Evidence of Improved Diagnosis and Management of Malaria from Bangladesh

Professor Md. Abul Faiz

Professor of Medicine (PRL), SSMC, Dhaka

&

Malaria Research Group, Chittagong, Bangladesh

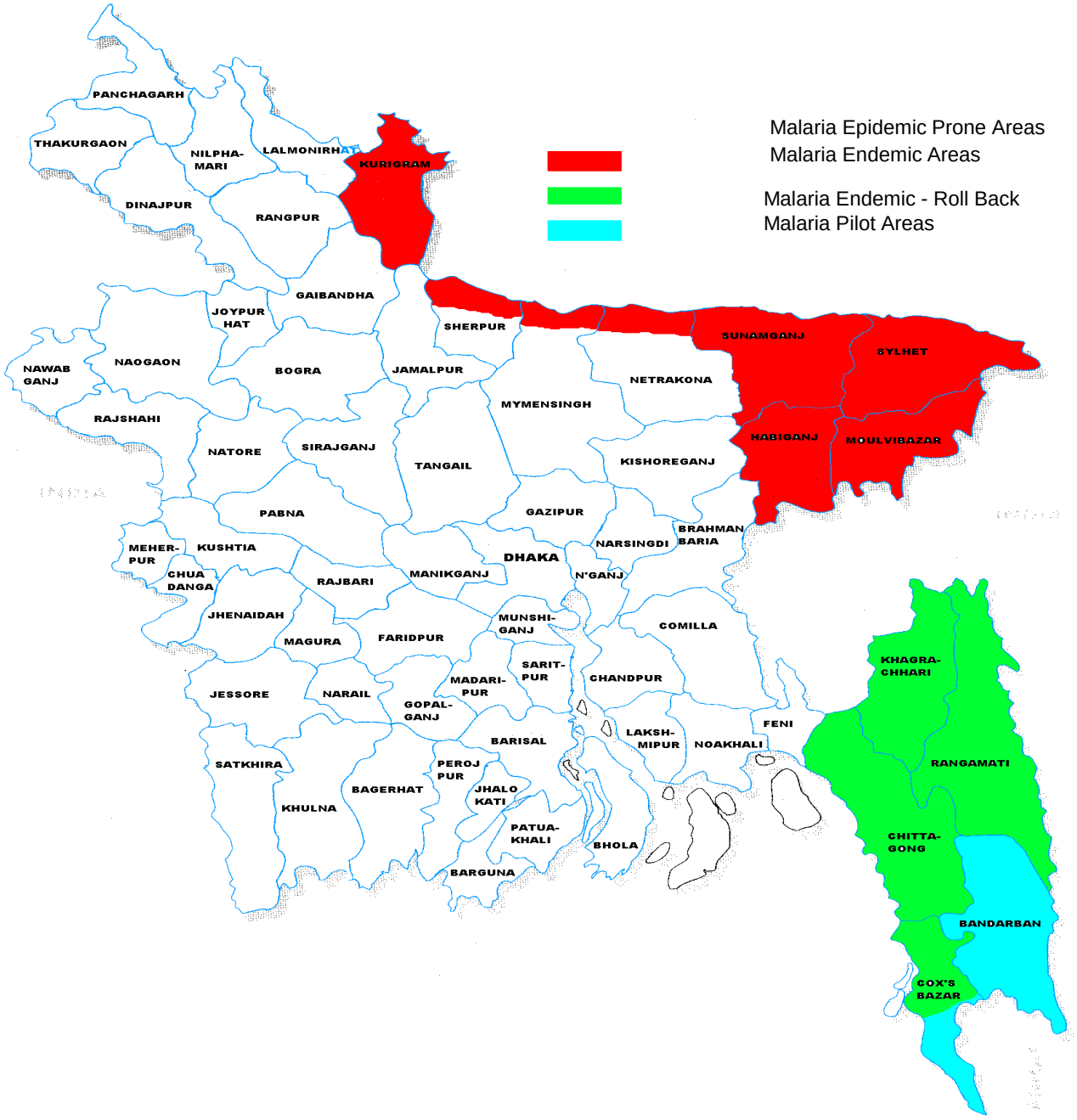
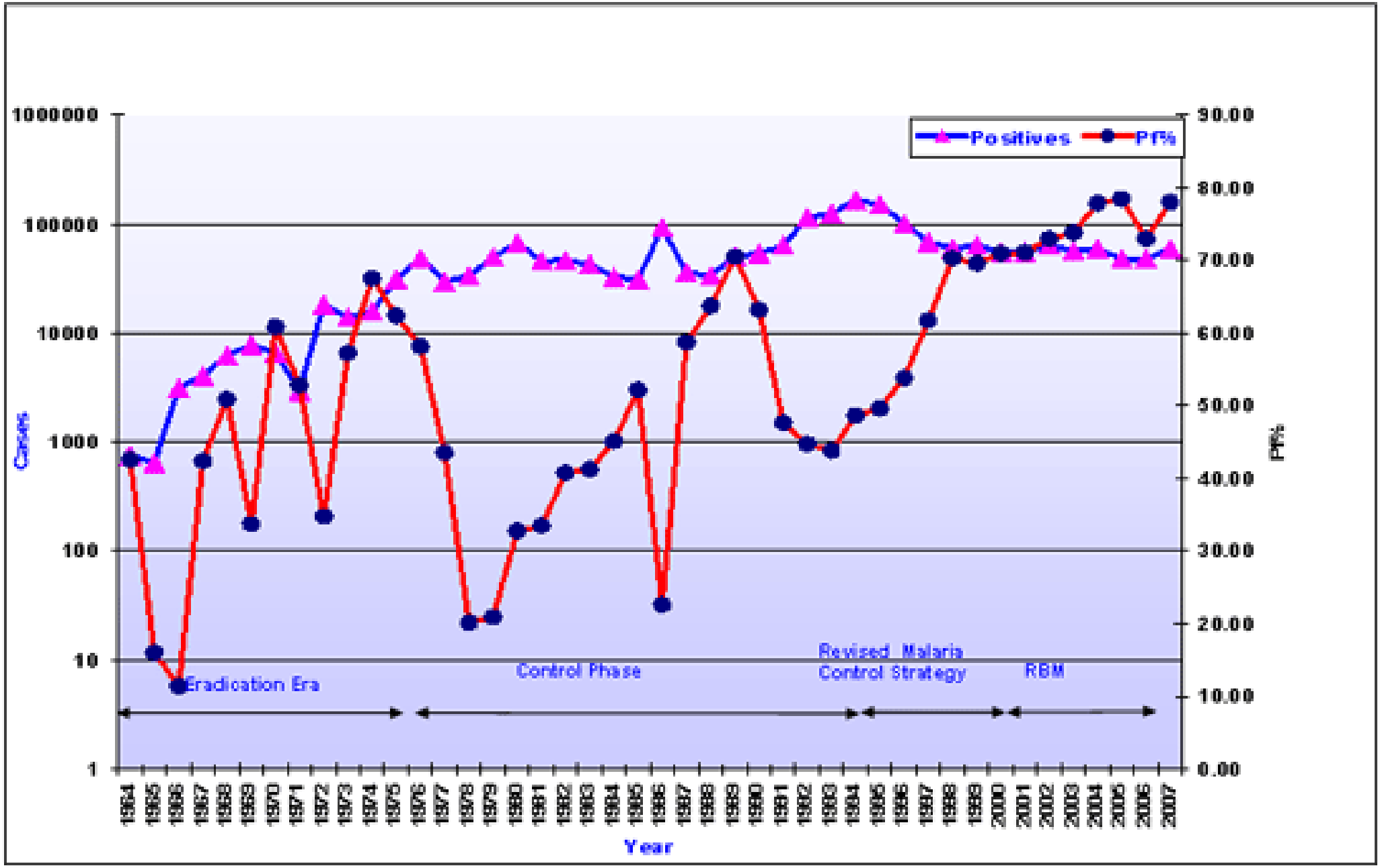

Malaria Epidemic Prone Areas
Malaria Endemic Areas
Malaria Endemic - Roll Back
Malaria Pilot Areas
PANCHAGARH
THAKURGAON
NILPHA-MARI
LALMONIRHAT
KURIGRAM
DINAJPUR
RANGPUR
GAIBANDHA
JOYPUR HAT
SHERPUR
SUNAMGANJ
SYLHET
NAWAB GANJ
NAOGAON
BOGRA
JAMALPUR
NETRAKONA
MYMENSINGH
RAJSHAHI
HABIGANJ
MOULVIBAZAR
NATORE
SIRAJGANJ
TANGAIL
KISHOREGANJ
PABNA
GAZIPUR
BRAHMAN BARIA
MEHER-PUR
KUSHTIA
DHAKA
NARSINGDI
CHUA DANGA
RAJBARI
MANIKGANJ
N'GANJ
JHENAIDAH
MUNSHI-GANJ
COMILLA
MAGURA
FARIDPUR
KHAGRA-CHHARI
SARIT-PUR
MADARI-PUR
CHANDPUR
JESSORE
NARAIL
GOPAL-GANJ
FENI
LAKSH-MIPUR
BARISAL
NOAKHALI
SATKHIRA
PEROJ PUR
RANGAMATI
BAGERHAT
JHALO KATI
KHULNA
PATUA-KHALI
CHITTA-GONG
BHOLA
BARGUNA
BANDARBAN
COX'S BAZAR

Fig 1: Reported Malaria Cases in Bangladesh, 1964-2007



Review of the current evidence on malaria

Case Definition (previous)

- Uncomplicated malaria
- Treatment failure malaria
- Severe malaria

- Clinical diagnosis: correct in 32% cases
  - (684 patients, 8 UZHC)

  - Incorporation of laboratory diagnosis: RDT or microscopy

Am J Trop Med Hyg 2002; 67: 396-399

Efficacy trial of Antimalarials

- High degree of failure to CQ, S-P, Q3 + S-P
- High equal efficacy of A-L (97%), MQ+ AS (100%)
  - (N=364)

  - New Bangladesh Treatment Guidelines – treatment of Uncomplicated falciparum malaria- ACT (A-L)

Trans R Soc Trop Med Hyg 2001, 2005

Adherence & Efficay of A-L

- Directly observed treatment (DOT) vs Non-directly observed treatment (NDOT)
- (n=320)
- PCR-corrected 42-day parasitological and clinical cure rate 100 % vs 99.3%

Trans R Soc Trop Med Hyg 2008, 102: 861-867

Study to document pre admission risk factors for development of severe malaria and the spectrum of it and outcome in different categories of hospitals in malaria endemic zone of Bangladesh.

Faiz MA, Yunus EB, Rahman MR, Hossain MA Rahman ME, Bhuiyan SN
J. Bangladesh Coll Phys Surg. 22: 3, 83 – 88.

Outcome of patients of SM Categories of Hospital N = 909

Outcome	Total =909 N (%)	PHC = 339 N (%)	SHC = 382 N (%)	THC N = 188 N (%)	
Full Recovery	747 (82.2)	286 (84.4)	321 (84.0)	140 (74.5)	P> 0.05
Recovery with sequelae	13 (1.4)	9 (2.7)	2 (0.5)	2 (1.1)	P< 0.05
Death	58 (6.4)	5 (1.5)	19 (5.0)	34 (18.1)	P> 0.01
Not known	91 (10.0)	39 (11.5)	40 (10.4)	12 (6.4)	P< 0.05

A Randomized Controlled Trial Comparing Artemether and Quinine in the Treatment of Cerebral Malaria in Bangladesh

Indian Journal of Malariology Vol. 38, March-June 2001, pp. 9-18

Comparison of treatment groups

Clinical criteria	Artemether	Quinine
Total number of patients	51	54
Age (years) (mean + SD)	28+10	30+10
Sex-Male	36(71%)	42(72%)
Weight in kg (Mean + SD)	47.5+ 8.7	48.1 + 9.6
Pre-treatment parasitaemia range (n/cm)	500-500000	500-500000
Duration of coma at presentation (hrs)	17.7+12.3	17.4+12
Prior quinine n (per cent)	24(57%)	25(58%)
H/0 convulsion	22(53%)	23(42%)
Splenomegaly	11(21%)	16(29%)
Retinal haemorrhages	7(14%)	8(15%)
Papilloedema	5(10%)	3 (6%)
n = No. of patients.		

Comparison of treatment groups (Important laboratory parameters)

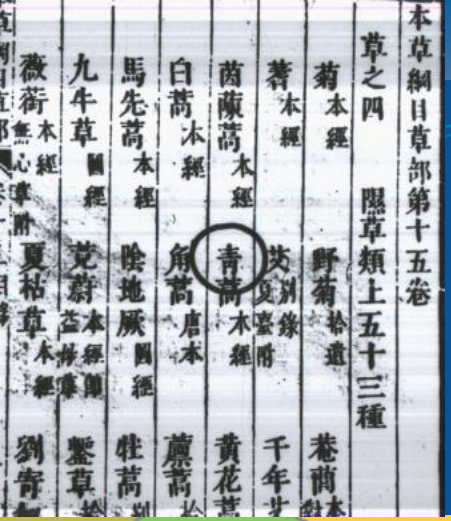
Lab. characters	Artemether	Quinine
Blood glucose (mg/dl ± SD)	135 ± 91	152 ± 99
Blood urea (mg/dl ± SD)	68 ± 17.5	59.5 ± 35
S. Creatinine (mg/dl ± SD)	1.6 ± 1.3	1.5 ± 1
S. Sodium (mmol/1 ± SD)	128.7 ± 7.3	129 ± 4.9
S. Potassium (mmol/dl ± SD)	3.6 ± 0.6	3.7 ± 6.0
S. Bilirubin (mg/dl ± SD)	2.3 ± 1.5	2.1 ± 1.2
CSF protein (mg/dl ± SD)	41.4 ± 24.6	40.8 ± 28.3
CSF cell (n ± SD)	8 ± 3	9 ± 7
CSF pressure raised	7(15%	13(25%)
Hb<9g/dl	21 (42%)	19 (35%)
n = No. of observations.		

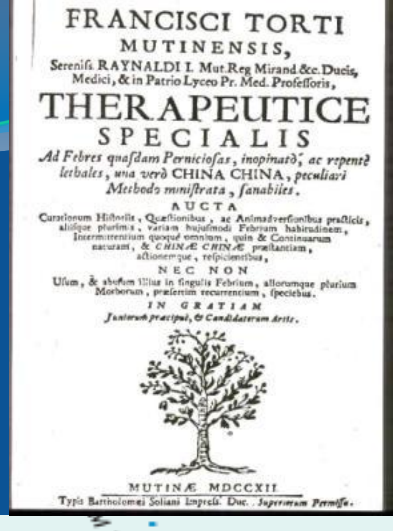
Comparison of outcome of treatment groups: Outcome of treatment

Group	Complete recovery	Death n(%)	Recovery with sequelae n(%)
Artemether	39(76)	9(18)	3(6)
Quinine	43(79)	10(19)	1(2)
Prior quinine	43(88)	6(12)	0
Other outcome variables			
Variables	**Artemether**	**Quinine**	**p-value**
Coma resolution time (hours ± SD)	74.2 ± 51.8	53.4 ± 36	0.0306
Parasite clearance time (hours ± SD)	52.1 ± 33.3	60.7 ± 39	028
Fever clearance time (hours ± SD)	58 ± 15.6	47 ± 31.5	0.18
Recrudescent parasitaemia [n (%)]	4(10)	1(2)	0.18
n = No. of patients.			

SEAQUAMAT study

Multicentre randomised trial of IV artesunate vs IV quinine for treatment of severe malaria





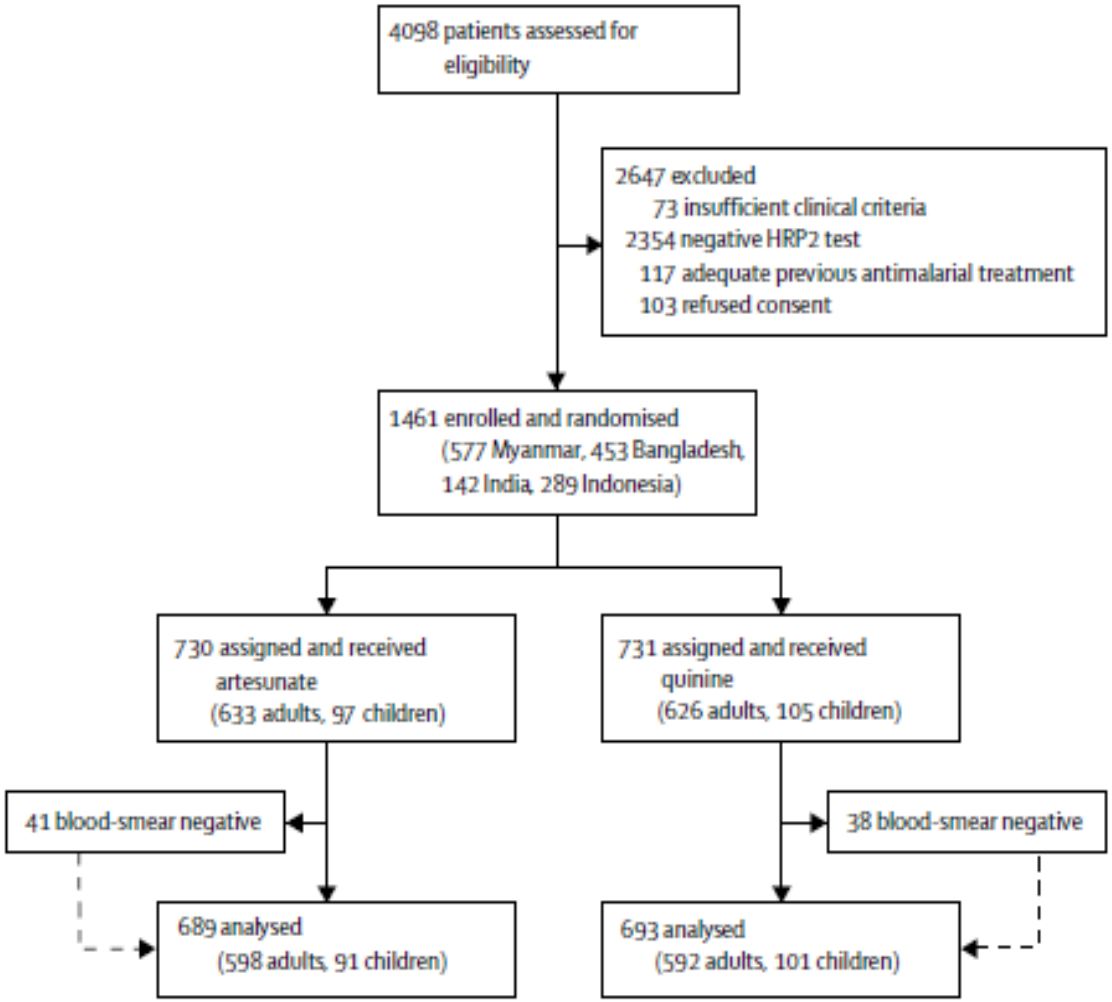
*South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group**

SEAQUAMAT Study

www.thelancet.com Vol 366 August 27, 2005

Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group*



2003-2005

453/1461 patients from CMCH

Categorical Baseline Characteristics

	Artesunate (n=730)	Quinine (n=731)
Sex		
Male	546 (75%)	529 (72%)
Female	184 (25%)	202 (28%)
Child (age <15 years)	97 (13%)	105 (14%)
Pregnant	23 of 133 (17%)	26 of 143 (18%)
Pretreatment with antimalarial drug	167 (23%)	142 (19%)
Pretreatment with quinine	103 (14%)	84 (11%)
Pretreatment with artemisinin derivative	25 (3%)	42 (6%)
Pretreatment with chloroquine	43 (6%)	21 (3%)
Pretreatment with sulphadoxine-pyrimethamine	9 (1%)	10 (1%)
Pretreatment with mefloquine	0	5 (1%)
Pretreatment with an effective antimalarial*	125 (17%)	118 (16%)
Severe malaria†	509 (70%)	541 (74%)
Malaria parasites on blood film	708 (97%)	716 (98%)
Hyperparasitaemia (>10%)	121 (17%)	108 (15%)
Complications on admission		
Coma (Glasgow coma scale <11 or Blantyre coma scale <3)	284 (39%)	304 (42%)
Convulsions	89 (12%)	87 (12%)
Jaundice (clinical)	355 (49%)	349 (48%)
Severe anaemia (haemoglobin <50 g/L)	40/683 (6%)	54/675 (8%)
Shock (clinical)	78 (11%)	92 (13%)
Acidosis (base excess less than −3·3 mmol/L)	308/662 (47%)	334/648 (52%)
Hypoglycaemia (blood glucose <2·2 mmol/L)	8/701 (1%)	17/693 (3%)
Respiratory distress	79 (11%)	96 (13%)
Blackwater fever	20 (3%)	16 (2%)
History of anuria	99 (14%)	135 (18%)

Continuous Baseline Characteristics

	Artesunate (n=730)	Quinine (n=731)
Age (years); mean (95% CI)	27·9 (26·8–29·0)	27·9 (26·8–29·0)
Days of fever	5 (3–7, 0–120)	5 (3–7, 0–120)
Days of coma	0 (0–0·75, 0–4)	0·1 (0–1, 1–7)
Physical examination		
Weight (kg)	50 (43–55, 9–85)	50 (43–60, 9–100)
Temperature (°C)	38 (37·2–38·9, 35–41·5)	37·9 (37–38·9, 33·8–41·5)
Adult respiratory rate per min	24 (20–32, 12–103)	26 (20–32, 12–68)
Systolic blood pressure (mm Hg)	100 (90–115, 30–200)	100 (90–110, 30–180)
Diastolic blood pressure (mm Hg)	60 (60–70, 0–120)	60 (54–70, 0–100)
Glasgow coma scale (n=1425)	12 (9–15, 3–15)	12 (8–15, 3–15)
Blantyre coma scale (n=36)	4 (3–5, 1–5)	4 (3–5, 0–5)
Investigation		
Parasite count (per µL); geometric mean (95% CI)	39 850 (33 300–47 700)	31 050 (25 800–37 450)
Sodium (mmol/L)	134 (130–137, 108–159)	134 (130–138, 100–165)
Potassium (mmol/L)	3·9 (3·4–4·3, 2–8·8)	3·8 (3·4–4·3, 2–7·4)
Chloride (mmol/L)	101 (98–104, 77–130)	101 (98–105, 71–128)
Blood urea nitrogen (mmol/L of urea)	9·2 (5·4–17·8, 1·1–104)	10·4 (5·7–21·4, 1·1–86·8)
Haematocrit (%)	30 (22–36, 9–60)	29 (21–36, 5–62)
Haemoglobin (g/L)	100 (71–120, 26–200)	100 (70–120, 80–200)
pH	7·407 (7·352–7·448, 6·5–7·696)	7·4 (7·347–7·45, 6·542–7·582)
$paCO_2$ (mm Hg)	33 (28–38, 6–68)	32 (27–37, 7–83)
Total CO_2 (mmol/L)	22 (18–25, 2–45)	22 (17–25, 3–42)
Base excess (mmol/L)	−3 (−8 to 0, −30 to 22)	−4 (−9 to 0, −30 to 12)
Anion gap (mmol/L)	12·5 (0 to 16, −30 to 38)	13 (−1 to 16, −28 to 58)

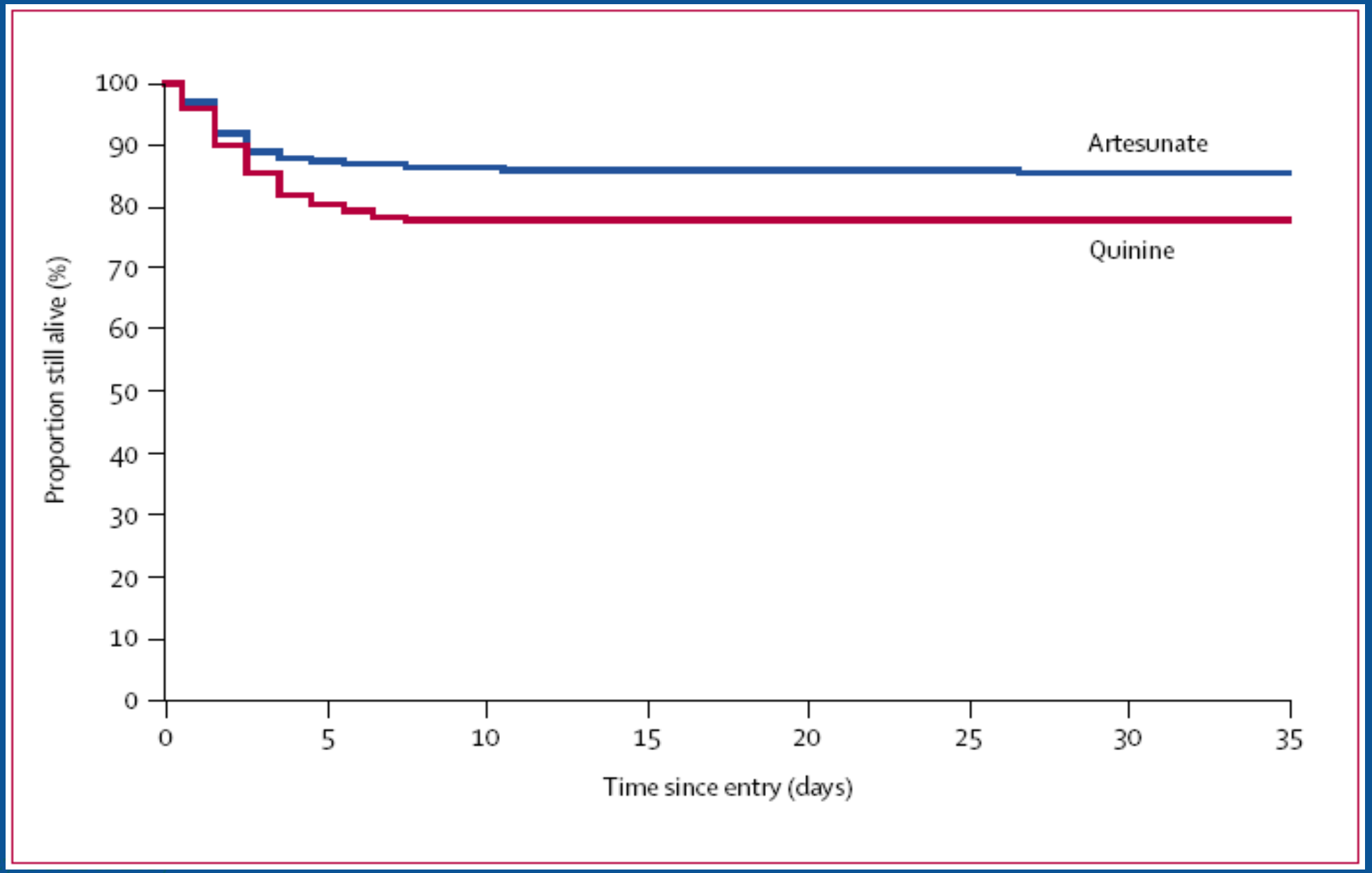
Data are median (IQR, range) unless otherwise stated.

Results by Treatment Group

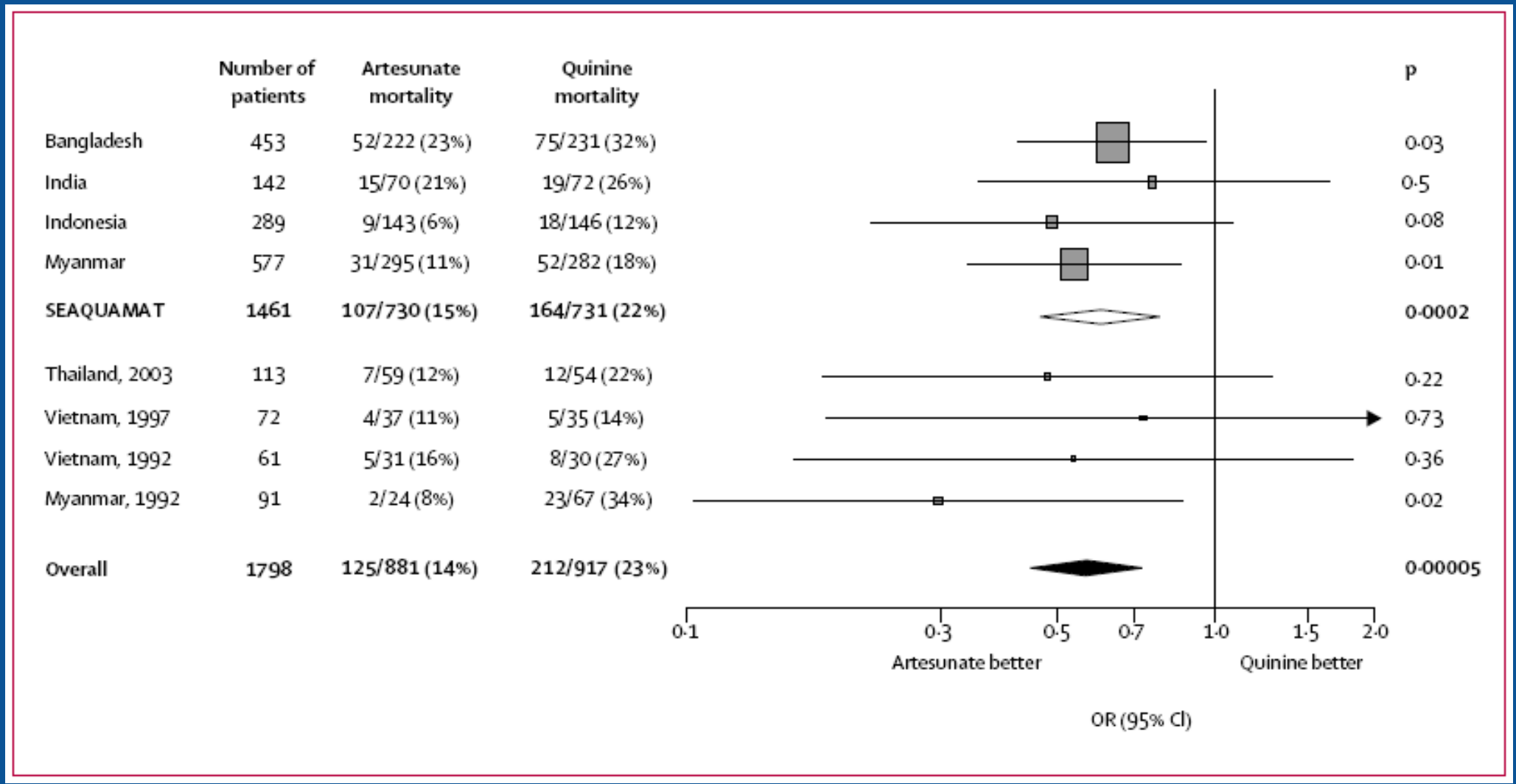
	Artesunate (n=730)	Quinine (n=731)	Mantel-Haenszel stratified OR/hazard ratio [hr] (95% CI)	p (stratified)	p for homogeneity
In-hospital death	107 (15%)	164 (22%)	0·60 (0·45–0·79)	0·0002	0·39
Death within 48 h of entry	61 (8%)	75 (10%)	0·81 (0·57–1·16)	0·25	0·67
Death after 48 h of entry	46 (6%)	89 (12%)	0·48 (0·33–0·70)*	0·0001	0·73
In-hospital death (blood-smear positive)	105 of 689 (15%)	157 of 693 (23%)	0·62 (0·47–0·82)	0·0007	0·29
Neurological sequelae	7 (1%)	3 (<1%)	2·3 (0·59–8·8)	0·22	0·34
Combined outcome: in hospital death or neurological sequelae	114 (16%)	167 (23%)	0·63 (0·48–0·82)	0·0007	0·36
Fetal death	5 of 23 (22%)	5 of 26 (19%)	1·33 (0·28–6·18)	0·72	0·34
Time to discharge (days); median (IQR, range)	5 (4–8, 0–54)	5 (4–8, 0–45)	hr 0·93 (0·83–1·04)	0·20	0·77
Time to speak (days); median (IQR, range)	1 (0–2, 0–35)	1 (0–2, 0–21)	hr 0·97 (0·84–1·13)	0·73	0·82
Time to eat (days); median (IQR, range)	2 (0–3, 0–21)	2 (0–4, 0–47)	hr 0·91 (0·79–1·04)	0·17	0·69
Time to sit (days); median (IQR, range)	2 (0–3, 0–30)	2 (0–3, 0–45)	hr 0·91 (0·80–1·05)	0·19	0·82
Convulsions after entry	31 (4%)	43 (6%)	0·70 (0·44–1·12)	0·14	0·09
Shock developing after entry	26 (4%)	36 (5%)	0·72 (0·43–1·21)	0·22	0·59
Hypoglycaemia after entry	6 (<1%)	19 (3%)	0·31 (0·12–0·78)	0·009	0·94
Blackwater fever developing after entry	49 (7%)	33 (5%)	1·58 (0·94–2·65)	0·08	0·54
Dialysis after entry	60 (8%)	48 (7%)	1·25 (0·85–1·85)	0·25	0·011
Vasopressor treatment after entry	23 (3%)	24 (3%)	0·92 (0·52–1·64)	0·78	0·28
Mechanical ventilation after entry	26 (4%)	39 (5%)	0·65 (0·39–1·1)	0·11	0·40

Data are number (%) unless otherwise stated. Analysis by intention to treat unless otherwise indicated. Results stratified by study site. * Excludes patients who died within 48 h.

Survival curve of in-hospital mortality

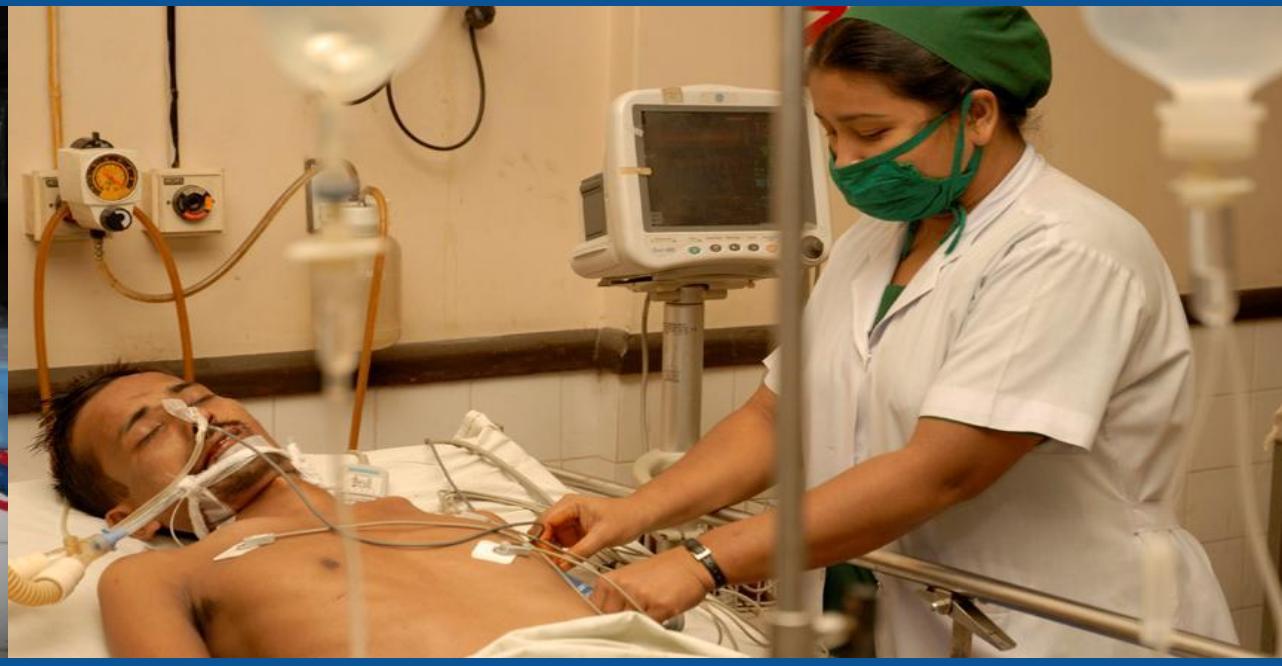


Forest plot of mortalities comparing parenteral quinine and artesunate in treatment of severe malaria in SEAQUAMAT and previously published studies

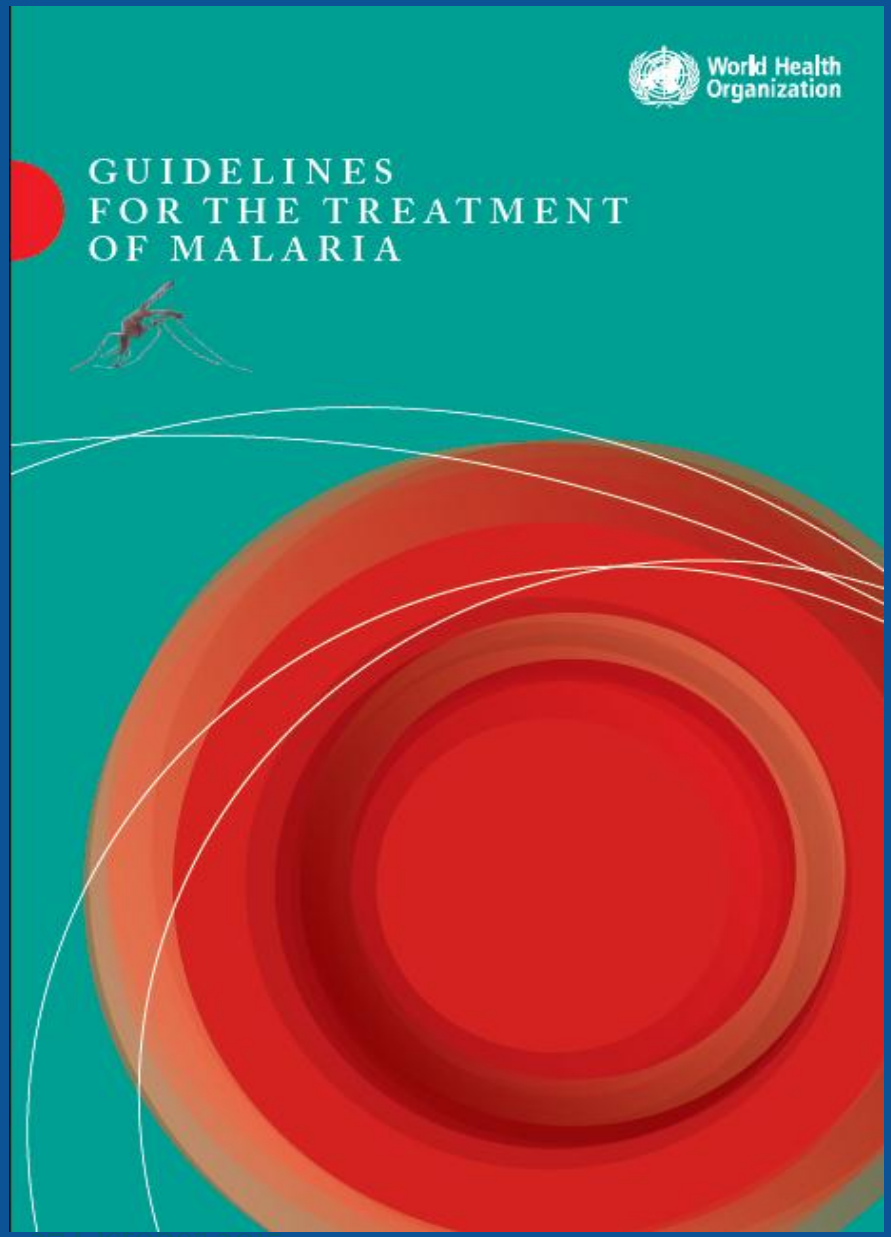


SEAQUAMAT Study

Intravenous artesunate reduces the mortality of severe malaria by 35%



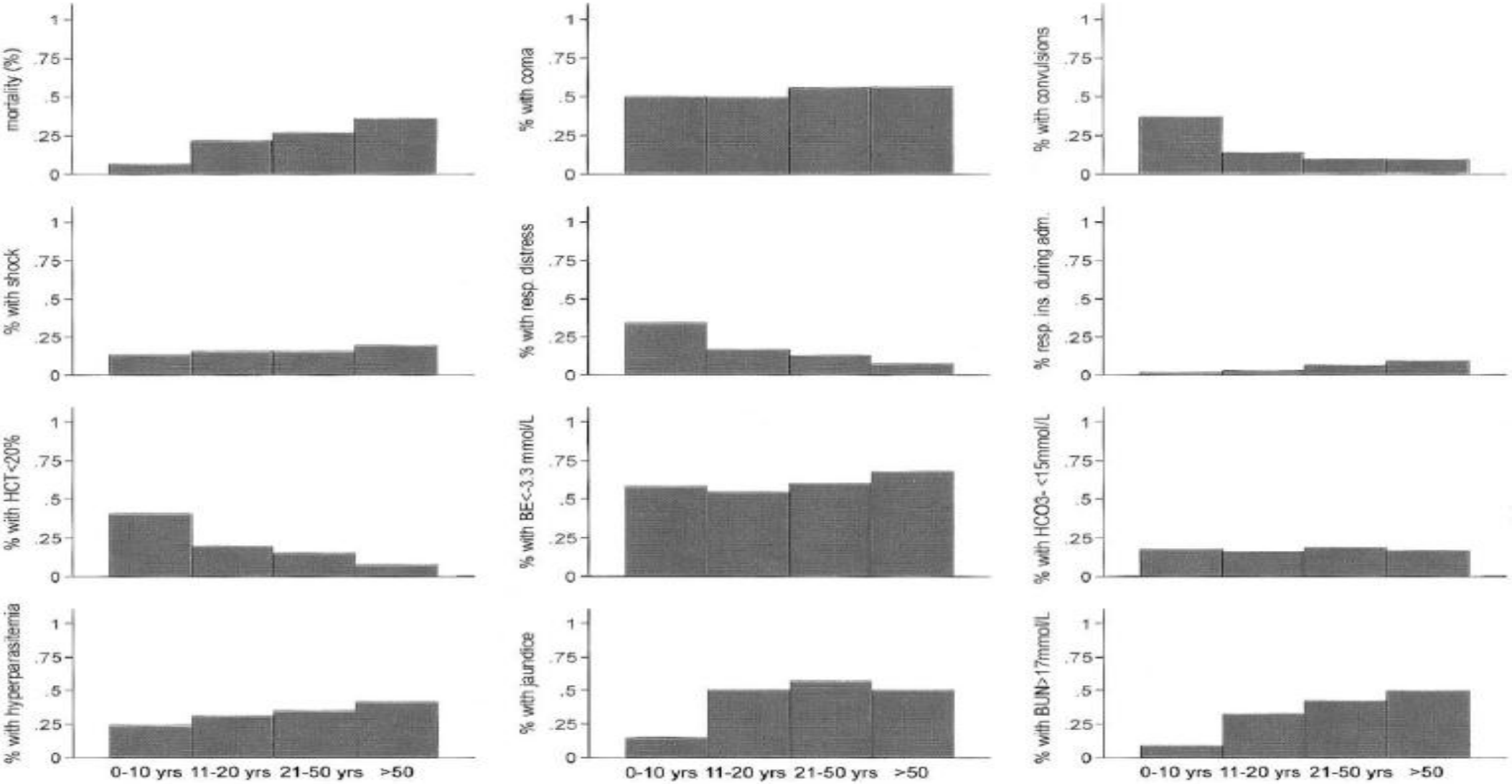
SEAQUAMAT Study



2006
WHO Malaria Guidelines

IV artesunate is now recommended first-line treatment for adult severe malaria worldwide

Mortality and presenting severity syndromes among 1050 patients with severe malaria, by age group



Treatment Cost per Patient

Country	Bangladesh	India	Indonesia	Myanmar	Pooled
Quinine					
Drug cost	$5.0	$5.5	$4.6	$4.8	$4.8
Drug administration cost	$8.2	$9.3	$9.0	$8.5	$8.7
Inpatient care cost	$21.8	$45.6	$50.2	$12.7	$27.6
Total	$35.0	$60.4	$63.8	$26.0	$41.1
Artesunate					
Drug cost	$15.8	$21.6	$13.4	$13.0	$14.7
Drug administration cost	$1.1	$1.4	$1.0	$1.0	$1.1
Inpatient care cost	$27.0	$47.3	$52.6	$12.9	$28.3
Total	$44.0	$70.3	$67.0	$26.9	$44.1

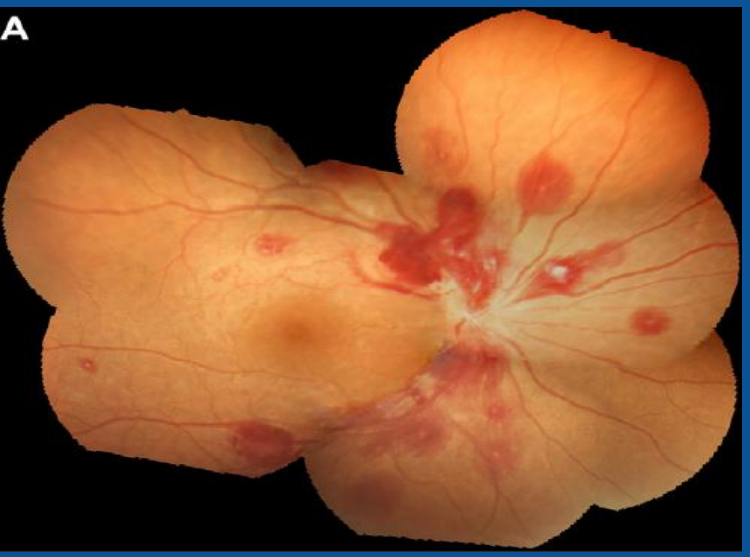
Tropical Medicine and International Health; Vol. 14 (3): 332–337.

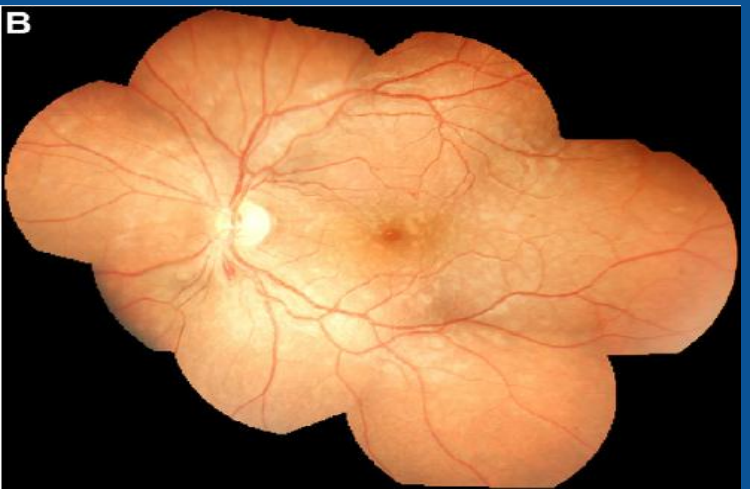
Costs for each of the treatments, combined with the relative risk to produce the numbers needed to treat and the incremental cost per death averted

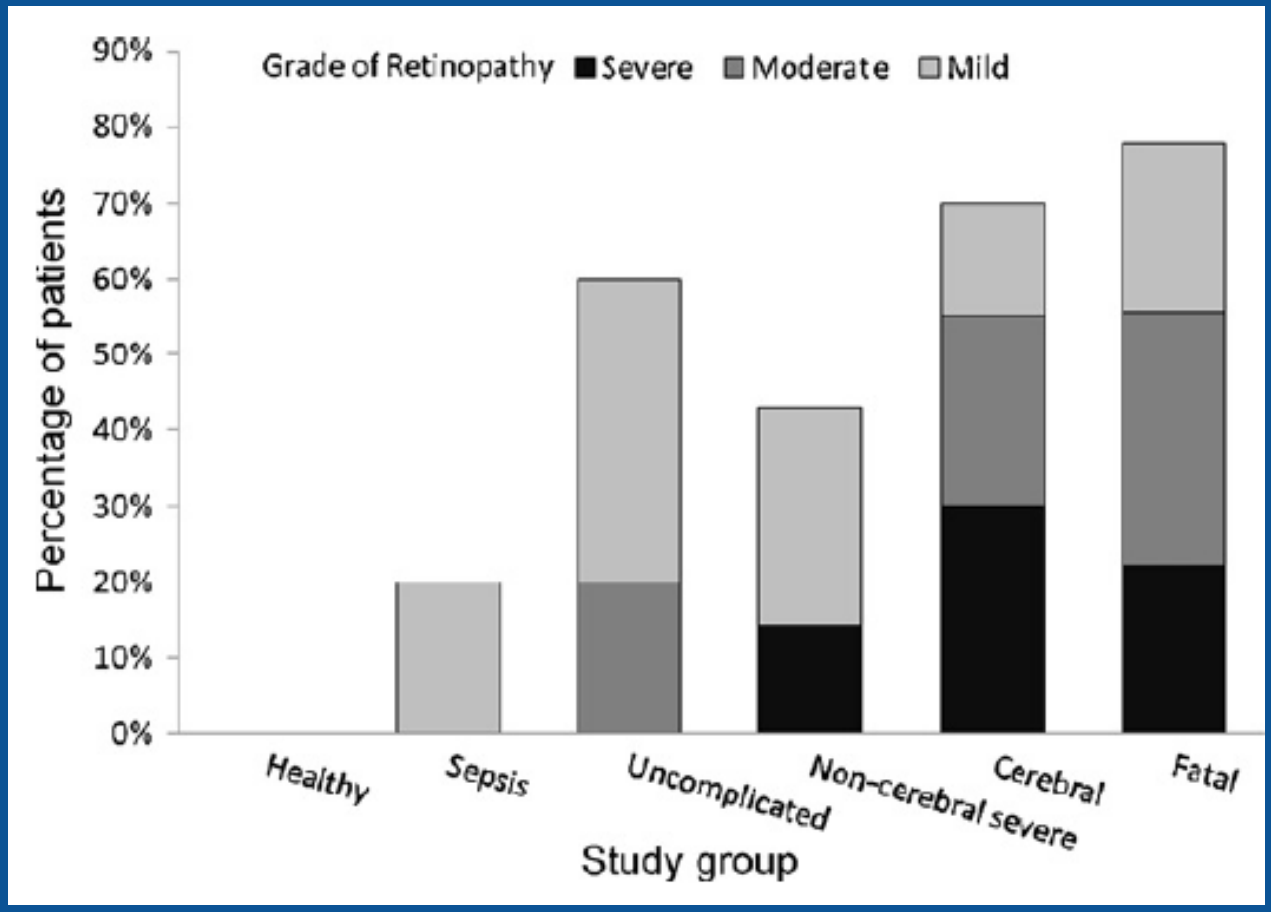
Country	Bangladesh	India	Indonesia	Myanmar	Pooled
Mean cost for patients treated with quinine	$26.8	$51.1	$54.8	$17.5	$32.4
Mean cost for patients treated with artesunate	$42.8	$68.9	$66.0	$25.8	$43.0
Relative risk for treatment with artesunate	0.72	0.81	0.51	0.57	0.65
Numbers needed to treat to avert a death	11	20	17	13	13
Incremental cost per death averted	$177.2	$358.9	$185.7	$104.8	$135.6

Tropical Medicine and International Health; Vol. 14 (3): 332–337.

Severity of retinal changes consistent with malarial retinopathy in patients with *Plasmodium falciparum* malaria or sepsis and healthy volunteers.

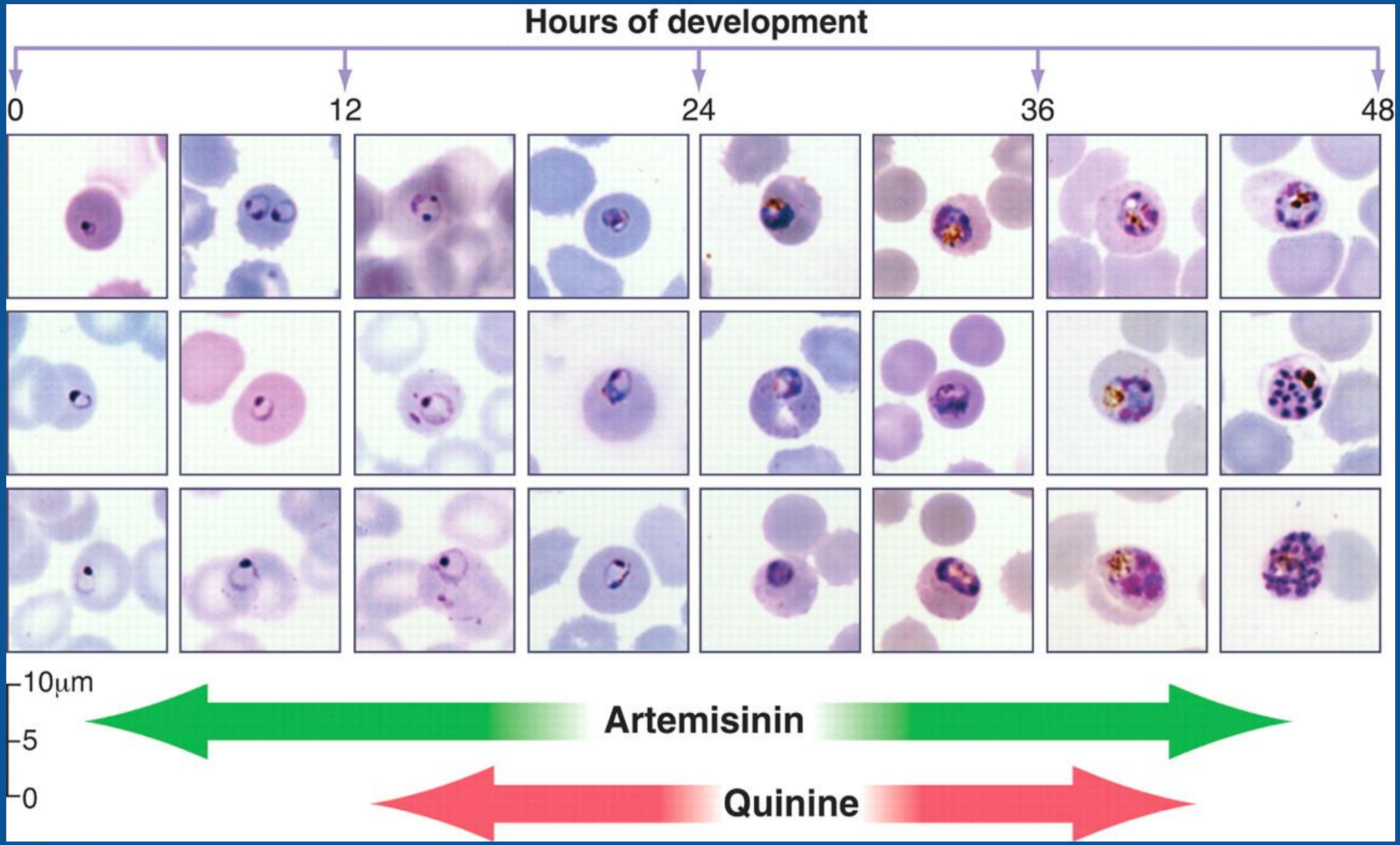




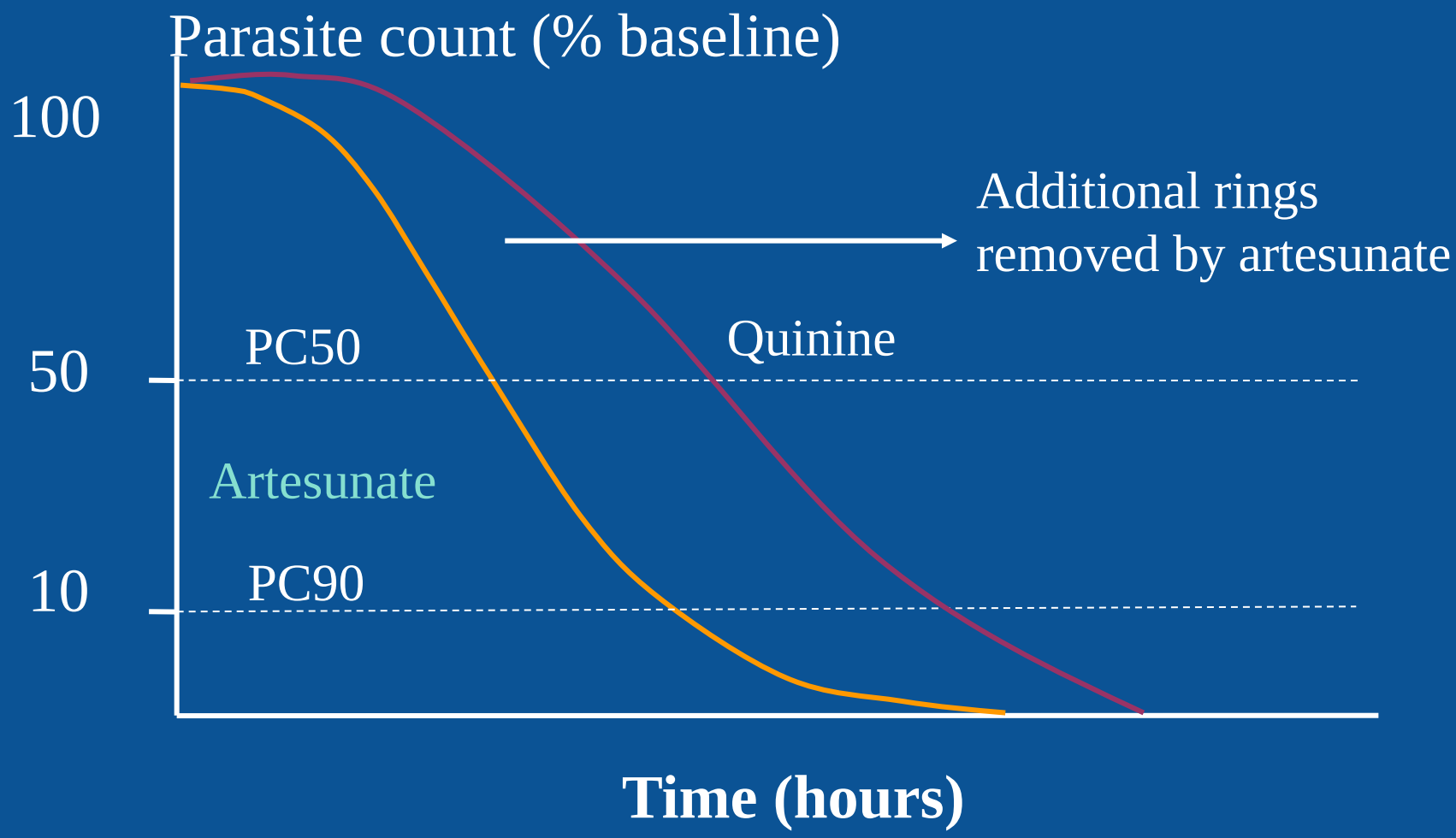


Transactions of the Royal Society of Tropical Medicine and Hygiene; 2009;103: 665—671.

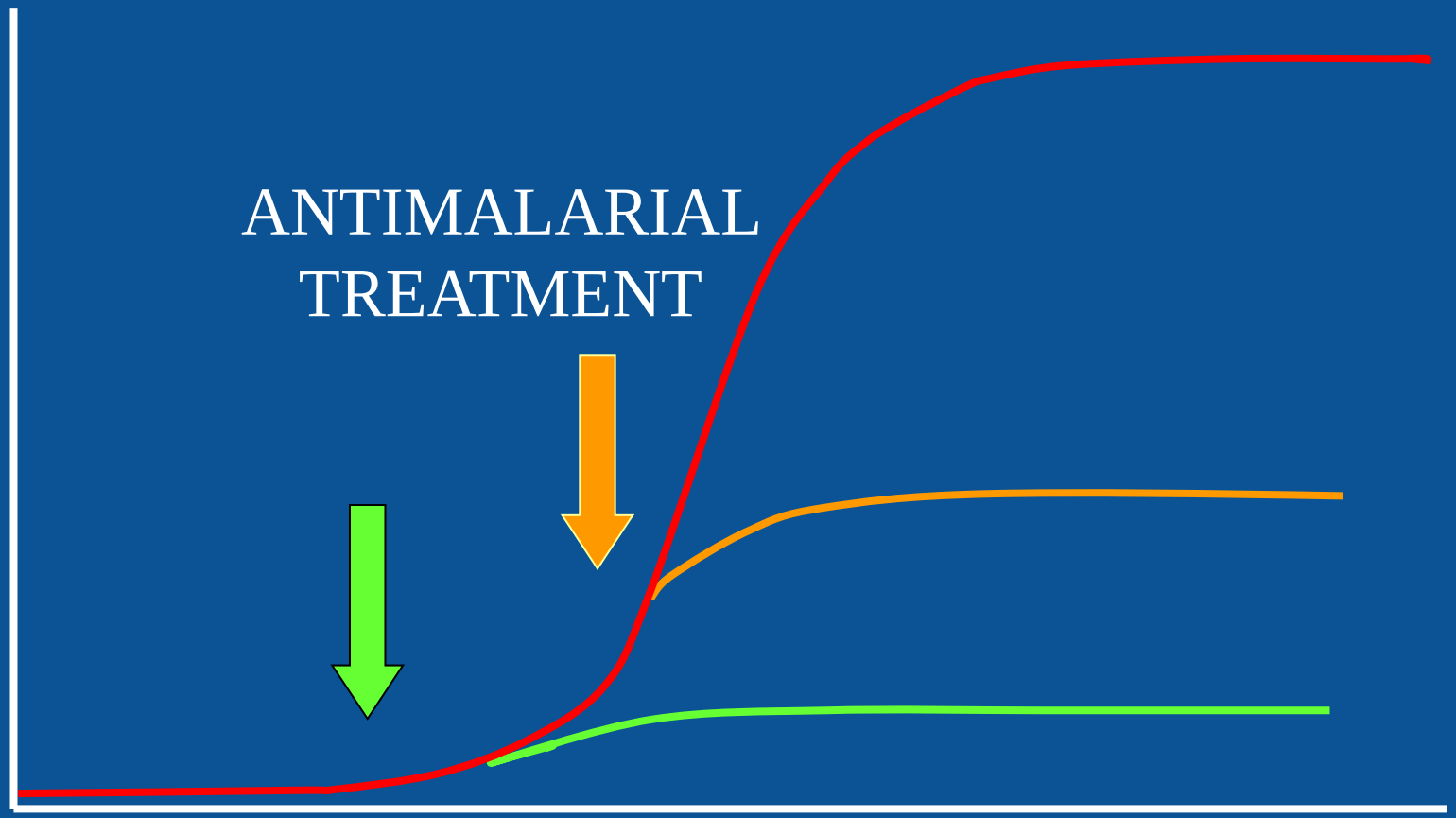
Plasmodium Falciparum



Removing parasites before they can cytoadhere



CUMULATIVE PROBABILITY OF DEATH



WHO developed the Indication and the drug for the indication – rectal artesunate

For the initial management of acute malaria in patients who cannot take medication by mouth and for whom parenteral treatment is not available

Artesunate suppositories offer hope for reducing mortality.

Pre-referral rectal artesunate to prevent death and disability in severe malaria: placebo-controlled trial

Gomes MF, Faiz MA, Gyapong J, Warsame M, Agbenyega T, Babiker A, Baiden F, Bin Yunus E, Binka F, Clerk C, Folb P, Hassan R, Hossain Md A, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ

for the Study 13 Research Group

Background

- Death from malaria reflects delay in administering effective anti-malarial treatment.
- Antimalarial treatment might not rescue moribund patients
- But if given earlier, could prevent permanent disability or death.
- If rectal artesunate is given before referral to patients who are several hours from injections it acts rapidly on parasites.
- If rectal artesunate is given before referral to patients who are several hours from injections it acts rapidly on parasites.
- *But can it save lives and prevent neurological sequelae?*

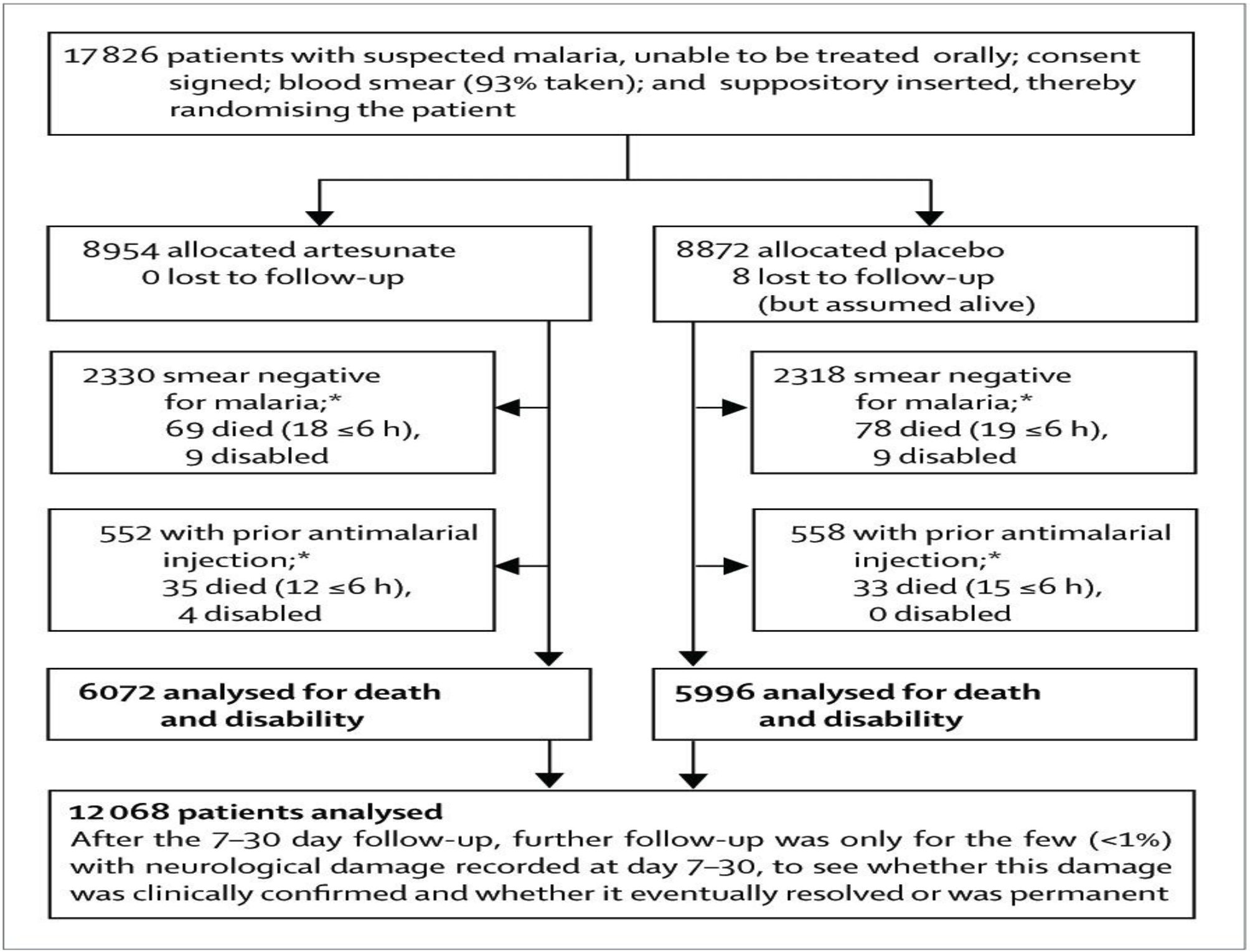
Study 13: Research question

"In patients with acute malaria who cannot take medication by mouth, and cannot yet reach a medical facility where injections can be given,

Is rectal artesunate plus referral better than rectal placebo plus referral, in terms of survival and/or neurological sequelae?"

Study 13: Inclusion criteria

- Patients clinically suspected to have malaria with history of fever
- Unable to take oral medication because of one of following
  - Unable to eat, drink or suck
  - Repeated vomiting
  - Repeated convulsions
  - Unable to sit, stand or walk unaided
  - Altered consciousness or in coma
- Aged ≥ 6-72 months Africa and ≥ 6 months Asia


17 826 patients with suspected malaria, unable to be treated orally; consent signed; blood smear (93% taken); and suppository inserted, thereby randomising the patient
8954 allocated artesunate
0 lost to follow-up
8872 allocated placebo
8 lost to follow-up
(but assumed alive)
2330 smear negative for malaria;*
69 died (18 ≤6 h),
9 disabled
2318 smear negative for malaria;*
78 died (19 ≤6 h),
9 disabled
552 with prior antimalarial injection;*
35 died (12 ≤6 h),
4 disabled
558 with prior antimalarial injection;*
33 died (15 ≤6 h),
0 disabled
6072 analysed for death and disability
5996 analysed for death and disability
12 068 patients analysed
After the 7–30 day follow-up, further follow-up was only for the few (<1%) with neurological damage recorded at day 7–30, to see whether this damage was clinically confirmed and whether it eventually resolved or was permanent

Study 13: Condition at recruitment

- 8% coma
- 20% repeated convulsions
- 72% prostrated

Non-adherence to referral advice

- Most of the patients went to a facility: 92% in Africa and 98% in Asia
- ¾ of the study population reached a referral facility within 6 hours

Study 13: Results

- Mortality was 154 of 6072 artesunate versus 177 of 5996 placebo (2·5% *vs* 3·0%, p=0·1).
- Two artesunate versus 13 placebo (0·03% *vs* 0·22%, p=0·0020) were permanently disabled; total dead or disabled: 156 *vs* 190 (2·6% *vs* 3·2%, p=0·0484).

Effects of treatment on early & later mortality and permanent disability in Africa, Asia and all 4 study sites

	Africa (three study sites)		Asia (one study site)		All four study sites		
	Artesunate (N=3041)	Placebo (N=2999)	Artesunate (N=3031)	Placebo (N=2997)	Artesunate (N=6072)	Placebo (N=5996)	Significance
Death by 7–30 day follow-up*							
Death in 0–6 h (at a median of 2 h)	42	39	14	12	56	51	NS
Reached clinic in 0–6 h (~3 h†), died after hour 6	42	47	29	28	71	75	NS
Still not in clinic at 6 h (~15 h†), died after hour 6	25	47	2	4	27	51	p=0·0039
Alive at 7–30 day follow-up, but with permanent disability‡							
CNS HIV or CNS tuberculosis	1	0	0	1	1	1	NS
Sequelae of cerebral malaria	1	12	0	0	1	12	p=0·0020
Overall							
Death/permanent disability	111 (3·6%)	145 (4·8%)	45 (1·5%)	45 (1·5%)	156 (2·6%)	190 (3·2%)	p=0·0484

NS=not significant. *Seven *vs* seven of the deaths (all in Africa) could not have been affected by the trial capsule (four *vs* four patients: capsule expelled intact and not re-inserted, plus three *vs* three patients: death attributed blindly by endpoint review committee to a disease other than malaria). †Median time (for those with an adverse outcome) to arrival at clinic, or prior death (ie, death without arrival at clinic). ‡One *vs* one permanent disability could not have been affected by trial capsule (one HIV CNS disease in Africa, one tuberculosis meningitis in Asia; both died after 7–30 day follow-up). All other cases of permanent disability were from CNS malaria in children in Africa, and all were severe; five, all in the placebo group, died after 7–30 day follow-up.

Effect of treatment on mortality or permanent disability by time to reach clinic: all malaria patients

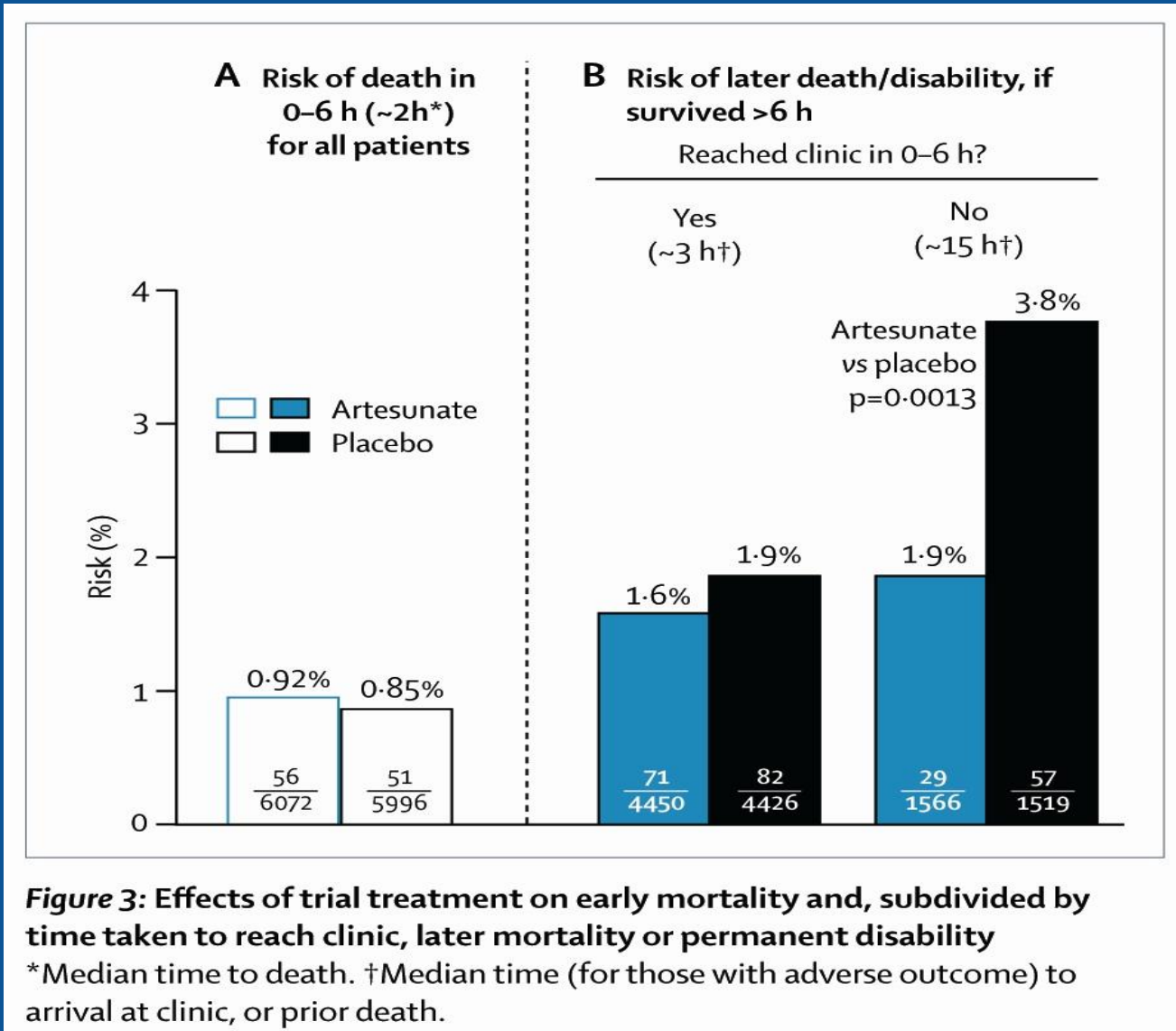


Figure 3: **Effects of trial treatment on early mortality and, subdivided by time taken to reach clinic, later mortality or permanent disability**
*Median time to death. †Median time (for those with adverse outcome) to arrival at clinic, or prior death.

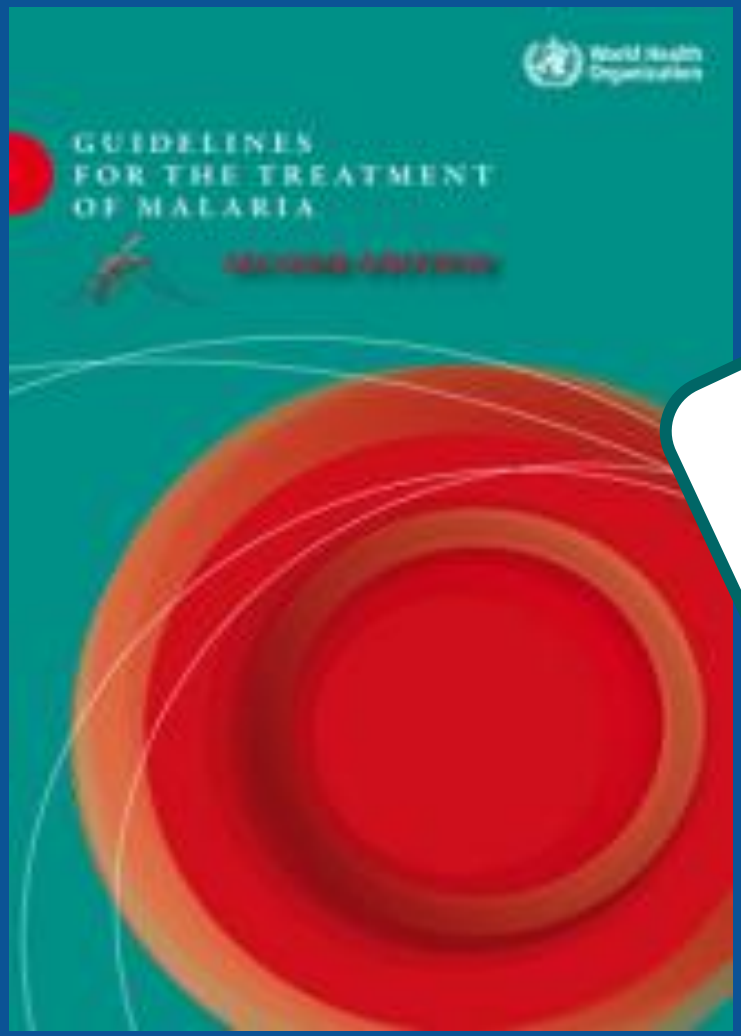
- A single dose of rectal artesunate plus referral reduced by about half the risk of mortality and permanent neurological disability in malaria patients who had delays in reaching a clinic
- A single dose of rectal artesunate plus referral improved the probability that neurological sequelae would resolve – and therefore reduced the risk of permanent neurological damage

Delay Kills and Damages

Conclusions and Implications

- One dose of rectal artesunate will not cure severe malaria; referral of a treated patient to the nearest clinic is important both to complete the treatment of malaria and to diagnose any other underlying life-threatening infection.
- Easy to use by non-medical community members
- Safe, inexpensive

Malaria Treatment Guidelines: Second Edition



Launched
9 March 2010

Recommendations in the Second Edition of the *Guidelines* (2010)

- **Malaria Diagnosis**
- Prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started.
- Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

Treatment of Uncomplicated *P. Falciparum M*alaria

- Artemisinin-based combination therapies should be used in preference to sulfadoxinepyrimethamine (SP) plus amodiaquine (AQ) for the treatment of uncomplicated *P. falciparum* malaria.
  - *Strong recommendation, moderate quality evidence.*
- ACTs should include at least 3 days of treatment with an artemisinin derivative.
  - *Strong recommendation, high quality evidence.*
- Dihydroartemisinin plus piperaquine (DHA+PPQ) is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.
  - *Strong recommendation, high quality evidence.*
- Addition of a single dose primaquine (0.75 mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme.

Treatment of Severe *P. Falciparum* Malaria

- Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.
  - *Strong recommendation, high quality evidence.*
- *AQUAMAT:* Intravenous (IV) artesunate found to be superior to quinine

Treatment of Uncomplicated *P. Vivax* Malaria

- In areas with chloroquine resistant *P. vivax*, artemisinin-based combination therapies (particularly those whose partner medicines have long half-lives) are recommended for the treatment of *P. vivax* malaria.
  - *Weak recommendation, moderate quality evidence.*
- At least a 14-day course of primaquine is required for the radical treatment of *P. vivax.*
  - *Strong recommendation, very low quality evidence.*

Thank You

27 October 2015