Efficacy & safety of artesunate-amodiaquine (AS&AQ) for treating uncomplicated falciparum malaria in Sub-Saharan Africa: A systematic review with Aggregate (APD) & Individual Patient (IPD) Meta-Analyses

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BACKGROUND

Artesunate combined with amodiaquine (AS&AQ) is first-line treatment of acute uncomplicated falciparum malaria in numerous countries in Africa. The accumulated data of AS&AQ have not been reviewed systematically against other antimalarial treatments.

OBJECTIVES

Perform a systematic search and meta-analysis to summarise efficacy & safety profile.

METHODOLOGY

Studies identified through electronic searches of MEDLINE, EMBASE, LILACS, the Cochrane Infectious Diseases Group's trials register and the Cochrane Central Register of Controlled Trials (CENTRAL) using the search terms: malaria, amodiaquine, artesunate, and artemisinins. Unpublished studies identified through personal contacts and by manuaL searches, contacting individual researchers working in the field, and examining WHO records.

APD (Systematic review + Aggregate Patient Data meta-analysis): investigators contacted for data by site + PCR.

IPD (Individual Patient Data pooled analysis): investigators contacted for individual patient data.

Quality of trials assessed.

66 studies identified → 42 eligible
(Tot = 19,209 pts; AS&AQ = 8,296)
- **38 African studies with 28-day follow-up**
  - **17,755 pts; AS&AQ = 7,692 (33 comparative trials: 6,435 AS&AQ vs. 9,964 comparators)**
    - **IPD: Total 11,700 pts; AS&AQ = 5,987 (comparative trials: 4,896 AS&AQ vs. 5,713 comparators)**

EFFICACY – main analyses

PRIMARY EFFICACY parameter = crude & PCR-adjusted parasitological outcome by Day 28

APD

- Per-protocol (PP) & Modified Intent-to-treat (MITT) populations by site
- Comparisons: logit normal and bi-variate random effect model PCR corrected failure - Risk Ratios (95%CIs) (WHO, 2003) heterogeneity tested.

IPD

- Kaplan-Meier efficacy estimate on modified ITT results stratified by site
- Cox regression stratified by site (Adjusted Hazard Ratio).

SAFETY APD DATABASE

- 22/46 studies contained safety data. (n = 4,693 / 8,296 patients).
- Rates of Adverse Events (Events / 4,693 Patients).
  - Vomiting was most commonly observed event (223, 4.75%)
  - Cough (123, 2.62%)
  - Abdominal pain (110, 2 .3%)
  - Anorexia (103, 2.13%)
  - Fever (67, 1.43%),
  - Pruritus (53, 1.13%)
  - Diarrhea (51, 1.08%).
  - All the remaining were AE's events reported were n<40 (1%) events.

RESULTS- EFFICACY

Figure 1. IPD analysis: risk of failure -all trials

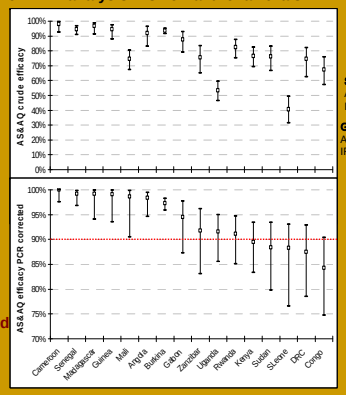


Figure 2. Day 28 Efficacy PCR-corrected APD & IPD

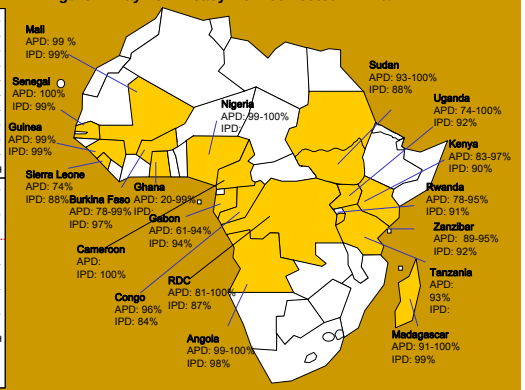


Figure 3. IPD analysis: risk of failure -comparative trials

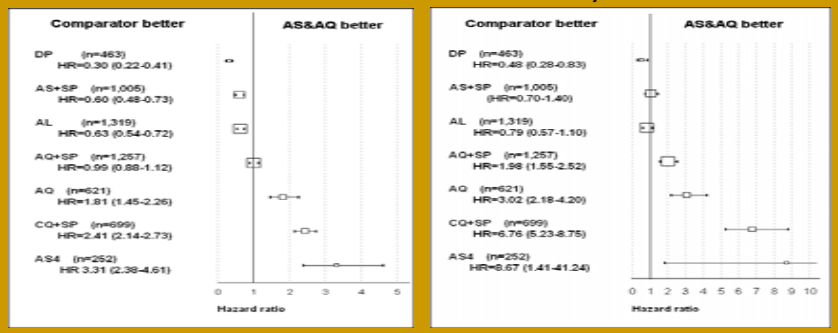
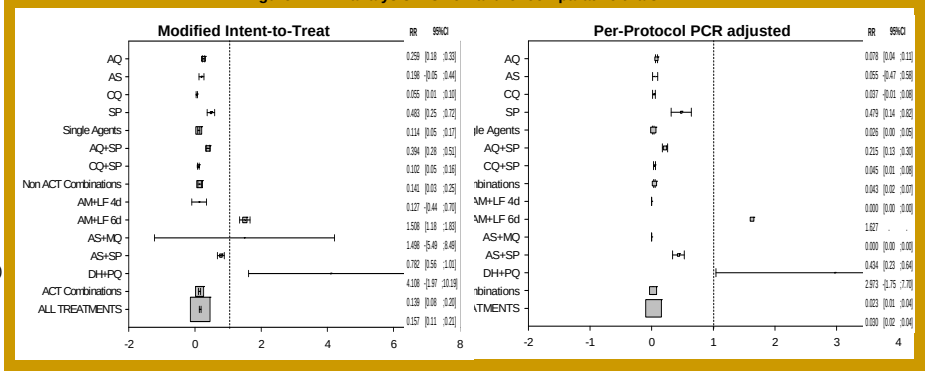


Figure 4. APD analysis: risk of failure -comparative trials



CONCLUSIONS

EFFICACY

- ❑ Variable efficacy across Africa (and sites within countries).
- ❑ Efficacy >90% (WHO threshold) In 11/16 countries.
- ❑ AS&AQ overall compares well with other Artemisinin-based Combination Therapies on PCR-adjusted day 28 outcomes but has more re-infections than other ACTs.

SAFETY

- Generally reported as "well-tolerated", not significantly different from comparator, BUT:
- Inconsistently/insufficiently reported in APD → difficult to summarize & quantify risk.
- Too few studies had lab tests for asymptomatic (haematological, liver) toxicities.
- In IPD → Still small database for rare events - Too few had lab tests for asymptomatic (haematological, liver) toxicities - Too few adults for neurological assessment.

THE AS&AQ GROUP

Systematic Review + meta-analysis:
Review/Analyses: P.Mussano, R.Phalkey, P.Millet; Data: JP.Guthmann, G.Dorsey, P.Brasseur, U.D'Alessandro, A.Mårtensson, K.Koram, B.Faye, P.Menard, K.Mugittu, S.B.Sirima, WRJ Taylor
IPD:
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The views expressed are those of the authors and may not represent those of their employing organizations.

SUMMARY

- ❑ **The question** – Artesunate+amodiaquine (AS&AQ) is an Artemisinin-based Combination Therapy (ACT) widely used in Africa for treating uncomplicated falciparum malaria but summaries are not available for policy decisions.
- ❑ **How was the question addressed** – a systematic review of published & unpublished trials with meta-analyses based on aggregate (APD) and individual (IPD) data.
- ❑ **What did we find** –
  - ❑**AS&AQ meets the WHO-recommended minimum PCR corrected efficacy of ≥90% in 11/16 countries** where it was tested. Its use is therefore justified in these countries.
  - ❑**The re-infection rate after AS&AQ is higher than with other ACTs –** this means patients may need more treatments were transmission intensity is high, but drug selective pressure by AQ may be low.
  - ❑**Safety was poorly documented and thus inconclusive**.
  - ❑**More comparative trials and continued surveillance of efficacy and safety are needed**, including studies in real life conditions and with repeat exposure.
  - ❑**The uptake by regulators and policy makers of knowledge from research should be optimised.** The WHO uses and grades evidence for preparing the Malaria Treatment Guidelines.