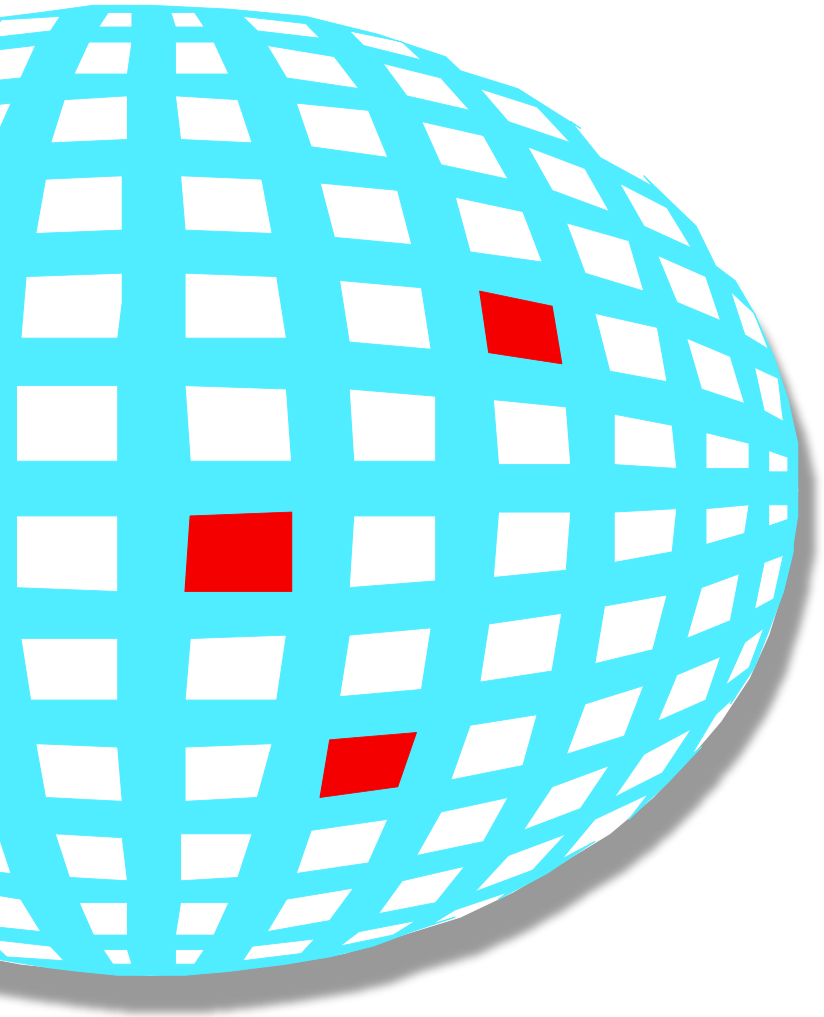


The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data

WWARN AL Dose Impact Study Group*

Study Groups → Collaborations

Define Scientific Question

↓

Bring together Collaborative Partnership

↓

Agree on Analytical Plan

↓

Collate Data in WWARN Format

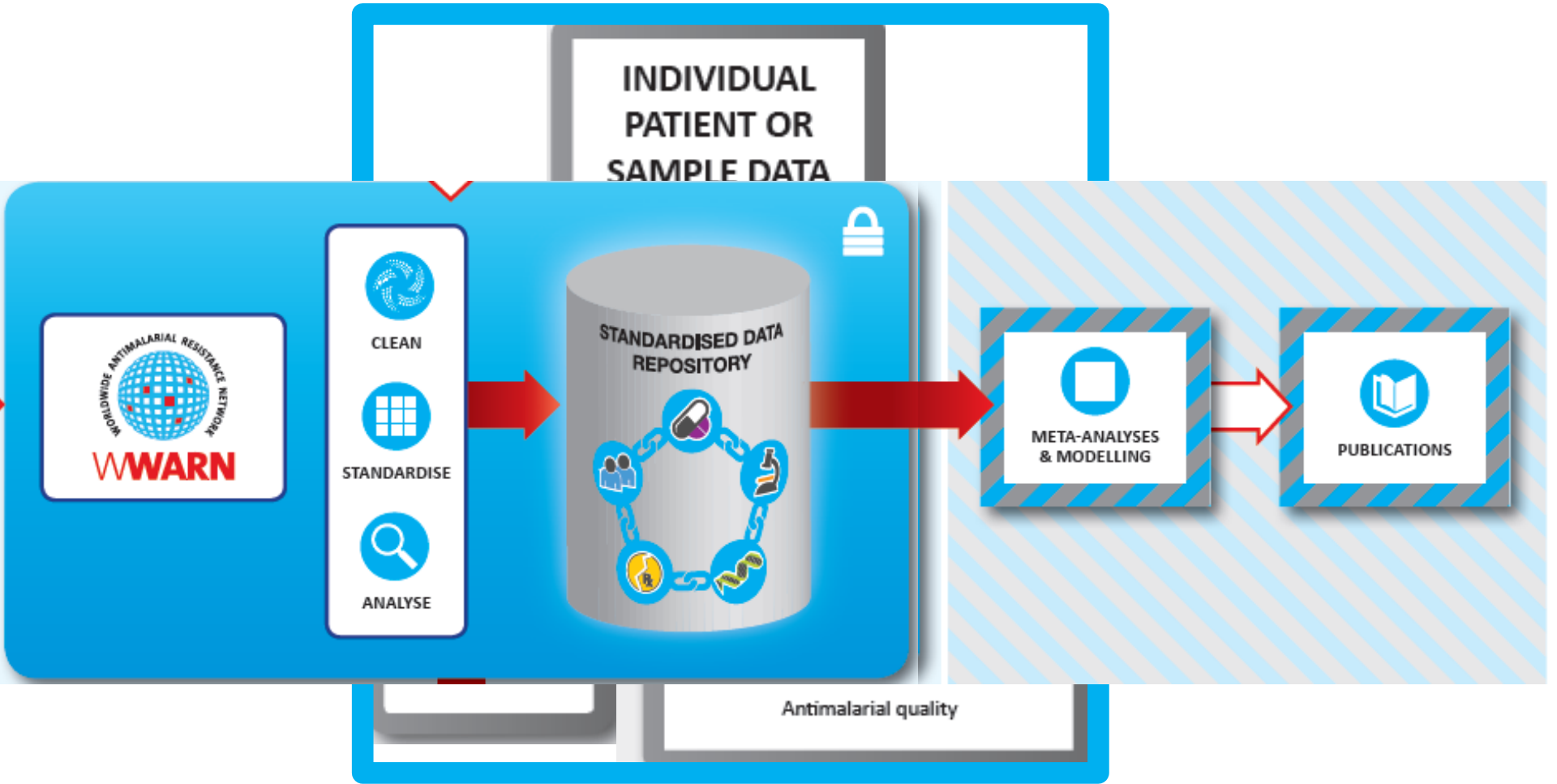
↓

Meta-analysis : Power, Temporal & Geographic variation

↓

Joint Publication with Open Access to additional material

Data processing



Artemether lumefantrine (AL)
Dose Impact Study Group

- **Objectives**

  - Determine mg/kg distribution of AM and LUM
  - Investigate influence of mg/kg dosing on early and late parasitological response
  - Identify major risk factors associated with treatment failure
  - Assess relationships between dose and tolerability

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- Active search of unpublished studies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
  - Relationship between drug dose and gastrointestinal side effects explored using logistic regression with random effects fitted for individual study & sites

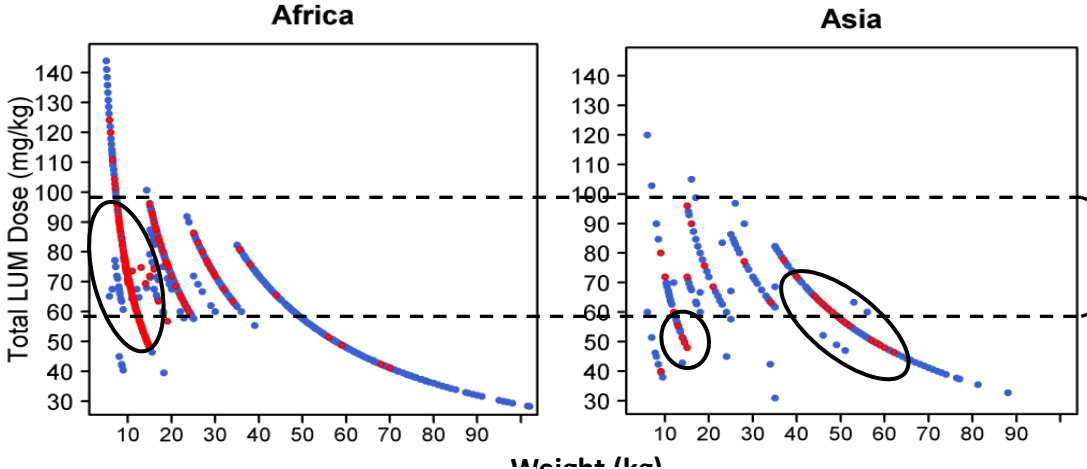
AL Dose impact study group sites

- 53 published studies (n=12,586) & 8 unpublished studies (n=1741)
- 14,327 patients between 1998–2012

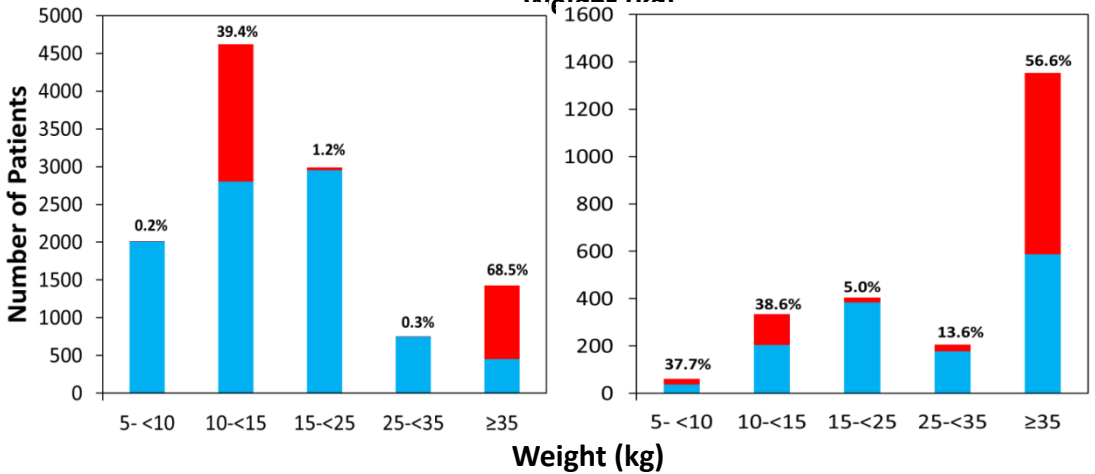
Baseline characteristics

	Asia	Africa	South America	Overall
N	2359 (16.5%)	11809 (82.4%)	159 (1.1%)	14327
Study period	1998-2010	2002-2012	2007-2008	1998-2012
Age (years)				
Median age [Range]	16.0 [0.5-77]	3.5 [0-77]	23.0 [12-56]	4.0 [0-80]
<1	0.3%	6.9%	0.0%	5.7%
1 to <5	15.81%	**58.9%**	0.0%	51.2%
5 to <12	21.3%	21.0%	0.0%	20.8%
≥ 12	**62.6%**	13.2%	**100.0%**	22.3%
Treatment supervision				
Full	77.3%	76.9%	100.0%	77.3%
Drug trade name				
Coartem® (Novartis)	100.0%	94.2%	100.0%	95.2%
Enrolment clinical variables				
Median parasitaemia (parasites/µl) [IQR]	9559 [13-450440]	**21360 [16-420360]**	4241 [1008-44744]	19921 [13-450440]
Children underweight for age (UWA)	36.7%	17.3%	-	18.4%

Dosing of lumefantrine and efficacy



Current WHO recommended therapeutic range 60-96 mg/kg for Lumefantrine



Dosing implications for AL efficacy

Patients with low AM daily dose:

Greater Risk of Parasitaemia on day 1

Patients with low AM total dose:

Greater Risk of gametocyte carriage on day 14

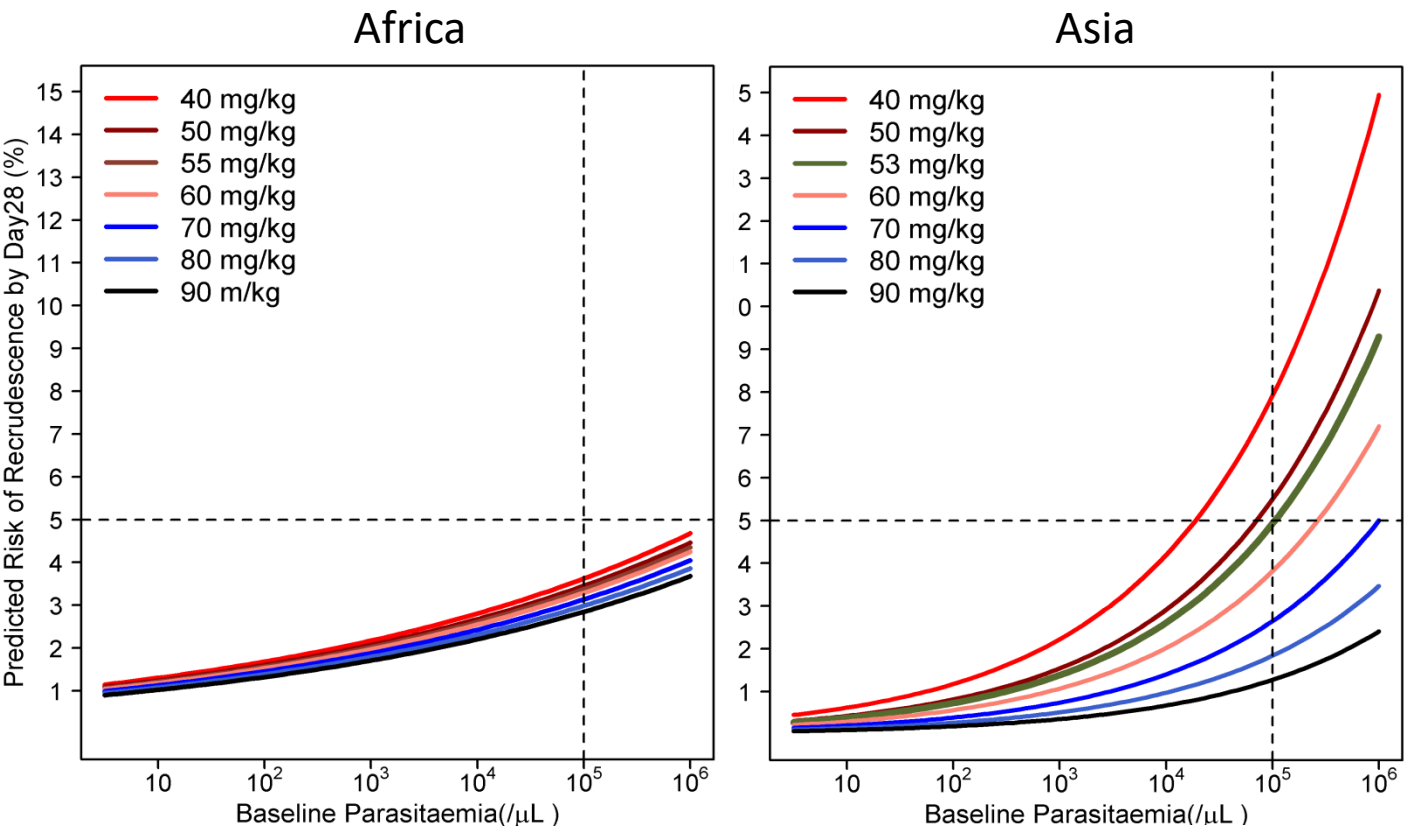
	Kaplan-Meier Survival Estimates	
	Day 28 n=11,923	Day 42 n=4,279
Overall	97.6 %	96.0 %
Age group (years)		
<1	97.0 %	95.2 %
1 to 3 (underweight)	94.3 %	92.5 %
1-3	96.8 %	95.1 %
3 to 5 (underweight)	98.1 %	94.7 %
3 to 5	97.2 %	94.1 %
5 to <12	98.4 %	97.3 %
≥12	98.9 %	98.3 %
Region		
Africa	97.5 %	95.4 %
Asia	98.0 %	97.5 %
S America	99.4 %	98.7 %

Risk factors for recrudescence and PARs

	Multivariable Analysis		Population attributable risks (PARs)	
	Adjusted HR [95% CI]	***p*-Value**	**Freq.**	**PARs**
Lumefantrine dose (every 5 mg/kg increase)	0.98 [0.94-1.02]	0.380	27.46%	6.30%
Enrolment clinical variables				
Parasitemia (log scale)	**1.41 [1.15-1.74]**	**0.001**	**9.51%**	**4.01%**
Age category (years)				
≥ 12 (reference)				
<1	1.78 [0.89-3.55]	0.100	5.72%	4.76%
1 to <5	**2.00 [1.23-3.23]**	**0.005**	**51.14%**	**37.92%**
5 to <12	1.27 [0.76-2.12]	0.360	20.79%	7.96%

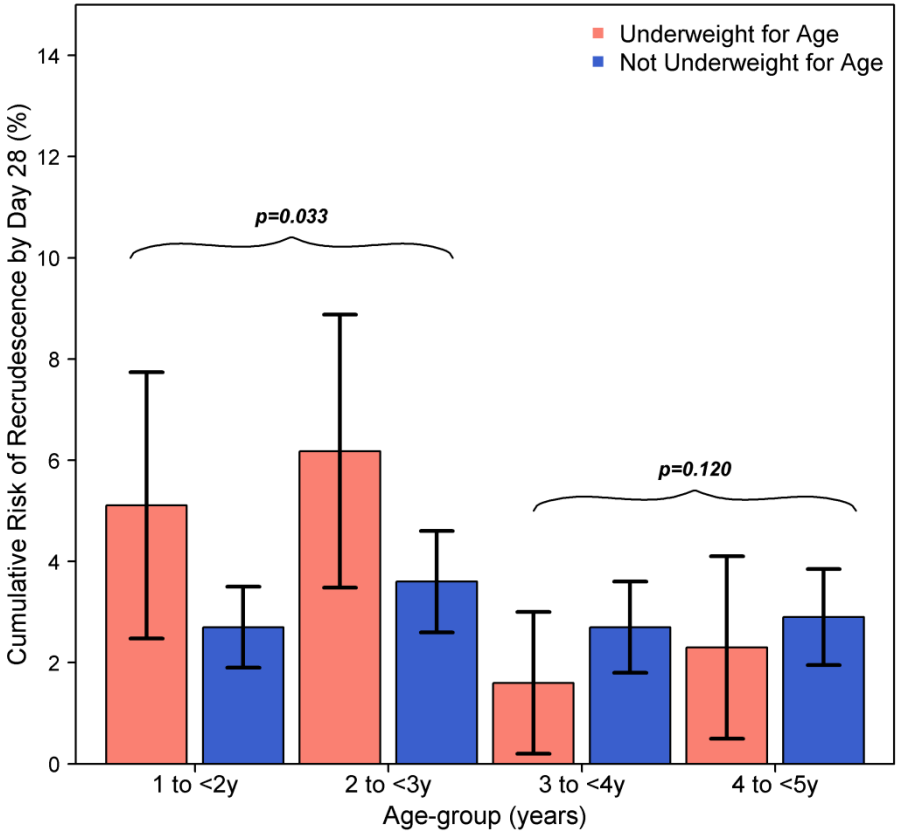
Overall PAR for model: 54.1 %
However, interaction between region, parasitemia and LUM dose

Africa vs Asia



In Asia, the LUM dose associated with recrudescence

Africa



Malnutrition associated with recrudescence in Africa

Conclusions

- AL is highly effective in most of patients
- Cure rates were lowest in young children from Asia, especially those with high parasitemia and young underweight children from Africa
- A higher dose regimen should be evaluated in these groups, especially in young patients between 13 and 15kg

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- Novartis

WWARN

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References

- Worldwide Antimalarial Resistance Network (WWARN) AL Dose Impact Study Group. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data. *The Lancet Infectious Diseases 2015*; D-14-00566R1; DOI 10.1016 S1473-3099 (15)70024-1

- WWARN newsletter article

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