

Intermittent preventive treatment in children with Piperaquine



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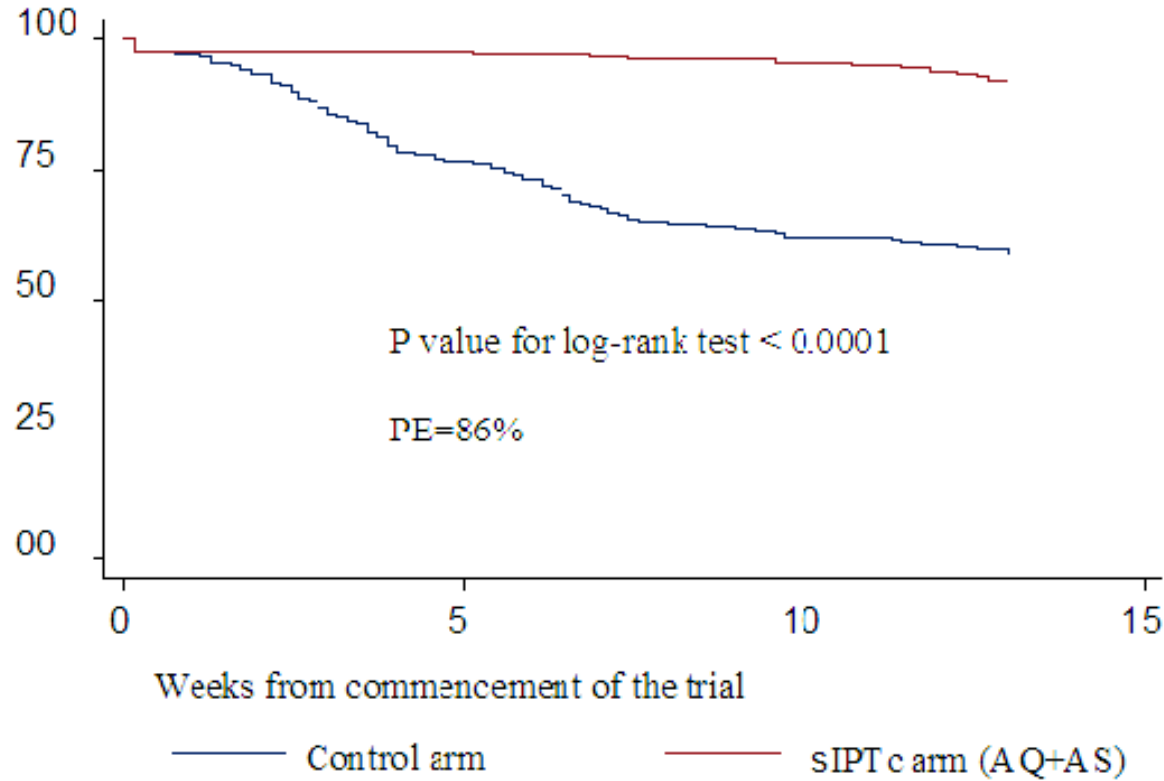
LSHTM/University of Dakar

5th EDCTP Forum, Arusha, October 2009



Intermittent preventive treatment protective efficacy

Cisse et al. The Lancet, 2006



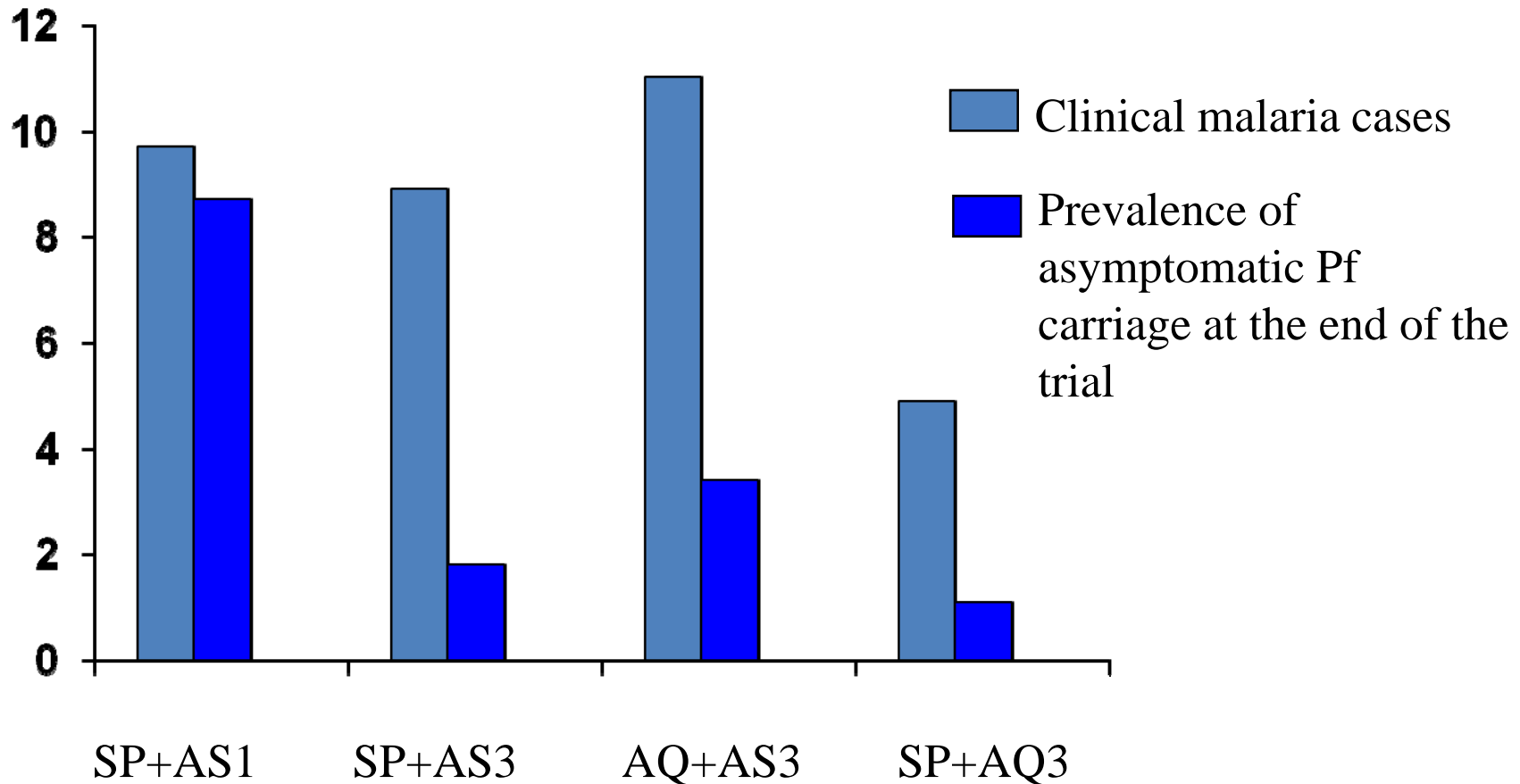
Number at risk

Placebo	546	447	356
sIPTc	542	529	522

Best drugs regimen for seasonal IPT?

Sokhna et al. PLoS one, 2008

Percentage



Treatment arms

≈ 450 children per arm

Piperaquine ?

- **Piperaquine** is an antimalarial compound belonging to the 4-aminoquinolines
- In 1966, the Shanghai Research Institute of Pharmaceutical Industry synthesized this new antimalarial, with a chemical structure identical to “13228 RP” earlier synthesized by Rhone Poulenc, France. In 1978 it replaced chloroquine as first line monotherapy in China for malaria. It is estimated that approximately 200 metric tons were dispensed between 1978 and 1992 for mass prophylaxis until resistance became too high.
- Piperaquine has recently been the object of renewed interest as a partner drug in ACTs.
- The long half life of piperaquine (terminal elimination **half life 33 days or more**) make it suitable for preventive treatment but no studies of its use for prevention have been done in Africa.
- **Hypothesis: A combination of two long acting drugs of similar half life is most suitable for prevention.**

Non-inferiority cluster randomised trial

- **Study population:** all children <5yrs in the 29 villages in the zone of responsibility of Keur Soce health post, Ndoffane district, Senegal.
- **Inclusion criteria:** aged 2-59 months at time of first dose in September; consent of parent or guardian; resident of the study area
- **Exclusion criteria:** history of allergy to study drugs
- **Intervention:** administration of treatment dose in September, October and November of either
 1. Dualkin[®] (sulfalene-pyrimethamine plus amodiaquine over 3 days) SP+AQ, or:
 2. Duocotexcin (piperavaquine plus dihydroartemisin over 3 days) PQ+DHA, or:
 3. Sulfadoxine-pyrimethamine plus piperavaquine over 3 days SP+PQ
 - Mefloquine (withdrawn upon request of the Ethics Committee)
- **Pragmatic design:** drug delivery by health post volunteer workers, dosage based on age, doses on days 2 and 3 unsupervised

Trial design

- **Endpoints:**

Efficacy: cum incidence of clinical malaria; prevalence of parasitaemia; Hb concentration in December

Safety and acceptability: tolerability, adverse events: incidence of vomiting immediately after first drug administration and of vomiting and other common adverse events by day 4.

- **Powered to establish:**

- **non-inferiority** of efficacy (5% non-inferiority margin for incidence of malaria)
- superior tolerability and acceptability, of SP+PQ and PQ+DHA relative to SP+AQ

- **Design:**

- Cluster randomized, unit of randomization being the community health worker circuit.
- Less efficient than individual randomization but simpler and compatible with pragmatic design;
- Less risk of contamination by sharing tablets or mis-attributing symptoms; and parents may be less aware of differences in tablet appearance

Trial design

- 1800 children in 33 clusters of 40 to 70 children per cluster, 2 strata large central village/outlying villages
- Passive detection of malaria and adverse events at health post September-December
- Home visit day 4 of each round to check for adverse events, and ask about adherence
- Active follow-up one month after each intervention round, just before the next round, to check for malaria
- All children finger prick sample for parasitology and Hb one month after the final round.



Dakar

Kaolack, Senegal

Keur Soce

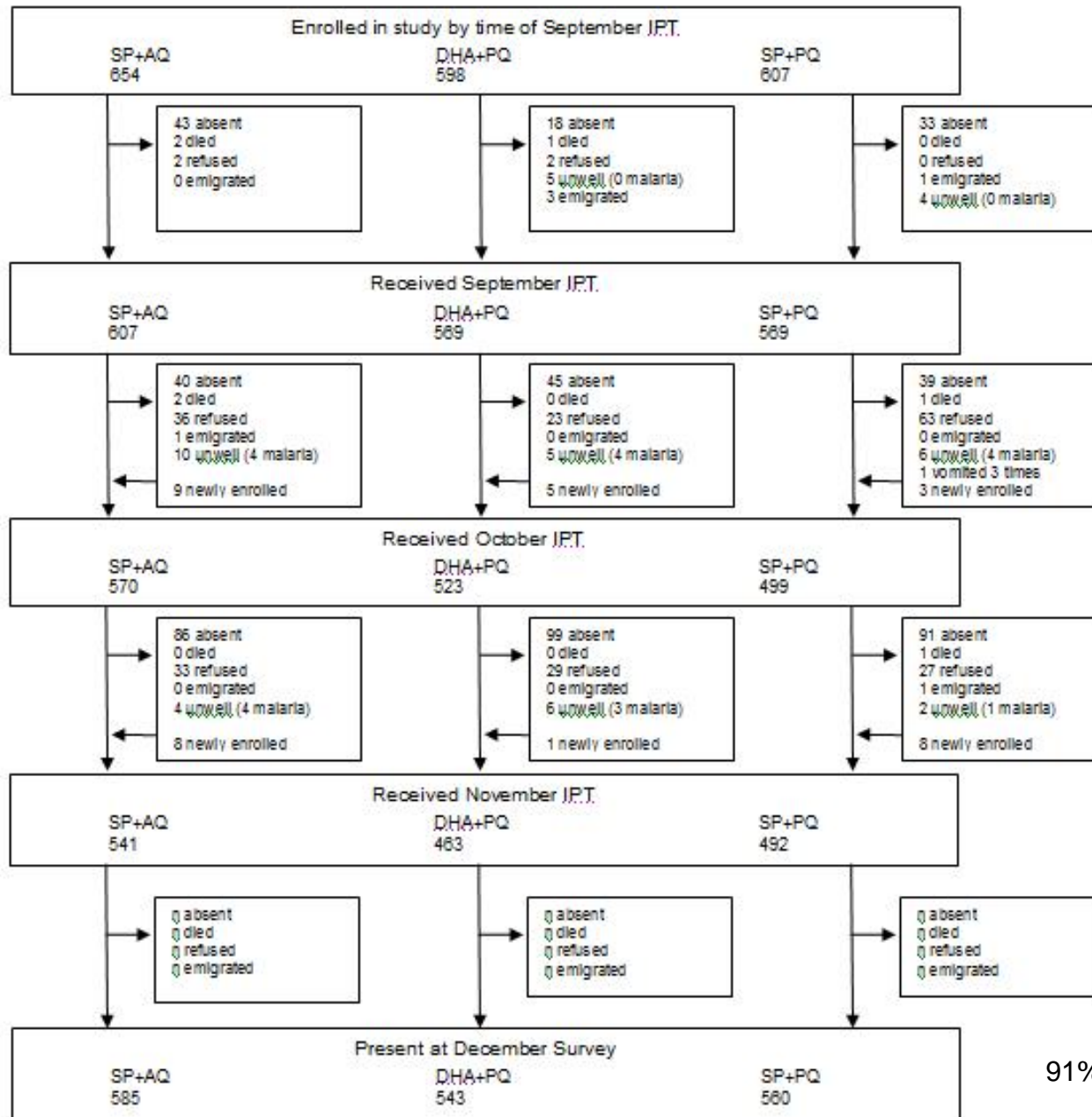
Banjul

Image © 2008 TerraMetrics
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Image NASA

Pointer 14°33'46.14" N 15°35'30.53" W elev 32 m

Streaming ||||| 100%

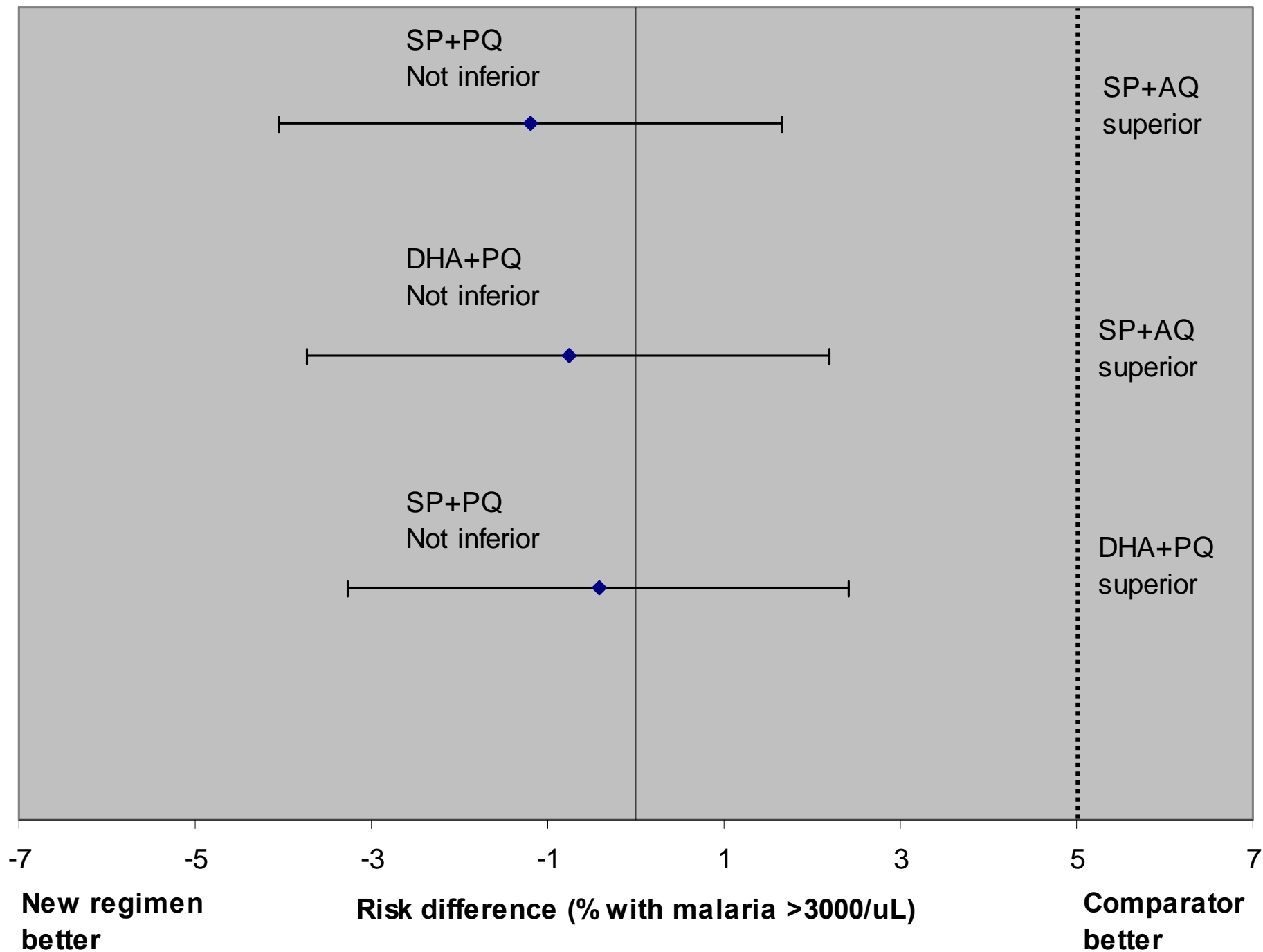
Trial profile



91% followed to study end

Malaria incidence

According to protocol			
	SP-AQ	DHA-PQ	SP-PQ
Malaria (>3000/μl)			
Cumulative incidence	4.1% (20/485)	3.5% (15/433)	2.4% (10/410)
Malaria (any parasitaemia)			
Cumulative incidence	5.0% (24/485)	4.9% (21/433)	2.7% (11/410)
Intention to treat			
	SP-AQ	DHA-PQ	SP-PQ
Malaria (>3000/μl)			
Cumulative incidence	4.2% (28/671)	3.5% (21/604)	2.8% (17/618)
Malaria (any parasitaemia)			
Cumulative incidence	5.2% (35/671)	5.1% (31/604)	3.4% (21/618)



AEs by trial arm – pre-specified outcomes

Adverse event	SP-AQ		SP-PIP		DHA-PIP		Total	
	%	no.	%	no.	%	no.	%	no.
vomited/regurgitated or spat out	31,4	217	16,5	75	13,6	76	21,6	368
rash	2,0	14	1,1	5	0,5	3	1,3	22
itching	3,9	27	1,8	8	1,3	7	2,5	42
fever	31,4	217	19,6	89	17,6	98	23,7	404
headache	12,5	86	4,0	18	5,7	32	8,0	136
any*	67,9	469	46,5	211	45,0	251	54,7	931

* 'any' includes adverse events other than those in this table

Results of cross-sectional survey at the end of the transmission season

1. Prevalence of parasitaemia:

	RDT or slide positive*	Asexual parasites \$	Risk difference (95% CI)	Gametocyte prevalence \$
SP-AQ	5.9% (26/444)	3.8% (13/342)	reference	0.9% (3/342)
DHA-PQ	5.4% (21/392)	3.8% (12/313)	-3.05 (-10.56, 4.46)	0.6% (2/313)
SP-PQ	4.2% (16/380)	3.2% (11/343)	-0.13 (-7.64, 7.38)	0.6% (2/343)

* denominator: protocol compliant children with slide or rdt result.

\$ denominator: protocol compliant children with slide result.

Results of cross-sectional survey at the end of the transmission season

2. Prevalence of parasite genotypes associated with resistance to sulfadoxine and pyrimethamine:

	dhfr triple mutant (51, 59, 108)		dhps-437		quadruple mutant	
	Overall prevalence*	Proportion of genotypes\$	Overall prevalence*	Proportion of genotypes\$	Overall prevalence*	Proportion of genotypes\$
SP-AQ	2.3% (10/444)	50% (10/20)	1.4% (6/444)	30% (6/20)	1.1% (5/444)	25% (5/20)
DHA-PQ	0.8% (3/392)	30% (3/10)	0.8% (3/392)	30% (3/10)	0.5% (2/392)	20% (2/10)
SP-PQ	1.1% (4/380)	40% (4/10)	0.5% (2/380)	22.2% (2/9)	0% (0/380)	0% (0/10)

* denominator: protocol compliant children with slide or rdt result

\$ denominator: protocol compliant who had parasite genotyped

Anaemia at the end of the transmission season

		All children	SP-AQ	DHA-PQ	SP-PQ
Anaemia (Hb<9 g/dl)		27.2% (332/1222)	23.2% (103/444)	33.5% (133/397)	25.2% (96/381)
Severe anaemia (Hb<5 g/dl)		1.1% (14/1222)	0.7% (3/444)	2.3% (9/397)	0.5% (2/381)
Haemoglobin (g/dl)					
Individuals	N	1222	444	397	381
	Mean	9.90	10.10	9.61	9.95
Clusters	N	33	11	11	11
	Mean	9.90	10.09	9.62	10.01
Mean difference	Crude	-	reference	-0.47 (-0.91, -0.03)	-0.08 (-0.49, 0.334)

Key findings:

- Similar results between Senegal and Gambia
- SP+PQ and DHA+PQ better tolerated than SP+AQ
- Excellent compliance with all regimens
- PQ combinations equally as good as SP+AQ in preventing clinical malaria
- Very low prevalence of gametocytes with all combinations
- Low prevalence of SP-resistant genotypes with SP+PQ
- Combination of two long acting drugs most suitable for prevention
 - *highly effective against malaria*
 - *most effective at limiting impact on resistance*
 - *allows ACTs to be reserved for treating acute cases*

Acknowledgments

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- **Colleagues & collaborators** (*University of Dakar, London School of Hygiene and Tropical Medicine*)

more @

- Clinicaltrials.gov NCT00529620
- <http://dx.plos.org/10.1371/journal.pone.0007164>