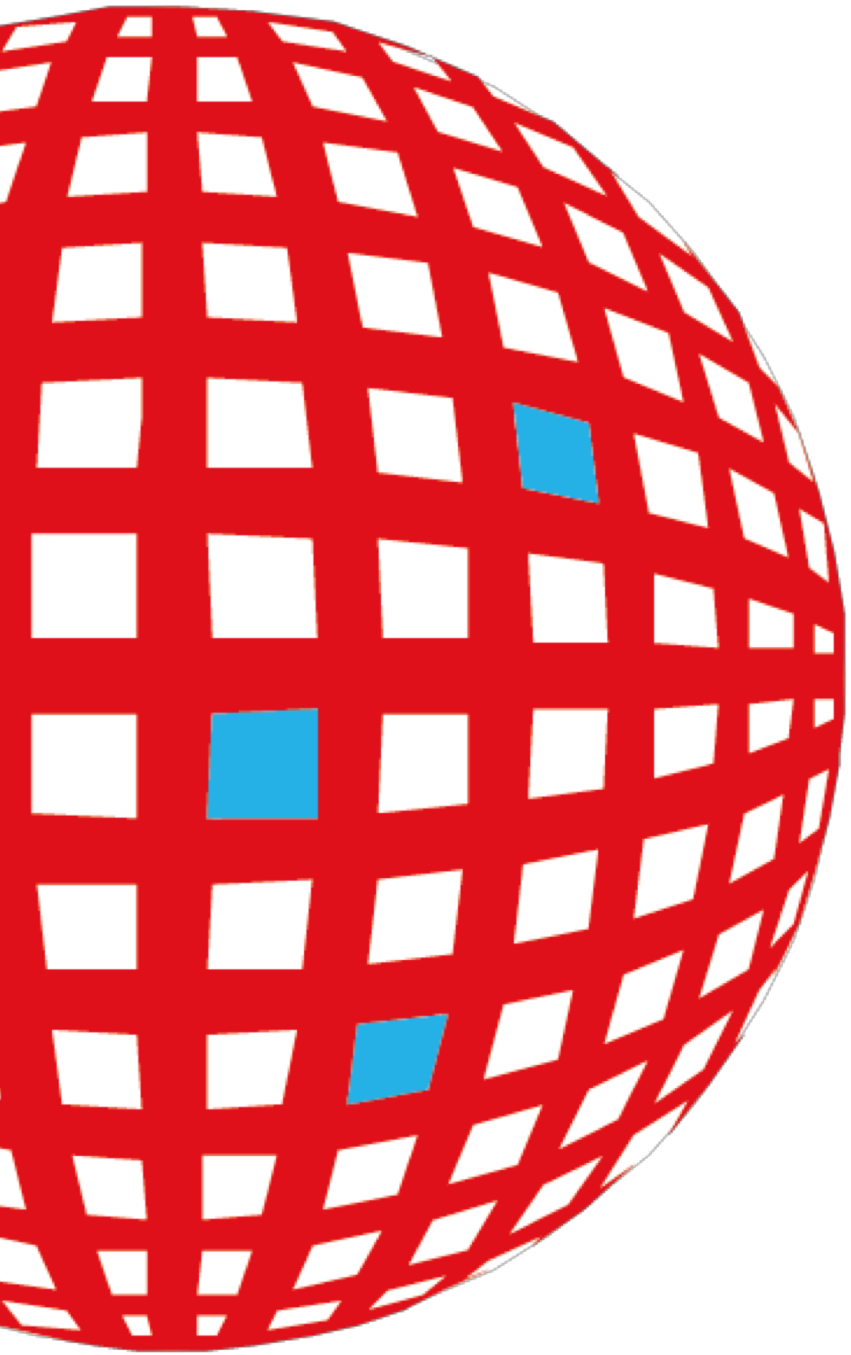

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INFECTIOUS DISEASES DATA OBSERVATORY

A global clinical trial data platform for poverty-related diseases: The potential and value for regulatory agencies

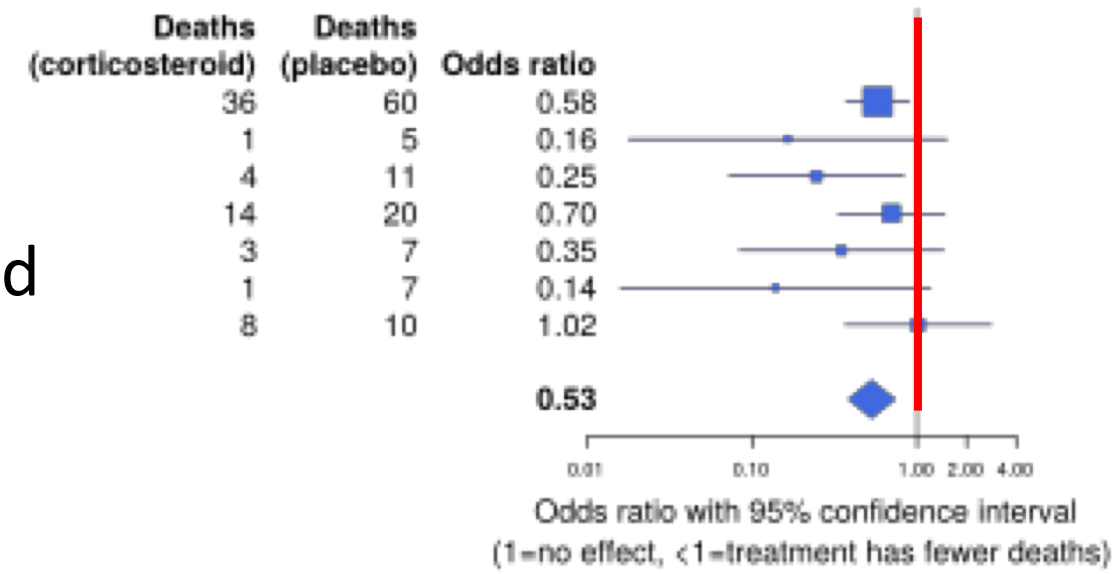
Laura Merson

www.iddo.org

Twitter: @IDDOnews

Standard evidence pathway: Aggregated meta-analyses from publications

The evidence we would like to see



Limitations

- Requires data from randomised controlled clinical trials
- Subject bias
- Unable to tease out heterogeneity across disease area, methodology, standards…
- Limited analysis of sub-groups: lack of granularity

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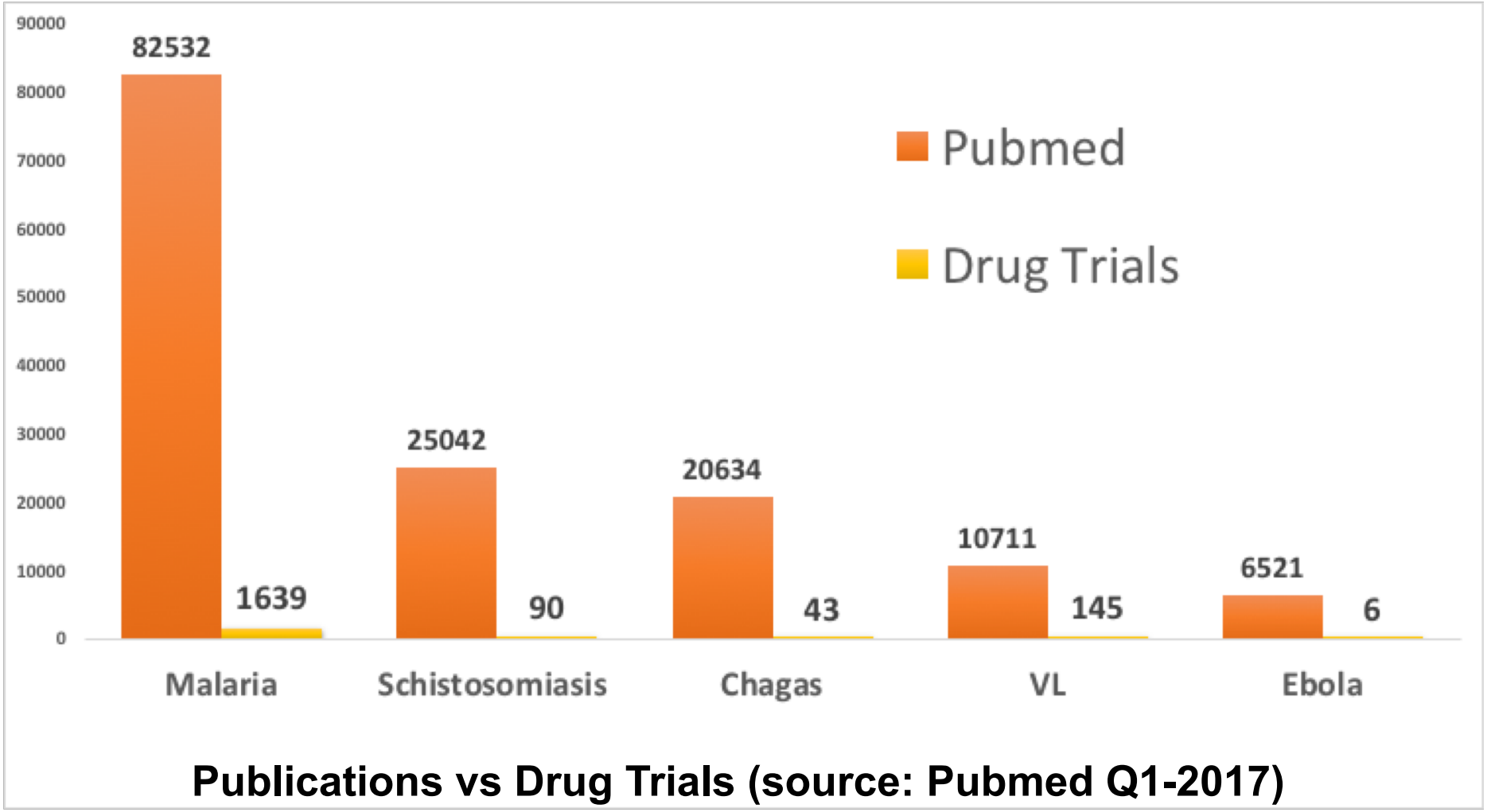
Volume of data available



Publications vs Drug Trials (source: Pubmed Q1-2017)

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Scarce data on poverty-related diseases

- Limited commercial interest
- Challenges in patient recruitment
- Small sample sizes

Thus strengthening the case of journals, funders and public health agencies that sharing data is necessary to maximise health benefits.

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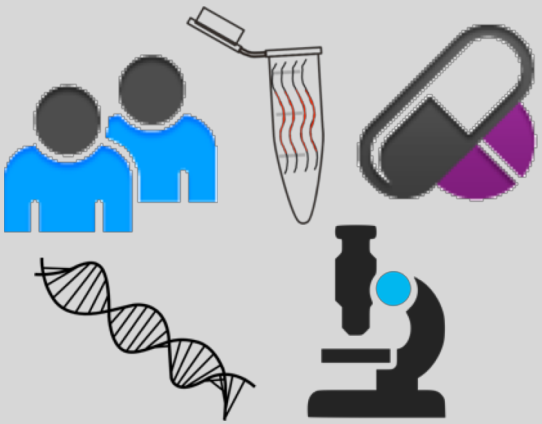
Barriers to accessing data on poverty-related diseases

- Perceived disadvantage for researchers in low-resource settings
- Risk vs. benefit
- Political sensitivities
- Concerns regarding consent and data privacy
- Lack of confidence in data quality
- Challenges of sharing benefits with communities of data origin
- Geographically scattered
- Methodologically diverse

The IDDO Data Platform

Individual patient data
(any format)



Clean

Standardise

Map

Repository

Publication

Treatment guidelines

Policy

Meta-analysis

Policy makers

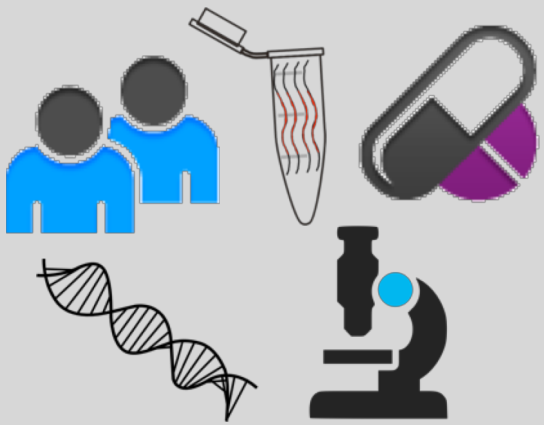
Contributor

Curator

Collaborators

The IDDO Data Platform

Individual patient data
(any format)



Clean

Standardise

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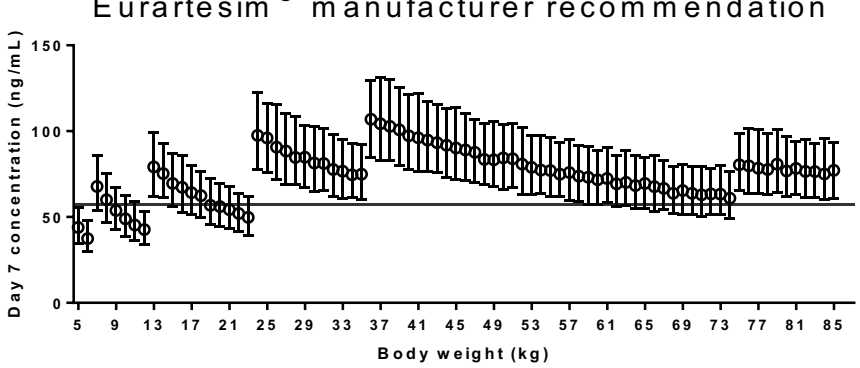
Dihydroartemisinin-Piperaquine (DHA-PPQ)

Case reports:
high failure rates in young children

Dose by weight band



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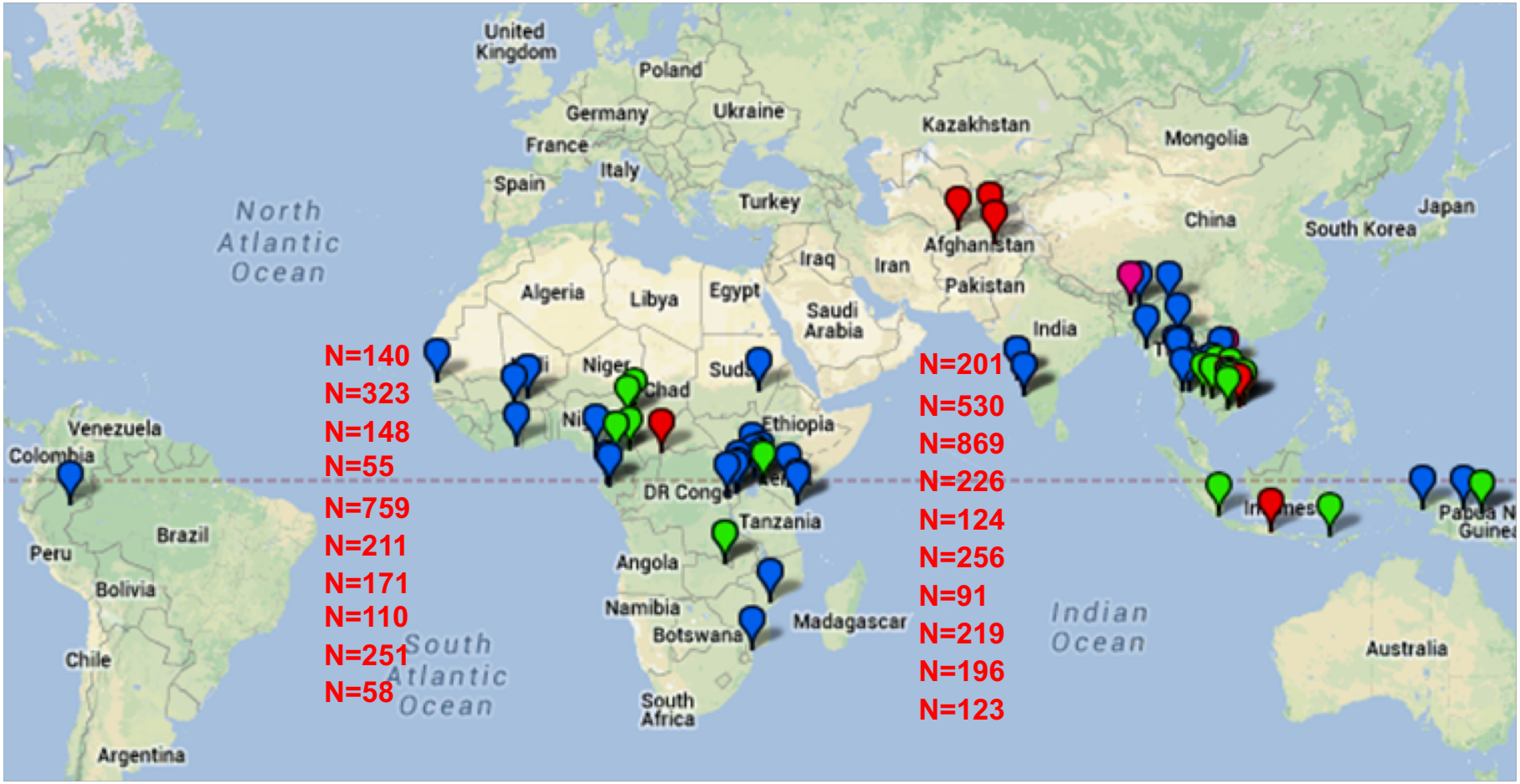
Dihydroartemisinin-Piperaquine (DHA-PPQ)



26 studies over 10 years - 7,072 patients

individual patient-level data (IPD)

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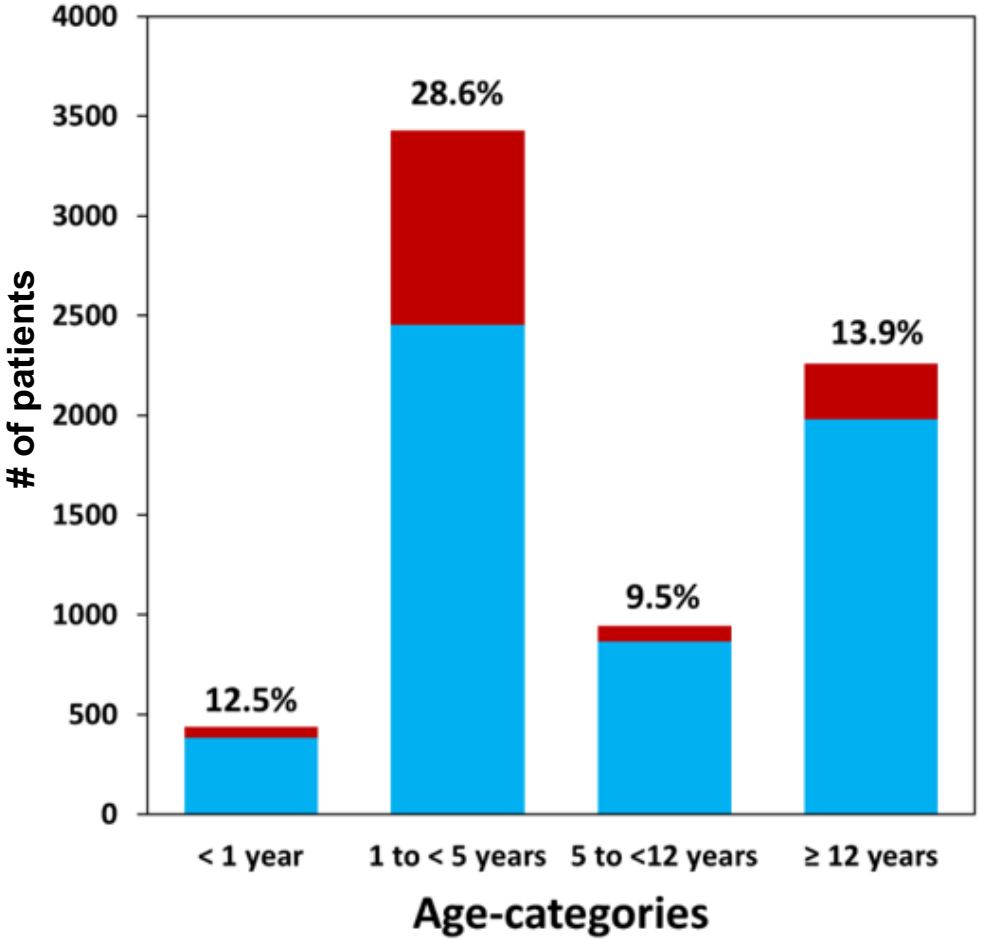
Dihydroartemisinin-Piperaquine (DHA-PPQ) IPD meta-analysis



¼ of children were under-dosed

WWARN DP Study Group. PLoS Med. 2013 Dec;10(12):e1001564

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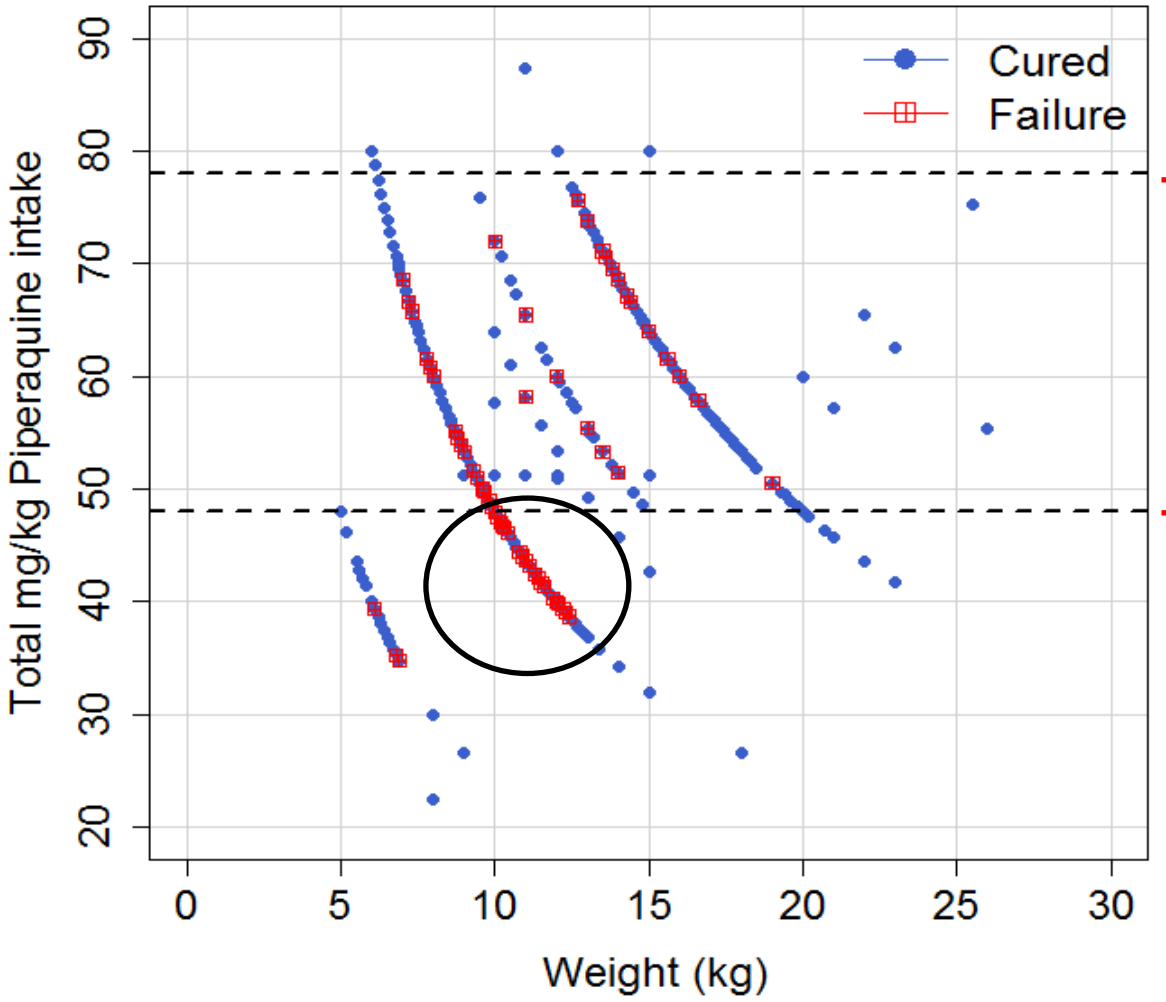
Dihydroartemisinin-Piperaquine (DHA-PPQ) IPD meta-analysis



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

WWARN DP Study Group. PLoS Med. 2013 Dec;10(12):e1001564

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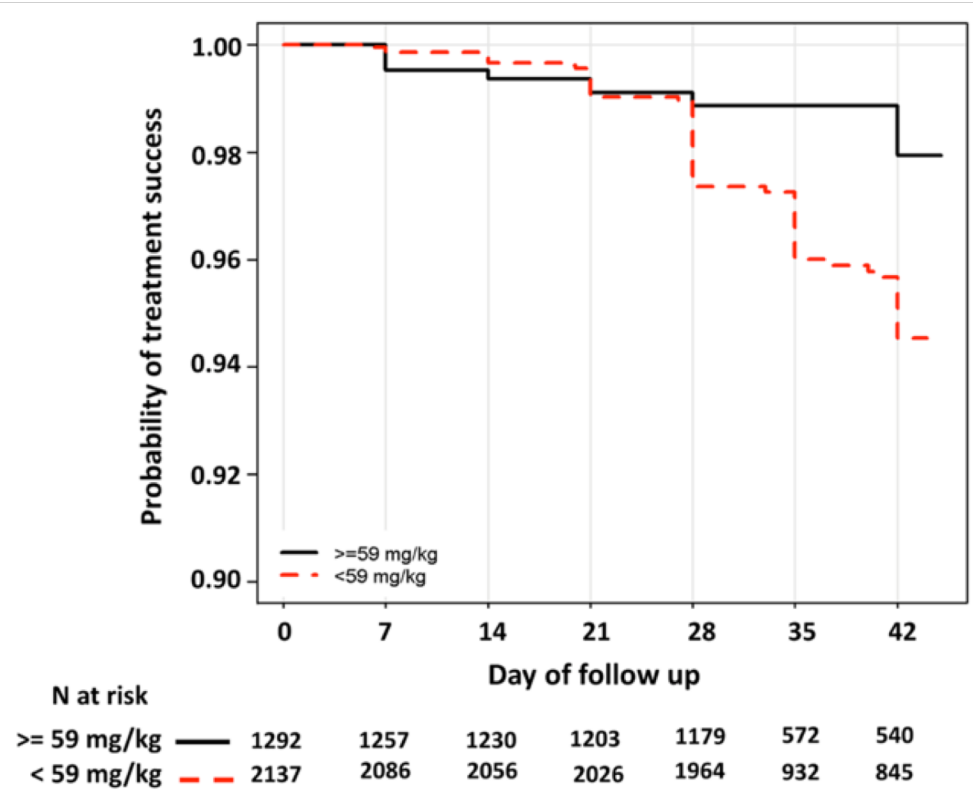
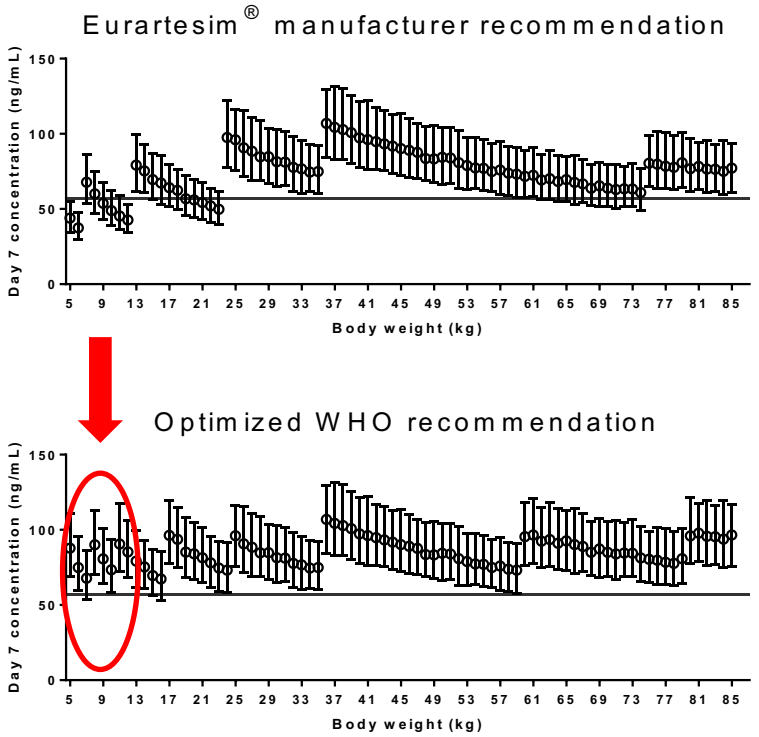
Dihydroartemisinin-Piperaquine (DHA-PPQ)

Double the risk of treatment failure for patients receiving <59 mg/kg





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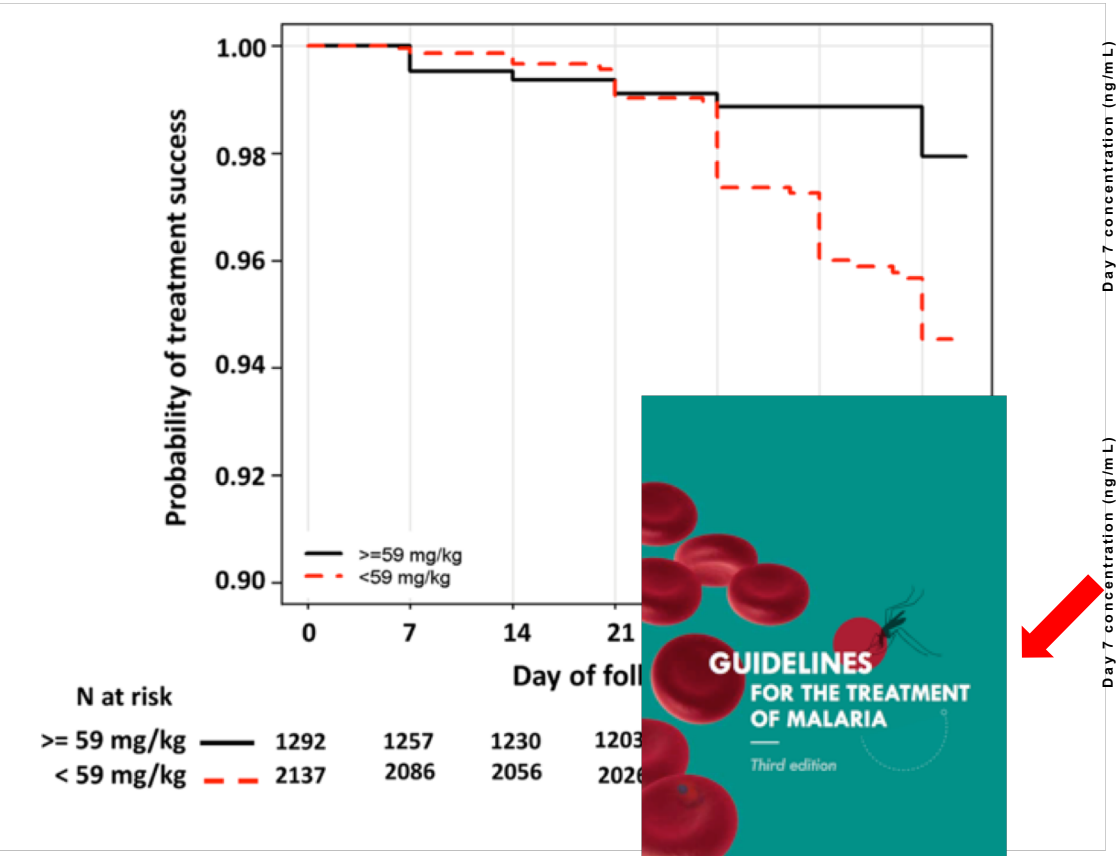
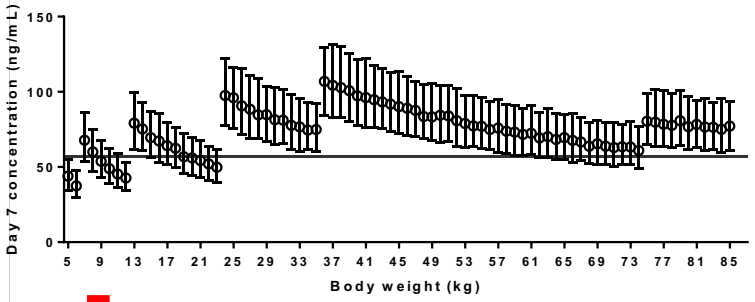
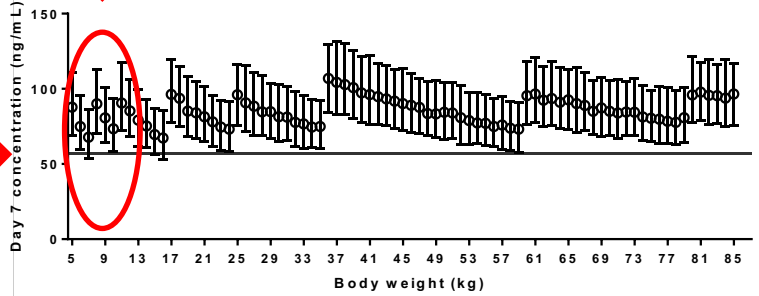


Eurartesim® manufacturer recommendation



Optimized WHO recommendation



POLICY IMPACT.

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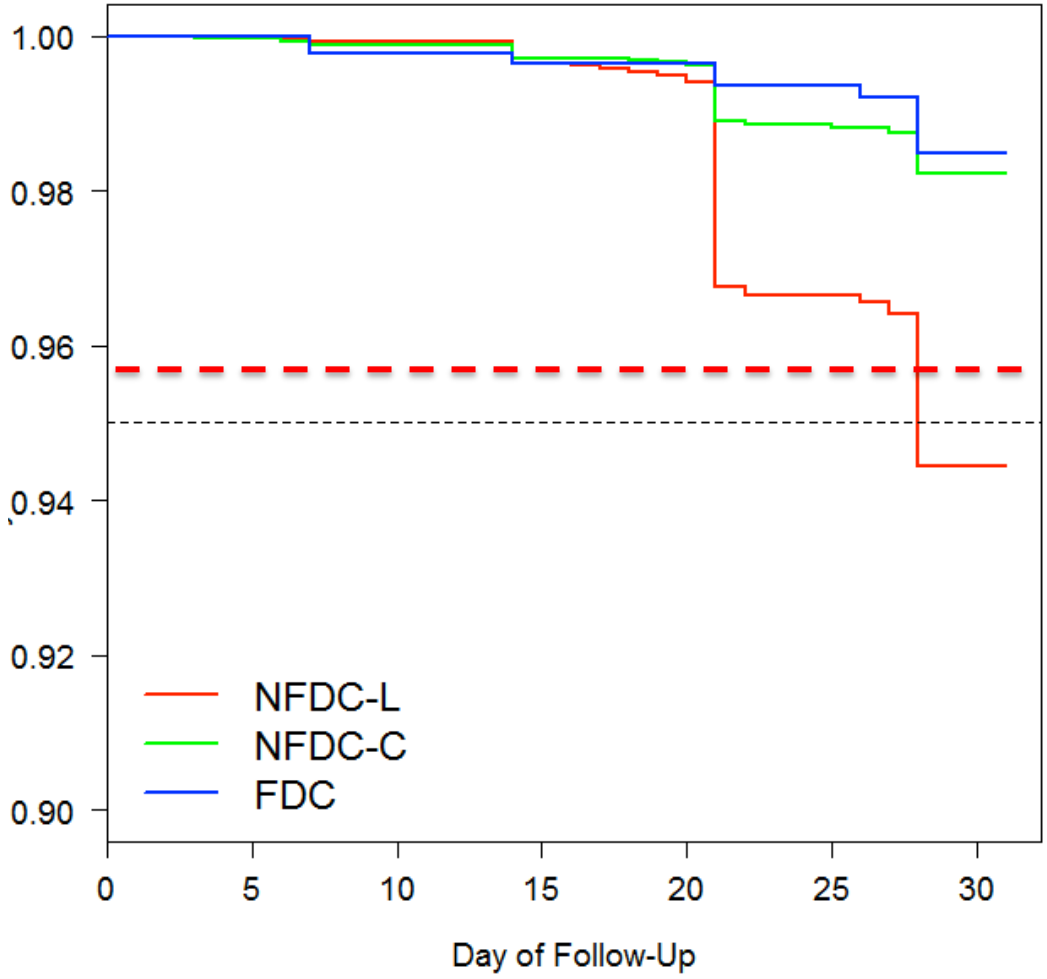
Artesunate – Amodiaquine (ASAQ)

1st line treatment in 25 countries: Signs of reduced efficacy

7796 patients, 36 studies



Fixed dose
Blister pack

Loose dose

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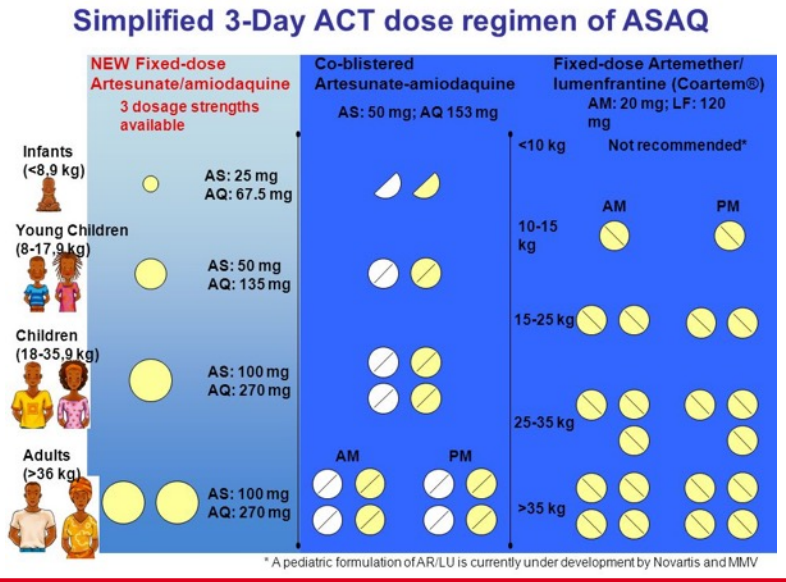
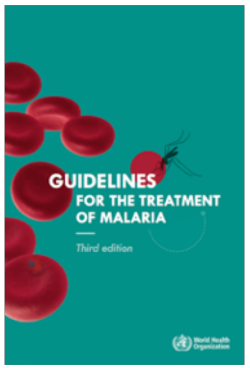
Artesunate – Amodiaquine (ASAQ)

Differentiate incorrect dosage from resistance

- ≠ conclusion to meta-analysis based on aggregated data
- ≠ formulations lead to ≠ outcomes
- Prevent premature withdrawal of one of few effective ACTs





POLICY IMPACT.

PRODUCTION IMPACT.

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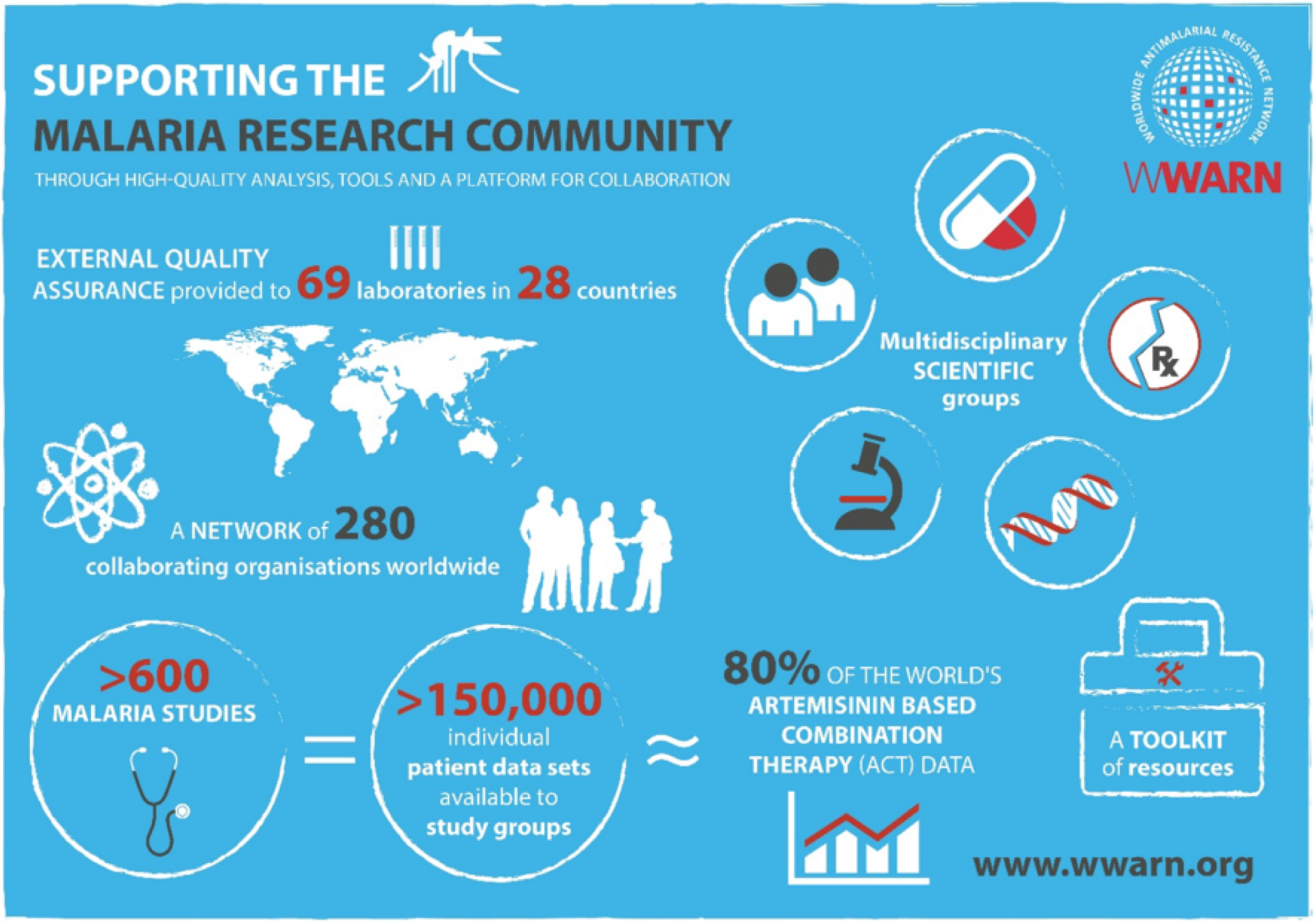
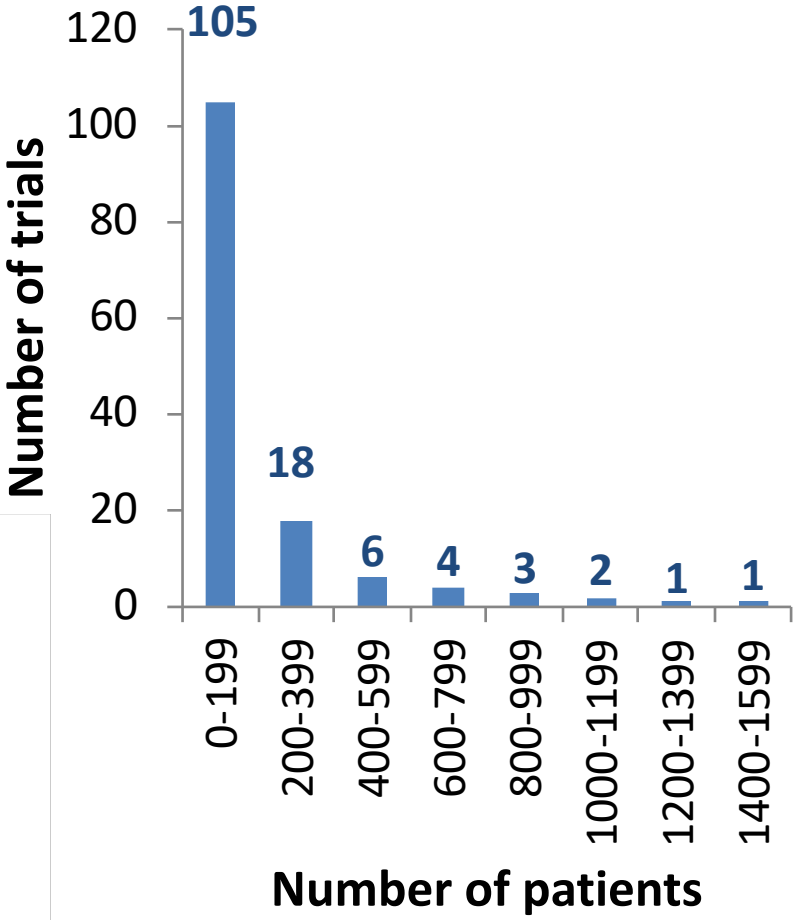
PATIENT IMPACT.



Visceral Leishmaniasis clinical trials landscape

- 141 clinical studies on VL drugs
  - 25,865 patients
  - **N < 200 for most trials**
- >10,000 patients in active trials



PLOS | NEGLECTED TROPICAL DISEASES

Systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform

Jacob T. Bush[1,2], Monique Wasunna[3], Fabiana Alves[4], Jorge Alvar[4], Piero L. Olliaro[1,5], Michael Otieno[1,2,3], Carol Hopkins Sibley[1,2,6], Nathalie Strub Wourgaft[4]*, Philippe J. Guerin[1,2]*

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Understanding factors affecting efficacy

Drugs	SSG	Ampho B Liposomal	Ampho B deoxycholate	MIL	PM sulphate	SSG+PM	LAB+SSG	LAB+MIL	PM+MIL
Clinical efficacy									
Asia	35-95% (depending on areas)	> 97% all regions	> 97%; single dose: > 96%	94-97% (India)	94% (India)	**93,8% (India)**	> 97%	> 97%	> 97%
Africa	93%	33 - >97% (depending on areas)	Not fully established	72%	84%	91%	87%	79%	Not documented
Resistance	As high as 60% (India)	Not documented	Not documented	20% (Nepal)	Lab isolates (easily)	Lab isolates (easily)	Lab isolates	Lab isolates	Lab isolates (easily)

- *Extreme variations in treatment response observed by drugs and regions (source DNDi)*
- ***Can the 35,000 patients enrolled in clinical trials help to answer thee questions?***

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Repurposing medicines in tropical medicine

The norm, rather than the exception.

- From animal health
  - Ivermectin, Moxidectin, Albendazole
- From other human indications
  - Oncology → miltefosine for VL, eflornitine for HAT
  - Mental health →thalidomide for erythema nodosum leprosum
  - Other ID → amphotericin B for VL

Access to data can support the innovation of better treatment. A data platform enables access to data that could not otherwise be considered.

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Repurposing drugs: Ivermectin as novel malaria control measure

- Ivermectin mass drug administration (MDA) under evaluation to aid malaria elimination
- Current label indications prohibit treatment of children <15kg for MDAs → weakens strategy
- Safety evidence for children <15kg exists in Strongyloidiasis - Onchocerciasis - Scabies
- Safety parameters for this population are not reported in the literature – IPD can provide the evidence base for re-labelling (on-going)

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Other examples

- **Visceral Leishmaniasis**
  - Miltefosine single dose and Liposomal amphotericin B

  → Now considered in combination
- **Human African Trypanosomiasis**
  - Recently registered fexinidazole for HAT (EMA CHMP Article 58) – now considered for Chagas disease
- **Malaria**
  - Primaquine registered for P. vivax to FDA in 1952

  → Repurpose for P. falciparum

Cost-effectiveness: IPD vs. standard evidence pathway

- Access to IPD reduces the time to evidence
- Every study can accelerate treatment optimisation
  - greater health benefits (improved health outcomes, limit resistance, QALYs)
  - cost-savings (avoid rescue therapy, AE treatment, economic loss)
- Reduce waste in clinical research and surveillance
- Expedite change to policy and treatment guidelines

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The place of a data platform for regulators?

STAMP 10/43

Objective 1: Supporting the framework

- Resources, expertise, access to data

Objective 2: Real-life examples

- Repurposing is at the forefront of treatment options for poverty-related diseases

Objective 3: Communications

- Network of academics, policy makers and clinicians
- Connection to expert input and dissemination of EMA messages

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Place of data platform for regulators?

Value pre-registration

- Lessons learned from the past
- Inform new drug development

Value post-registration

- Phase IV and post-marketing clinical trials
- Capture safety signals: especially in settings with weak pharmacovigilance
- Critical for sub-populations
  - "vulnerable populations" usually excluded from trials: pregnant women, obese, malnourished, HIV, co-infections

Specific value for poverty related diseases

- Sufficient size to examine **vulnerable populations**
  - **Often excluded/under represented in registration trials**
- Better historical baseline for evaluating treatments
  - Produce evidence not otherwise accessible
  - Prevent irremediable knowledge lost
    - Drug repurposing
- Ethical imperative
- Increase life span of registered drug
  - Optimisation of dose → role in AMR for antimicrobials

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Reflections for the future

- Started a dialogue with US-FDA
- Regulators could help to define priorities for data pooling
  - Drug developers may not realise the potential of data
- Quality and integrity of data
  - Open source standards (CDSIC) and improved methodology
- Cost effectiveness approach
  - Consolidate a registration dossier
  - Accelerate the development process
- Neutral role

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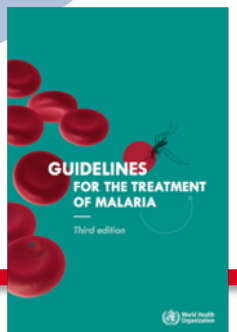
Clinical trial outputs

	1	2	3	4	5	6	7
Name	Sex	Fold	Pulse	Age	Clap	Exer	Smoke
Label							
Type	Factor	Factor	Number	Number	Factor	Factor	Factor
Format							
Levels	Female#...	L on R#,...			Left#,#...	Freq#,#...	Heavy#,...
1	Female	R on L	92	18.25	Left	Some	Never
2	Male	R on L	104	17.583	Left	None	Regul
3	Male	L on R	87	16.917	Neither	None	Occas
4	Male	R on L		20.333	Neither	None	Never
5	Male	Neither	35	23.667	Right	Some	Never
6	Female	L on R	64	21	Right	Some	Never
7	Male	L on R	83	18.833	Right	Freq	Never
8	Female	R on L	74	35.833	Right	Freq	Never
9	Male	R on L	72	19	Right	Some	Never
10	Male	R on L	90	22.333	Right	Some	Never

- IDDO, in collaboration with the research community
- Researchers and Policy Makers



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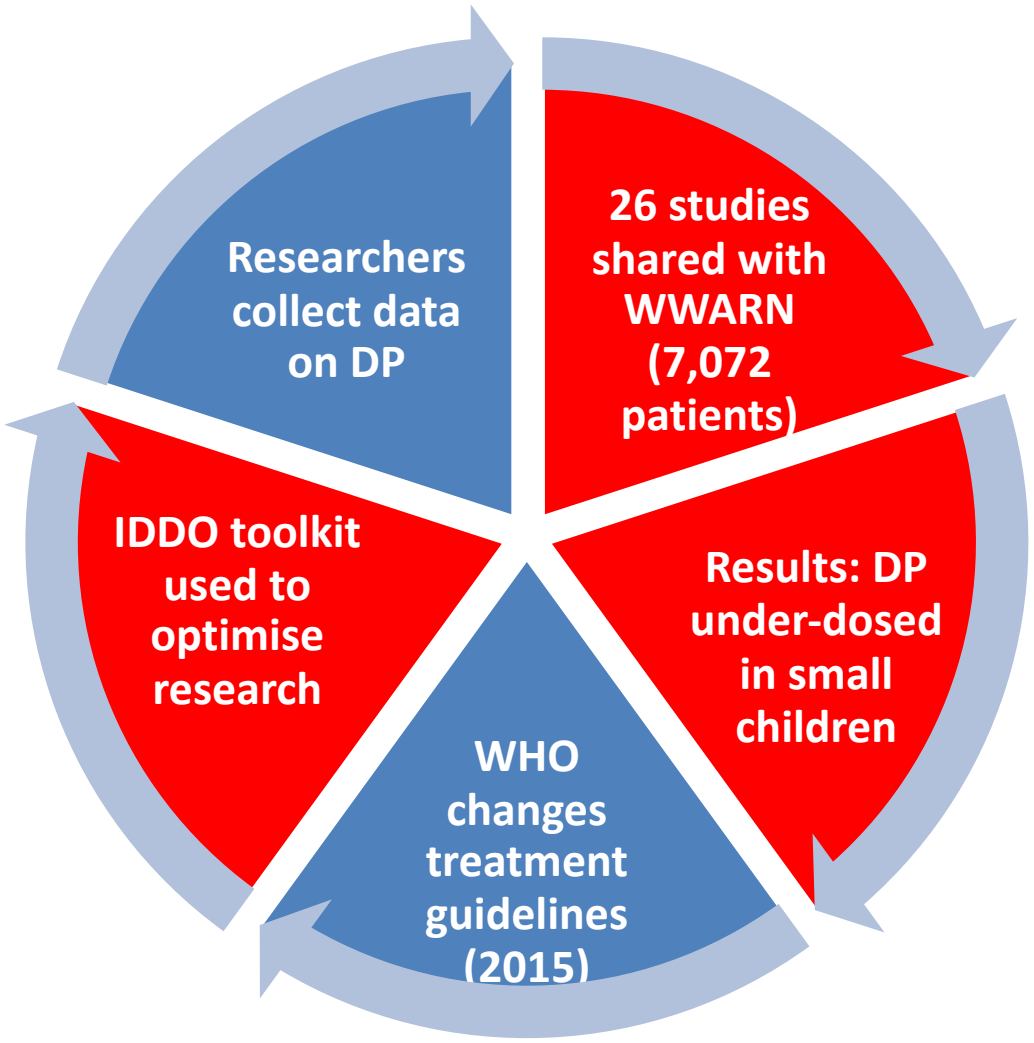
Efficacy of Dihydroartemisinin-Piperaquine (DP)



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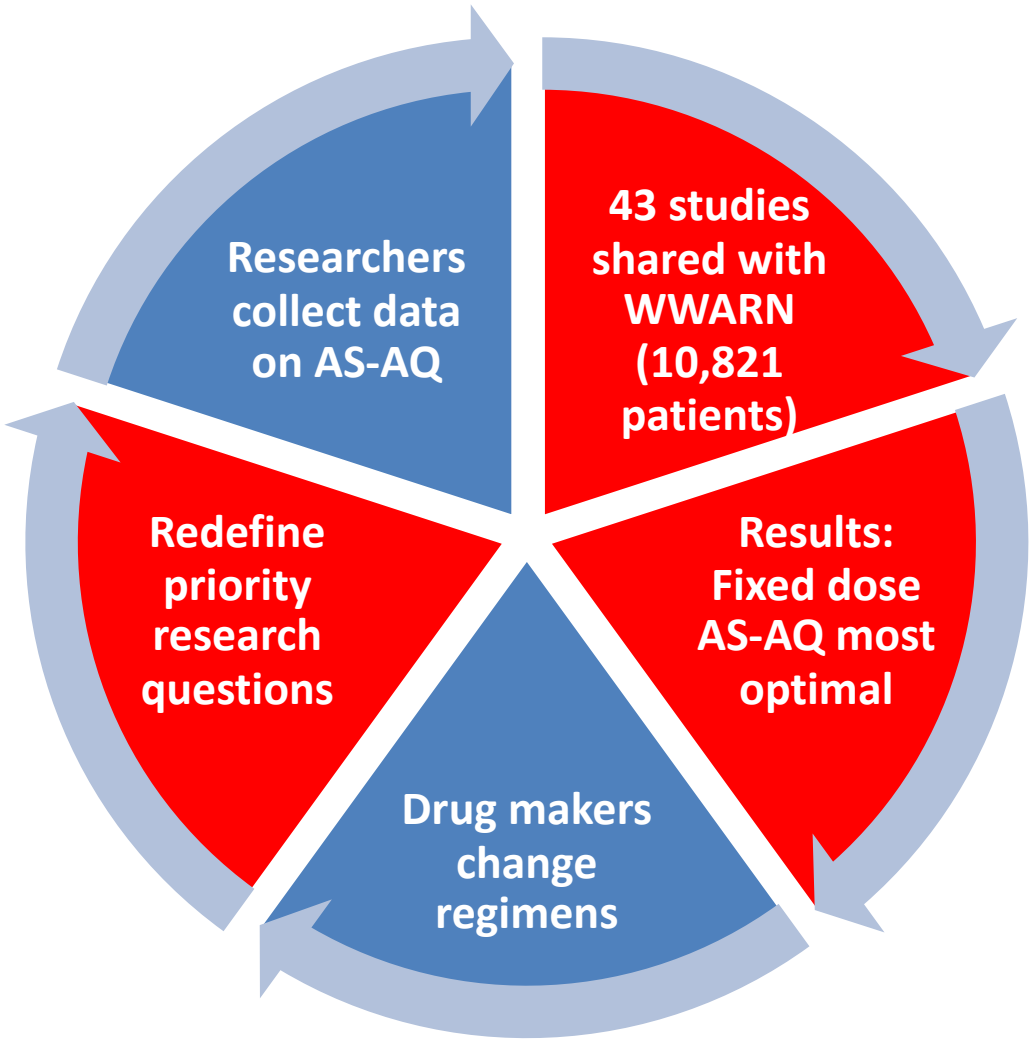
Efficacy of Artesunate Amodiaquine (AS-AQ)



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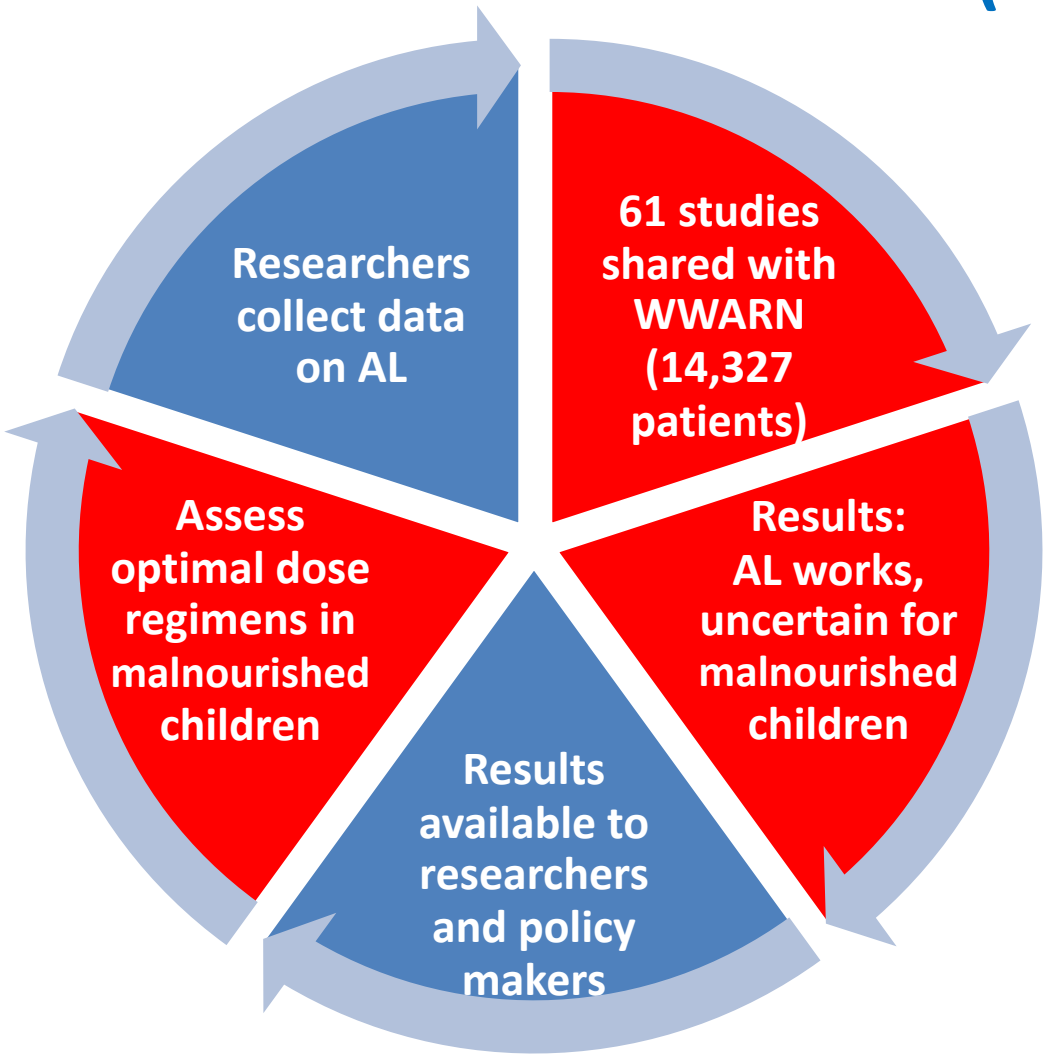
Efficacy of Artemether Lumefantrine (AL)



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