Assessment of the Public Health Benefit of Artemisinine based combination therapies for uncomplicated Malaria treatment in Mali

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Rationale

- Day 14 or 28 efficacy may not adequately reflect the true public health impact of a treatment regimen.
- Long term efficacy, safety and overall public health impact of ACTs in the African context is not known.

- We proposed to assess the public health benefit of the repetitive use of a given ACT in Mali

Objective of the projects

1. Test the hypothesis that repeated administration of AS/AQ, AS/SP and AR-L for the treatment of consecutive episodes of uncomplicated malaria reduces the incidence of uncomplicated falciparum malaria and malaria attributable anemia,
2. Measure the impact of the repeated administration of AS/AQ, AS/SP and AR-L on antimalarial immunity and malaria transmission.
3. Measure the efficacy and *safety* of the three ACTs in this context of repeated administration

Methods

- Started July 2005
- Randomized controlled trial in Bougoula-Hameau
  - malaria is hyper-endemic with
  - seasonal transmission in Southern Mali.
- Drugs: AS/AQ (Arsucam® from Sanofi-Aventis), AS/SP or AR-L (Coartem®, Novartis).
- Subsequent malaria episodes: re-treated with same ACT
- 2 years follow up: clinically and biologically (Hb, Creatinin, Liver enzymes, WBC) to record any AEs.
- Protocol approved by EC of FMPOS, written consent
- Study sponsored AND monitored by Sanofi-Aventis

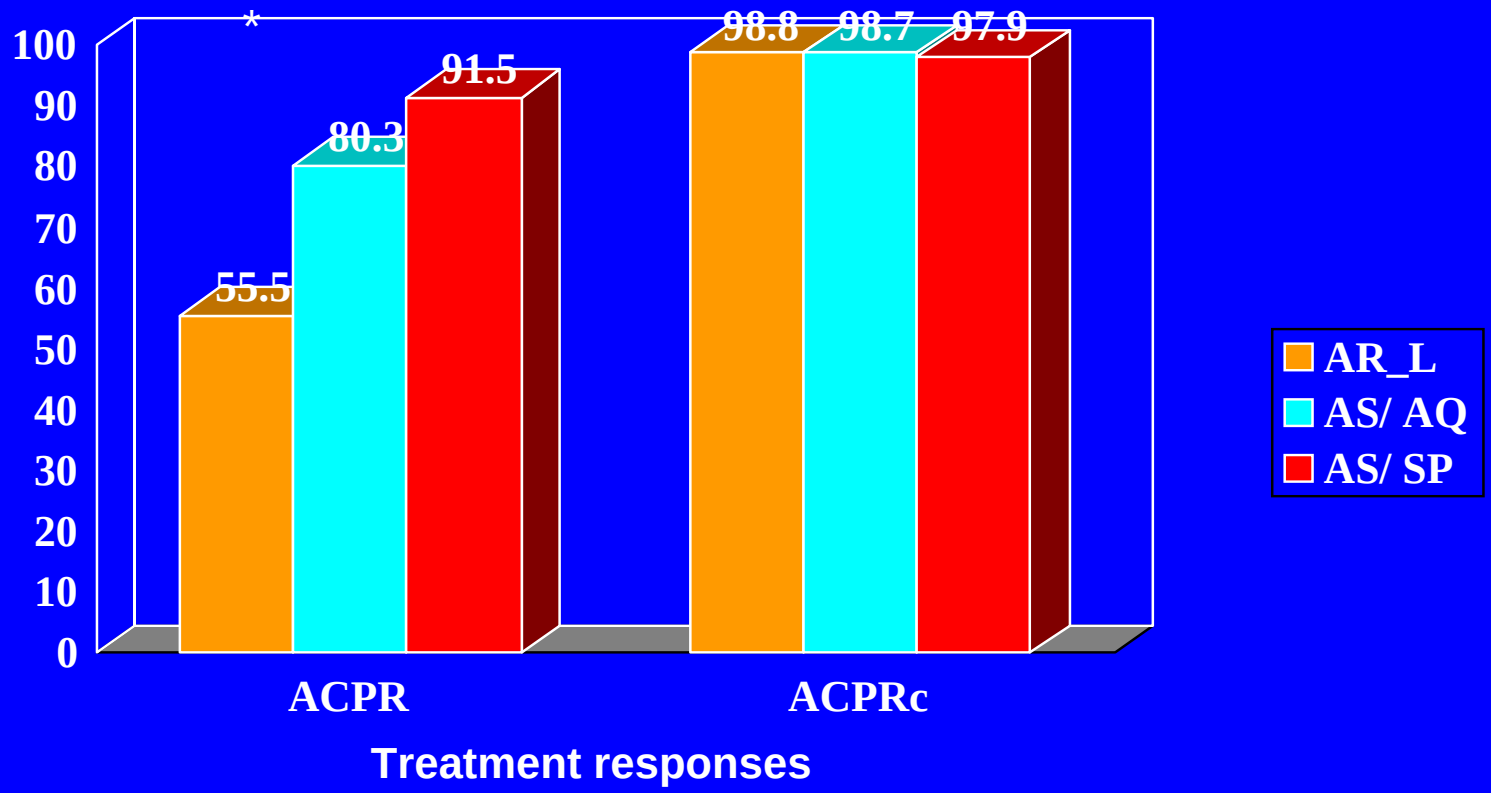
Descriptive Results

- ~4000 screened, 780 included
  - 260 patients/treatment arm
- 2019 episodes of malaria
- >95% successful follow up
- Three arms comparable at baseline for Age, sex, parasitemia, gametocyte carriage, anemia

Efficacy

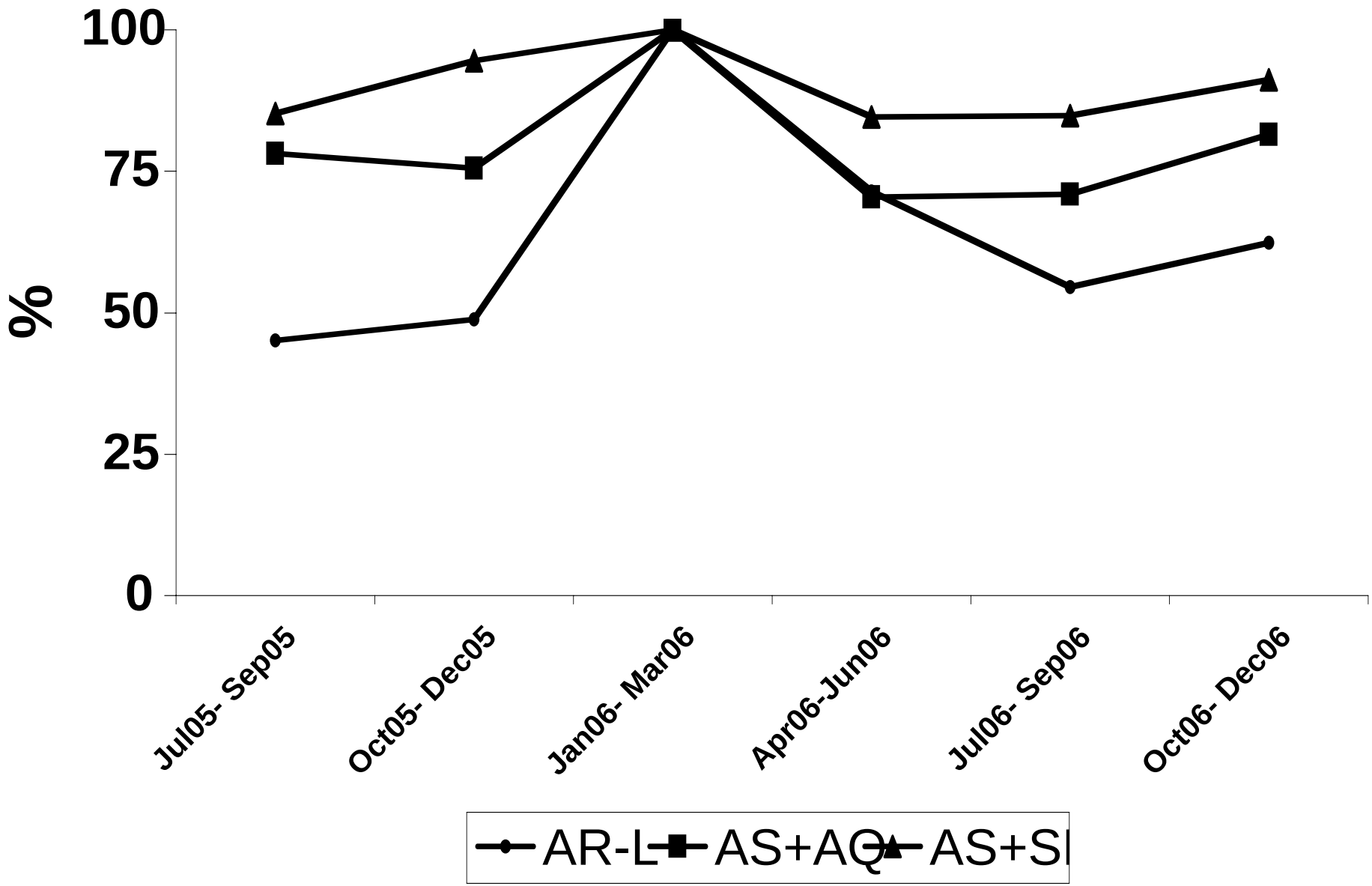
Day 28 Efficacy
non-Corrected vs. PCR Corrected

* P < 0.05



All the three treatment groups were comparable after PCR correction (p>0.05)

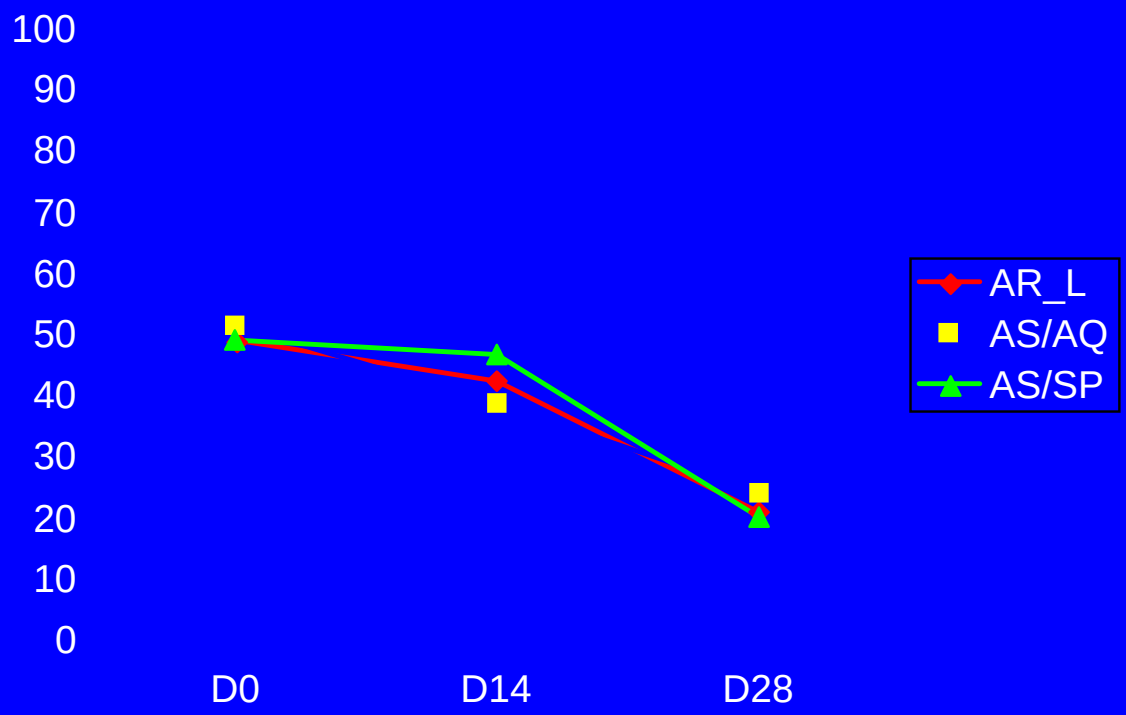
Evolution of Treatment Efficacy (non



Incidence of uncomplicated malaria during study period

treat	mean	N	min	max
AR-L	2.644788	259	1	8
AS-AQ	2.498069	259	1	12
AS-SP	2.673077	260	1	9
Total	2.605398	778	1	12

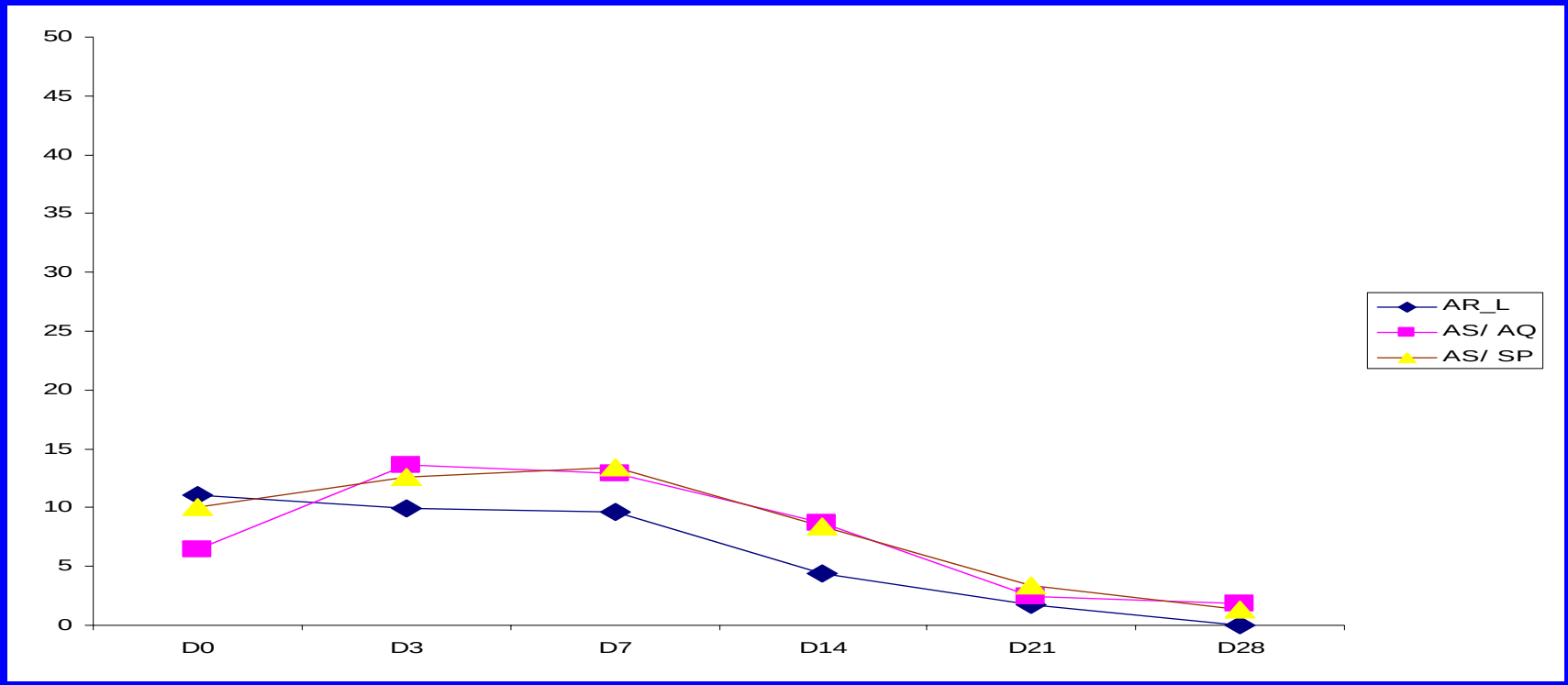
Evolution of anemia during follow up



Significant decrease of anemia after ACTs treatment,

the three arms are comparable in the correction of anemia.

Evolution of gametocyte carriage by treatment arm on follow up days



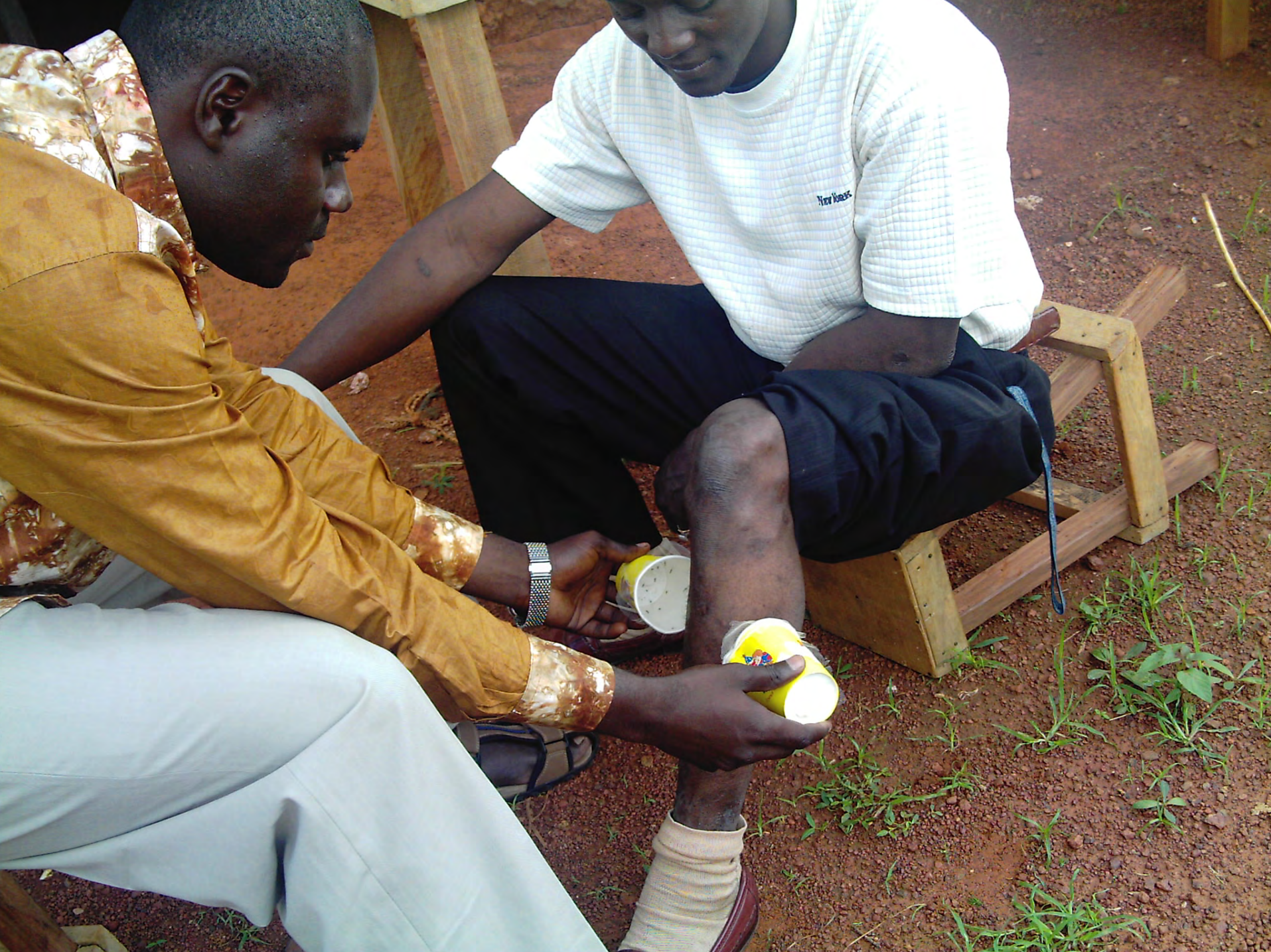
Gametocyte carriage decreased following ACT treatment.

Transmission

Methods

- Drug efficacy study
- Screening for gametocyte carriers
- Include gametocyte carriers aged 6 – 18 y.
- Direct feed starved F1 generation *An. gambiae*
- Maintain mosquitoes in field Insectaries for 8 days
- Presence and number of oocysts measured by dissection
- Compare the infectivity of pre-treatment *vs.* post-ttt gametocytes to *Anopheles gambiae*


gambiae 13-09-06
gambiae 15-09-06
Béghin Say




MALI
PNLP

Infectivity of Post-ACT gametocytes

	Baseline % (N)	Post-AS/AQ % (N)	Post AR-L % (N)	Post AS/SP % (N)
Oocyst +	12%(728)	34%(224)	28%(288)	8%(602)

AS/AQ or AR-L vs. D0: P<0.0001;
AS/SP vs. D0: P = NS

Ongoing analyses and studies

- Detailed analysis on incidence density of clinical malaria,
- Immunity
  - Cytokine kinetics per treatment arm over 24 months
  - Antibody responses per treatment arm
- Clinical and biological safety of the three regimens over time

Summary & Conclusion

- Preliminary results suggest that
  - all three regimens are comparable in molecular corrected efficacy over 1 year of follow up
  - Delay in re-infection: AS/SP > AS/AQ > AR-L
  - ACTs significantly decrease malaria attributable anemia

- ACTs decreased gametocyte carriage HOWEVER ACT reduction of malaria transmission may be questionable

Remerciements

- **MRTC/DEAP**
  - **Pr O. Doumbo**
  - **Dr I. Sagara, Mr O. Toure and Dr A. Dicko**

- **Bougoula residents and local authorities**

- **Sponsor:**
  - **Access to Medicines, Sanofi-Aventis, France**

- **Funder: EDCTP Senior Fellowship Program**