

# **Amodiaquine-Artesunate vs. Artemether-Lumefantrine:**

## **Efficacy and Safety After Single or Multiple Episodes of Uncomplicated Malaria in Ghanaian Children.**

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## Background- drug efficacy

Amodiaquine-Artesunate (A-A)

Artemether- Lumefantrine (A-L)

- There are few direct comparisons between these two ACTs
- 42-day ff-up schedule is recommended in trials involving lumefantrine
- Longer follow-up desirable - diff impact on longer term outcomes
- Few trials have studied the effect of new treatments on subsequent episodes

*Martensson et al,  
Clin Inf Dis, 2005*

*Stepniewska et al,  
Antimicrob Agents  
Chemother 2004*

*White NJ,  
Trends in  
Parasitol. 2002*

*Dorsey et al,  
Lancet 2002*

## Background II-safety of ACT

### Agranulocytosis / Neurotoxicity / Cardiotoxicity

- a) - rare side-effect of AQ prophylaxis,
    - possibility of ↑ toxicity with repeated treatment.....
    - serial neutrophil count ↓ reported after A-A.
  - b) - animal studies - evidence of brainstem toxicity
    - clinical studies - no consensus on neurotoxicity
    - audiometric evaluation for A-A not available
  - c) -Amodiaquine → bradycardia
    - bradycardia- risk factor for ↑ QT interval
    - no report on Q-T interval for A-A in spite of A-L, ART-M etc been evaluated
- *Adjuik et al, Lancet 2002*
- *Brewer et al, Am J Trop Med Hyg 1994*
- *Kissinger et al, Am J Trop Med Hyg 2000*
- *van Vugt et al, Am J Trop Med Hyg 2000*
- *Toovey and Jamieson, Trans R Soc Trop Med Hyg 2004*
- *Ngouesse et al, Am J Trop Med Hyg 2001*
- *Qilin et al, Bull WHO 1988*

## This study - questions.....

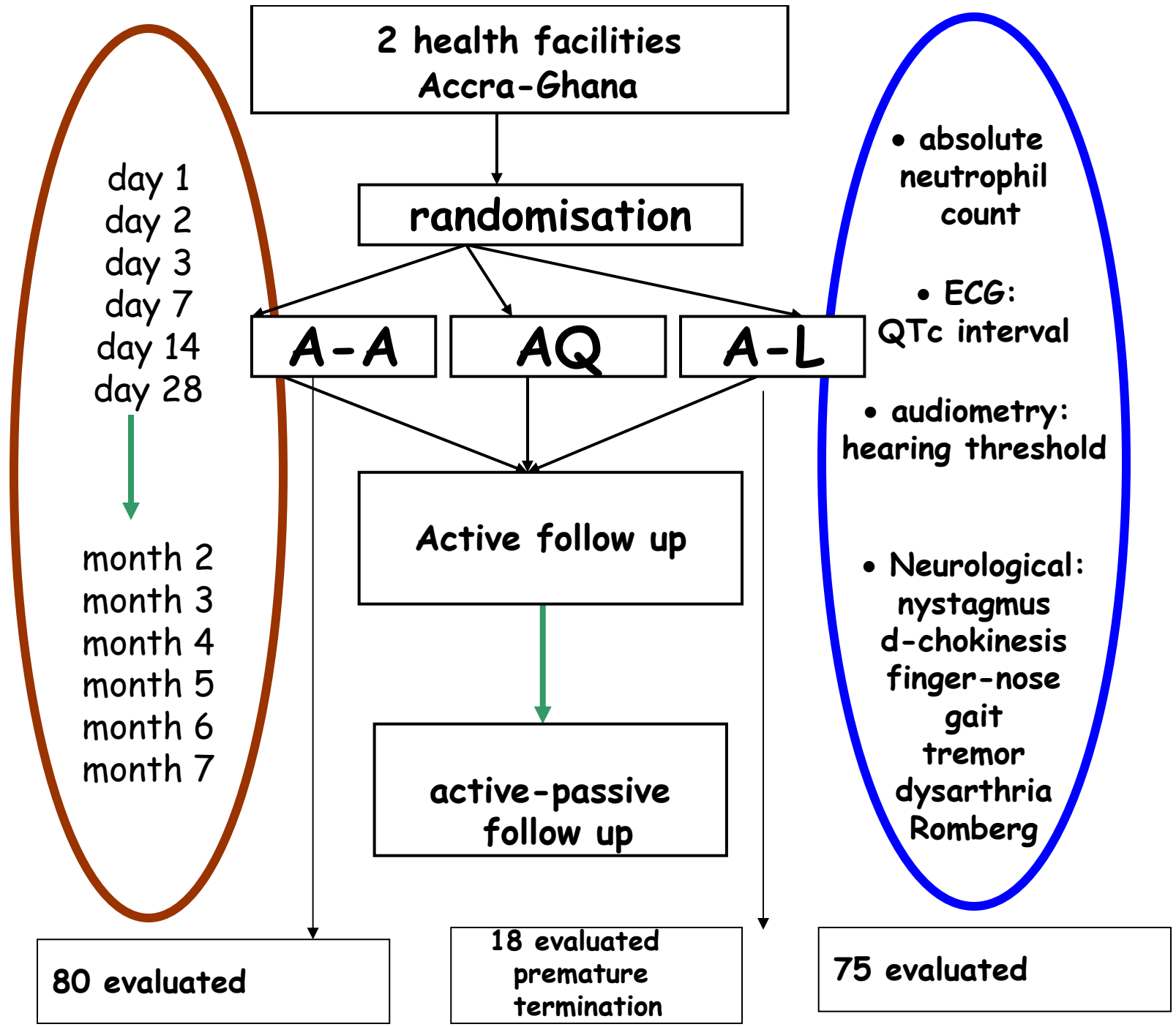
- **Clinical trial with extended ff-up:**

? re-treatment rates different between the A-A and A-L over extended follow up

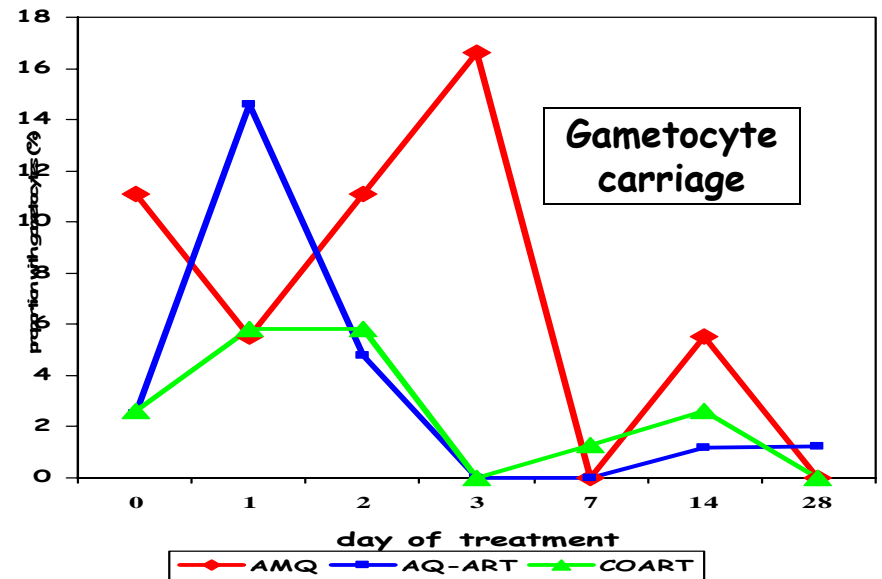
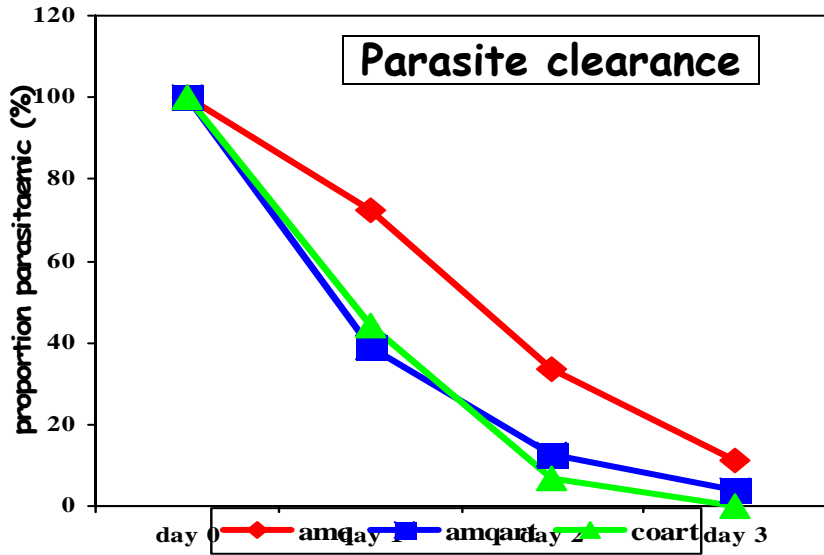
### **2. Side effects profile after ACT:**

a) ? more frequent after ACT treatment than after monotherapy

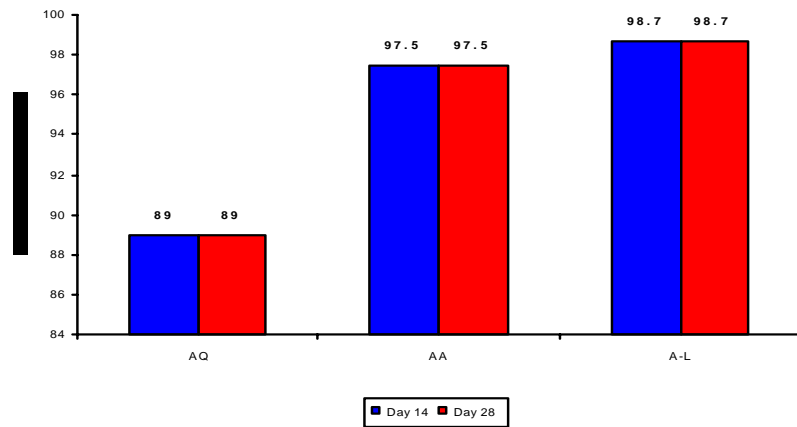
b) ? exacerbated after re-treatment than after treatment for single episode



## Summary of short-term (day 28) assessment



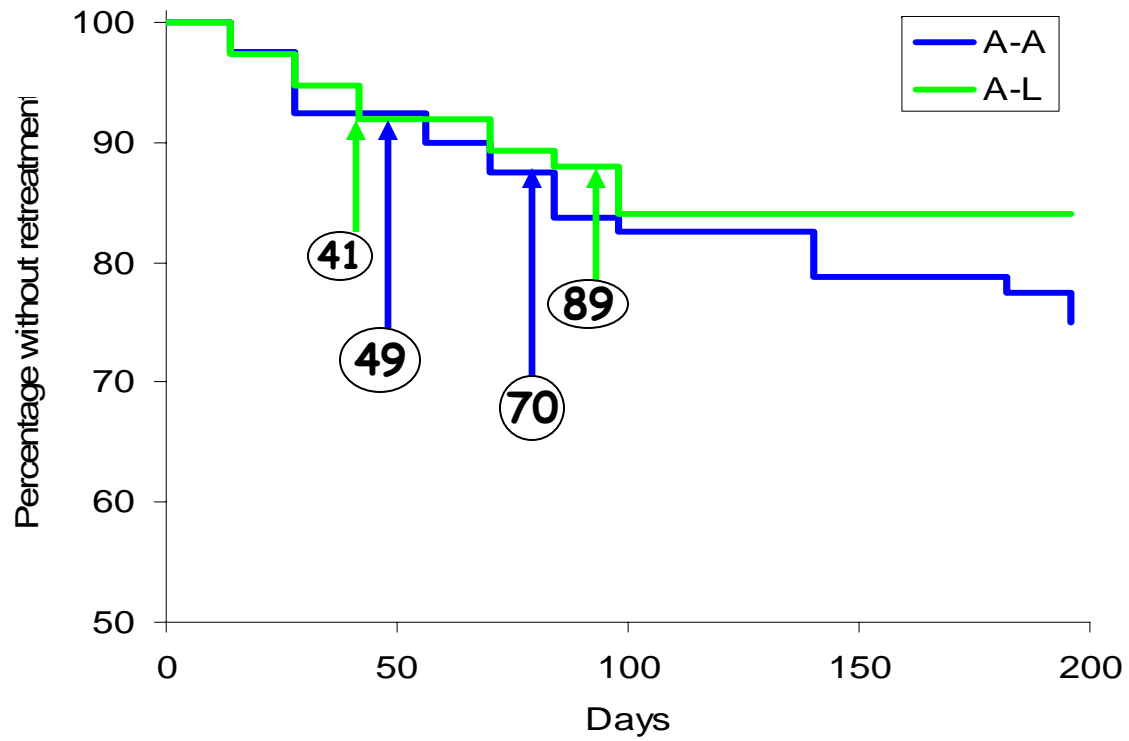
### PCR-corrected cure rates- day 14 and day 28



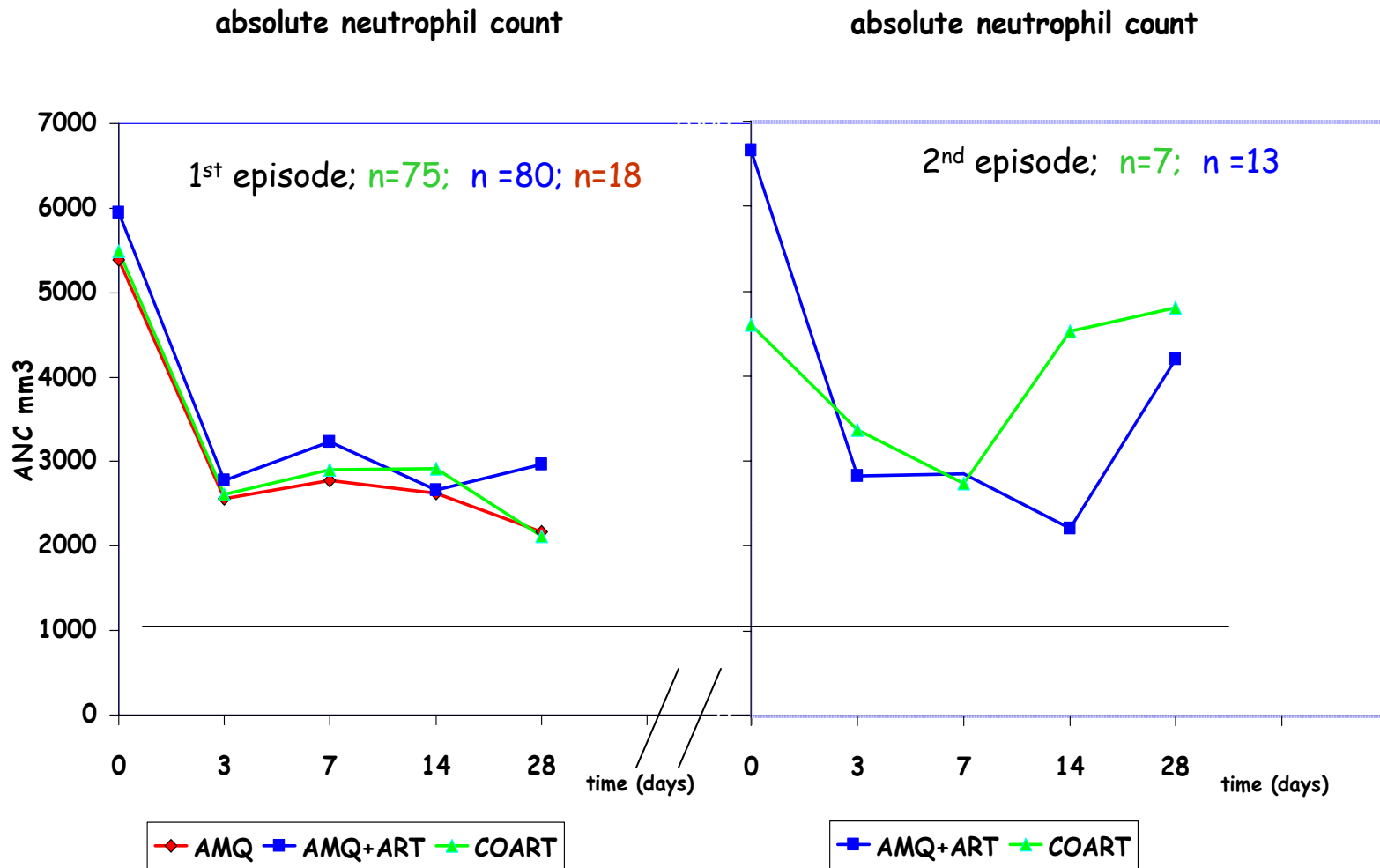
Reported  
resolution of  
symptoms after  
24 hrs-

A-A > A-L > AQ  
(p<0.05)

# Extended follow up: Re-treatments and Recrudescence:

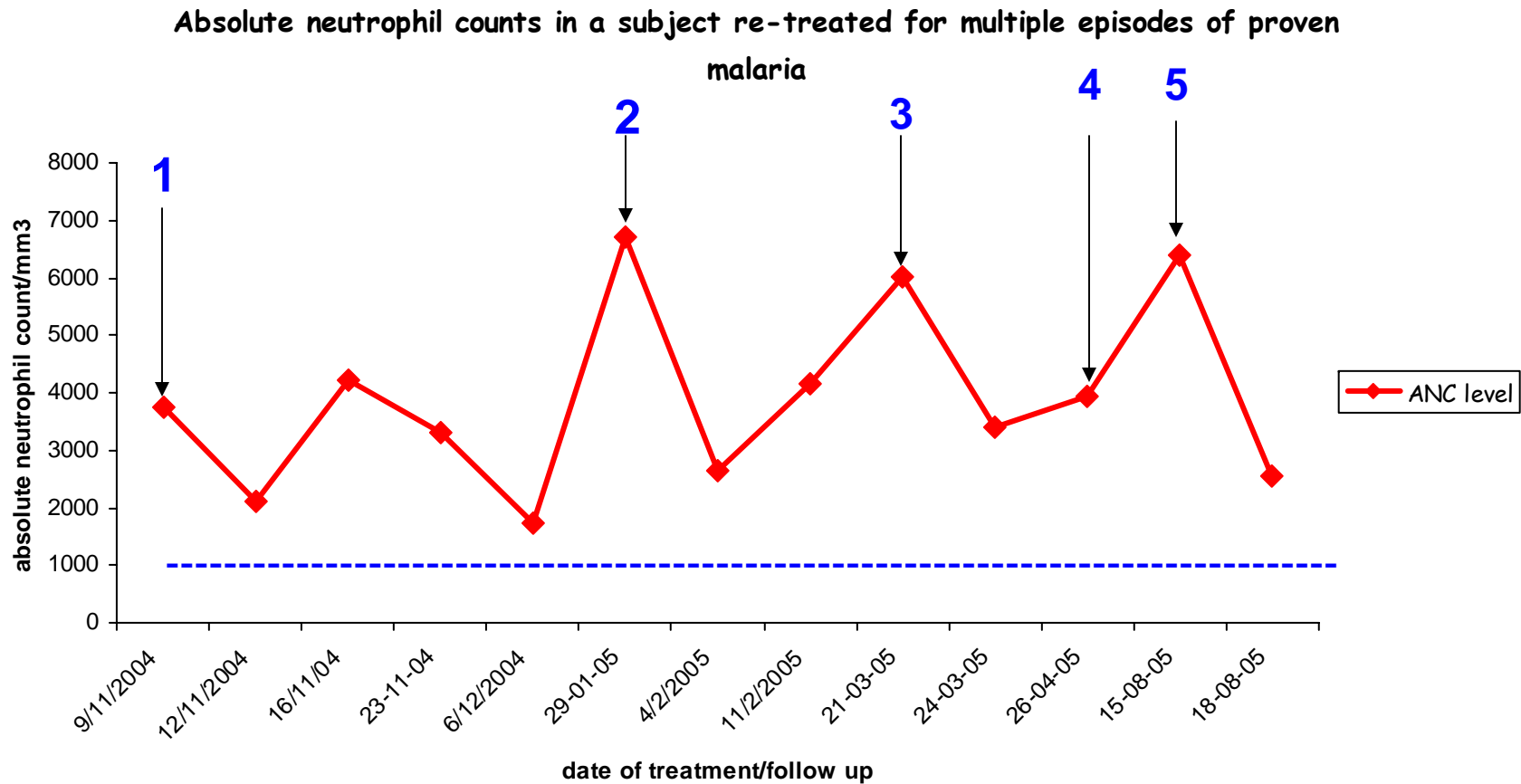


# Side effect profiles: Absolute Neutrophil counts-episodes I and II

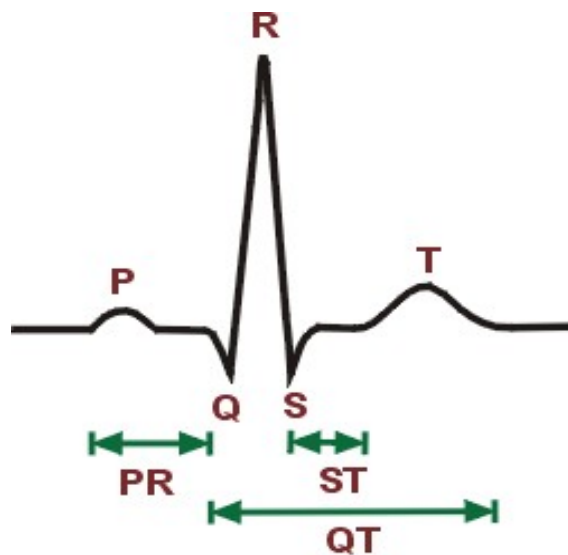
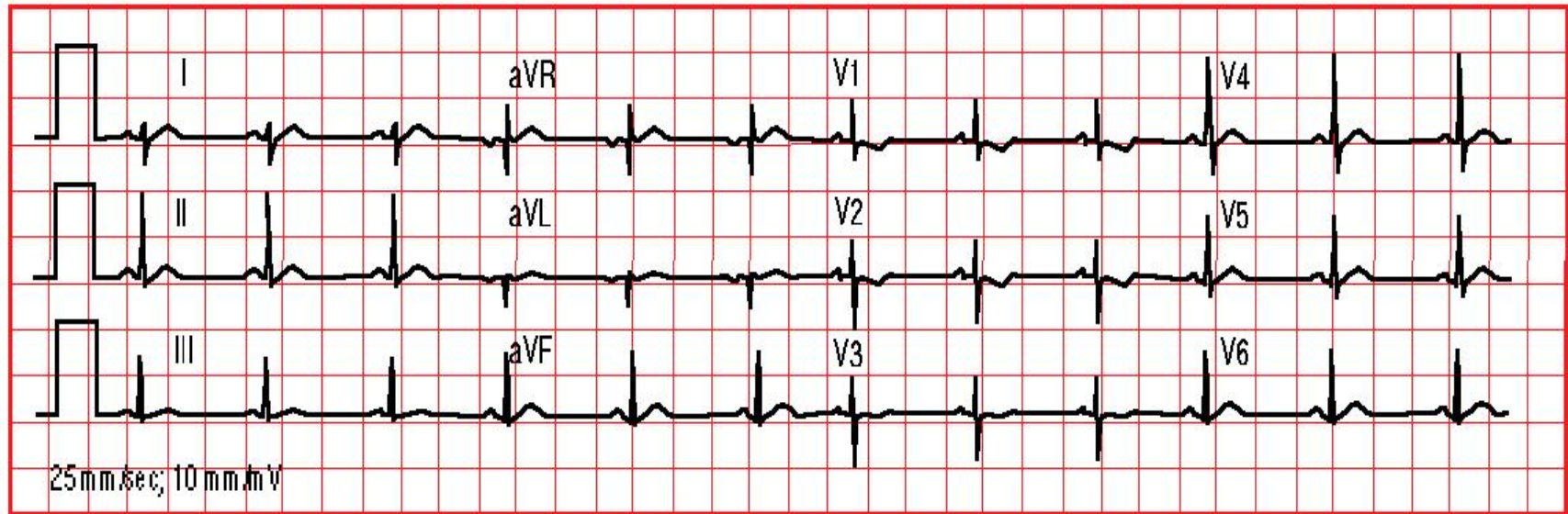


# Side effect profiles:

- absolute neutrophil counts- in a child with multiple treatments

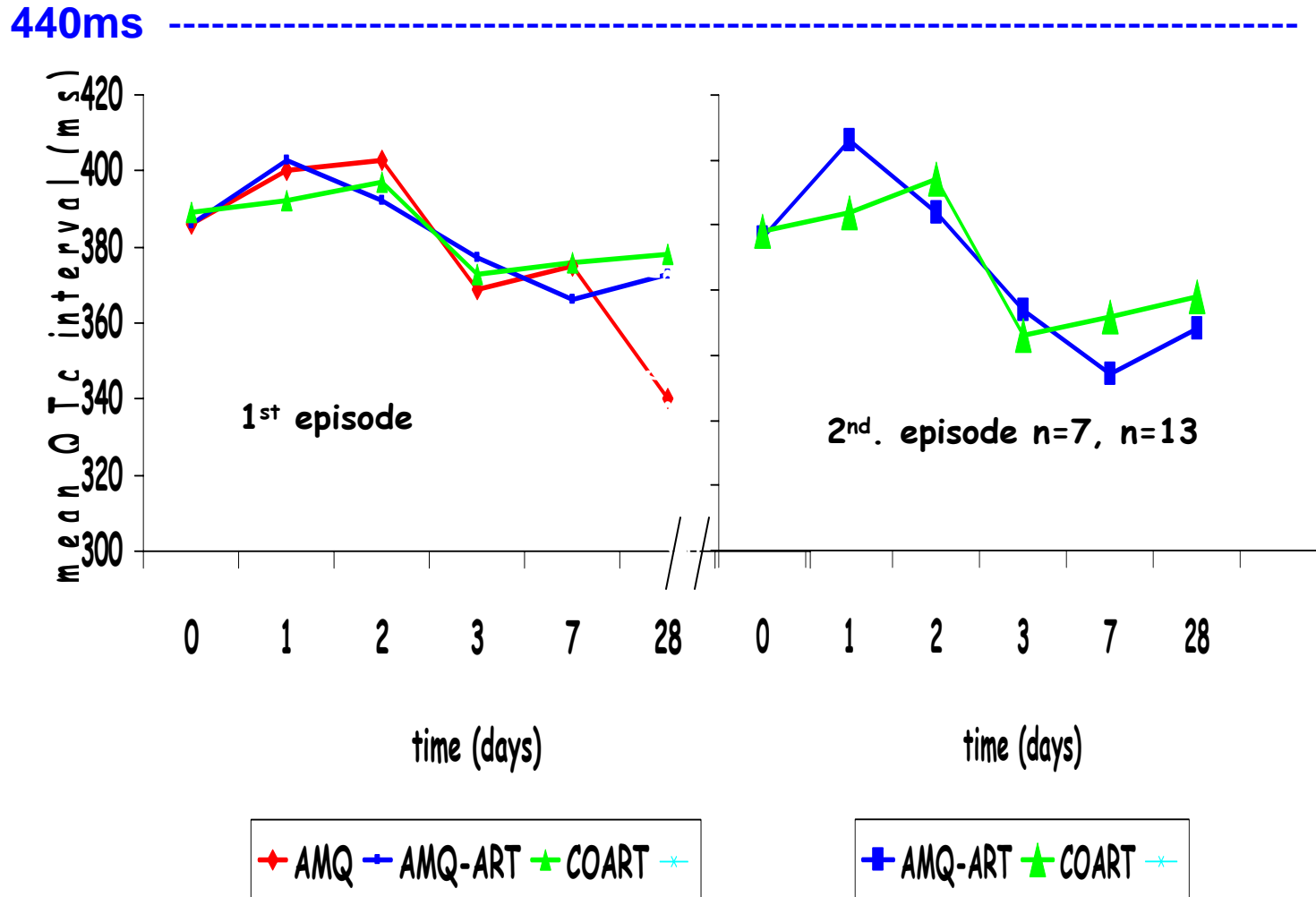


# ECG- corrected QT interval

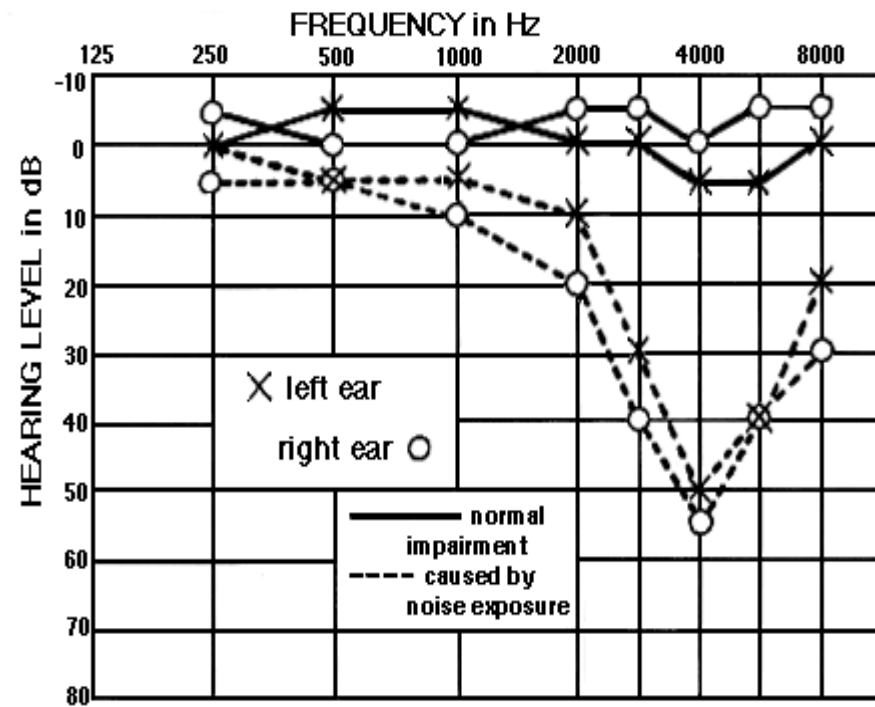


$$QTc = \frac{QT}{\sqrt{RR}}$$

# Side effect profiles: QTc intervals on ECG-episodes I and II

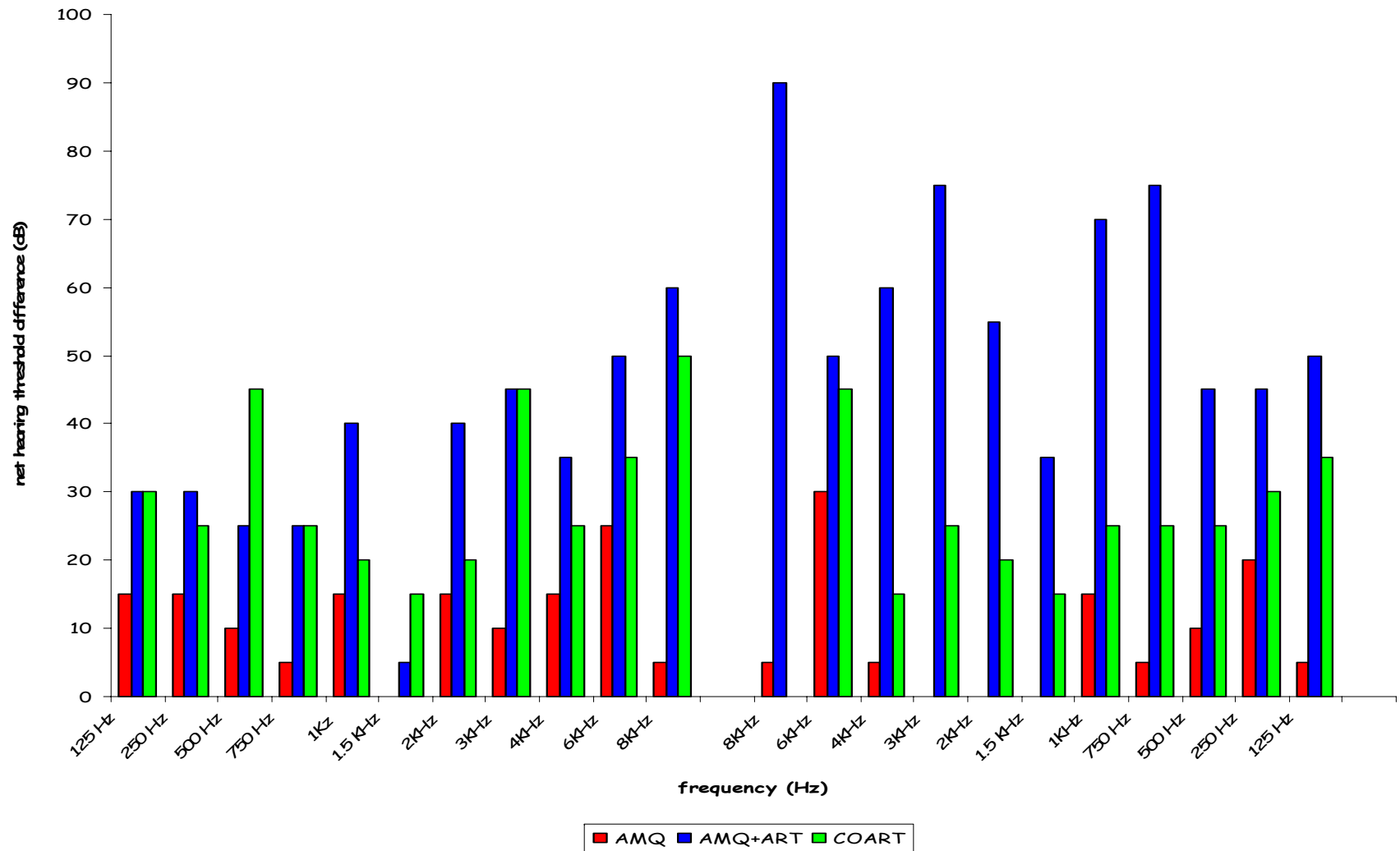


# Audiometry



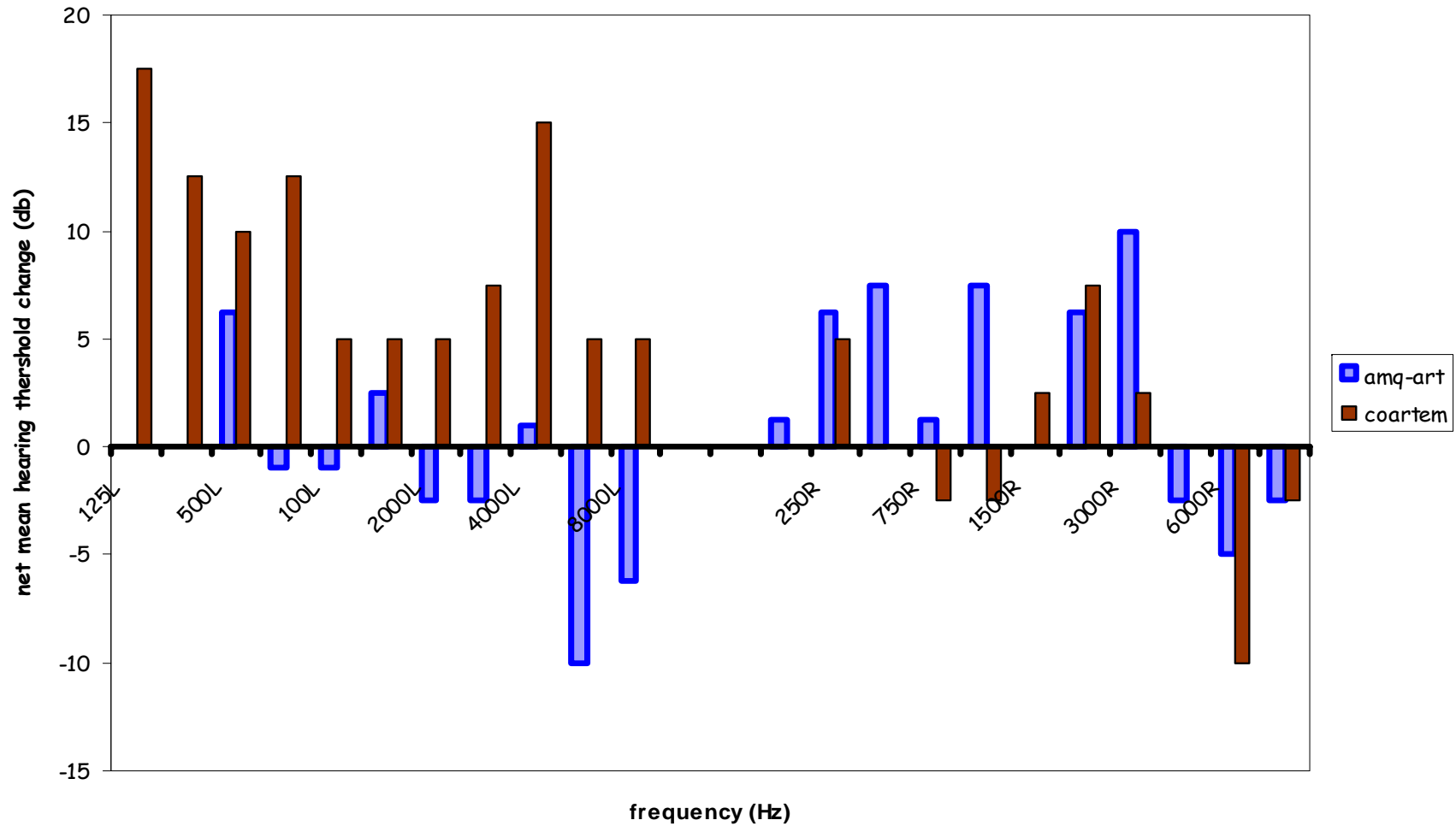
# Side effect profiles: audiometry mean hearing thresholds in (17/59 chn)

children with increased hearing thresholds after treatment

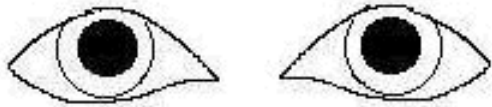
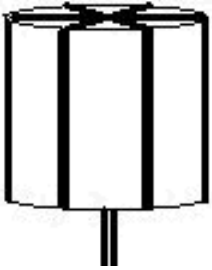


# Side effect profiles: mean hearing thresholds differences- after repeat treatment

thresholds after retreatment



## Side effect profiles: abnormal events

	AQ	A-A	A-L
agranulocytosis	-	2	1
↑ QTc		-	1
nystagmus		2	1
↑ hearing threshold	-	2	2
bradycardia	1	-	-

*chua*

# Conclusions

- 1 • First report of direct comparison b/n A-A/A-L with extended follow up > 42 days
  - A-L assoc. with fewer retreatments and fewer re-infections
  - longer follow ups may be desirable to detect impact on medium-term outcomes in high transmission areas
  
- 2 • First report evaluating QT intervals after treatment with A-A
  - QTc intervals increase during acute phase of malaria, reflecting heart rate changes during convalescence, and is independent of treatment type
  
- 3 • - Mean hearing threshold differences greater in the subset who received ACT than those who received AQ
  - these were not exacerbated after re-treatment
  
- 4 • Possible drug-related adverse effects may occur in a subset of treated patients - ! ↑ pharmacovigilance required



# KORLE BU

## TEACHING HOSPITAL



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