



Pan American Health Organization



*Regional Office of the
World Health Organization*

MONITORING ANTIMALARIAL DRUG RESISTANCE Contributions of AMI/RAVREDA and results in past ten years:

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**PAHO/WHO Regional Advisor for Malaria
AMI / RAVREDA Annual Evaluation Meeting
Panama City, Panama • 22 - 24 March 2011**

AMI Thematic Areas

1

Surveillance of antimalarial resistance

a. In vivo

b. In vitro

c. Molecular markers

2

Drug policy implementation

3

Access and quality of diagnosis and treatment

a. Improve access to diagnosis (Microscopy & Rapid tests)

b. Quality of diagnosis

c. Drug quality

d. Drug availability and use

4

Vector control based in evidence

5

Epidemiological stratification

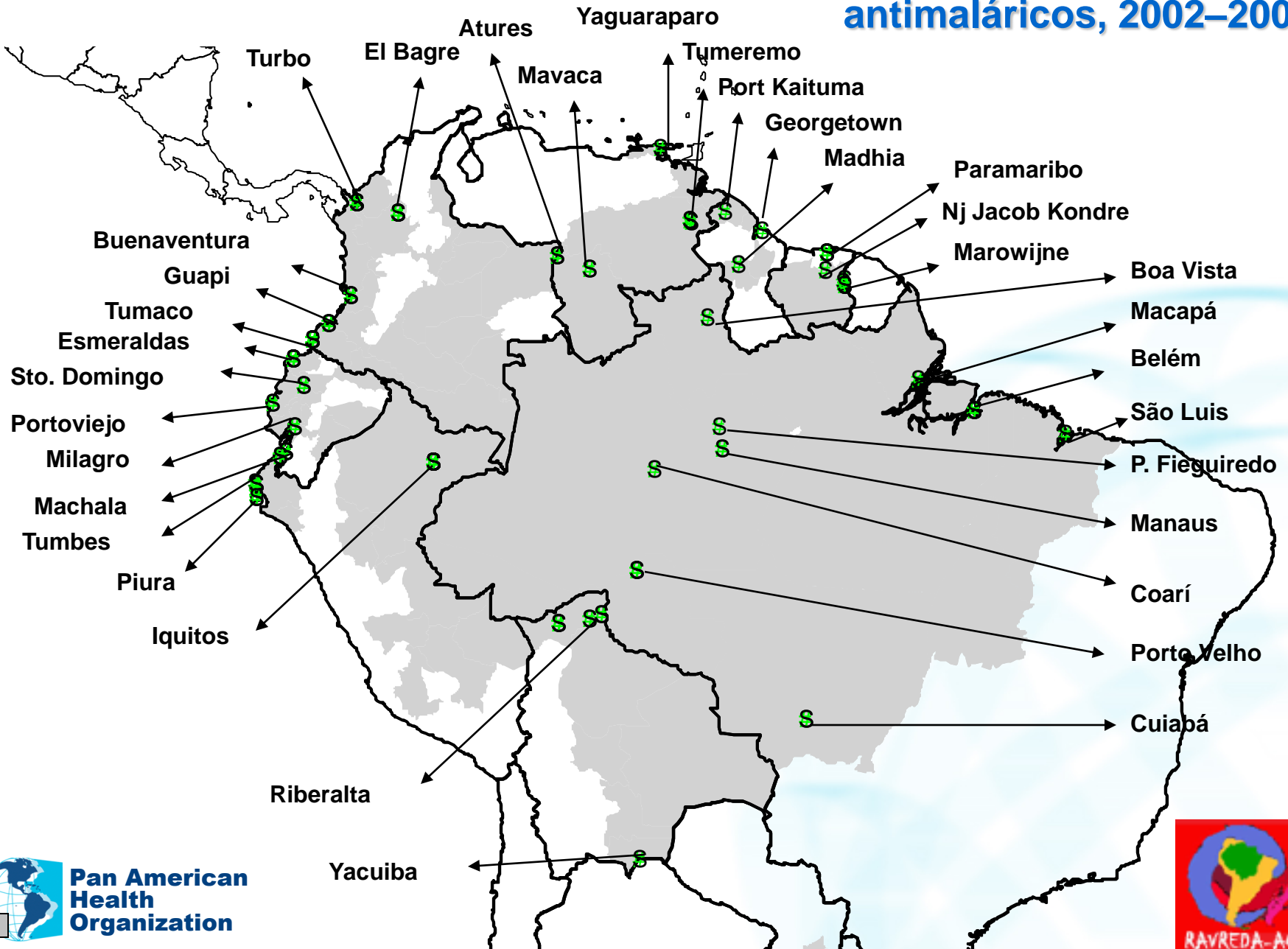
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Communications and Information Dissemination

1 Monitoring antimalarial drug resistance

- *In vivo* drug efficacy trial results used in first line treatment policy decision making: use of Artemisinin-based Combination Therapy (ACT) for *P. falciparum* infection
- Selective use of *in vitro* monitoring of susceptibility to antimalarial drugs and molecular markers as an early warning system
- Molecular studies

RAVREDA/AMI: Sitios centinelas para vigilancia de la resistencia a los antimaláricos, 2002–2008



AMI



USAID
FROM THE AMERICAN PEOPLE

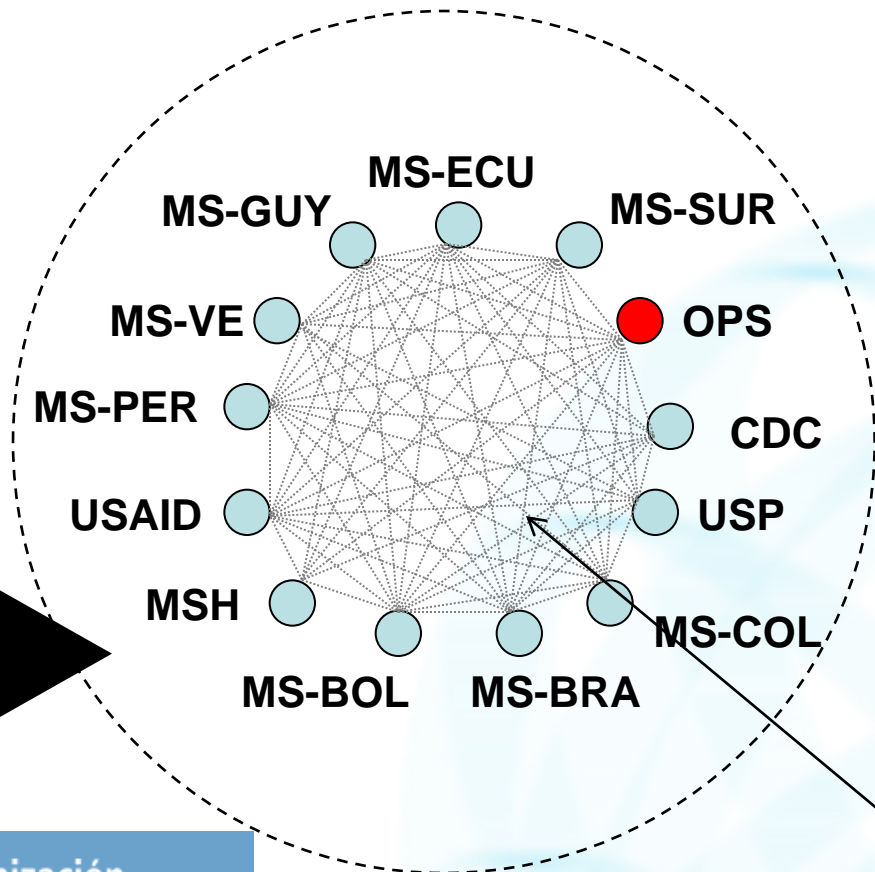
MS-BOL
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USAID
USP
MSH
CDC

OPS



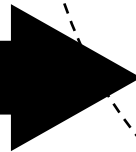
RAVREDA



(Coordinación)

- MS-NIC
- MS-HON
- MS-BLZ
- MS-PAN
- MS-GUT

Vigilancia de la resistencia a los antimicrobianos



OPS/OMS

MS = Ministerio de Salud

Resultados estudios de eficacia, 2002-2009

#	Pais	Especie de <i>Plasmodium</i>	Droga Antimalárica testada	Año de finalización del estudio	Localidad / Municipalidad	Numero de pacientes que completaron el estudio	Falla terapéutica (%)	Fuente
1.	BOLIVIA	Pv	CQ	2003	YAQUIBA	60	0	RAVREDA / AMI
2.	BOLIVIA	Pv	CQ	2003	RIBERALTA	59	15	RAVREDA / AMI
3.	BOLIVIA	Pv	CQ	2007	YAQUIBA	57	0	RAVREDA / AMI
4.	BOLIVIA	Pv	CQ	2007	GUAYARAMERIN	75	12.1	RAVREDA / AMI
5.	BOLIVIA	Pv	CQ	2007	RIBERALTA	81	6.1	RAVREDA / AMI
6.	BRASIL	Pf	MQ	2004	MACAPA	33	6	RAVREDA / AMI
7.	BRASIL	Pf	AS+MQ	2007	MACAPA	58	0	RAVREDA / AMI
8.	BRASIL	Pv	CQ	2004	CAREIRO	40	25	RAVREDA / AMI
9.	BRASIL	Pv	CQ	2004	COARI	98	2	RAVREDA / AMI
10.	BRASIL	Pf	AS+MQ	2006	COLNIZA	49	0	RAVREDA / AMI
11.	BRASIL	Pf	AT+LM	2006	PORTO VELHO	54	0	RAVREDA / AMI
12.	BRASIL	Pf	MQ	2004	SAO LUIS	11	9	RAVREDA / AMI
13.	BRASIL	Pf	MQ	2004	MANAUS	73	1	RAVREDA / AMI
14.	BRASIL	Pv	CQ	2004	MANAUS	108	19	RAVREDA / AMI
15.	BRASIL	Pv	CQ	2004	MACAPA	136	18	RAVREDA / AMI
16.	BRASIL	Pv	CQ	2004	SAO LUIS	46	13	RAVREDA / AMI
17.	BRASIL	Pv	CQ	2004	BELEM	165	10	RAVREDA / AMI
18.	BRASIL	Pf	Q+DOX	2004	MACAPA	63	18	RAVREDA / AMI
19.	BRASIL	Pv	CQ	2004	PORTO VELHO	87	8	RAVREDA / AMI
20.	BRASIL	Pf	MQ	2004	PORTO VELHO	54	7	RAVREDA / AMI
21.	BRASIL	Pv	CQ	2004	CUIABA	75	13	RAVREDA / AMI
22.	BRASIL	Pf	Q+DOX	2007	COARI	86	33.6	RAVREDA / AMI
23.	BRASIL	Pf	AT+LM	2007	COARI	117	0	RAVREDA / AMI
24.	BRASIL	Pf	AS+MQ	2006	PORTO VELHO	86	0	RAVREDA / AMI
25.	BRASIL	Pf	Q+DOX	2004	BELEM	79	11	RAVREDA / AMI
26.	COLOMBIA	Pf	AQ+SP	2004	BUENAVENTURA	5	50	RAVREDA / AMI
27.	COLOMBIA	Pf	AQ+SP	2003	TURBO	44	2.3	RAVREDA / AMI
28.	COLOMBIA	Pf	AS+SP	2004	TURBO	47	2.1	RAVREDA / AMI
29.	COLOMBIA	Pf	AS+SP	2004	EL BAGRE	51	1.9	RAVREDA / AMI
30.	COLOMBIA	Pf	MQ+SP	2004	EL BAGRE	33	0	RAVREDA / AMI
31.	COLOMBIA	Pf	AQ	2004	EL BAGRE	12	42	RAVREDA / AMI
32.	COLOMBIA	Pf	MQ+SP	2004	TURBO	20	0	RAVREDA / AMI
33.	COLOMBIA	Pf	AQ	2004	TURBO	21	23	RAVREDA / AMI
34.	COLOMBIA	Pv	CQ	2004	BUENAVENTURA	42	0	RAVREDA / AMI
35.	COLOMBIA	Pf	AQ	2004	BUENAVENTURA	14	57	RAVREDA / AMI
36.	COLOMBIA	Pf	AQ	2003	TUMACO	29	38	RAVREDA / AMI
37.	COLOMBIA	Pv	CQ	2003	TURBO	45	2.2	RAVREDA / AMI
38.	COLOMBIA	Pf	MQ	2003	TURBO	45	2.2	RAVREDA / AMI
39.	COLOMBIA	Pf	MQ	2003	TUMACO	50	0	RAVREDA / AMI



#	País	Especie de <i>Plasmodium</i>	Droga Antimalárica testada	Año de finalización del estudio	Localidad / Municipalidad	Numero de pacientes que completaron el estudio	Falla terapéutica (%)	Fuente
40.	COLOMBIA	Pf	AQ+SP	2003	EL BAGRE	46	2.2	RAVREDA / AMI
41.	COLOMBIA	Pv	CQ	2003	EL BAGRE	47	0	RAVREDA / AMI
42.	COLOMBIA	Pv	CQ	2003	GUAPI	34	0	RAVREDA / AMI
43.	COLOMBIA	Pf	SP	2003	GUAPI	44	0	RAVREDA / AMI
44.	COLOMBIA	Pf	AQ	2003	GUAPI	40	15	RAVREDA / AMI
45.	COLOMBIA	Pf	AQ+SP	2003	TUMACO	49	0	RAVREDA / AMI
46.	COLOMBIA	Pv	CQ	2003	TUMACO	49	2	RAVREDA / AMI
47.	COLOMBIA	Pf	MQ	2003	EL BAGRE	47	6.4	RAVREDA / AMI
48.	ECUADOR	Pf	AQ+SP	2004	ESMERALDAS	34	0	RAVREDA / AMI
49.	ECUADOR	Pf	CQ	2003	PORTOVIEJO	22	81	RAVREDA / AMI
50.	ECUADOR	Pv	AQ	2003	ESMERALDAS	22	0	RAVREDA / AMI
51.	ECUADOR	Pf	AQ	2004	SANTO DOMINGO	60	47	RAVREDA / AMI
52.	ECUADOR	Pf	SP	2003	PORTOVIEJO	29	0	RAVREDA / AMI
53.	ECUADOR	Pf	SP	2003	MILAGRO	49	0	RAVREDA / AMI
54.	ECUADOR	Pf	CQ	2003	MILAGRO	15	80	RAVREDA / AMI
55.	ECUADOR	Pf	CQ+SP	2004	ESMERALDAS	50	0	RAVREDA / AMI
56.	ECUADOR	Pf	AS+SP	2004	MACHALA	48	0	RAVREDA / AMI
57.	ECUADOR	Pf	AT+LM	2005	Esmeraldas-Milagro-Santo Domingo	62	0	RAVREDA / AMI
58.	ECUADOR	Pf	AS+SP	2003	ESMERALDAS	61	0	RAVREDA / AMI
59.	GUYANA	Pf	MQ	2003	PORT KAITUMA	37	28	RAVREDA / AMI
60.	GUYANA	Pf	AT+LM	2008	GEORGETOWN	63	1.7	RAVREDA / AMI
61.	GUYANA	Pf	AS+MQ	2005	MADHIA	82	1.2	RAVREDA / AMI
62.	GUYANA	Pf	MQ	2005	MADHIA	82	3.6	RAVREDA / AMI
63.	GUYANA	Pf	AS+MQ	2003	PORT KAITUMA	27	7.5	RAVREDA / AMI
64.	GUYANA	Pf	AT+LM	2004	GEORGETOWN	72	0	RAVREDA / AMI
65.	GUYANA	Pf	SP	2002	PORT KAITUMA	52		RAVREDA / AMI
66.	GUYANA	Pv	CQ	2006	GEORGETOWN	68	32.3	RAVREDA / AMI
67.	GUYANA	Pv	CQ+PQ	2006	GEORGETOWN	8	25	RAVREDA / AMI
68.	HONDURAS	Pf	CQ	2009	Puerto Lempira	67	0	RAVREDA / AMI
69.	NICARAGUA	Pf	SP	2006		28	0	RAVREDA / AMI
70.	NICARAGUA	Pf	CQ	2006		30	0	RAVREDA / AMI
71.	PERU	Pf	AS+MQ	2005	IQUITOS	95	1.01	RAVREDA / AMI
72.	PERU	Pv	CQ	2002	IQUITOS	132	4	RAVREDA / AMI
73.	PERU	Pf	CQ	2002	ULLPAYACU	20	90	RAVREDA / AMI
74.	PERU	Pf	SP	2002	ULLPAYACU	34	12	RAVREDA / AMI
75.	SURINAME	Pf	AT+LM	2003	PARAMARIBO	53	1.9	RAVREDA / AMI
76.	SURINAME	Pf	MQ	2002	PARAMARIBO	55	7	RAVREDA / AMI
77.	SURINAME	Pf	AT+LM	2006	PARAMARIBO	44	4.5	RAVREDA / AMI
78.	SURINAME	Pf	AS+MQ	2002	PARAMARIBO	52	6	RAVREDA / AMI
79.	SURINAME	Pf	AT+LM	2003	MAROWIJNE	49	2	RAVREDA / AMI
80.	SURINAME	Pf	AT+LM	2005	PARAMARIBO	36	2.8	RAVREDA / AMI
81.	SURINAME	Pf	Articom	2005	PARAMARIBO	31	6.5	RAVREDA / AMI



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82.	SURINAME	Pf	AS+DOX	2003	PARAMARIBO	49	18	RAVREDA / AMI
83.	SURINAME	Pf	Artecon	2006	PARAMARIBO	43	4.6	RAVREDA / AMI
84.	SURINAME	Pf	AS+MQ	2003	PARAMARIBO	41	2	RAVREDA / AMI
85.	VENEZUELA	Pv	CQ+PQ	2002	YAGUARAPARO	102	0	RAVREDA / AMI
86.	VENEZUELA	Pf	AS+MQ	2005	ATURES	60	0	RAVREDA / AMI
87.	VENEZUELA	Pv	CQ	2005	ATURES	65	1.5	RAVREDA / AMI
88.	VENEZUELA	Pf	AT+LM	2005	ATURES	60	0	RAVREDA / AMI
89.	VENEZUELA	Pf	CQ	2002	ATURES	17	100	RAVREDA / AMI
90.	VENEZUELA	Pv	CQ+PQ	2002	ATURES	102	0	RAVREDA / AMI
91.	VENEZUELA	Pf	Q+PQ	2003	ATURES	52	9.6	RAVREDA / AMI
92.	VENEZUELA	Pf	CQ	2002	TUMEREMO	21	76	RAVREDA / AMI
93.	VENEZUELA	Pf	Q+PQ	2003	TUMEREMO	45	22.2	RAVREDA / AMI
94.	VENEZUELA	Pv	CQ	2003	KM 88	44	0	RAVREDA / AMI
95.	VENEZUELA	Pv	CQ+PQ	2003	TUMEREMO	94	0	RAVREDA / AMI

Pf: *Plasmodium falciparum*, Pv: *Plasmodium vivax*

Resumen de los resultados - estudios de eficacia

- 95 estudios de eficacia finalizados,
- Resistencias comprobadas a CQ en áreas de la Amazonia, tratamientos modificados uso de ACT's,
- Eficacia CQ comprobada en Centroamérica, Republica Dominicana y Haití

http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=11789&Itemid=

Información de la Región incluida
en el reporte global de OMS



Amazon Countries. *P. falciparum* First Line Treatment 1998 y 2008. ²⁰⁰⁷

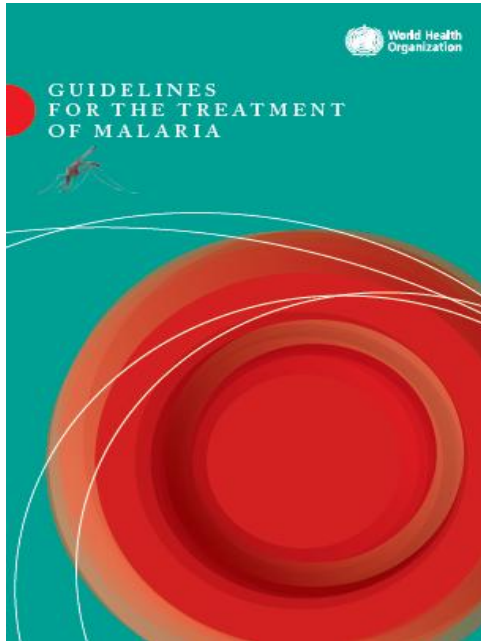
Scheme	1998	2008
Bolivia	Q7d	ASU+MQ
Brasil	Q3d+D5d	LUM+ATM
Colombia	CQ + SP	AQ+SP ASU+MQ LUM+ATM
Ecuador	CQ	SP+ASU
Guyana	Q5d+SP	LUM+ATM
Perú Costa Amazonas	CQ / SP / Q7d+T7d	SP+ASU ASU+MQ
Suriname	Q 5d	LUM+ATM
Venezuela	CQ	ASU+MQ

TREATMENT Guidelines

- *P. vivax* : Chloroquine 25mg/kg over three days
Amodiaquine 30mg/kg over three days
+ Primaquine 0.25-0.5mg/kg daily 14 days
- *P. falciparum*: Chloroquine, if sensitive
Artemisinin based combination
therapy where resistance detected
- Severe or complicated malaria : clinical care and
monitoring
- National treatment guidelines

WHO treatment guidelines

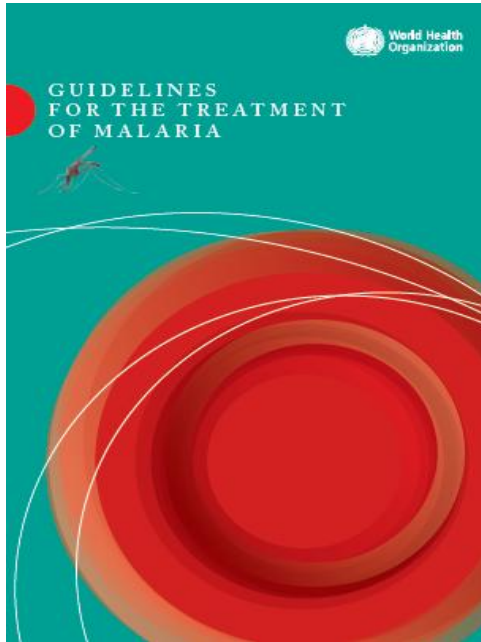
Combinations recommended against *P. falciparum*



- Artemisinin based combinations
 - Artemether + lumefantrine
 - Artesunate + amodiaquine
 - Artesunate + mefloquine
 - Artesunate + sulfadoxine-pyrimethamine
 - ACT + Tet or Dox or Cln (special groups)
 - Dihydroartemisinin + Piperaquine
 - ACT + PQ (0.75mg/kg single dose)

WHO calls for use of ACTs and careful monitoring of their efficacy (2006)

WHO treatment guidelines

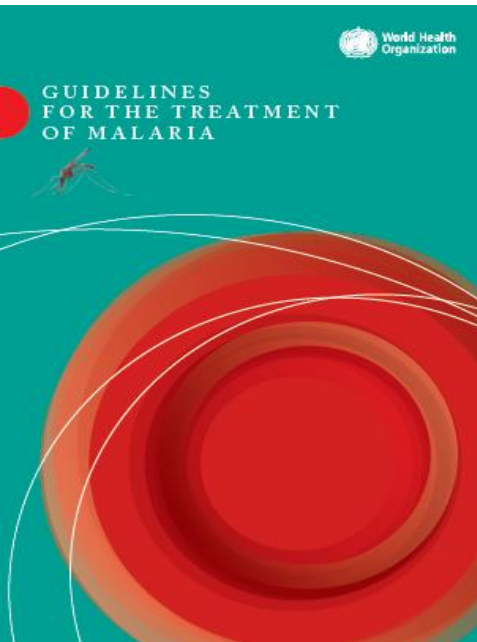


Recommendations against *P. vivax*:

- Sensitive to Chloroquine:
(CQ) 25mg/kg divided over three days +
(PQ) 0.25mg/kg daily for 14 days
- Resistant to Chloroquine
Suggest ACT+PQ (with AQ, MQ or PPQ)
(DHA+PPQ; AL; AS+AQ; AS+MQ)
exception AS+SP – not effective in many
places

**WHO calls for use of ACTs and careful monitoring
of their efficacy (2006)**

WHO treatment guidelines



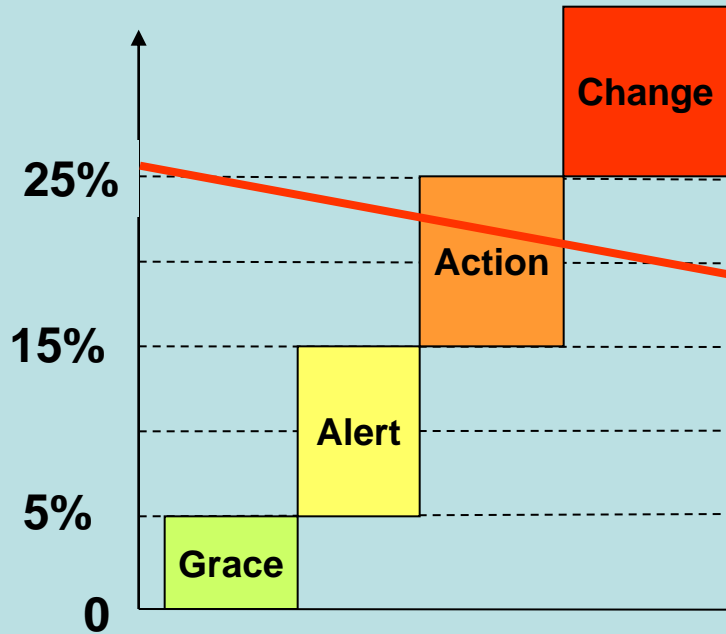
Recommendations against *P. vivax*:

- Severe *P. vivax* – cerebral malaria, severe anemia, thrombocytopaenia and pancytopenia, jaundice, splenic rupture, acute renal failure, acute respiratory distress syndrome, pulmonary oedema
- prompt and effective treatment same as for severe and complicated malaria

WHO calls for use of ACTs and careful monitoring of their efficacy (2006)

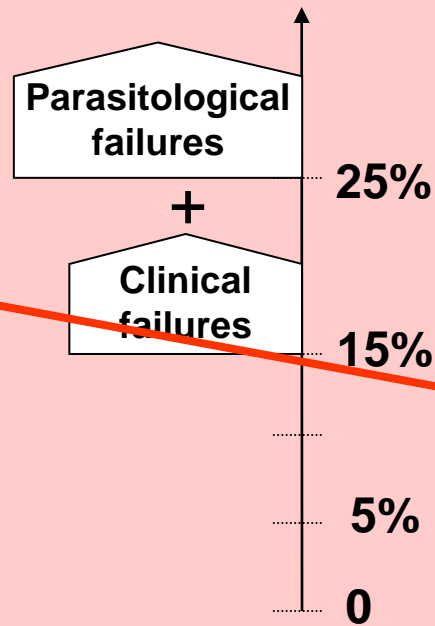
Threshold levels for changing malaria treatment policy

% clinical failures (14 d f/up)



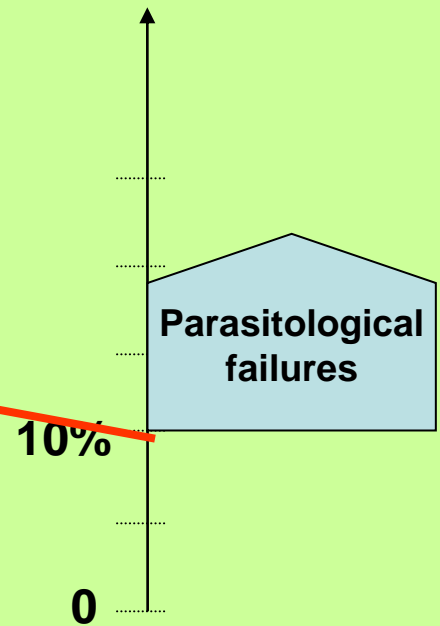
WHO criteria 1998

% failures (14 d f/up)



WHO criteria 2003

% failures (28 d f/up)



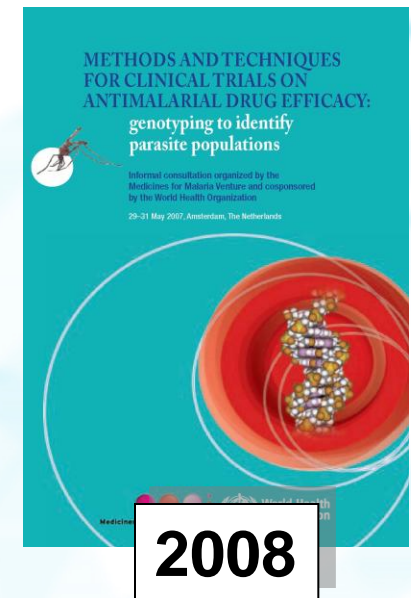
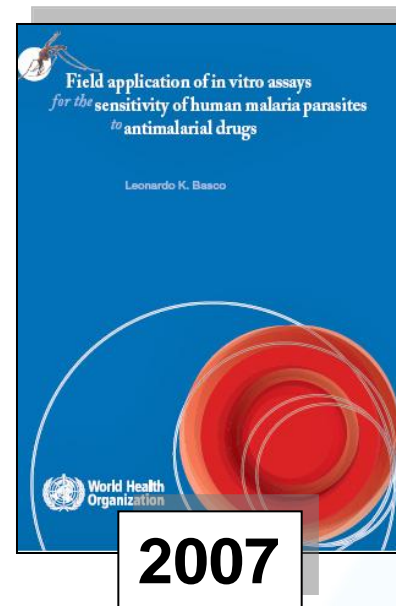
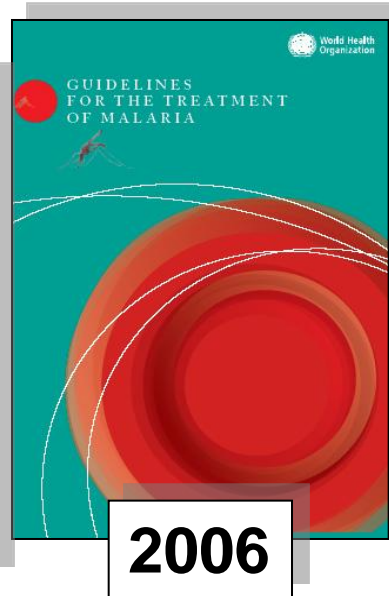
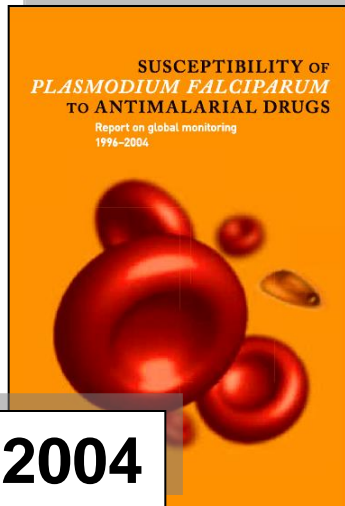
WHO criteria 2005

Monitoring antimalarial in very low transmission setting



Dr P. Ringwald
Global Malaria Programme

WHO/GMP Guidelines



Challenges

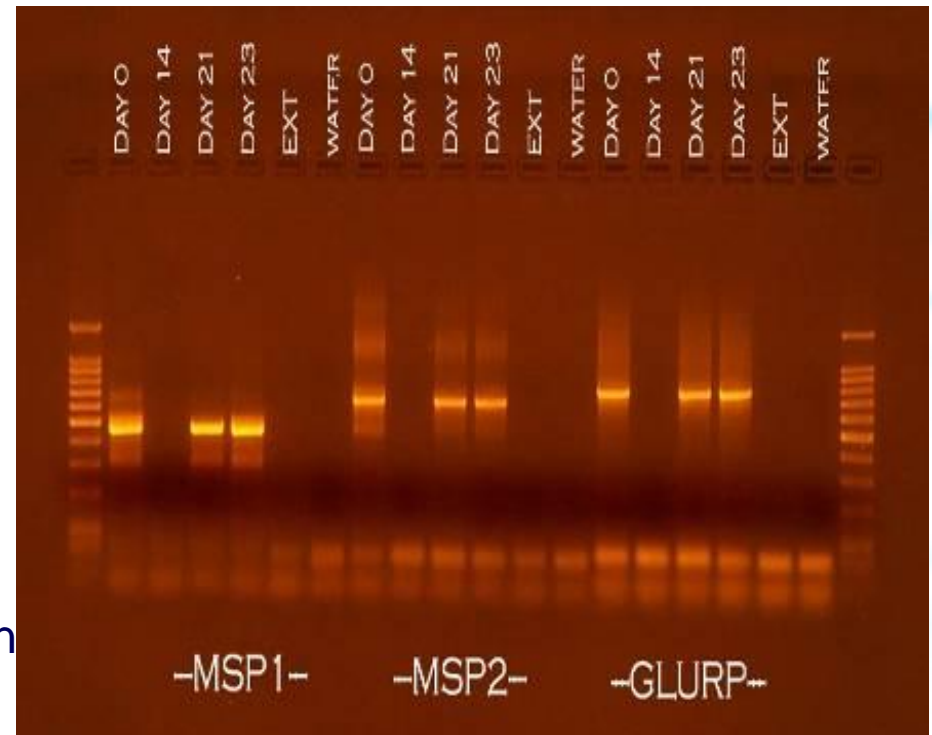
- **Routine monitoring of ACTs**
 - Most of the countries carried out TET to update drug policy
 - Rarely as a routine activity (change of sites, personnel, decentralization)
- **Funding**
 - GF, PMI (USAID), WB and bilaterals
 - Gaps for some countries and absence of sustainability
- **"Less but better studies"**
 - More expensive
 - Longer follow-up
 - More QA and QC
 - PCR becomes compulsory
 - Set up national or regional reference centres for molecular biology

Monitoring *P. vivax*

- **Major differences with falciparum protocol**
 - Inclusion criteria
 - Parasitemia > 250 μ l
 - History of fever 48 hours
 - Classification
 - Same as falciparum or simplified
 - Chloroquine blood concentration
 - D7, D failure, D 28, D0
 - 100 μ l on filter paper

Genotyping to distinguish between reinfection and recrudescence

- Compulsory for TET (longer follow-up)
- Sampling D0, D7, D14, D21, D failure, D28
- Genotyping only D0 and D failure
- Consensus on standardization during co-sponsored WHO MMV meeting
 - Sampling scheme
 - Methods of blood sampling and sample storage
 - Genotyping strategy
 - Analyses and outcome classification
 - Quality control
 - Genotyping of *P. vivax*



Monitoring therapeutic efficacy for countries targeting elimination

- Detection of patients – active or passive?
- Routine in vivo monitoring of therapeutic efficacy with modified inclusion criteria (age, parasitemia, fever)
- Hospitalise all *P. falciparum* patients
 - Tunisia and Morocco experience (≠ United Arab Emirates)
 - Monitor all patients regardless of parasitaemia
 - 28 day follow up
 - No loss to follow-up
 - Use PCR for distinguishing between recrudescence and re-infection
- Use in vitro and molecular markers as additional tools

Parasites vs. Drugs

- Treatment failure, development of resistance CQ
- Changes to Monotherapy: SP, MQ – further resistance
- Changes to Combination Therapy – possible resistance, how delay?
- Genetic changes – molecular epidemiology – treatment and diagnosis

Estudios de Eficacia

- Guia Practica para Estudios de Eficacia en Areas de Baja Transmision
- AMI/RAVREDA adaptacion del guia – reunion tecnica Panama 2010

Gracias

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