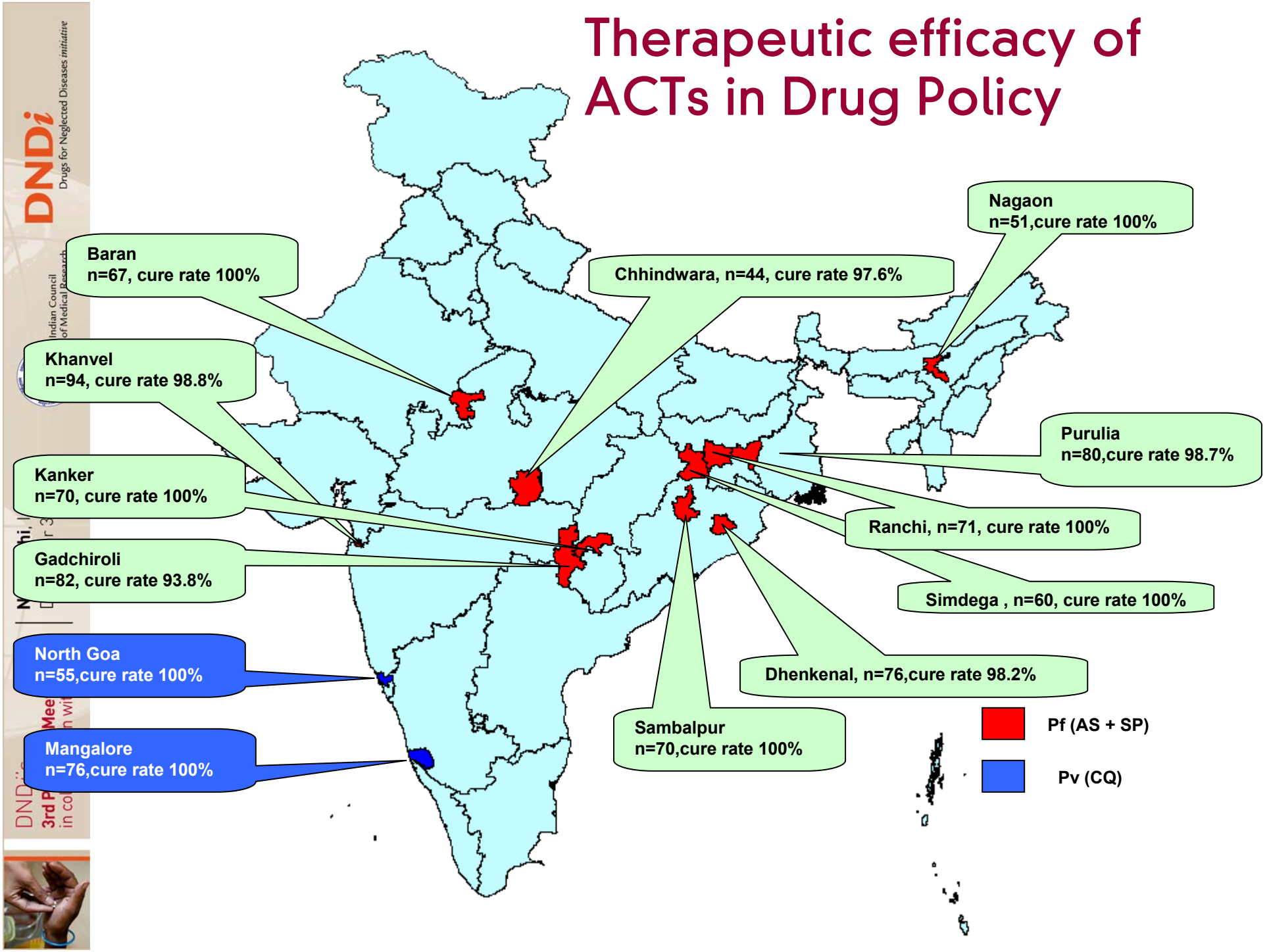
Districts with CQ treatment failure ≥10% (red) in any trial between 1978 and 2007 and Pf endemic areas (pink)

Lancet Infectious Diseases 2010 in Press

Evolution of ACTs in India

- **1973**
  - First evidence of CQ resistance
- **1982**
  - Drug policy drafted for the first time, Presumptive therapy CQ: (600 mg)
  - PQ RT (5d), SP introduced in resistant Pf areas
- **1995**
  - Presumptive treatment with full dose of Chloroquine
- **1997**
  - Registration of artemisinin derivatives
- **2001**
  - Introduction of αβ arteether for severe malaria in programme
- **2007**
  - No more presumptive treatment, PQ for 14 days
  - ACT (AS+SP) introduced in India in NER and clusters with >10% resistant Pf districts
- **2008**
  - Trials of AS+AQ, AS+MQ, Artekin, Pyramax accomplished
  - AS+SP extended to 117 districts
- **2009**
  - Registration of AS+AQ
  - Ban on Artemisinin monotherapy
- **2010**
  - ACT extended to Pf cases all over India
- **2011**
  - Registration of AS+MQ FDC ?

Therapeutic efficacy of ACTs in Drug Policy



Do we Need New ACTs/Antimalarials?

With effective ACT's, Insecticides being available and vaccine in phase III stage, do we need new medicines?

- Fixed dose ACTs are superior to blister packs
- Emergence of drug resistance is inevitable. Range of medicines with varying mechanisms needed to stem the tide of resistance.
- Safe medicines to tailor needs of vulnerable groups like pregnant mother and children.
- Safe medicine for relapsing malaria.
- For goal of eradication transmission blocking medicines are required

Need of partnerships

- Access to patients
- Treatment facilities
- Government approvals
- Funds
- Basic research to reach the level of clinical trials

DNDi
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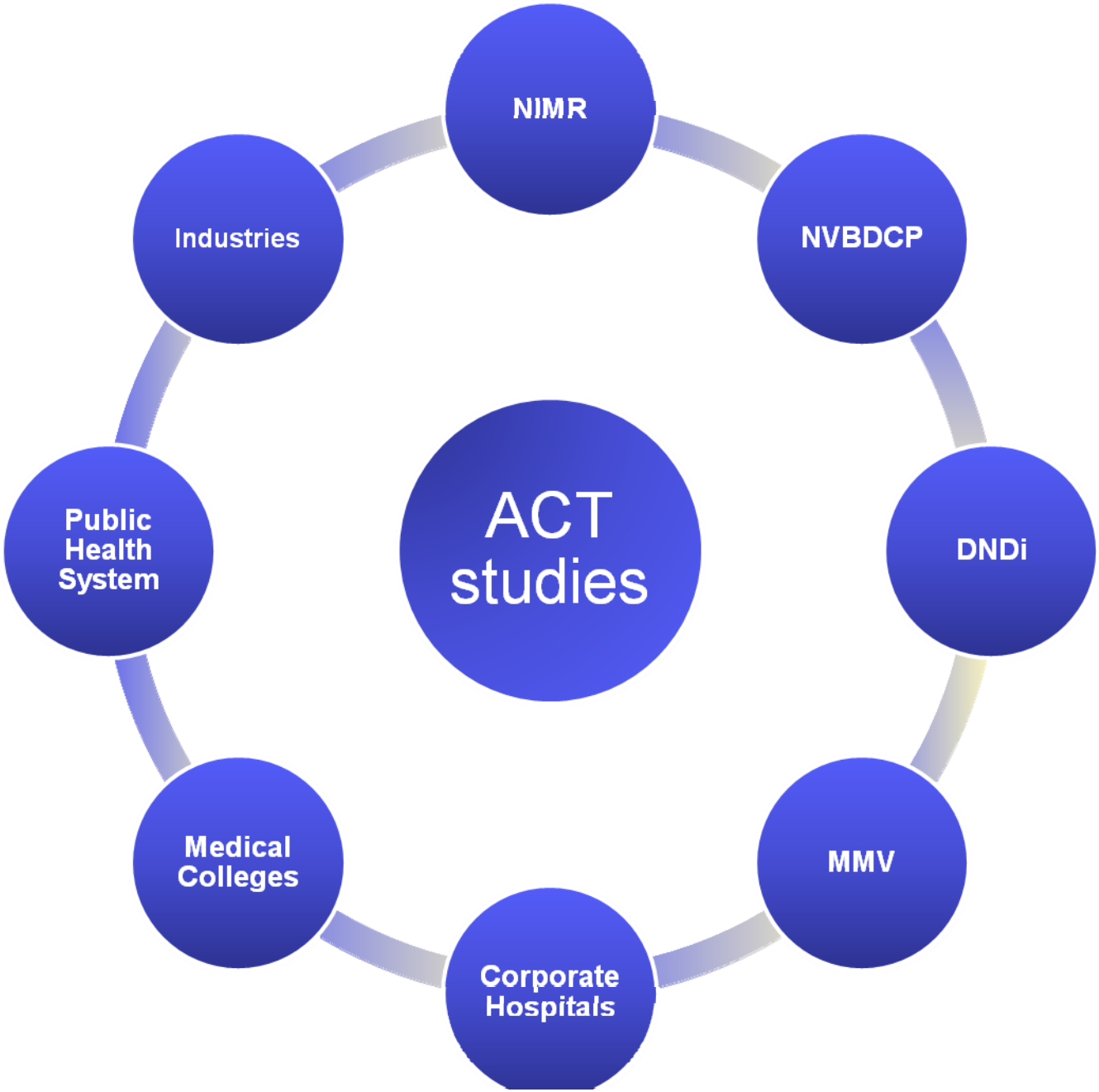
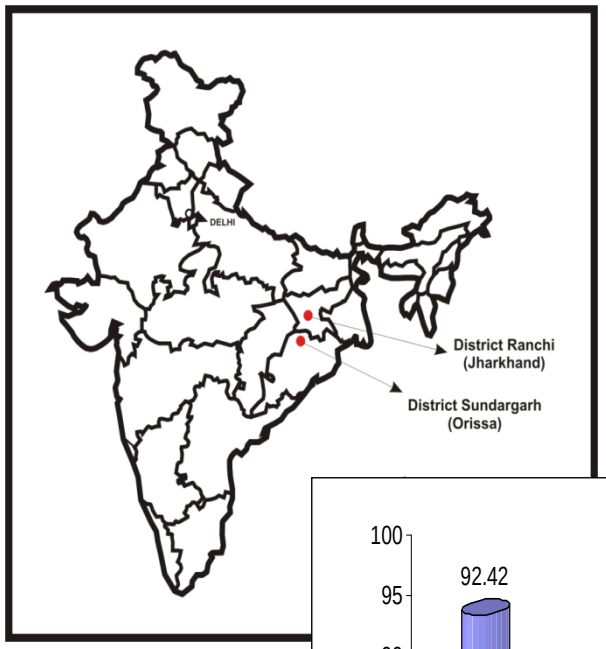
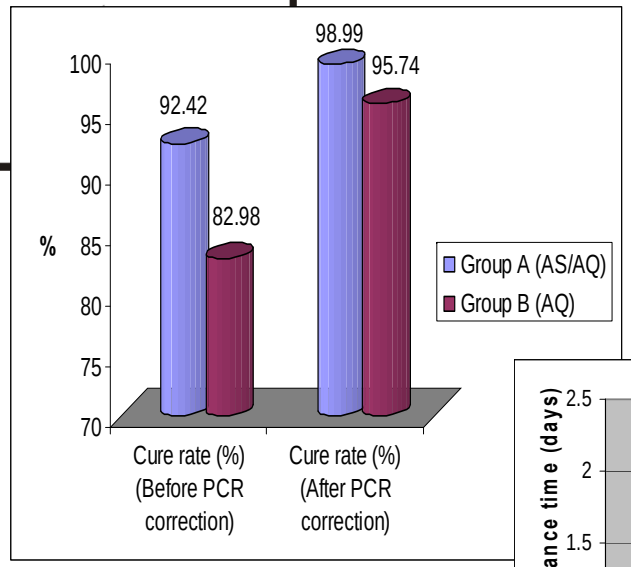
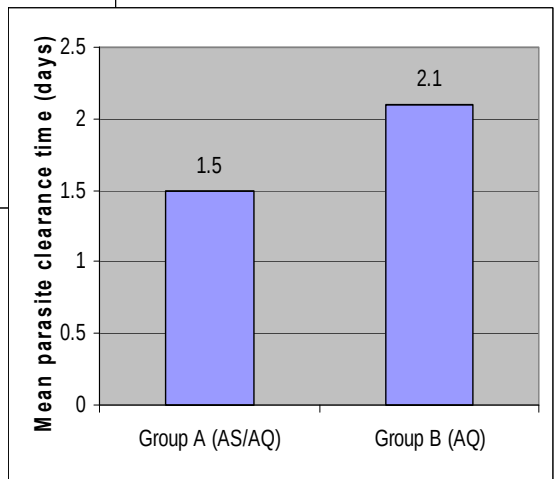
Partners for ACT studies



Partnership with DNDi for ASAQ

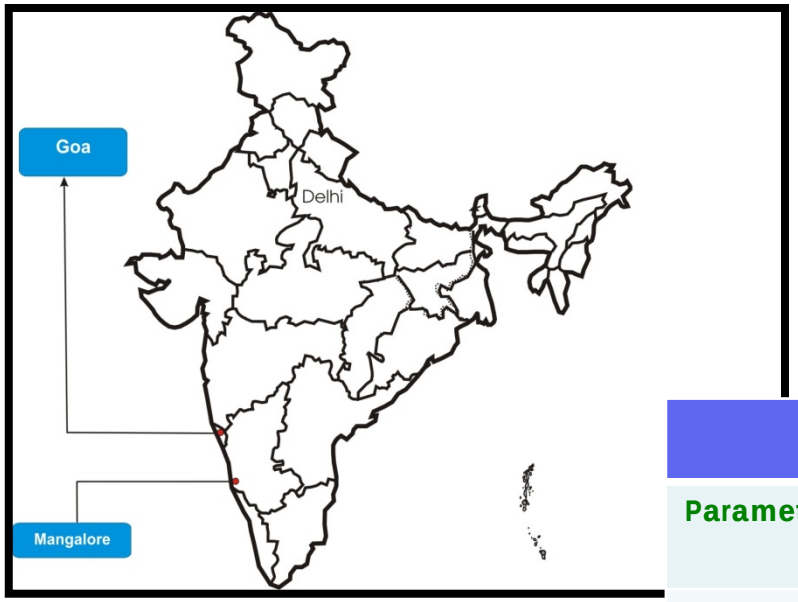






- ASAQ registered in 30 African countries
- 70 million doses distributed
- Phase III trials in India
- Registration with regulatory authority in 2009

Partnership with DNDi for ASMQ



63 Day Cure rate	
Parameter	n (%)
No. of patients with ACPR	65 (98.48)
Cure rate (%)	98.48
95% CI of cure rate	91.8, 100.0

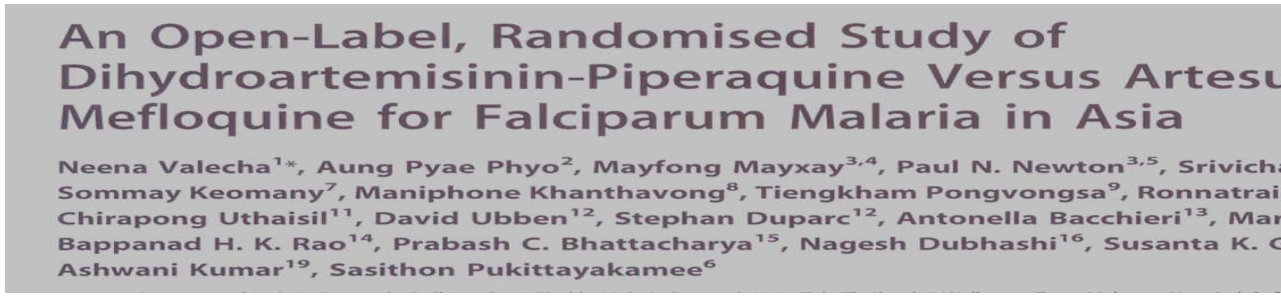
PCR corrected 63 Day Cure rate	
Parameter	n (%)
No. of patient available for PCR genotyping	1 (1.5)
No. of patients with new infection	1 (1.5)
No. of patients classified as cured after PCR genotyping	66 (100%)
95% CI of cure rate	94.6, 100.0

Partnerships with

MMV Medicines for Malaria Venture

- Development of FDC's
  Eurartesim
  Pyramax for Pf and Pv

- Packaging for Pyramax
- Plans for implementation research
- Representation in technical committees


An Open-Label, Randomised Study of Dihydroartemisinin-Piperaquine Versus Artesunate-Mefloquine for Falciparum Malaria in Asia

Neena Valecha[1*], Aung Pyae Phyo[2], Mayfong Mayxay[3,4], Paul N. Newton[3,5], Srivicha Krudsood[6], Sommay Keomany[7], Maniphone Khanthavong[8], Tiengkham Pongvongsa[9], Ronnatrai Ruangveerayuth[10], Chirapong Uthaisil[11], David Ubben[12], Stephan Duparc[12], Antonella Bacchieri[13], Marco Corsi[13], Bappanad H. K. Rao[14], Prabash C. Bhattacharya[15], Nagesh Dubhashi[16], Susanta K. Ghosh[17], Vas Dev[18], Ashwani Kumar[19], Sasithon Pukittayakamee[6]

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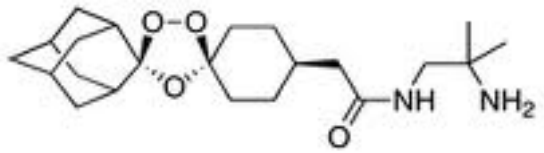
Partnership with Industry: Ranbaxy

Arterolane (150mg) and Piperaquine (750mg) New Oral combination for uncomplicated *P. falciparum* malaria, affordable with OD dosing for 3 days



Arterolane: Synthetic trioxolane

- No supply constraint
- Rapid clearance of parasitemia

- Piperaquine :
  - Proven effective, safe long-acting anti-malarial
  - Synthetic and long shelf-life with arterolane
- Combination:
  - In a study with 240 patients, safety and efficacy was established similar to Coartem®
- Adult formulation: FDC tablets (phase III ongoing ~300 pts in India, Bangladesh & Thailand, initiation in west Africa)
- Pediatric formulation: Dispersible FDC tablets (Phase II)

Arterolane, a New Synthetic Trioxolane for Treatment of Uncomplicated *Plasmodium falciparum* Malaria: A Phase II, Multicenter, Randomized, Dose-Finding Clinical Trial **Valecha et al *Clin Infect Dis* 2010 *51*: 684-691**

Clinical Trials for Efficacy of New ACTs

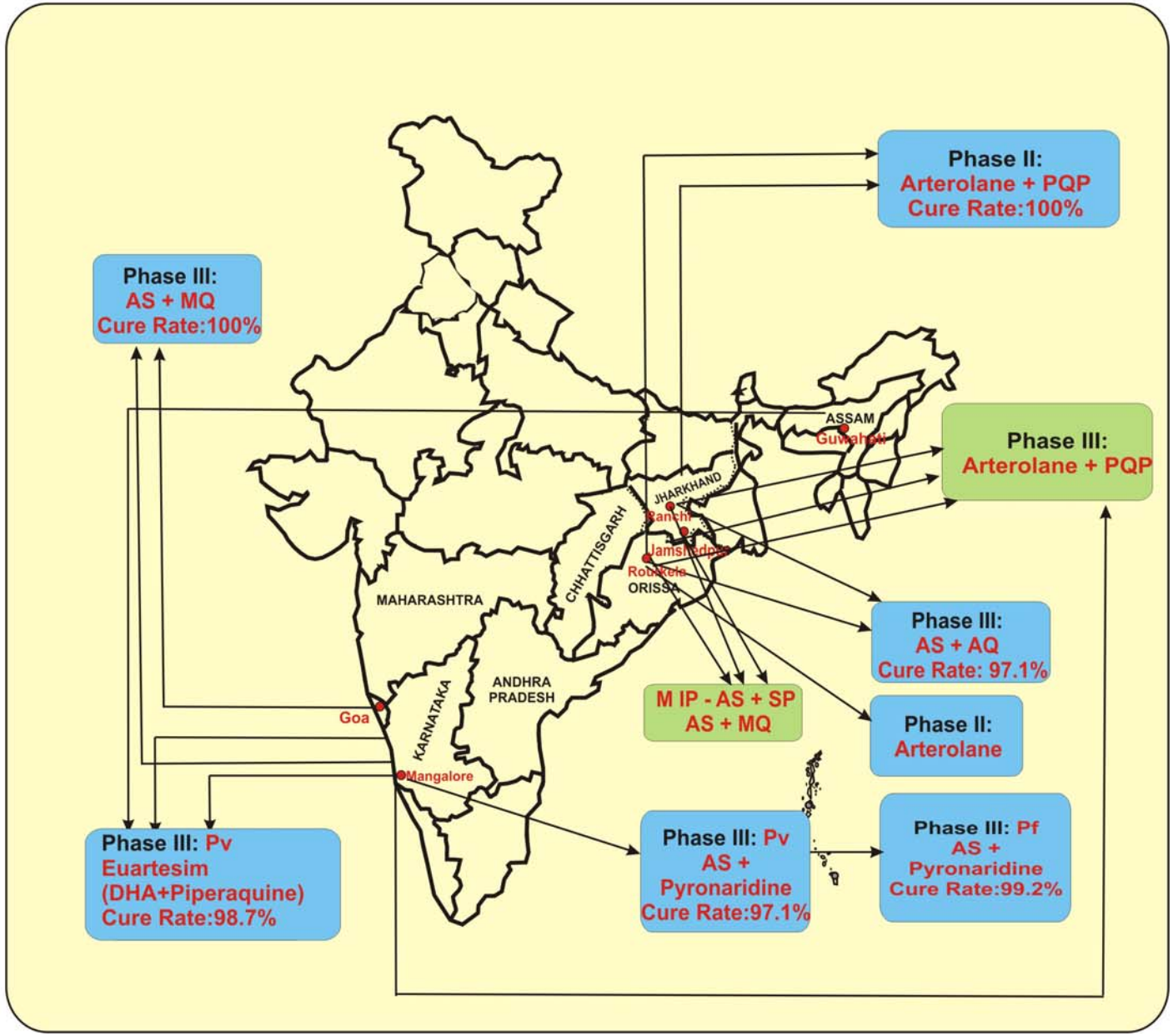
- Trials with fixed dose ACTs & new drugs
- Teams have been trained For GCP – ICH

Linkages

- Ispat General Hospital Rourkela
- Community Welfare Society Rourkela
- Kasturba Medical Hospital Mangalore
- Maha Devi Birla Hospital Ranchi
- Goa Medical College Goa
- Civil Hospital Maihar
- TATA Main Hospital Jamshedpur

Collaborators / Sponsors

- MMV
- DBT
- IISc, Bangalore
- Ranbaxy
- DNDi
- Sigma Tau
- Shing Poong



Partnership for Access / Implementation

- Collaborative process with Input from Govt./Stakeholders
- Work with manufacturer on no profit/no loss structure
- Focus on lowering price outside profit /competition motive and by technology transfer
- Farmanguinhos in Brazil, Cipla in Asia, Sanofi Aventis in Africa
- Advocacy to improve representation of products, pharmacovigilance

Next Steps and Challenges for New Tools

- Variable epidemiology
- Common protocols may not be acceptable
- Delay in approvals
- Restriction in material / data sharing

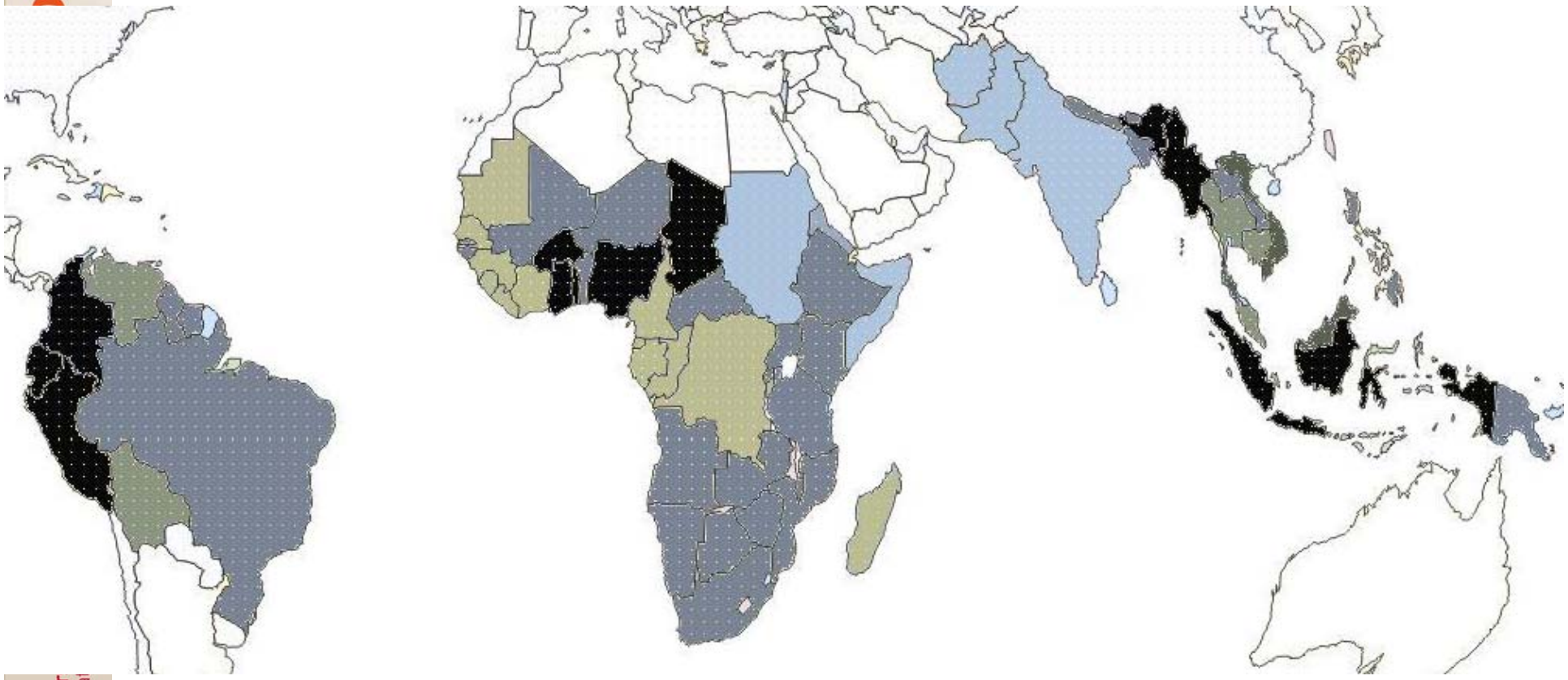
Key Strengths and Weaknesses of the Major In-Phase III and Available ACTs

Drug	Key Strengths	Key Weaknesses
Artesunate-Sulphadoxine+ Pyrethemine	•Effective •Safe	• Blister Pack • Pediatric formulation not available • Not effective in *P vivax* • Resistance to SP can compromise efficacy • ? Post Treatment Prophylaxis
Artemether-lumefantrine	•WHO prequalified •Stringently approved •Market leader •Comprehensive safety data •Pediatric formulation with a sweet taste •First-line therapy in many countries	•Twice daily admn. •Bioavailability variable •Half-life shorter than the other ACTs •Some reports of resistant strains
Amodiaquine-artesunate	•WHO prequalified •Pediatric tablets available	•Resistance to amodiaquine can compromise efficacy • GI side effects •No approval by stringent regulatory authority
Artesunate-mefloquine	•Satisfactory safety record •Effective in *P. vivax* malaria in chloroquine-resistant areas •Long half-life	•Psychiatric and GI adverse events •No approval by stringent regulatory authority •No prequalification by WHO •No pediatric formulation •High cost
Dihydroartemisinin-piperaquine	•Long Half life •Extensive safety data	•WHO prequalified •Pediatric formulation in development

Key Strengths and Weaknesses of the Major In-Phase III and Available ACTs

Drug	Key Strengths	Key Weaknesses
Pyronaridine-artesunate	•Clinical data and registration also for *P. vivax* malaria •Long half-life of pyronaridine	•Safety data limited to the current clinical trial data •Pediatric formulation (sachet) still in development
Naphthoquine-artemisinin	•Single administration of 400mg maphythoquine and 1000mg artemisinin •Published activity based on a number of small investigator-led studies	•No ICH clinical study, or large phase III study •Little information on the safety •Not submitted to a stringent regulatory
Arterolane maleate-piperaquine phosphate (Arterolane)	•Arterolane is free from concerns of embryotoxicity associated with artemisinin derivatives •Synthetic and therefore free from the variabilities of price from agriculturally derived material •Might be active against artemisinin-resistant strains •Dispersable paediatric tab available	•Concerns about efficacy, based on relatively poor activity as monotherapy in Phase IIa study. •In clinical Phase III. Indian launch expected in 2011.

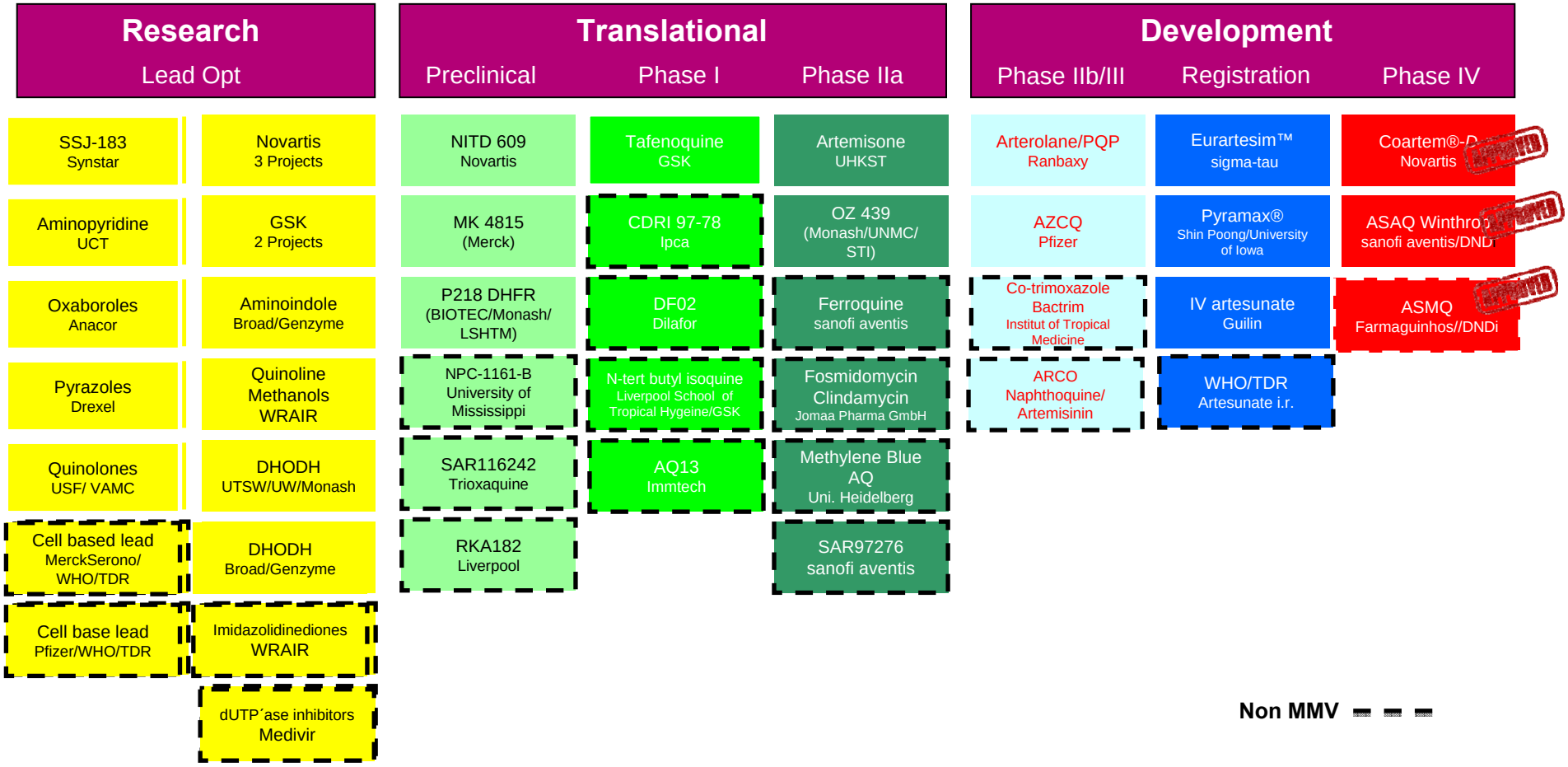
Country First line treatment for *P. falciparum*



A-L
ASAQ
ASMQ
Multiple 1st Line
AS-SP (co-blistered)

World Malaria Report 2009

Global Malaria Portfolio, Q3 2010



Source: MMV

Thank You