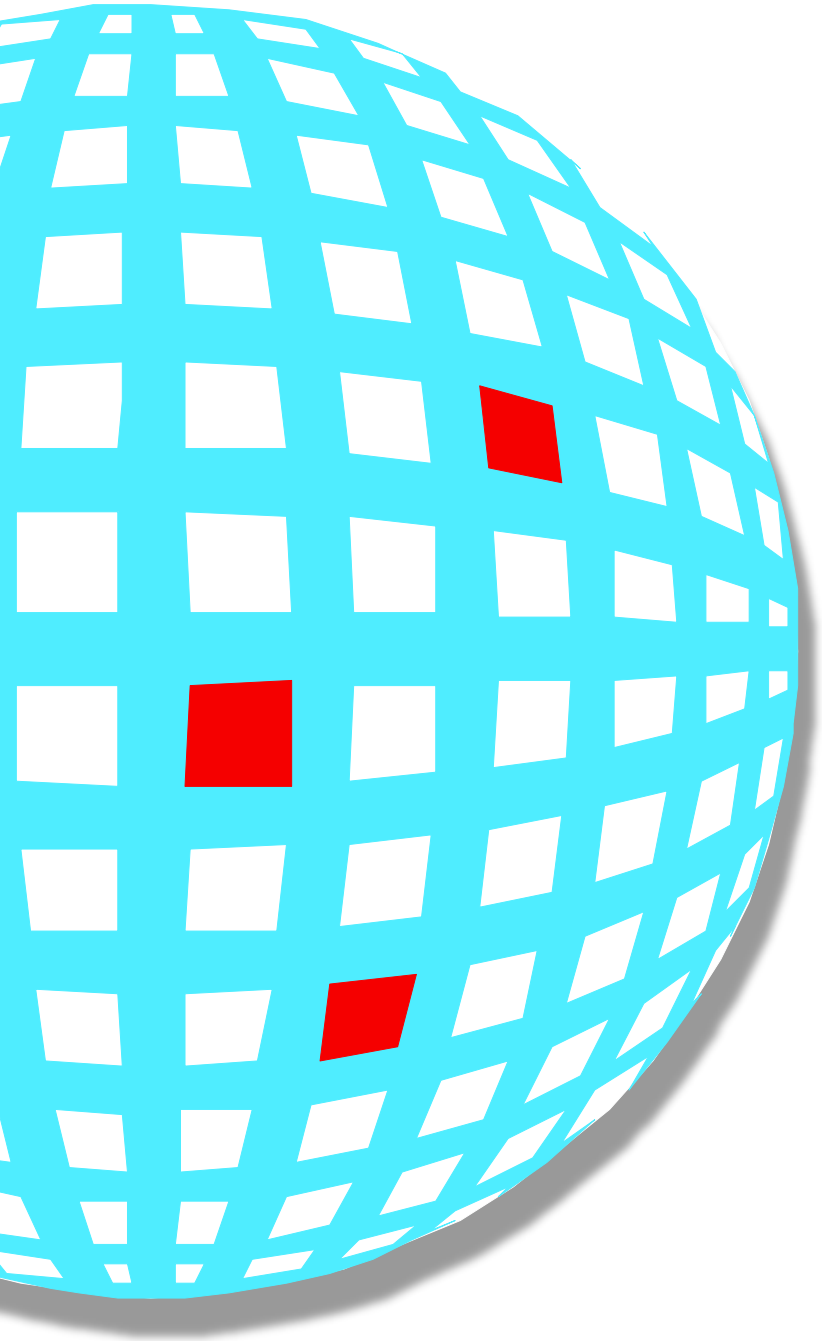


# The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data

WWARN ASAQ Dose Impact Study Group*

# Study Groups → Collaborations

**Define Scientific Question**

↓

**Bring together Collaborative Partnership**

↓

**Agree on Analytical Plan**

↓

**Collate Data in WWARN Format**

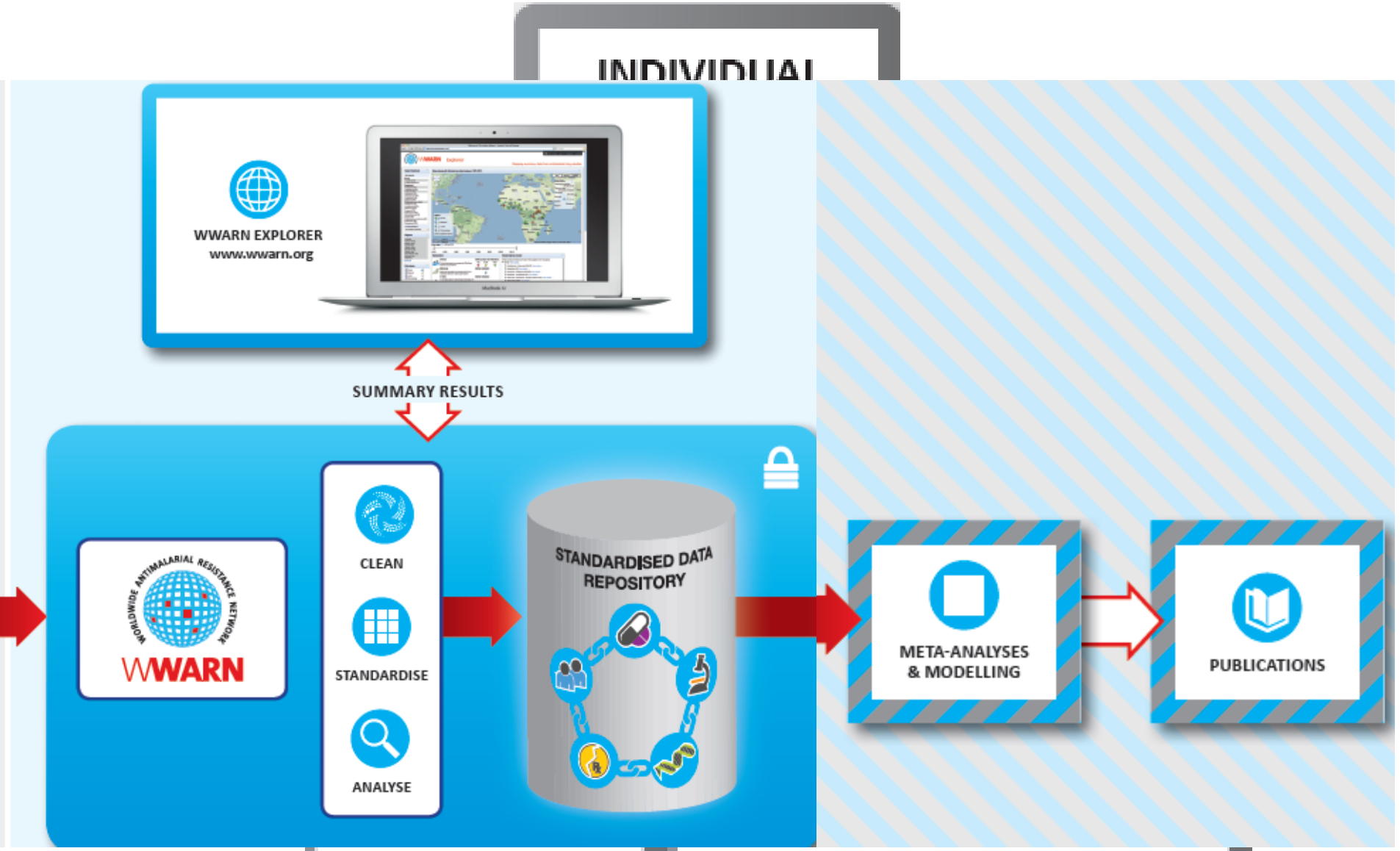
↓

**Meta-analysis : Power, Temporal & Geographic variation**

↓

**Joint Publication with Open Access to additional material**

# Data processing



# Artesunate Amodiaquine (ASAQ) Dose Impact Study Group

- **Background**
  - Efficacy of amodiaquine monotherapy is comprised in many areas
  - Combination with artesunate provides better efficacy but not universally

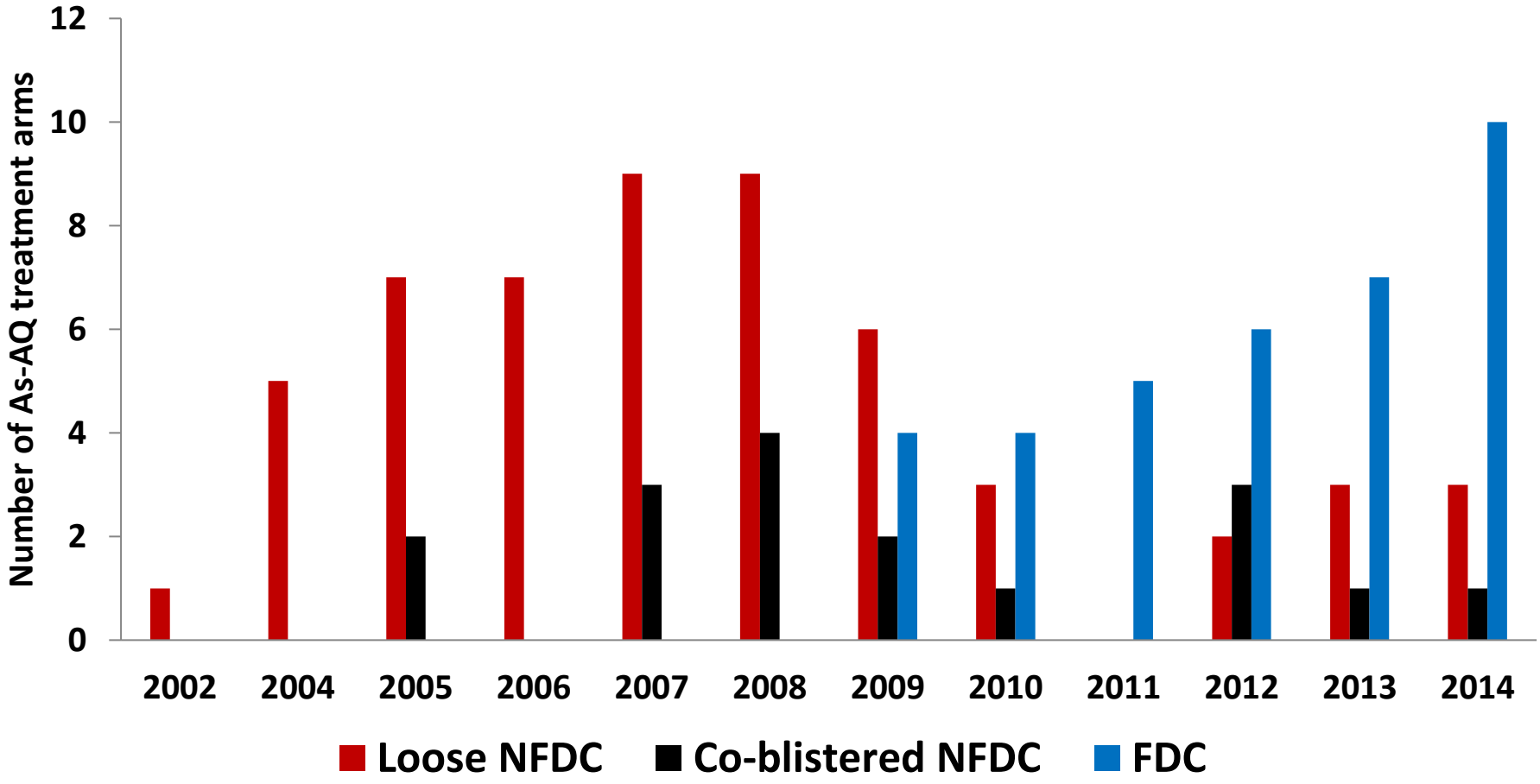
- **Objectives**
  - Identify major risk factors associated with treatment failure after ASAQ treatment for uncomplicated malaria
  - Investigate influence of mg/kg dosing on early and late parasitological response

# Methodology

- Literature Review to identify all published studies
- Active search of unpublished studies
- Data complied and standardised
  - http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf
- A priori Analytical Plan
  - Weight adjusted drug dosage calculated using
    - Tablet counts where available
    - Back calculation from study protocol (weight/age)
  - Survival analysis
  - Cox proportional hazards model with shared frailties to account for heterogeneous study sites
  - Population attributable risks (PARs) associated with recrudescent failures
  - Logistic regression with random effects to assess risk factors for GI side effects

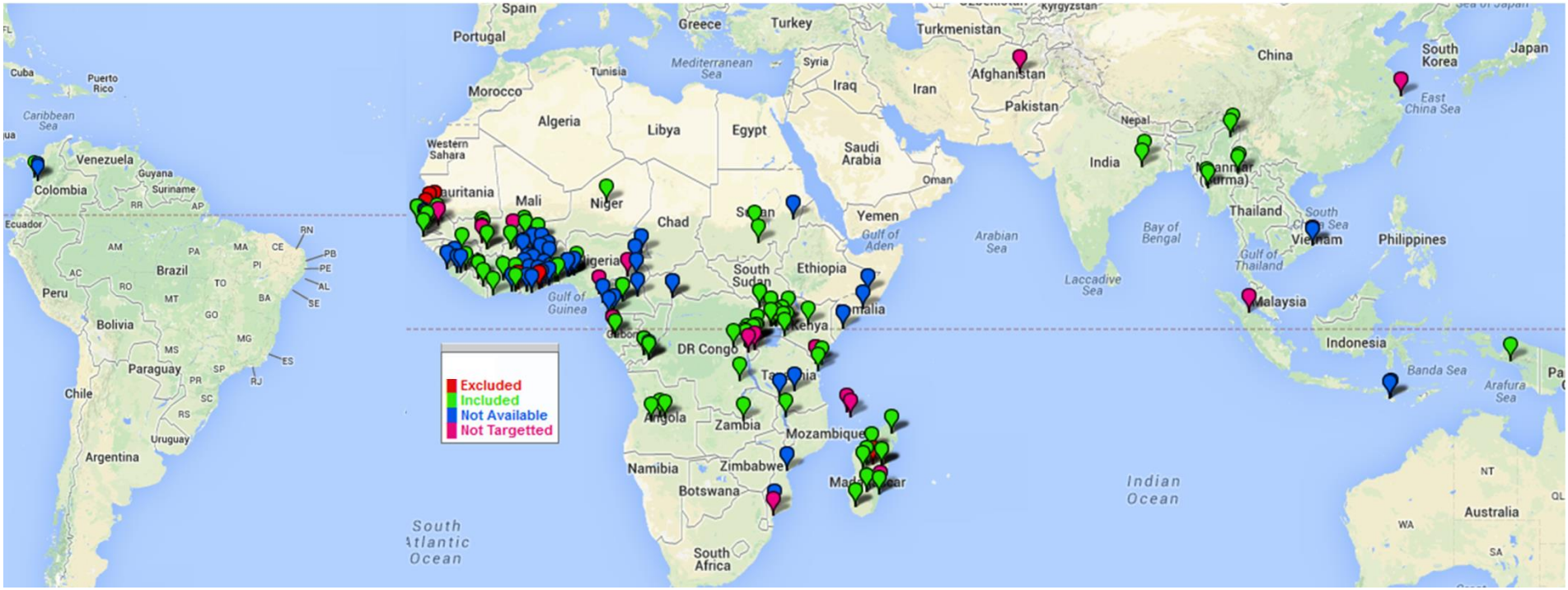
# AS-AQ Literature review

- AS-AQ is the first line treatment in 25 counties
  - Available as Fixed dose combinations (FDC) or Non-fixed dose combinations in loose formulation (Loose NFDC) or Co-packaged (Co-blistered NFDC)



# AS-AQ Dose impact study group sites

- 49 published studies (n=11,768) & 8 unpublished studies (n=1,505)
- 9,106 patients between 1999–2012

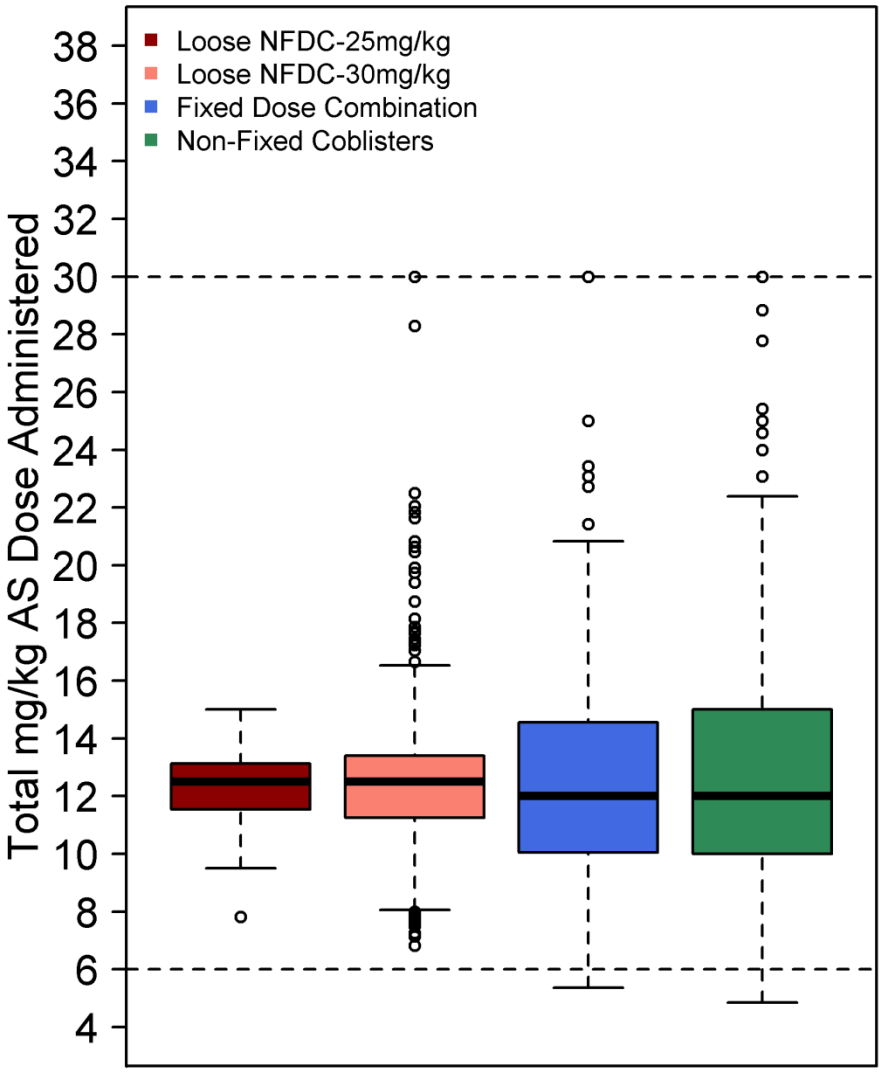


# Baseline characteristics

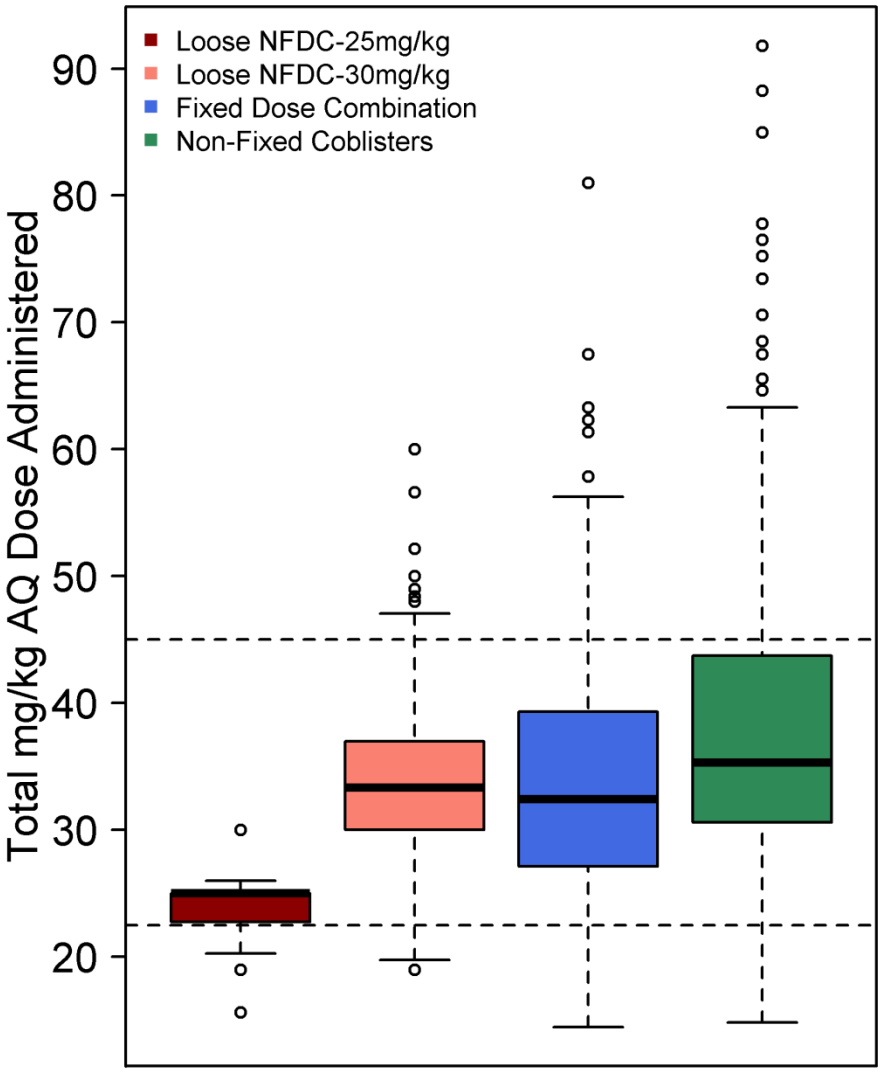
| Variable | Asia n=434 (4.8%) | Africa n=8,635 (94.8%) | South America n=37 (0.4%) |
|---|---|---|---|
| Study Period | 2005-2009 | 1999-2012 | 2000-2004 |
| Geometric mean parasitaemia [95% CI] in parasites/µl | 8,504 [7,409-9,761] | 19,508 [18,944-20,089] | 80 [55-116] |
| Median Age [IQR, Range] in years | 17 [8-28,0.6-80] | 3 [1.7-5,0-80] | 20 [16-25,8-58] |
| Drug Formulation | | | |
| Fixed Dose Combination (FDC) | 78.6% | 44% | 0% |
| Co-blistered non-fixed dose combination (co-blistered NFDC) | 0% | 14.6% | 0% |
| Non-fixed dose combination: Target dose 25 mg/kg ( Loose NFDC-25) | 0% | 15% | 0% |
| Non-fixed dose combination : Target dose 30 mg/kg (Loose NFDC-30) | 21.4% | 26.5% | 100% |

# Total mg/kg administered

Artesunate

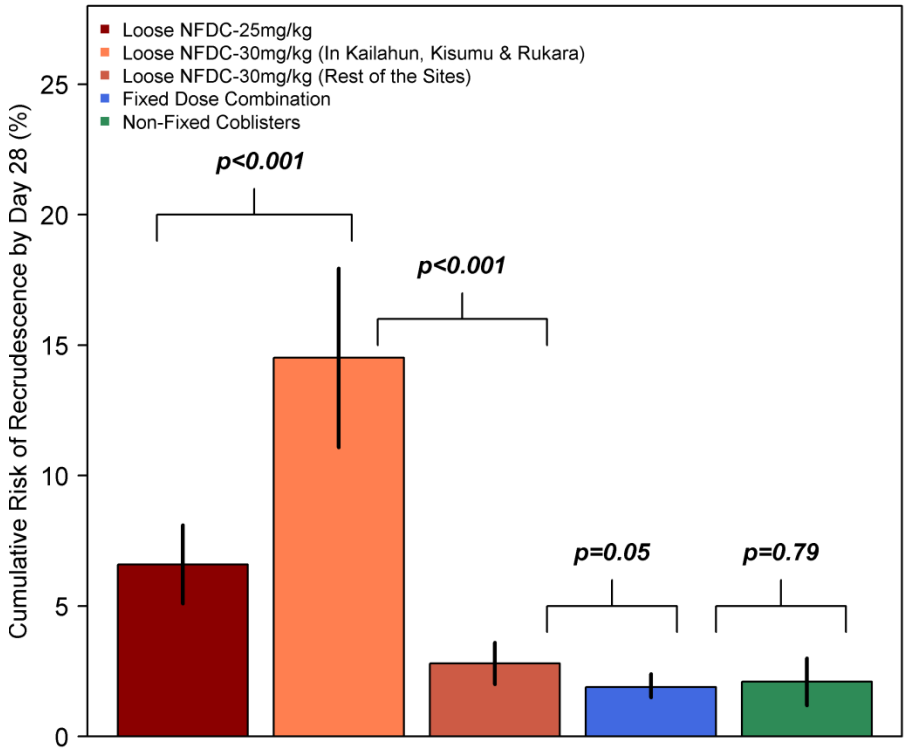



Amodiaquine



# PCR-Corrected cumulative risk of recrudescence

| Combination | Day 28 [95% CI] | Day 42 [95% CI] |
|---|---|---|
| FDC | 98.1% [97.8-98.6%] | 96.1% [95.4-97.6%] |
| Co-blistered NFDC | 97.9% [97.6-99.4%] | - |
| Loose NFDC 25 | **93.4%** [91.9 – 94.9] | - |
| Loose NFDC 30 | 95.0% [94.1-95.9%] | **92.1%** [89.8.1-94.4%] |



# Risk factors for recrudescence and PARs

| | Multivariable Analysis | | Population Attributable Risk | |
|---|---|---|---|---|
| **Variable** | Adjusted HR [95% CI] | p-Value | Freq. | PAR |
| Amodiaquine dose (5 mg/kg) | 0.94 [0.84-1.05] | 0.280 | - | - |
| Parasitaemia (per 10-fold) | 1.39 [1.10-1.74] | 0.005 | 10.4% | 3.7% |
| **Age Category** | | | | |
| ≥12 y (reference) | - | - | - | - |
| <1 y | 3.93 [1.76-8.79] | 0.001 | 8.6% | 20.9% |
| 1 to <5 y | 4.47 [2.18-9.19] | <0.001 | 62.3% | 69.2% |
| 5 to <12 y | 2.03 [0.96-4.28] | 0.064 | 16.9% | 15.1% |
| **Drug Formulation** | | | | |
| FDC (reference) | - | - | - | - |
| Co-blistered NFDC | 1.38 [0.75-2.57] | 0.300 | 13.9% | 5.1% |
| Loose NFDC- 25 | 3.51 [2.02-6.12] | <0.001 | 14.3% | 25.8% |
| Loose NFDC- 30 | | | | |
| In Rukara/Kailahun/Kisumu | 7.75 [4.07-14.76] | <0.001 | 5.1% | 26.3% |
| Rest of the sites | 1.47 [0.91-2.38] | 0.110 | 21.1% | 8.3% |
| **Region** | | | | |
| Africa (reference) | - | - | - | - |
| Asia | 7.39 [3.45-15.86] | <0.001 | 4.8% | 21.6% |
| S. America | - | - | | |

**Overall PAR for model: 92.6 %**

Combined PAR accounted by aged 1-5 years and loose combination: **69.2%**

# Conclusions

- Overall efficacy of AS-AQ is adequate in most settings
- Efficacy varies with the formulation
- Main risk factors for treatment failure
  - Baseline parasitemia
  - Age
  - Use of loose formulations
  - Certain regions with resistance to amodiaquine
- Power of pooled analysis
  - ≠ conclusion to meta-analysis based on aggregated data
  - Provide evidence and could prevent the withdrawal of an effective ACT

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WWARN

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# References


- Worldwide Antimalarial Resistance Network (WWARN) AS-AQ Dose Impact Study Group. The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data. *BMC Medicine 2015*; XXXXXXX DOI XXXXXXXXX

- Link to WWARN newsletter article


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