

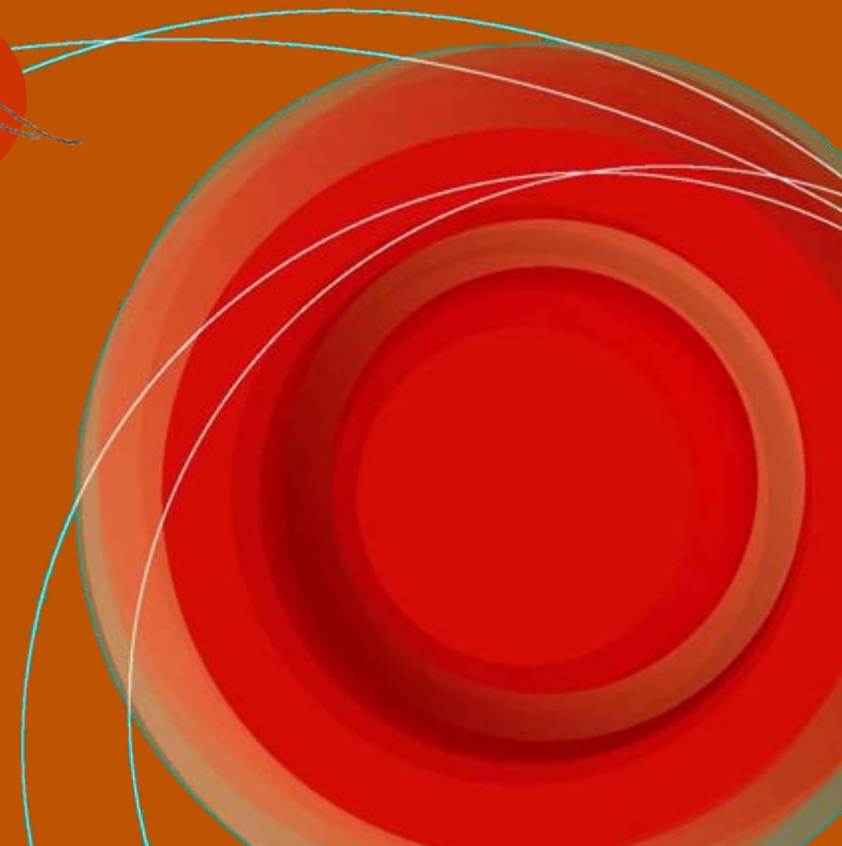
Gaps and challenges for paediatric antimalarial medicines

UNICEF Supplier Meeting
21 October 2008, Copenhagen, Denmark

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Global Malaria Programme



**World Health
Organization**



Outline

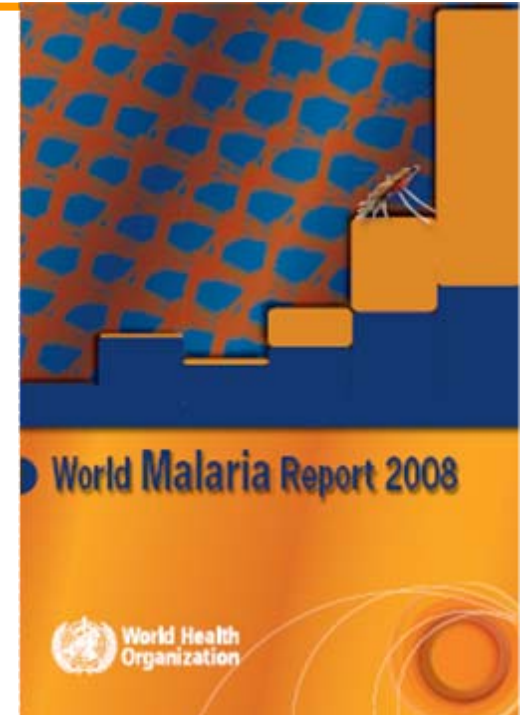
- Burden of disease
- Market situation, funding
- Requirements for children medicines
- Prequalification
- Monotherapy

Why paediatric antimalarial medicines?

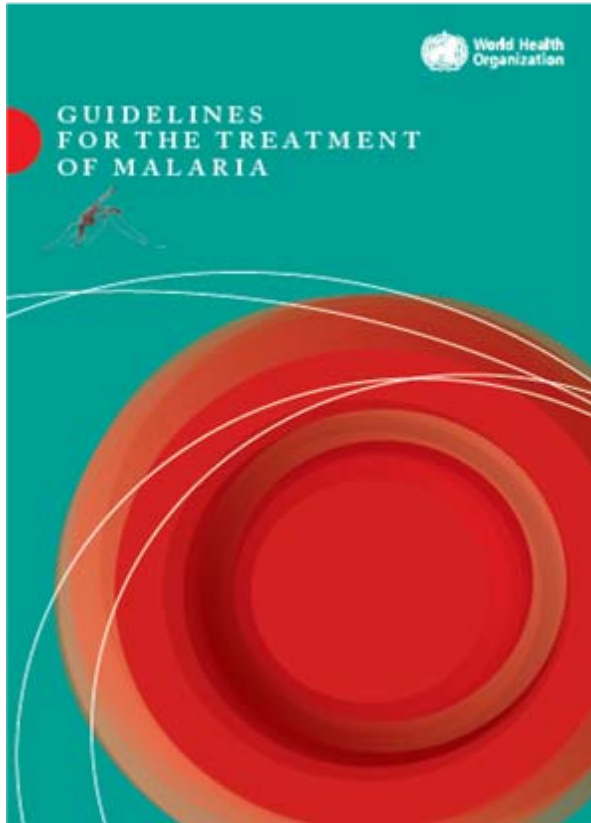
World Malaria Report 2008: Burden of disease

- 247 million malaria cases (2006)
86 % in the African region
- 881.000 malaria deaths (2006)
91 % in Africa
85 % among children under 5 years
- Use of antimalarial medicine not only in confirmed malaria cases, but also for **fever cases** (up to **600 million** fever cases in < 5)

➔ Major need for antimalarial medicines for children



WHO Guidelines for the Treatment of Malaria (2006)

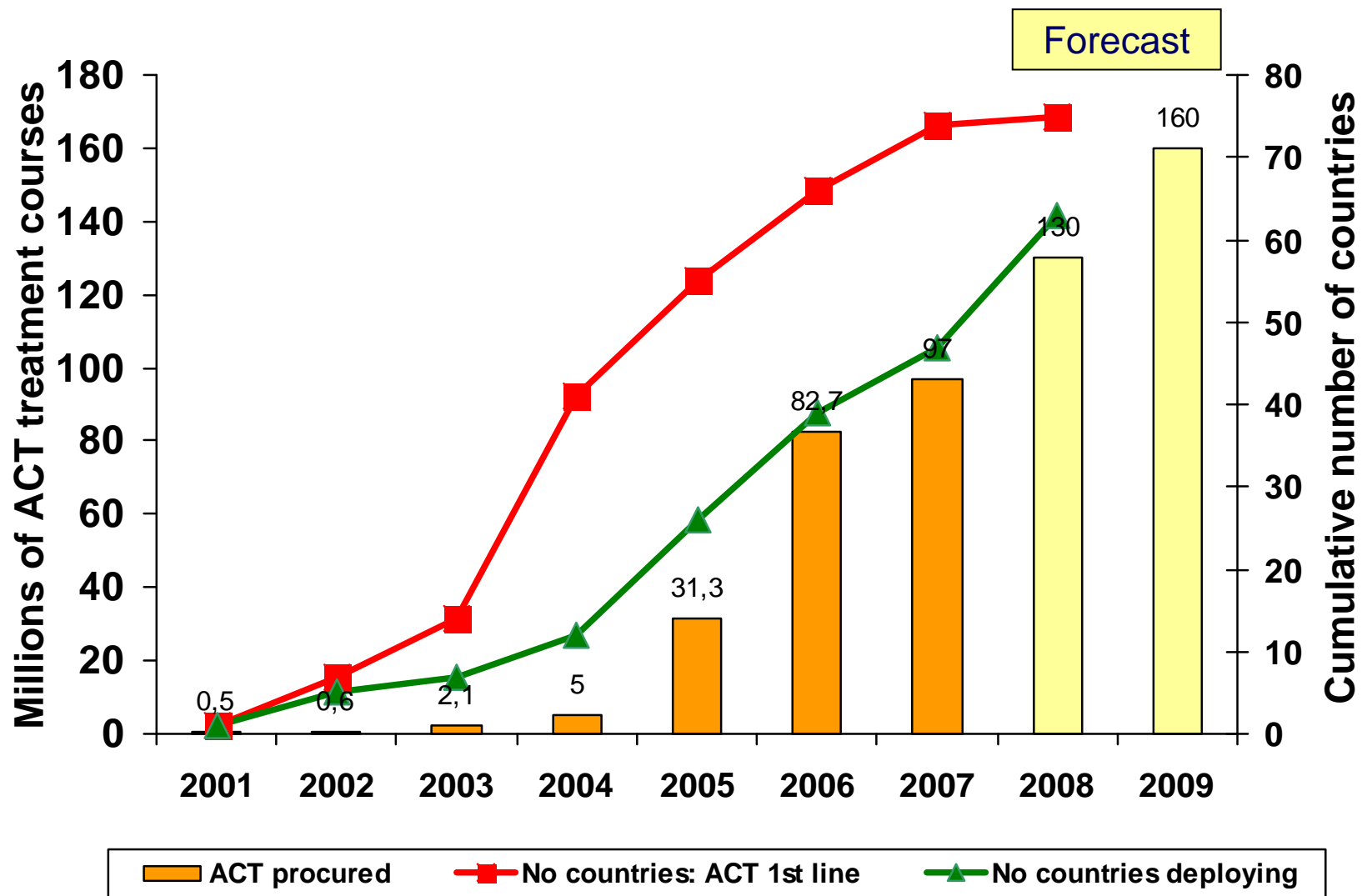


Artemisinin-based combination therapy (ACTs):

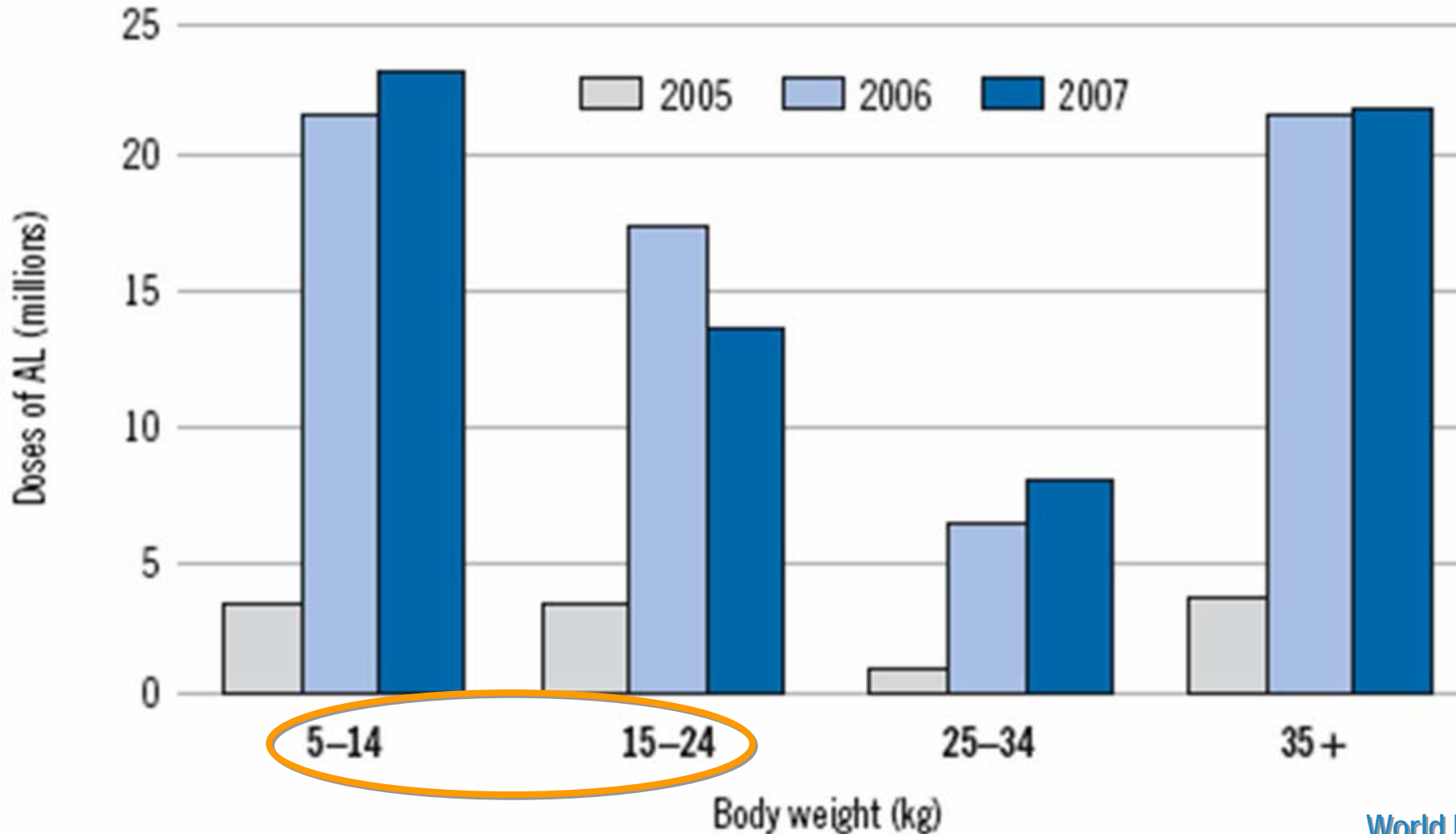
- Artemether-lumefantrine
- Artesunate + amodiaquine
- Artesunate + mefloquine
- Artesunate + sulfadoxine-pyrimethamine

WHO Malaria Treatment Guidelines are currently under review

ACTs: policy adoption, deployment, past procurement and 2008/09 forecast



Procurement of AL by patient body weight (orders placed in 2005 - 2007)

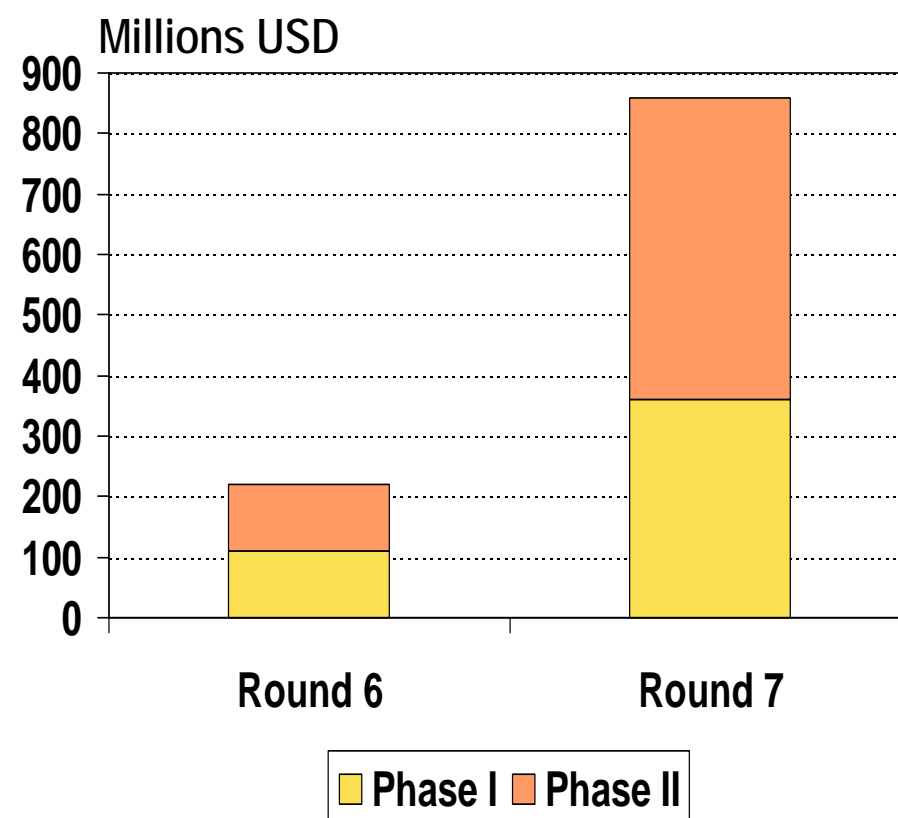


World Malaria Report 2008

Increasing resources for ACTs

- Round 7 GFATM quite successful for malaria, and in Round 8 TRP approved 68% of malaria grants
- UNITAID: new funding for AIDS, TB and malaria medicines
- Affordable Medicine Facility for malaria (AMFm) – initial roll-out plan for 11 countries in April 2009, will be submitted for approval to GFATM Board on 6-8 Nov 2008

Successful applications to Round 6 and 7 of GFATM



Why not adult medicines for children?



- **Sub-populations:**
 - (pre)term newborn infants
 - infants, toddlers: > 28 days - 23 months
 - children: pre-school 2 - 5 years
school 6 - 11 years
 - adolescents: 12 - 16/18 years
- **Pharmacokinetics and pharmacodynamics may be different**
(e.g. extracellular water, body fat, protein mass, liver/kidney development => absorption, distribution, metabolism, elimination)
- **Profile of adverse reactions and toxicity may differ**
- **Need for different, suitable for children pharmaceutical formulations**



Antimalarial medicine of the future

- Highly effective in curing illness – clinical and parasitological
- Very safe, including in infancy and pregnancy
- Guaranteed against resistance
- Potent anti-gametocyte (transmission blocking) activity
- Effective in all malaria species
- Have application in preventive treatment
- Fixed-dose combinations
- Simple regime – ideally single dose
- Long shelf-life (at least 3 years)
- Available in paediatric formulations and in unit-dose packaging

Additional requirements for children medicines

- Correct dosing: Need for appropriate dose-finding studies
- Ease of administration: taste, colour, flavour
- Excipients, e.g. alcohol, sugar, preservative
- Affordable price
- Formulations
 - Liquid: syrups, solutions, suspensions
 - Semi-solid: suppositories
 - Solid: tablets, (capsules, granules, pellets)



Paediatric medicines (I)

● Syrups

- Drug solubility (dose/volume)
- API(s) compatibility with diluents
- Preferably without sugar and alcohol
- Taste (taste masking), colour, flavour
- Stability (preservatives), pH: single dose vs multidose
- supply chain issues (large volume: transport, storage)

● Suspensions (and liquid products reconstituted from powders/granules)

- as above
- quality and quantity of clean water for reconstitution
- API particle sedimentation, redispersion
- particle size/crystallinity changes on storage/shelf life

● Suppositories

- heat stability
- rectal absorption
- cultural issues
- pre-referral treatment

Substandard ACT: content and efficacy of preservatives in artemisinin-based dry suspensions for paediatric use

(Atemnkeng *et al.* 2007)

Brand name/manufacturer	Preservative	Active ingredient/dose	Content stable*	Efficacy test ^o
Artenam®, arenco Pharmaceutica, Belgium	Sorbic acid	Artemether, 180 mg, dry powder 60 ml	✓	conforms
Gvither®, GVS Labs, India	Methylparaben Propylparaben	Artemether, 300 mg, dry powder 100 ml	failed	conforms
Artesiane®, Dafra Pharma, Belgium	Methylparaben Propylparaben	Artemether, 300 mg, dry powder 100 ml	failed	Not conforms
Alaxin®, GVS Labs, India	Methylparaben Propylparaben	Dihydroartemisinin, 160 mg, dry powder 80 ml	failed	Not conforms
Artexin®, Sphinx Pharma, Kenya	Benzoic acid	Dihydroartemisinin, 160 mg, dry powder 80 ml	✓	Not conforms
Santecxin®, Shsj, China	Benzoic acid	Dihydroartemisinin, 160 mg, dry powder 80 ml	✓	Not conforms
Cotecxin®, Jiaxing Nanhu Pharma, China	Chlorbutanol?	Dihydroartemisinin, 160 mg, dry powder 80 ml	No content	Not conforms

* preservative completely and immediately dissolved and levels unchanged during 7 days

^o preservative efficacy test against *P. aeruginosa*, *S. aureus*, *E. coli*, *C. albicans*, *Z. rouxii*, *A. niger*

Paediatric medicines (II)

- Oral solid dosage forms
 - Excipients: without sugar, alcohol
 - Easier to reach stability of product
 - Easier to mask bitter taste of API
 - Breakable or dispersible tablets easier to administer
 - Breakable or dispersible tablets support clinicians to adhere to accurate dose
 - Fixed-dose combinations are cost effective
 - Tablets simplify supply chain management (volume: transport, storage)

Disease	Name	Formulation and strength	Applicant	Manufacturing site	Packaging	Reference	Date of PQ
MA	Amodiaquine	Film-coated tablets 150mg	Guilin Pharmaceutical Co. Ltd	Guilin, Guangxi, China	PVC/Alu blisters 6; Cardboard box 2x6	MA045	2007-08-30
MA	Amodiaquine+Artesunate	Tablets 153mg + Tablets 50mg	Ipca Laboratories Limited	Dadra and Nagar Haveli (U.T.), India	PVdC/PVC/Alu blister 12+12, 6+6, 3+3	MA001	2008-04-23
MA	Amodiaquine+Artesunate	Tablets 150mg + Tablets 50mg	Guilin Pharmaceutical Co. Ltd	Guilin, Guangxi, China	PVC blisters sealed with an aluminium foil lid 4+4; Cardboard box 3x(4+4)	MA046	2007-08-30
MA	Amodiaquine+Artesunate	Tablets 67.5mg+25mg	Sanofi-Aventis	MAPHAR Laboratories, Casablanca, Morocco	Alu/Alu blister 3 x 1, 3 x 25	MA056	2008-10-14
MA	Amodiaquine+Artesunate	Tablets 135mg+50mg	Sanofi-Aventis	MAPHAR Laboratories, Casablanca, Morocco	Alu/Alu blister 3 x 1, 3 x 25	MA057	2008-10-14
MA	Amodiaquine+Artesunate	Tablets 270mg+100mg	Sanofi-Aventis	MAPHAR Laboratories, Casablanca, Morocco	Alu/Alu blister 3 x 1, 3 x 25, 6 x 1, 6 x 25,	MA058	2008-10-14
MA	Artemether+Lumefantrine	Tablets 20mg+120mg	Novartis Pharma	Beijing, China; Suffern, USA	Blister 6, 12, 18, 24	MA026	2004-04-26
MA	Artemotil	Solution injection 50mg/ml	Artecef BV	Rotexmedica, Trittau, Germany	Glass ampoules 1ml	MA027	2006-03-01
MA	Artemotil	Solution injection 150mg/ml	Artecef BV	Rotexmedica, Trittau, Germany	Glass ampoules 1ml	MA028	2006-03-01
MA	Artesunate	Tablets 50mg	Sanofi-Synthelabo	Guilin Pharmaceuticals, Guangxi, China	Blister 12	MA018	2004-04-26
MA	Artesunate	Tablets 50mg	Ipca Laboratories Ltd	Dadra and Nagar Haveli (U.T.), India	PVdC/Al blisters 12	MA038	2007-08-30
MA	Artesunate	Tablets 50mg	Guilin Pharmaceutical Co. Ltd	Guilin, Guangxi, China	Blister 12	MA044	2005-12-21

Co-blister

Fixed-dose

New invitation to manufacturers of antimalarial medicines - EOI for PQ (I)

1. Artemisinin-based fixed dose oral combination formulations

- Artemether + Lumefantrine: tablet 20mg+120mg; tablet 40mg+240mg; tablet 60mg+360mg; tablet 80mg+480mg
- Artesunate + Amodiaquine: tablet 25mg+67,5mg; tablet 50mg+135mg; tablet 100mg+270mg

2. Artemisinin-based fixed dose combination or co-blistered oral formulations

- Artesunate + Amodiaquine: tablet 25mg+76.5mg; tablet 50mg+153mg; tablet 100mg+306mg
- Artesunate + Mefloquine: tablet 25mg+250mg; tablet 50mg+250mg; tablet 100mg+250mg
- Artesunate + Sulfadoxine + Pyrimethamine: tablet 25mg+500mg+25mg; tablet 50mg+500mg+25mg;
tablet 100mg+500mg+25mg

3. Artemisinin-based fixed dose combination or co-blistered oral **paediatric** formulations, **preferably dispersible**

- Artemether + Lumefantrine
- Artesunate + Amodiaquine
- Artesunate + Mefloquine
- Artesunate + Sulfadoxine + Pyrimethamine

New invitation to manufacturers of antimalarial medicines - EOI for PQ (II)

4. Artemisinin-based single-ingredient formulations

- Artemether: oily injection 20mg/ml; 40mg/ml; 80mg/ml
- Artesunate: powder for injection 60mg (vial)
- Artesunate: suppositories 50mg; 100mg; 200mg; 400mg
- Artesunate: tablet* 25mg; 50mg; 100mg

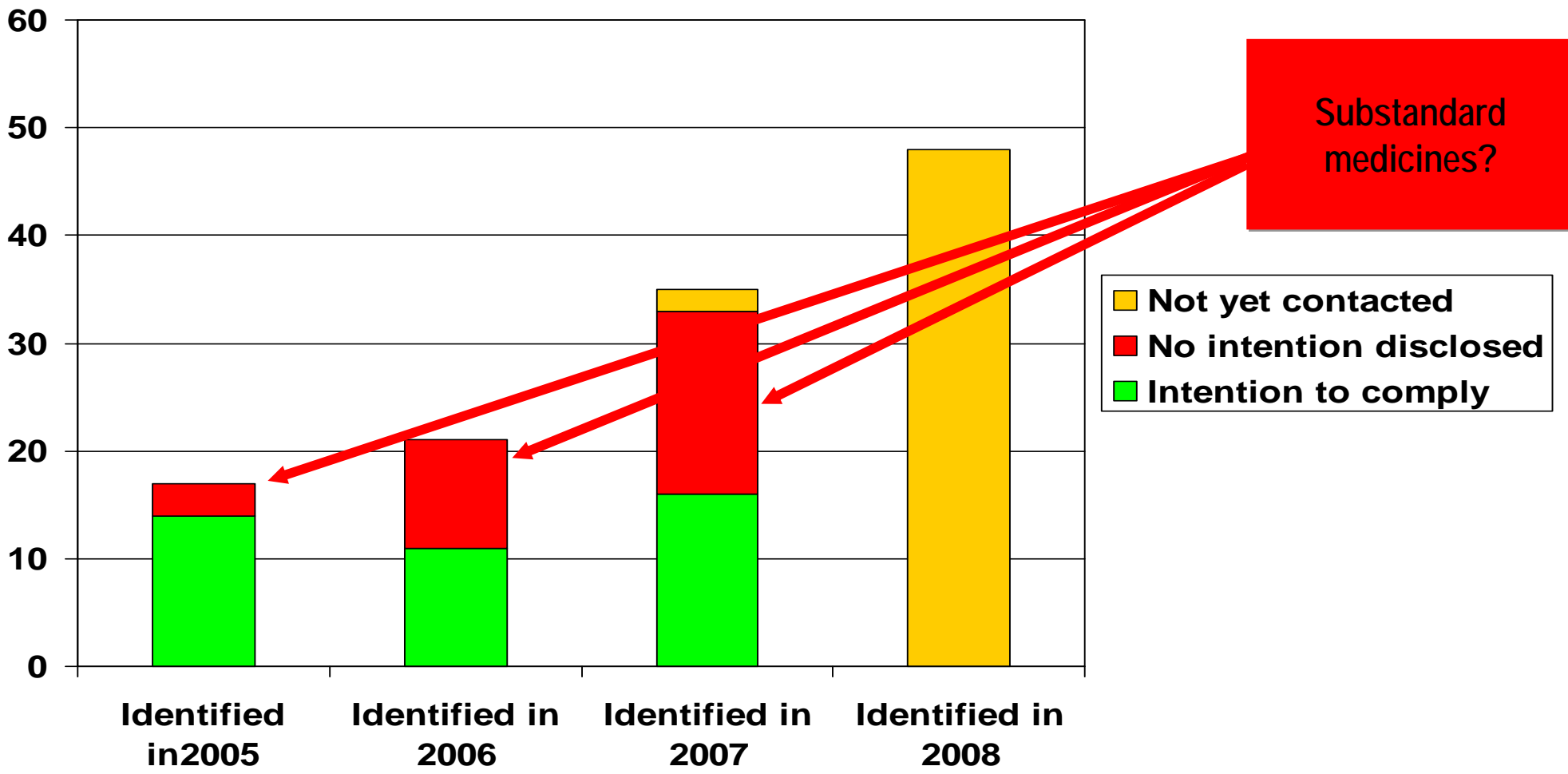
5. Other antimalarial medicines

- Amodiaquine: tablet 153mg (or 200mg as hydrochloride)
- Mefloquine: tablet 250mg
- Sulfadoxine + Pyrimethamine: tablet 500mg+25mg

* Artesunate tablets to be used only in combination with either Amodiaquine, Mefloquine or Sulphadoxine + Pyrimethamine

Manufacturers of artemisinin monotherapies: 41/121 expressed intention to comply with WHO

Number of companies



Thank you

