Latest evidence on artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapies from the markets

Asian Pacific Leaders Malaria Alliance – Access to Quality Medicines and Other Technologies Task Force Meeting
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Diagnosis, Treatment and Vaccines
Global Malaria Programme

World Health Organization

GLOBAL MALARIA PROGRAMME

Outline

- Oral artemisinin-based medicines (oAMTs)
- Development and spread of resistance
- Research and development pipeline for antimalarial medicines
- Monitoring the implementation of WHA60.18
  - WHO web-based monitoring system (national regulatory authorities, pharmaceutical companies)
  - ACTwatch survey results: oAMTs availability
- Regulatory action
  - Country examples
  - Generic Guide
  - Challenges
- Key messages

Oral artemisinin-based monotherapies (oAMTs)

World Health Assembly Resolution WHA60.18:
"...cease progressively the provision in both the public and private sectors of *oral* artemisinin monotherapies..."

Caveat: The Resolution refers to phasing out *oral** artemisinin-based monotherapies, i. e. tablets, capsules, suspensions.

Main factors contributing to development and spread of resistance

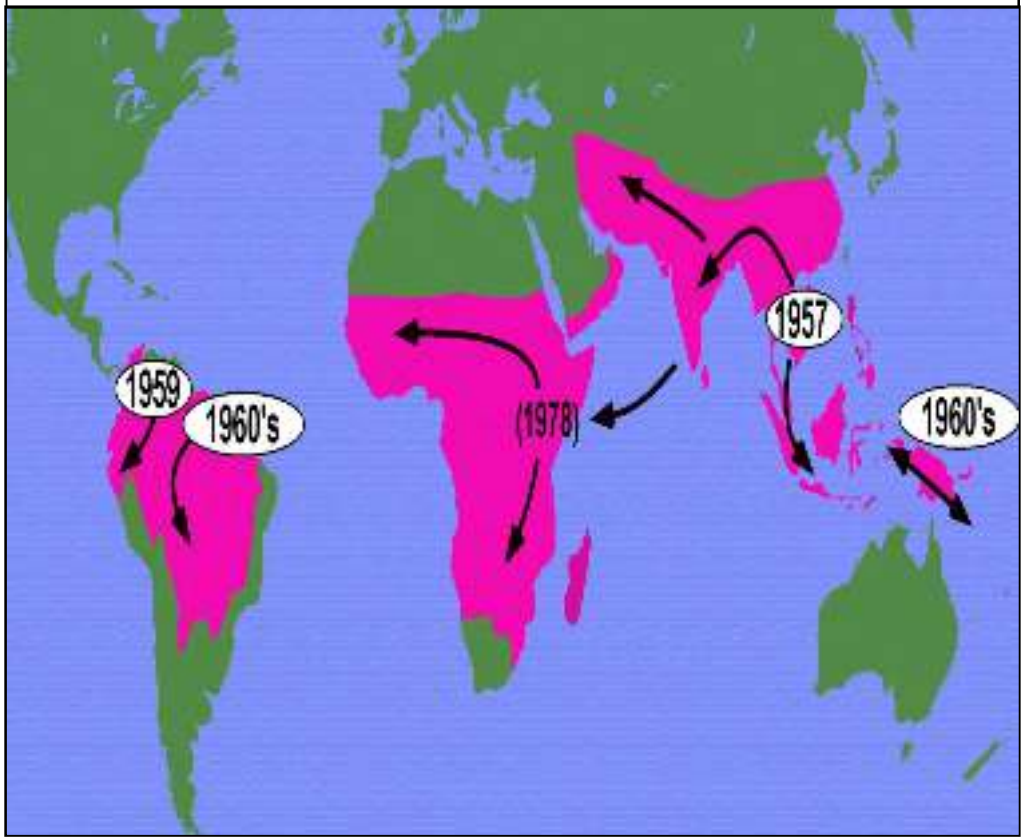
- Patient compliance / adherence to treatment
- Co-formulated products
- Quality of medicines (low amount of active pharmaceutical ingredients, due to e.g. poor stability or degradation)
- Migrating populations
- Weak regulatory systems
- Insufficient knowledge on prescriber and patent side
- Insufficient availability of quality artemisinin-based combination therapies (ACTs) at affordable prices

*Rectal and injectable formulations: Still required for pre-referral treatment and treatment of severe malaria

Rapid development and spread of resistance to monotherapies

Antimalarial compound	Year of intro-duction	First case of resis-tance	Duration until first resis-tance
Quinine	1632	1910	
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Sulfadoxine-pyrimethamine	1967	1967	<1
Mefloquine	1977	1982	5
Atovaquone	1996	1996	<1
Artemisinin derivatives	1990	2009	19

The spread of *Plasmodium falciparum* resistance to chloroquine



Latest evidence on artemisinin resistance

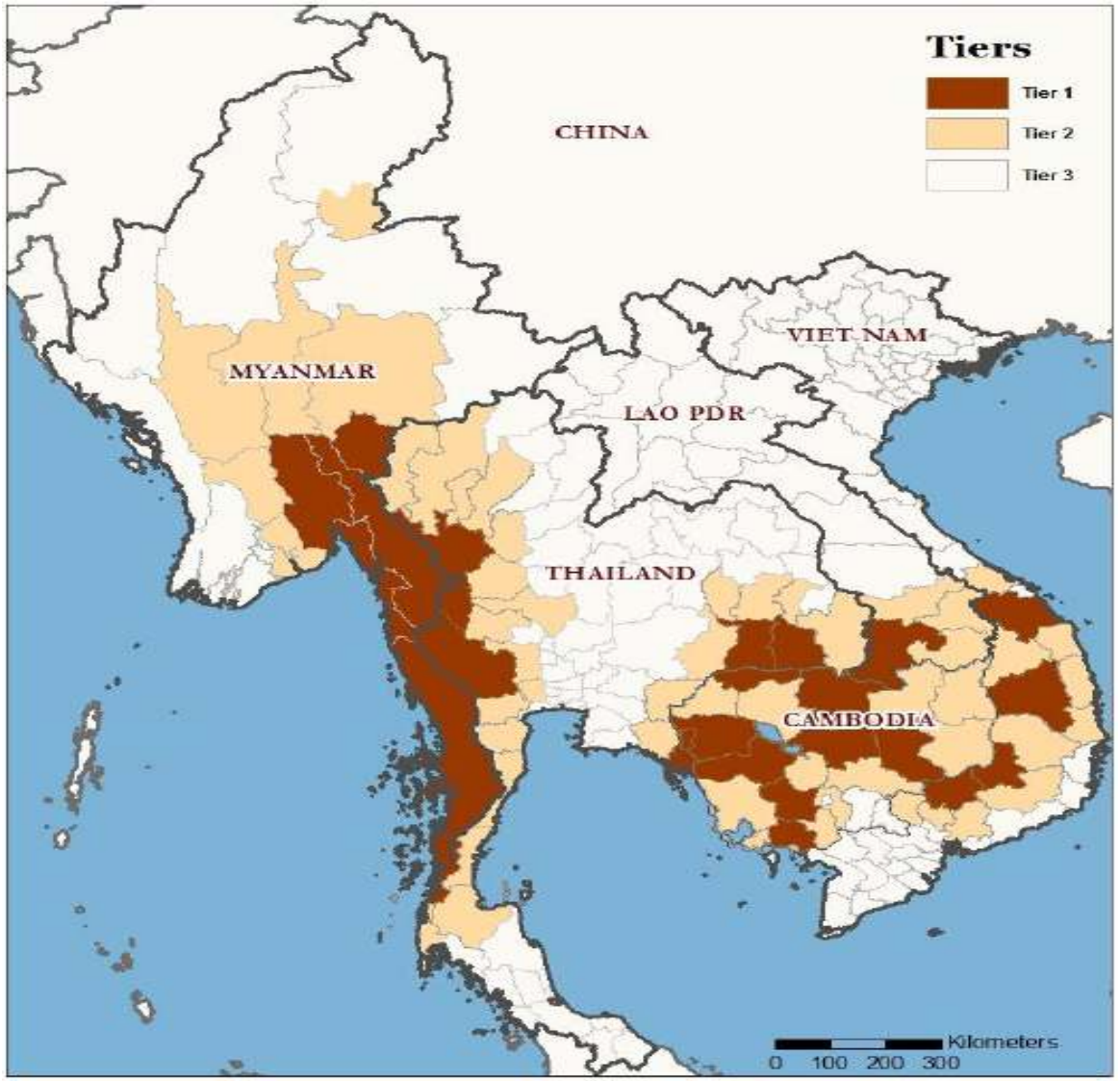
WHO Status report on artemisinin resistance (January 2014)

Confirmed foci

- Cambodia
- Laos
- Myanmar
- Thailand
- Viet Nam

Suspected foci

- Suriname
- Guyana
- French Guyana



Tier map of the Greater Mekong Subregion (January 2014)

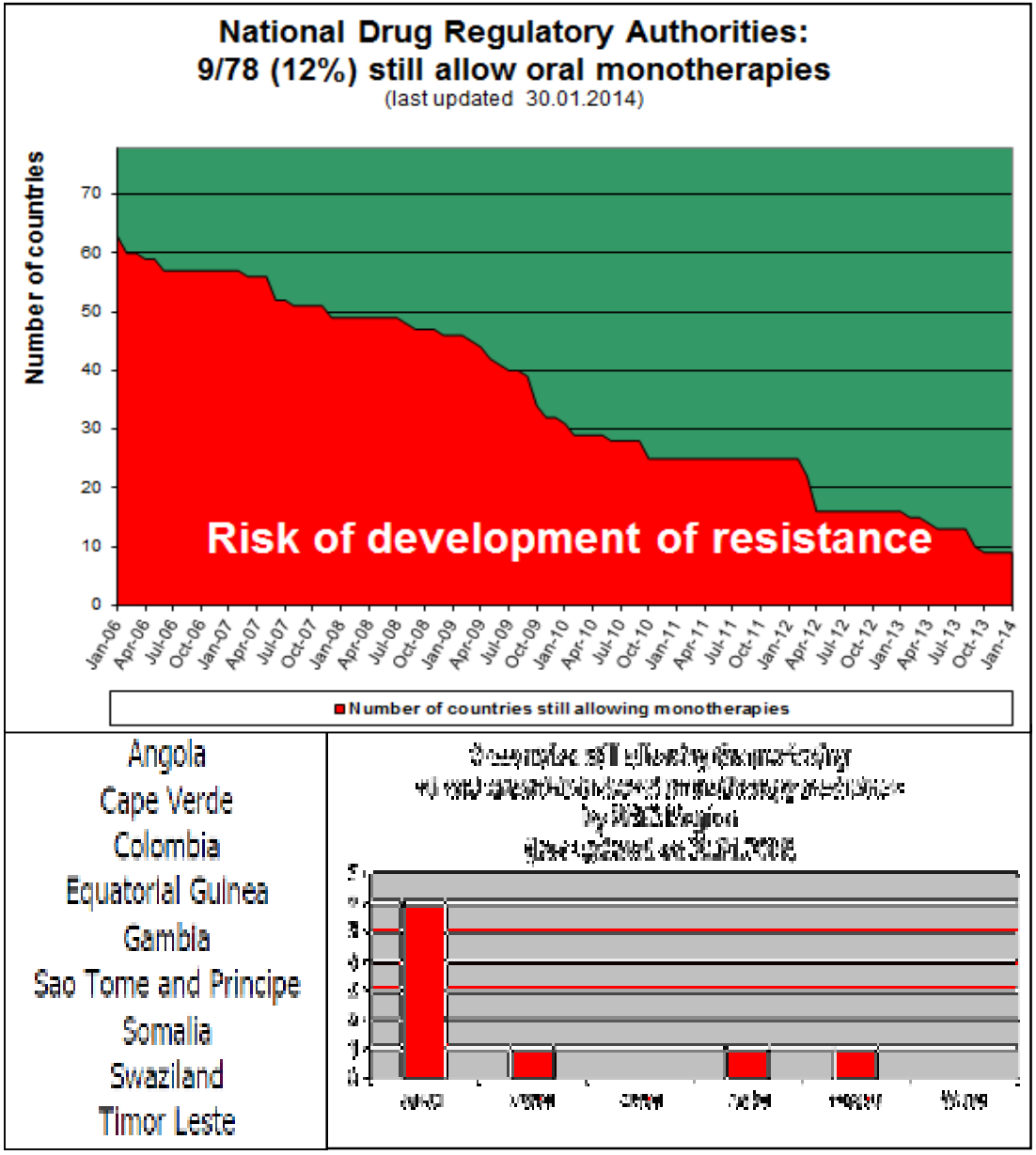
Medicines for Malaria Venture (MMV)
Current Research and Development Portfolio

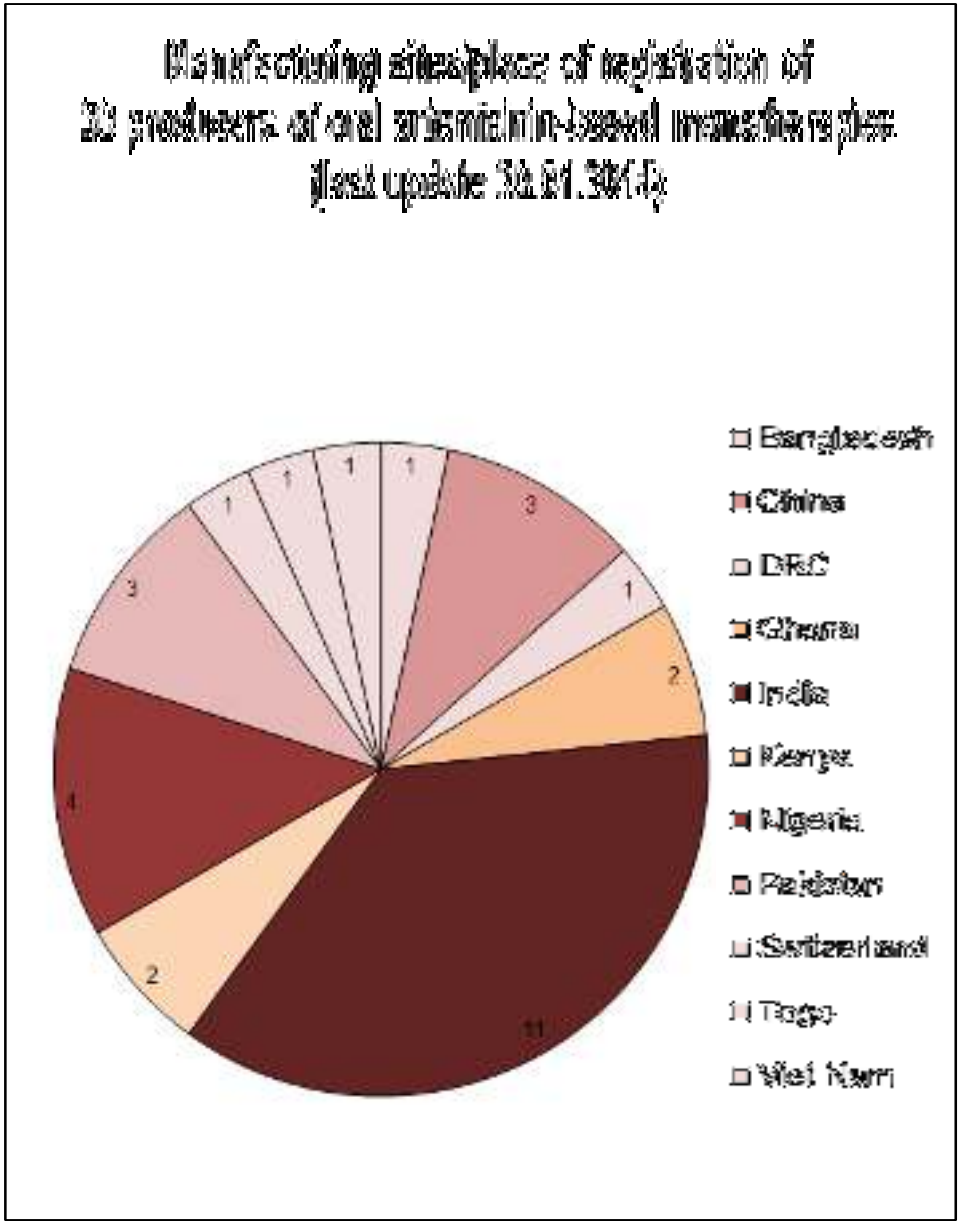
Research		Translational		Development			Access
Lead optimisation		Preclinical	Human volunteers	Patient exploratory	Patient confirmatory	Under review	Post approval*
Novartis MP	1 project Novartis	P218 DHFR	DSM265	OZ439	Azithromycin chloroquine	Rectal Artesunate	Artemether-Lumefantrine Dispersible **1**
GSK MP	3 projects GSK	ELQ-300	OZ439/FQ	KAE609	Tafenoquine	SP-AQ	Artesunate for injection **2**
Sanofi MP	Orthologue leads Sanofi	21A092		KAF156	Pyronaridine-Artesunate Paediatric		Dihydroartemisinin-Piperaquine **3**
AstraZeneca MP	Whole cell leads AstraZeneca	MMV390048			Dihydroartemisinin-Piperaquine Paediatric		Pyronaridine-Artesunate **4**
Heterocycles Celgene	Oxaboroles Anacor	SJ557733					Artesunate-Amodiaquine **5**
Heterocycles Univ Campinas	Tetraoxanes Liverpool STM/ Liverpool Univ						Artesunate-Mefloquine **6**
Screening Daiichi-Sankyo/GHIT	DHODH UTSW/UW/Monash						
Screening Takeda/GHIT	Aminopyridines UCT						
Screening Eisai/GHIT	Heterocycles Dundee						
Pathogen Box	Open Source Drug Discovery Univ Sydney						
16 Other Projects	Amino-alcohols Merck Serono						

MMV R&D Portfolio available via the following link:
http://www.mmv.org/research-development/rd-portfolio

Oral artemisinin-based monotherapies

Web-based WHO monitoring system



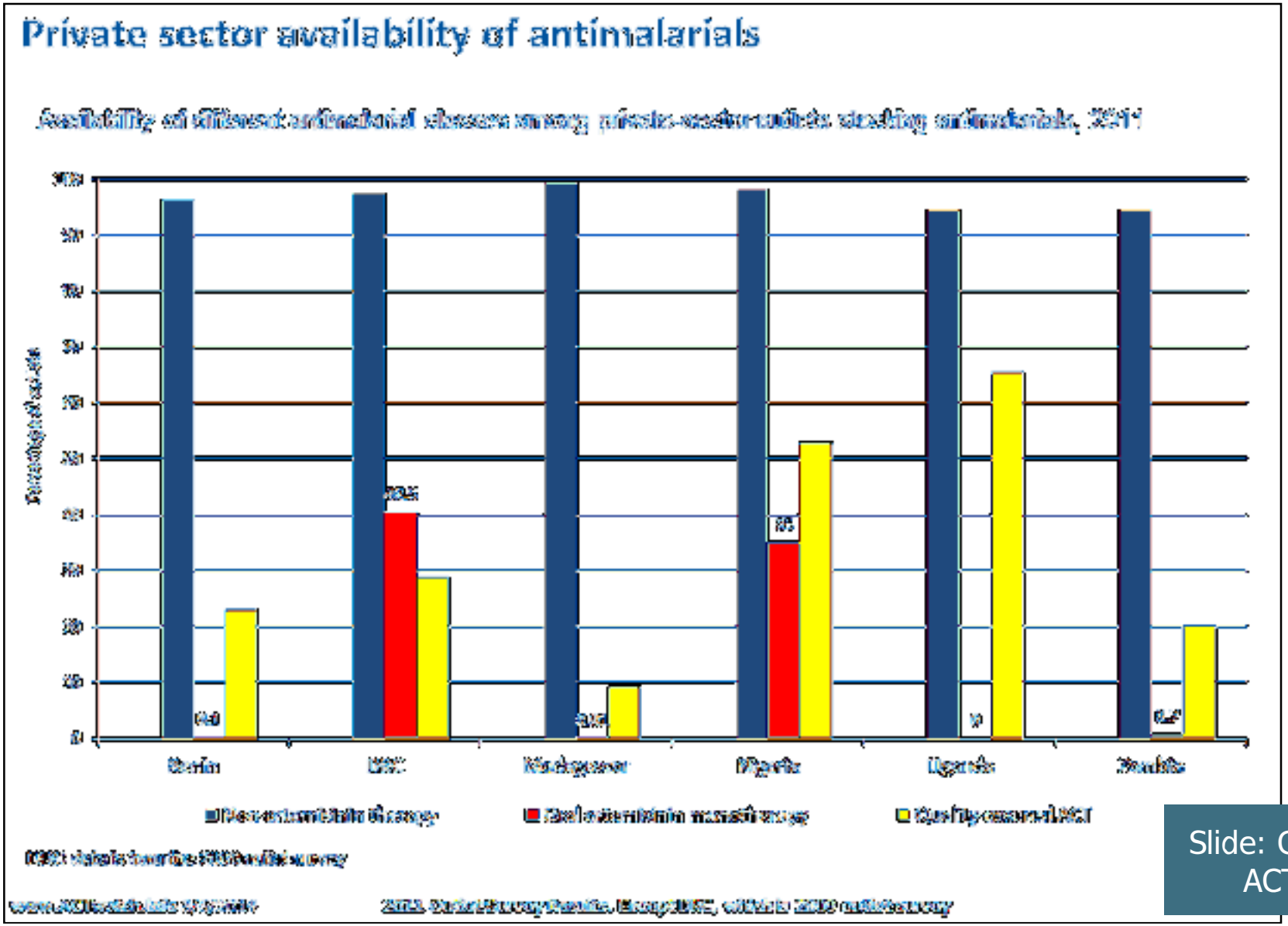


http://www.who.int/malaria/monotherapy_NDRAs.pdf

http://www.who.int/malaria/monotherapy_manufacturers.pdf

ACTwatch survey results: **Private sector availability of antimalarials**

DRC 40,5% (2009) and Nigeria 35% (2011)



Slide: Courtesy of ACTwatch

Regulatory action – Country examples

Benin

- Combined removal of oAMTs and chloroquine (ineffective due to P. falciparum resistance).
- Alignment of removal with large-scale deployment of ACTs.

India and Pakistan

- Coordination of initiative by the national regulatory authorities essential.
- Acceleration of procedures through support provided by the National Malaria Control Programme and WHO in both countries to accelerate the process.
- India: Need for close coordination between the federal drug regulatory authorities and the state regulatory authorities.

Cambodia and Malawi

- Comprehensive approach comprising withdrawal / suspension of marketing, manufacturing and import licenses for oAMTs.
- Cambodia: Active search and confiscation of all oAMTs, applying enforcement laws.
- Malawi: Disposal of all oAMTs in the market, followed by enforcement via quarterly inspections to all drug outlets in the private sector.

Generic guide
to phase out oAMTs from the markets

Action	Task	Suggested approximate timeline
Step 1	Agreement on time frame of phasing out oAMTs in synchrony with large-scale implementation of ACTs	Immediate
Step 2	Suspension of new approvals of marketing authorizations for oAMTs	Immediate
Step 3	Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies exclusively marketing oAMTs	3–4 months
Step 4	Large-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapies	Time X
Step 5	Widespread availability and affordability of quality ACTs in the private sector	Time Z
Step 6	Withdrawal of marketing authorization and of manufacturing licences for oAMTs as FPPs to protect domestic markets	6 months after time X
Step 7	Suspension of export license for oAMTs as FPPs to protect export markets	6 months after time X
Step 8	Active recall of oAMTs from the market	3 months after time Z
Step 9	Enforcement activities (e.g. regular outlet inspections, confiscation and destruction of products, suspension of selling licenses, fines, prosecution)	Regular intervals after Step 8
Step 10	Monitoring to ensure complete elimination of oATMs as FPPs from the market	10–12 months after time X

Main challenges

- Regulatory environment (Withdrawal of domestic licenses without suspension of export licenses in producing countries allows for oAMTs to enter poorly regulated pharmaceutical markets in endemic countries)

- Weak enforcement mechanisms (e.g. active recall, confiscation, destruction, regular inspections, suspension of selling licenses,...)

- Limited availability of quality ACTs at affordable prices in the private sector (Limited access to ACTs often caused by slow roll-out of ACTs in the public sector and limited penetration of ACTs in the private sector)

Key messages

- Artemisinin resistance – confirmed in five countries in the Greater Mekong Subregion, suspected in three countries in South America – requires intensified action to eliminate oAMTs from the markets

- Successful country examples show withdrawal of oAMTs from the markets is possible and requires a number of critical steps plus enforcement mechanisms

- Government commitment and strong stewardship of national regulatory authorities is crucial to protect both domestic and export markets

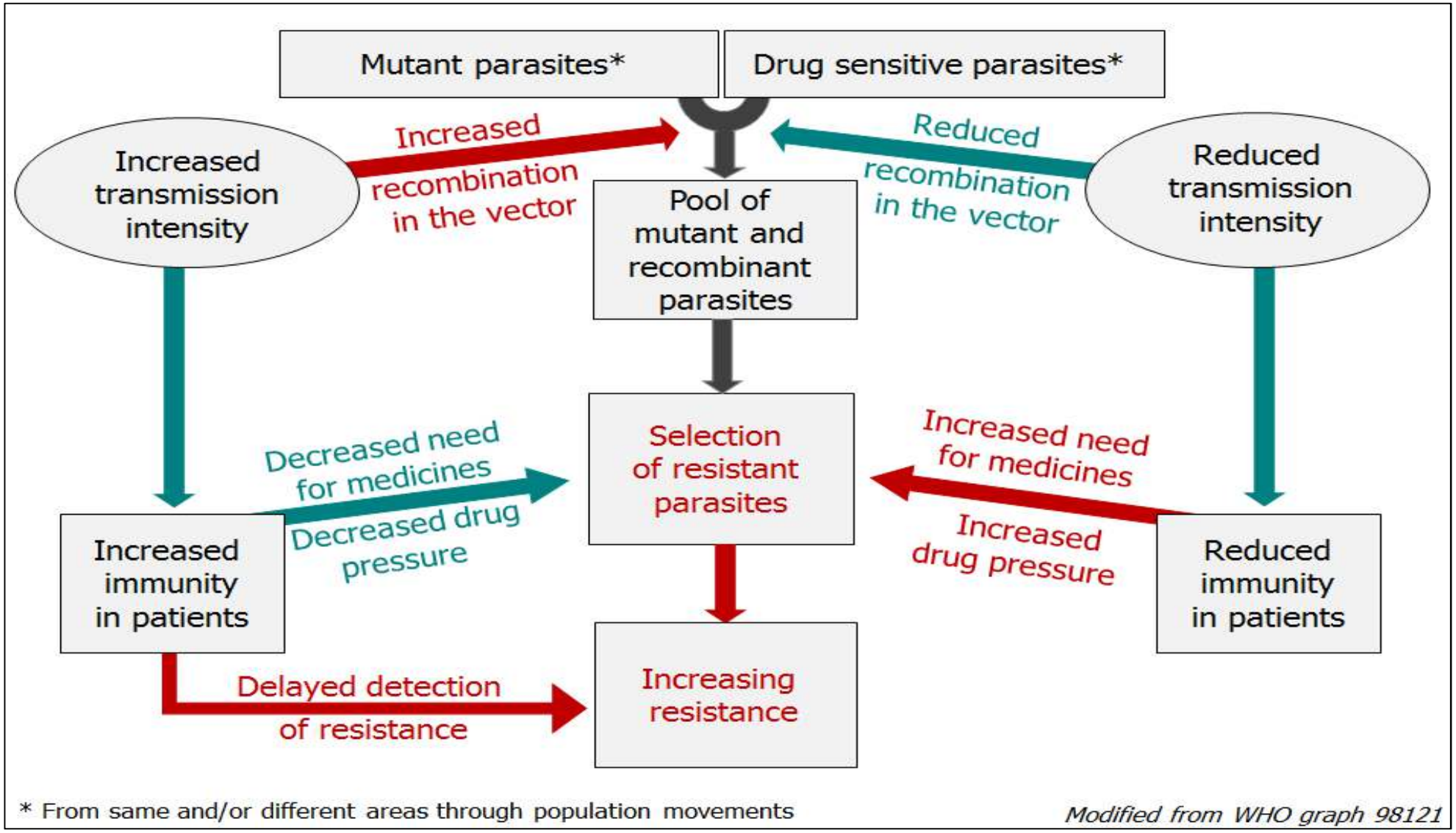
Thank you

Backup slides

Main factors contributing to the development and spread of artemisinin resistance

Issue	Potential solution
Patient compliance / adherence to treatment	• ACTs with 3-day treatment regimen • Patient information • Fixed-dose ACTs (quality, availability, price) • Elimination of oAMTs from the market
Co-formulated products	• Fixed-dose ACTs (quality, availability, price)
Quality of medicines (low amounts of active pharmaceutical ingredient, e.g. poor stability or degradation)	• Selection of pre-qualified antimalarial medicines for procurement • Functioning quality assurance and quality control measures at country level
Migrating populations	• Increase monitoring / surveillance (mass population movements from areas with high levels of resistance) • Improve access to rational treatment with ACTs
Weak regulatory system	• Strengthening of national regulatory systems • Capacity building and structural reforms
Insufficient knowledge on prescriber and patient side	• Training and communication to change prescriber habits • Information campaigns for patients
Insufficient availability of quality ACTs at affordable prices	Ensure large-scale availability of affordable quality ACTs and RDTs in both public and private sectors to help crowding out oAMTs and to promote rationale use of ACTs

Epidemiological determinants of drug resistance



Modified from WHO Epidemiological Approach to Malaria Control. WHO Reference Code 98121

Main initiatives to implement WHO recommendations

- 2006:
  - WHO Press Release
  - Web-based monitoring system for marketing practices and position of companies and national regulatory authorities (http://malaria.who.int/)
  - Dissemination of WHO position via WHO Offices
  - WHO staff briefings, inter-country and regional meetings with MOH officials
  - WHO technical briefing on malaria guidelines and artemisinin monotherapies, Alignment of funding and procurement agencies
- 2007:
  - World Health Assembly Resolution (WHA60.18)
  - WHO informal consultation with manufacturers of artemisinin-based antimalarials
- 2010:
  - Publication of the article in the WHO Drug Information "Regulatory action needed to stop the sale of oral artemisinin-based monotherapy"
  - International Conference of Drug Regulatory Authorities (ICDRA), Singapore
- 2011:
  - World Health Assembly Resolution (WHA64.17)
  - Global plan for artemisinin resistance containment (GPARC)
- 2013:
  - Emergency response to artemisinin resistance (ERAR) in the Greater Mekong subregion, Regional Framework for action 2013-2015

Regulatory targets for phasing out oAMTs