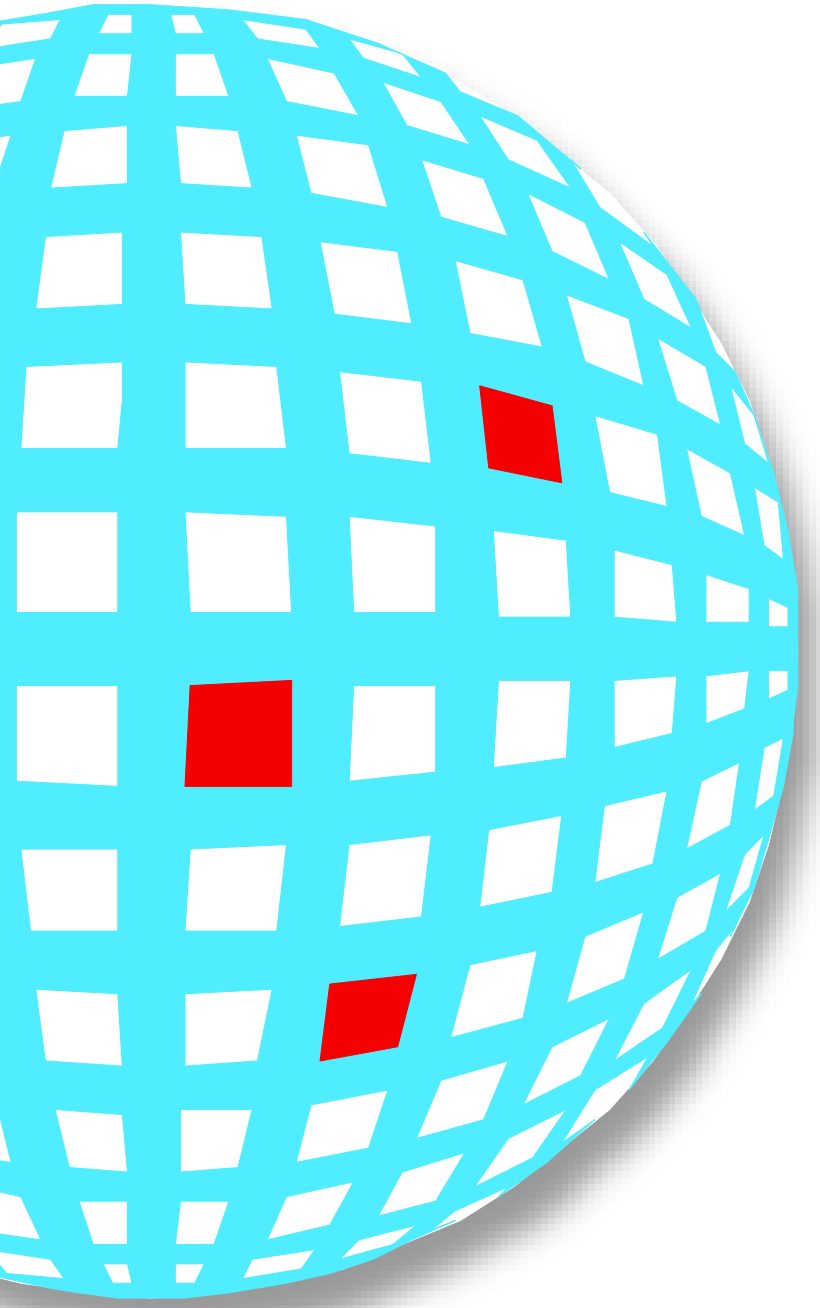
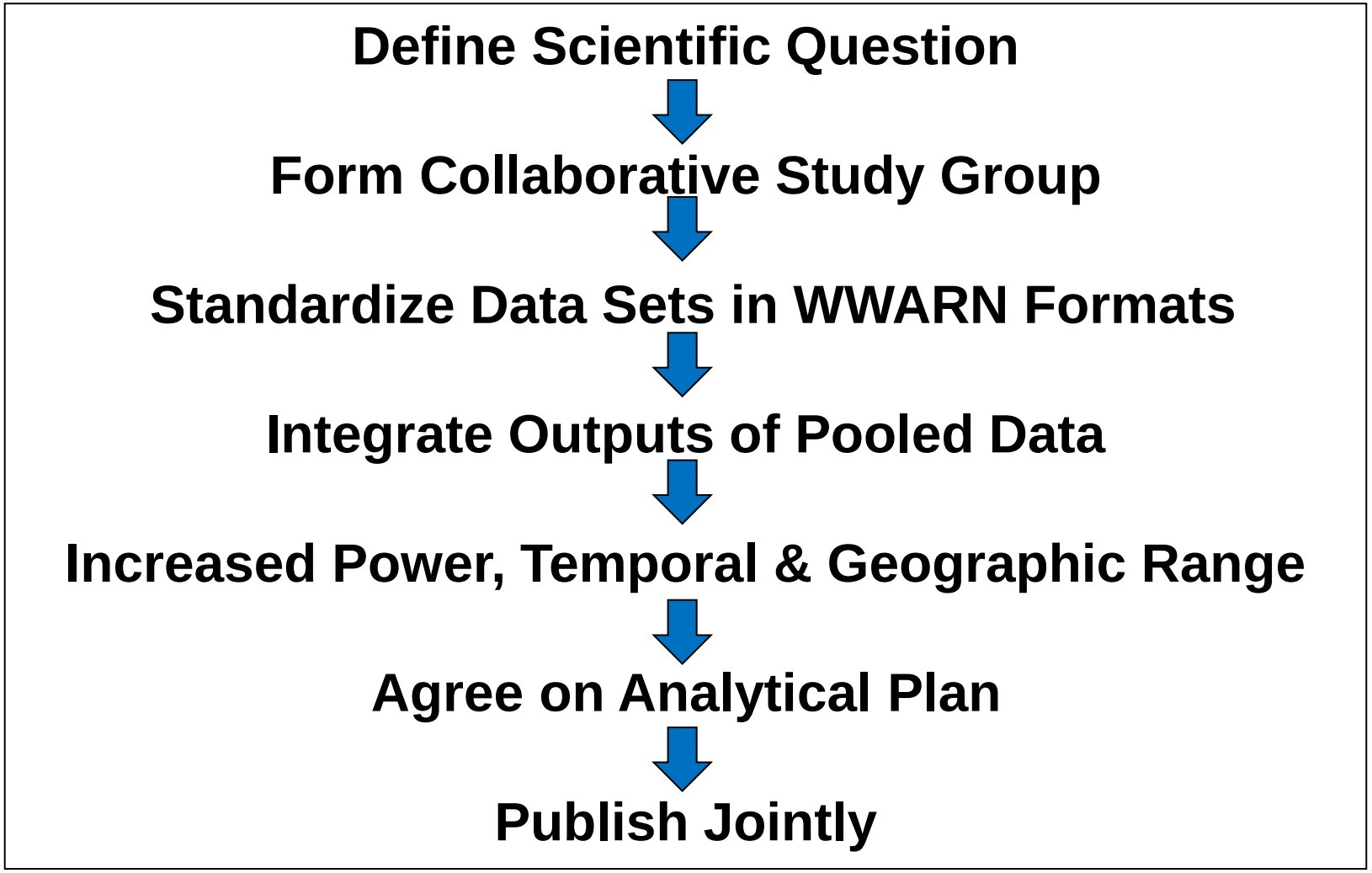


The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin piperaquine: a pooled analysis of individual patient data

WWARN DP Study Group*

Study Groups = Collaborations



DHA-PIP Dose Impact Study Group

- **Objectives**
  - Determine mg/kg distribution of DHA and PIP
  - 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

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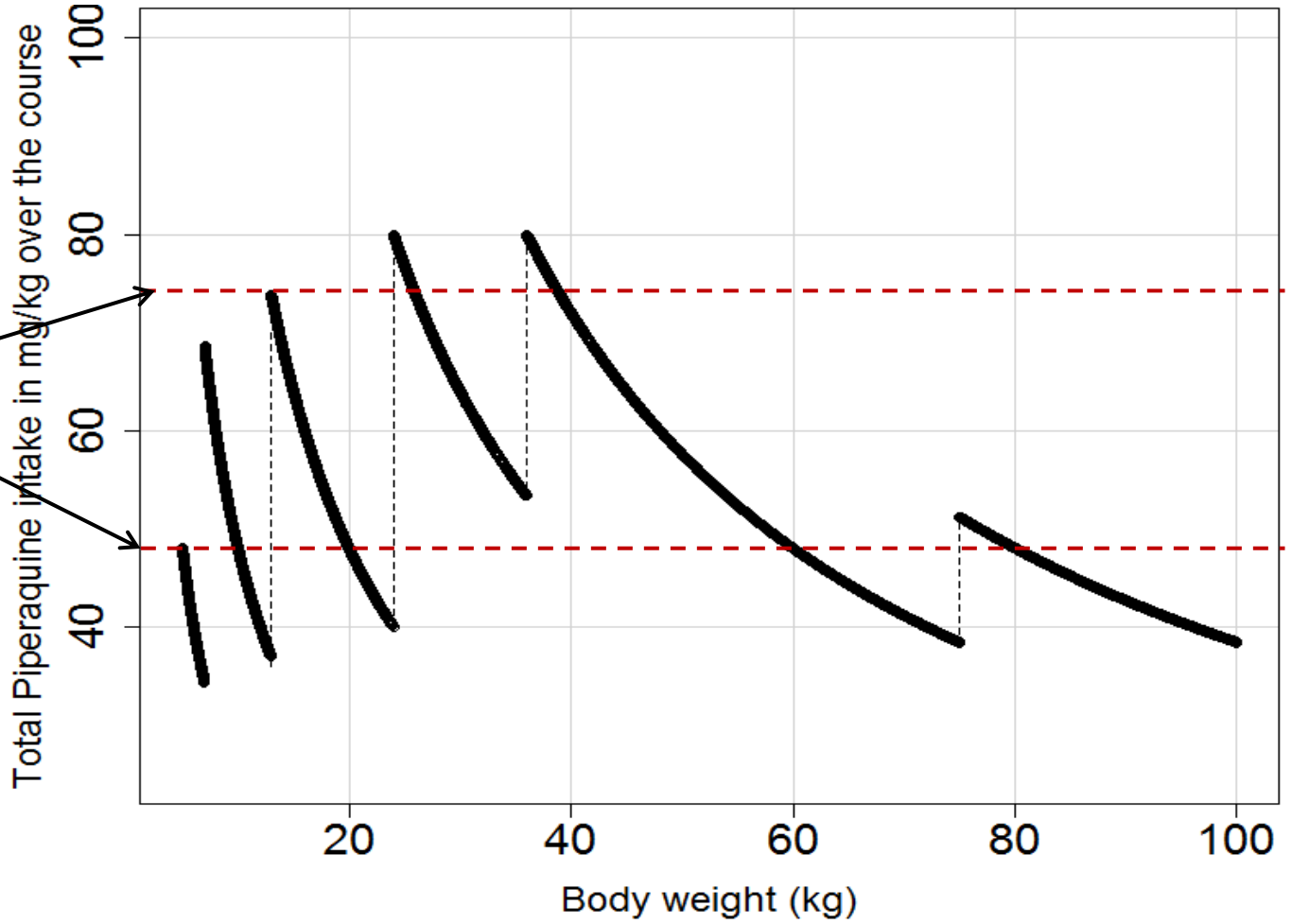
Wide range in mg/kg piperaquine dose administered

Current WHO recommended therapeutic range 48-78 mg/kg for PIP



Methodology

- Literature Review to identify all published studies
- Active search of unpublished studies
- Data complied and standardised
  - Transparent methodology: http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf
  - Public Policy: http://www.wwarn.org/sites/default/files/PublicationPolicy.pdf
- Weight adjusted drug dosage calculated using
  - Tablet counts where available
  - Back calculate from study protocol (weight/age)
- A priori Analytical Plan
  - http://www.wwarn.org/partnerships/study-groups/dha-pqp-dose-impact-study-group
  - Survival analysis
  - Cox proportional hazards model with shared frailties on study sites to account for heterogeneous nature of the data
  - Population attributable risks (PARs) associated with recrudescent failures assessed
  - Relationship between drug dose and gastrointestinal side effects explored using logistic regression with random effects fitted for individual study & sites

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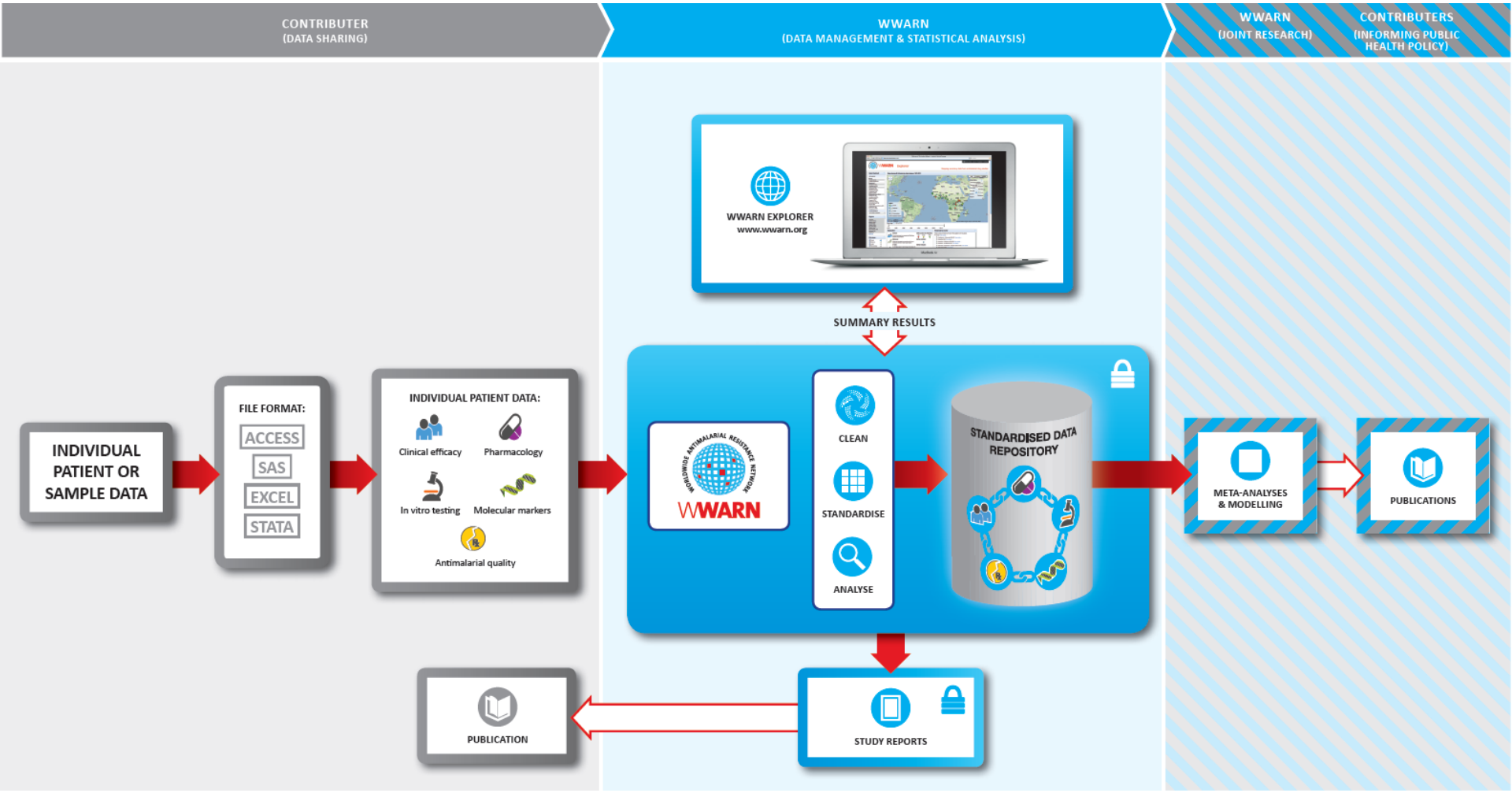
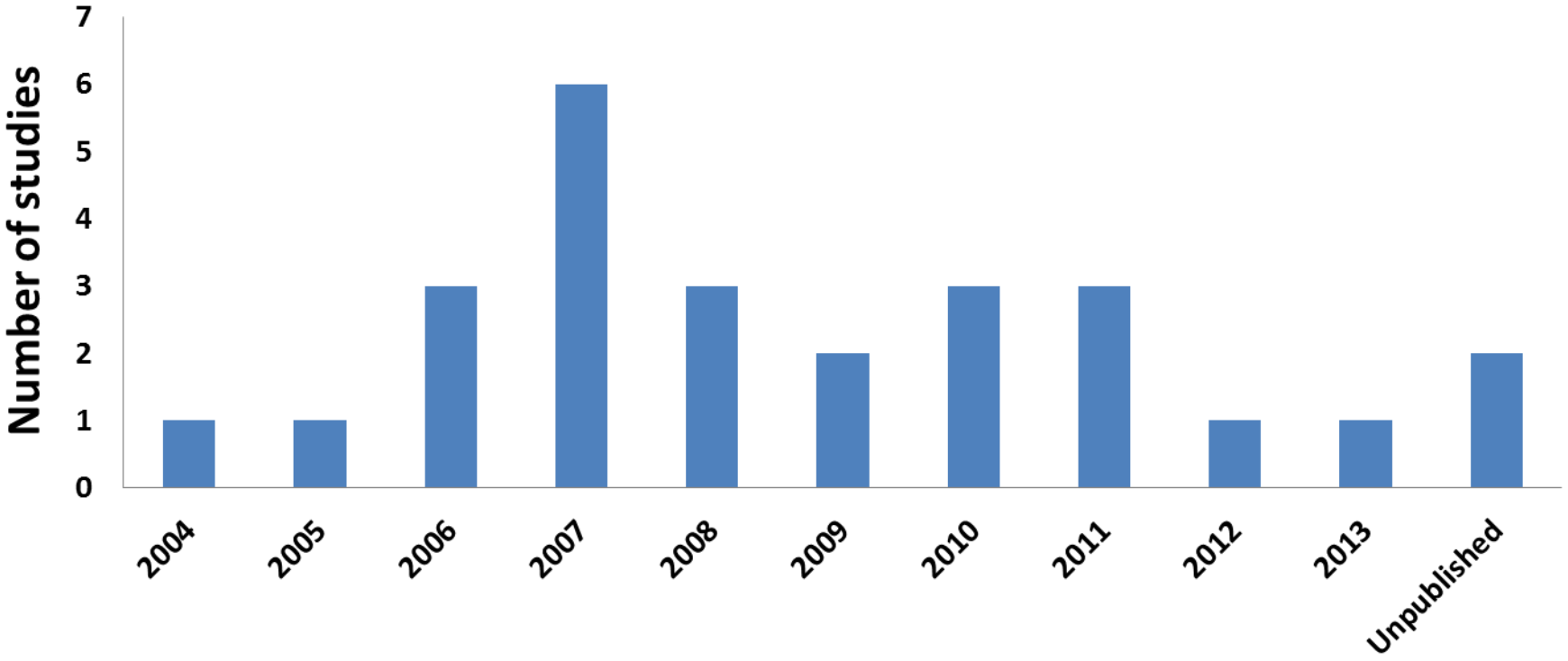
Data processing

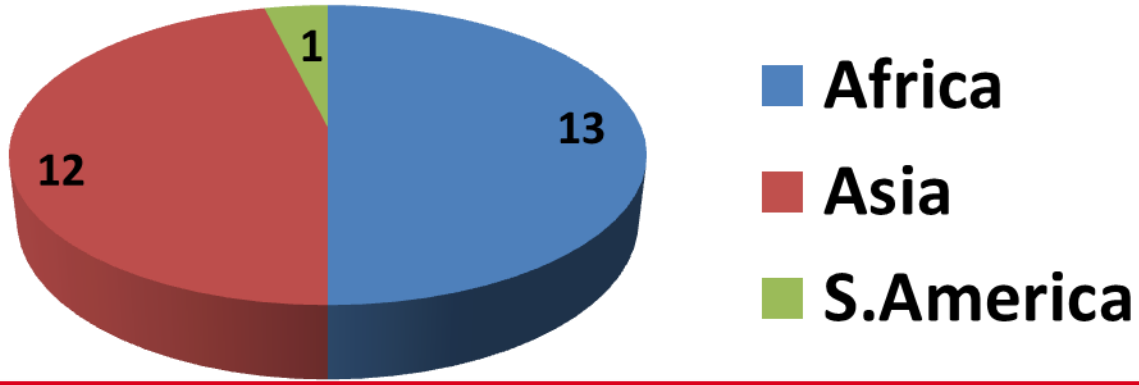


DHA-PIP study sites

- 24 published studies : 69% of targeted studies
- 2 unpublished studies
- Overall: 7,072 Patients between 2002–2011 (70% of 10,168)

Studies included in the pooled analysis





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Patients baseline characteristics

	Asia	Africa	South America	Overall
Number of patients	2807 (39.7%)	4009 (56.7%)	256 (3.6%)	7072 (100%)
Median Age in years [Range]	18 [0.7-65]	2.6 [0.35-75]	23.5 [5-59]	4.2 [0.35-75]
<1 year	0.2% [5/2807]	10.8% [434/4009]	0% [0/256]	6.2% [439/7072]
1 to <5 years	12.9% [361/2807]	**76.5% [3068/4009]**	0% [0/256]	48.5% [3429/7072]
5 to <12 years	20.9% [587/2807]	7.8% [312/4009]	17.6% [45/256]	13.4% [944/7072]
≥ 12 years	**66.1% [1854/2807]**	4.9% [195/4009]	**82.4% [211/256]**	31.9% [2260/7072]
Median parasitemia (μl^{-1}) [IQR]	8,530 [2240.5-29026.8]	**26,520 [8739-62400]**	6,274.5 [3272-9995]	16,580 [4782-473000]

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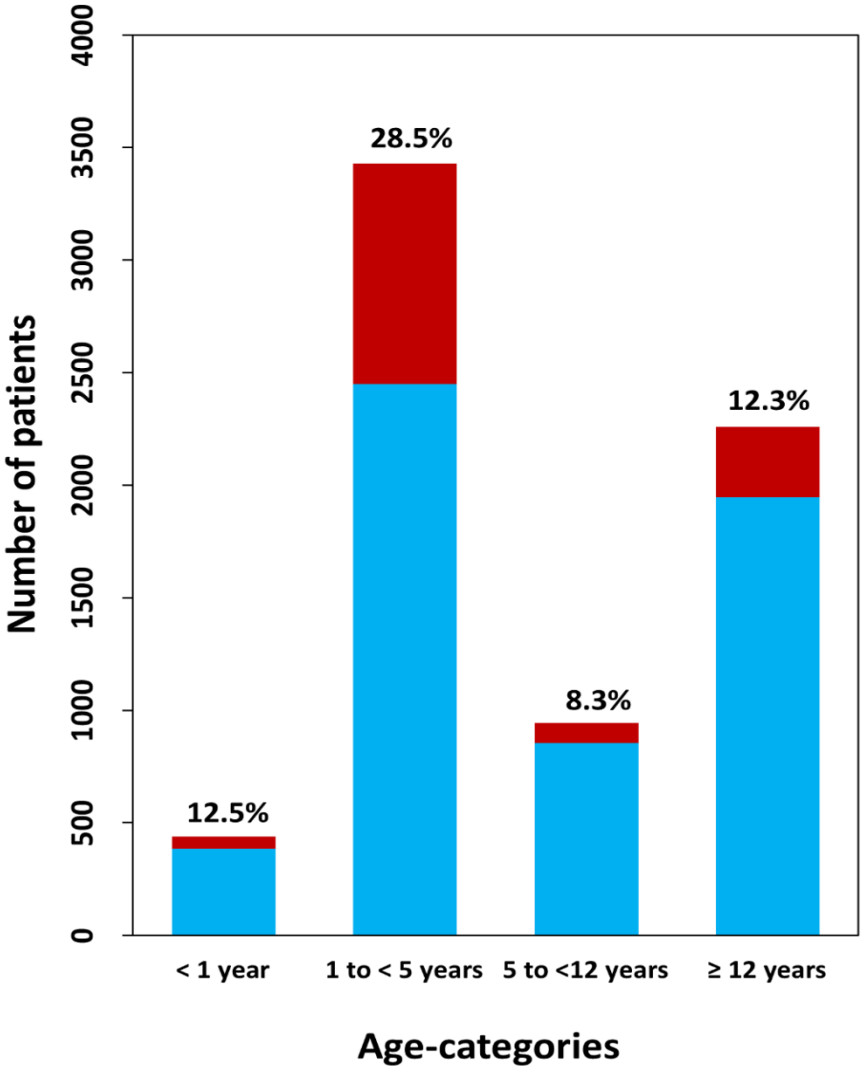
Dosing and Efficacy

- Overall: 22% of the patients exposed to a dose < 48mg/kg
- Children aged 1 to <5 years at greater risk of exposure [OR=2.3 [95% CI: 1.7-3.3]; p<0.001) to a dose below the recommended range for DHA and PIP
- overall PCR-adjusted efficacy of 98.8% at day 28, 97.6% at day 42 and 97.0% at day 63
- However, efficacy of 94.4% in children 1 to < 5 years at day 63



Proportion of patients below the WHO recommended the therapeutic range (48 -78 mg/kg) for piperaquine

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Risk factors for recrudescence and PARs

	Univariable Analysis		Multivariable Analysis		PAR	
Variable	Crude HR [95% CI]	p-Value	Adjusted HR [95% CI]	p-Value	Freq. (%)	PAR (%)
PIP dose (mg/kg) (every 5 unit increase)	**0.86 [0.78-0.94]**	**0.001**	**0.87 [0.79-0.95]**	**0.002**	**20.33**	**7.70**
Parasitaemia (log-scale)	**1.26 [1.10-1.44]**	**0.001**	**1.23 [1.08-1.41]**	**0.003**	**9.38**	**6.51**
Baseline gametocyte carriage	1.79 [1.05-3.04]	0.032	-	-	-	-
≥12 years (reference)	1					
<1 year	2.36 [0.79-7.06]	0.200	2.39 [0.79-7.25]	0.120	6.21	7.80
1 to <5 years	**3.71 [1.66-8.26]**	**0.002**	**3.22 [1.42-7.33]**	**0.050**	**48.50**	**53.52**
5 to <12 years	1.48 [0.56-3.91]	0.610	1.56 [0.59-4.13]	0.370	13.34	5.72

Overall PAR: 65.1 %

Age and low dosing accounted for 54% of the all recrudescent failures.

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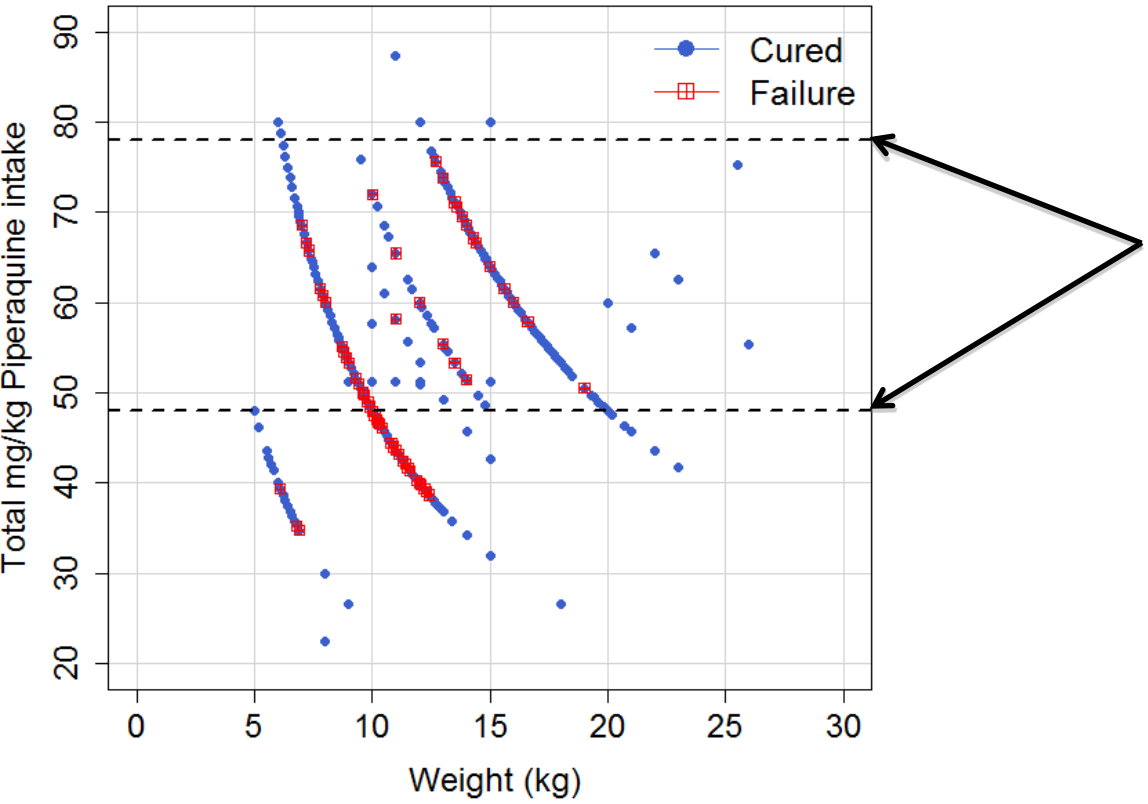
PIP dosing in children < 5 years

Mann-Whitney test: p<0.001

Outcome	N	25th	Median (mg/kg)	75th
Cured	2954	44.9	**53.3**	64.0
Recrudescence	92	42.5	**48.4**	53



Current WHO recommended therapeutic range 48-78 mg/kg for piperaquine

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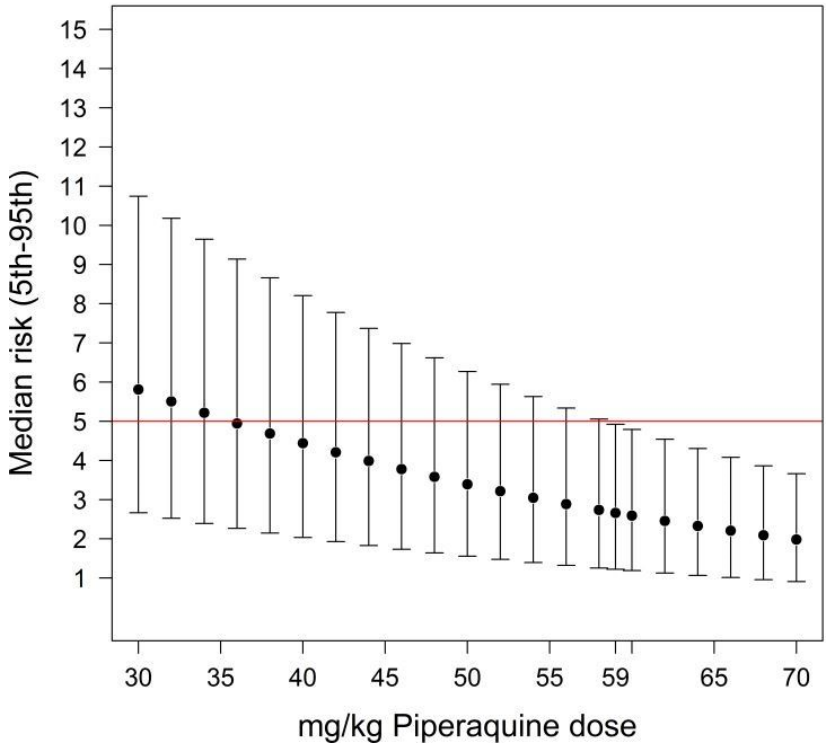
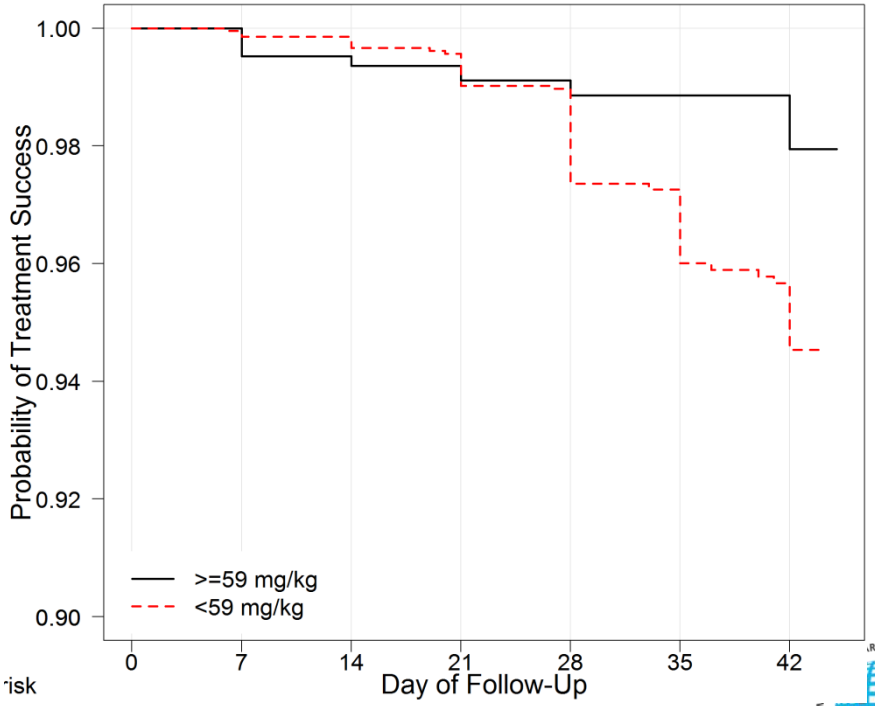
Optimising PIP Dosing in children < 5 years

- PIP dose of 59 mg/kg: day 42 cure rate ≥95%
- Patients with a dose < 59 mg/kg at higher risk of recrudescence (AHR=2.03 [95% CI: 1.2-3.42; p=0.008])
- Risk of recrudescence by Day 42: 5.5% vs 2.1%; p< 0.001





Other Therapeutic Parameters

Early Parasite response

- PPR: Day 1: 59% Day 2: 9.1% Day 3: 1.2%

- DP dose (mg/kg) risk factor for parasite positivity:
  - **0.81** [95% CI: 0.67-0.97]; p=0.022) for DHA
  - **0.97** [95% CI: 0.94-0.99]; p=0.026) for PIP per unit increase in mg/kg

Reinfections

448 New Infections

- PIP dose (mg/kg): **AHR 0.97** [0.96-0.98], p<0.001
- After controlling for young age and high transmission sites

Gametocyte Carriage

- DHA dose risk factor for gametocyte carriage on day 7
  - Dose < 6mg/kg: AOR=1.56 [95% CI: 1.08-2.24]; p=0.015

Conclusions

- Overall efficacy of DHA-PIP is excellent
- Main risk factors for treatment failure:
  - Age, baseline parasitaemia, and PIP dose (mg/kg)
- Dosing is suboptimal, particularly in young children
  - Increase risk of recrudescence
  - Slower parasite clearance
  - Increased risk of reinfection and gametocyte carriage
- Emphasises the need for paediatric formulations
- Need a combination of clinical, pharmacokinetic and safety data to review dosing strategies

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WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK
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References

- The Worldwide Antimalarial Resistance Network (WWARN) DP Study Group (2013) The Effect of Dosing Regimens on the Antimalarial Efficacy of Dihydroartemisinin-Piperaquine: A Pooled Analysis of Individual Patient Data. *PLOS Med* 10(12): e1001564. DOI:10.1371/journal.pmed.1001564

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