Antimalarial Drug Combinations

P.Olliaro MD, PhD
WHO/TDR

A bit of History

- Failing drugs + liberal practice + inappropriate test
- Mono-therapies deployed in sequence
  - Parasite resistance
  - Effects underestimated; over-reliance →
  - Excess morbidity & mortality
- Theory & trials in support of combinations
  - Evidence of efficacy/safety & effectiveness
  - Evidence on appropriate methodology
- Interaction: research-policy
- Informed policy decision

Why combining drugs ?

- Mutual protection against resistance -best if:
  - Independent mode of action (different targets)
  - Complementary pharmacodynamic effects
  - Comparable concentration/time profiles
- Prolong useful therapeutic life-span
- Broader spectrum -best if:
  - Younger and more mature asexual forms
  - Gametocytes; liver stages; …
- Long-time practice in other disciplines

Current combinations

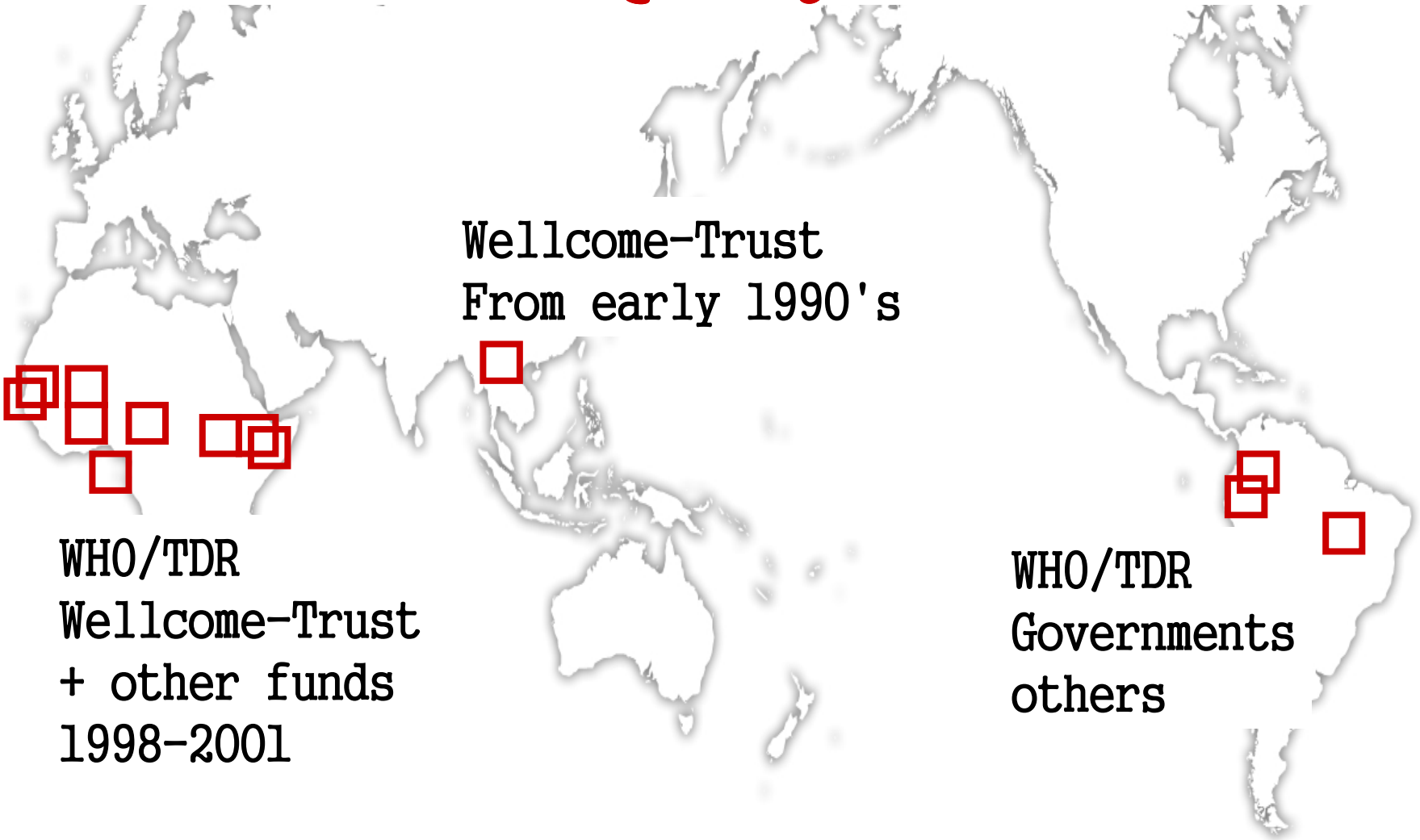
Artemisinin:

- Very rapid killing
- Short-lived
- Residual parasites
- Act on rings + more mature asexual parasites + young gametocytes
- Virtually no selective window
- No resistance (so far)? (slower clearance in Cambodia?)

Companion drug:

- Rapid killing (quinolines)
- Longer residence
- Killing residual parasites
- Act on mature asexual forms
- Variable selective window
- Variable (cross) resistance

Driver of change: parasite resistance to traditional antimalarial drugs
→ evidence-based policy recommendation



Evidence of efficacy

Day 28 failure rates

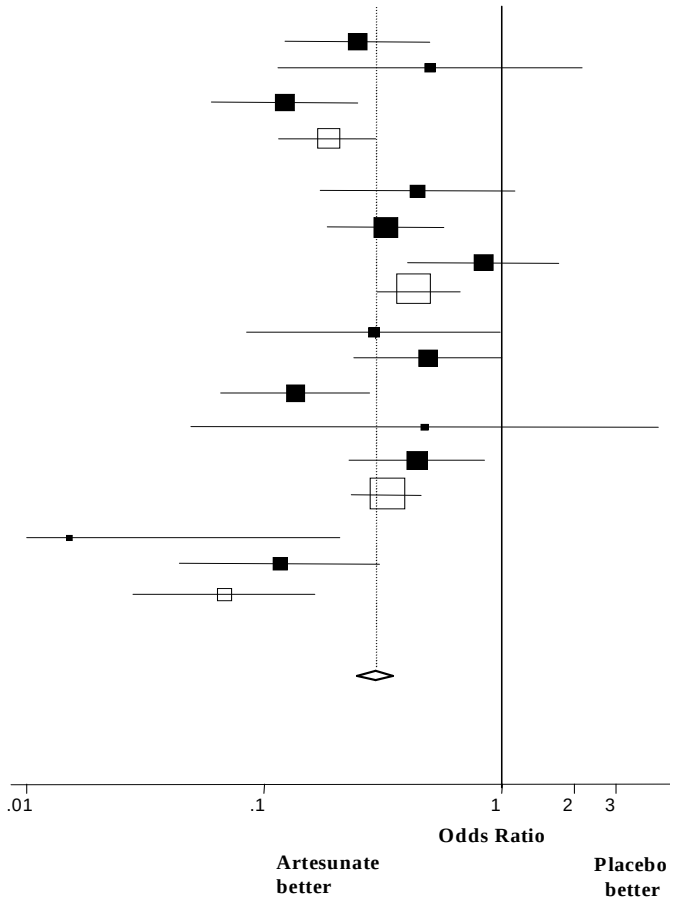
ACTs →

Accelerate therapeutic response

↑cure rates

(↓transmissibility)

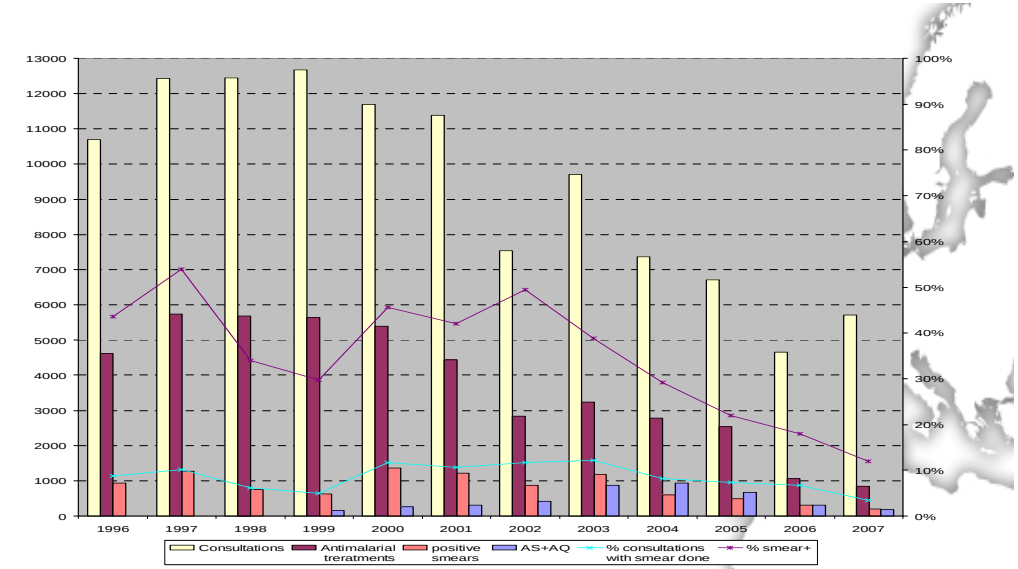
Companion Drug	Study	AS3	Placebo	O-E	V(O-E)
CQ	Burkina	74/145	115/142	-21.49	16.19
	C.Ivoire	115/124	129/134	-2.27	3.32
	Saotome	85/181	154/175	-36.51	19.69
	Subtotal	*274/450*	*398/451*	*-60.27*	*39.19*
AQ	Gabon	14/94	28/98	-6.56	8.24
	Ken_AMRF	57/180	108/183	-24.82	22.56
	Senegal	29/159	33/156	-2.30	12.49
	Subtotal	*100/433*	*169/437*	*-33.68*	*43.29*
SP	Gambia	6/187	20/193	-6.79	6.07
	Ken_KMRI	89/192	121/189	-16.83	23.62
	Malawi	41/134	99/129	-30.33	16.43
	Peru	2/97	4/93	-1.06	1.46
	Uganda	48/116	89/144	-13.12	16.08
	Subtotal	*186/726*	*333/748*	*-68.14*	*63.66*
MQ	Thai2	1/180	46/169	-23.24	10.19
	Thai3	9/179	57/181	-23.82	13.51
	Subtotal	*10/359*	*103/350*	*-47.06*	*23.70*
	Total	**570/1968**	**1004/1987**	**-209.41**	**169.91**



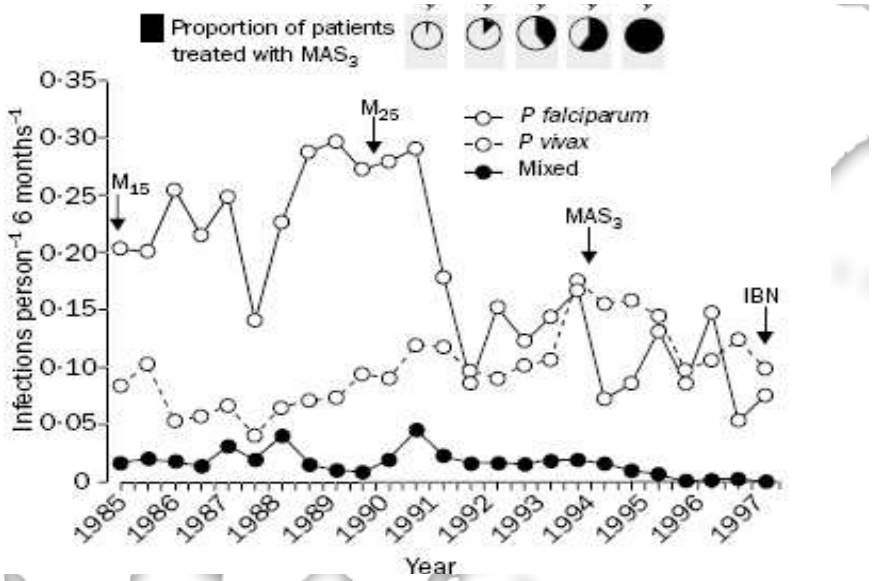
Adjuik et al, Lancet 2004

Background drug	OR	99% CI	p
CQ	0.19	0.12, 0.30	<0.0001
AQ	0.45	0.30, 0.68	<0.0001
SP	0.33	0.24, 0.46	<0.0001
MQ	0.07	0.03, 0.17	<0.0001
		95% CI	
Overall	**0.27**	**0.23, 0.32**	**<0.0001**

Evidence of effects



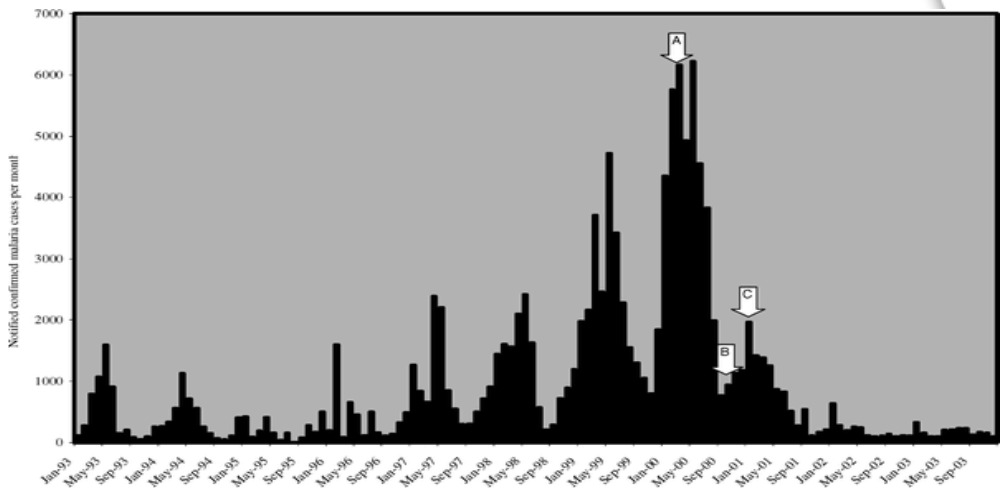
Casamance, Senegal



Thai-Myanmar borders

Zanzibar

Kwazulu-Natal, South Africa



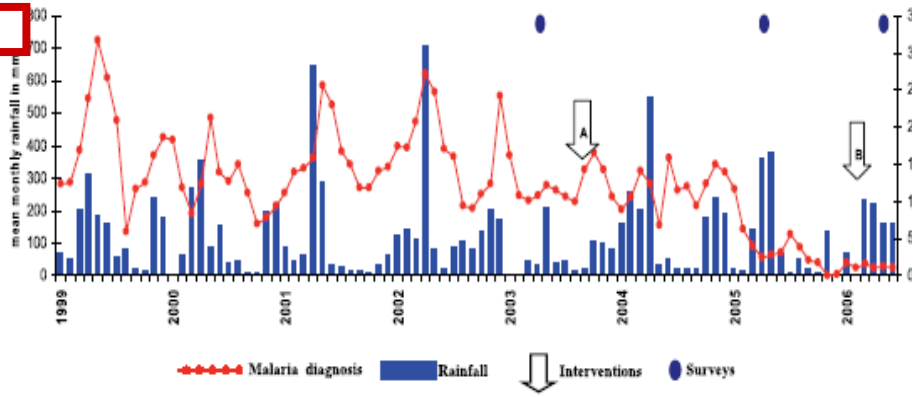


Figure 1. Malaria Interventions, Cross-Sectional Surveys, Monthly Rainfall, and Reported Clinical Malaria Diagnoses in Children under 5 Years of North A District, Zanzibar

(A) Start of the implementation of artemisinin-based combination therapy for treatment of uncomplicated malaria in September 2003.
(B) Introduction of LLINs in February 2006. Promotion of ITNs started in January 2004; the use of conventional ITNs, however, remained low, u introduction of LLINs. Outpatient data for 2006 are up to June.

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What have we learnt ?

- Deploying effective drugs reduces morbidity & mortality
- Combining effective interventions (ACTs + insecticide-treated nets, residual spraying) works - evidence from areas of low and moderate transmission
- Fixed combinations for improved adherence
- Adapted dosage forms & dosing schedules needed to avoid
  - underdosing (failure, resistance)
  - & overdosing (toxicity; non-compliance, resistance)

The Challenges Ahead

- Drug pressure: companion drugs = few chemical families & modes of action; compromised by (cross)resistance
- The pipeline: lacks novelty in the medium term; no immediate replacement for classical artemisinin derivatives
- Deployment & practice: misuse; coverage
- Looming resistance?
- P.vivax, mixed infections
- Multiple first-line therapies to dilute pressure?