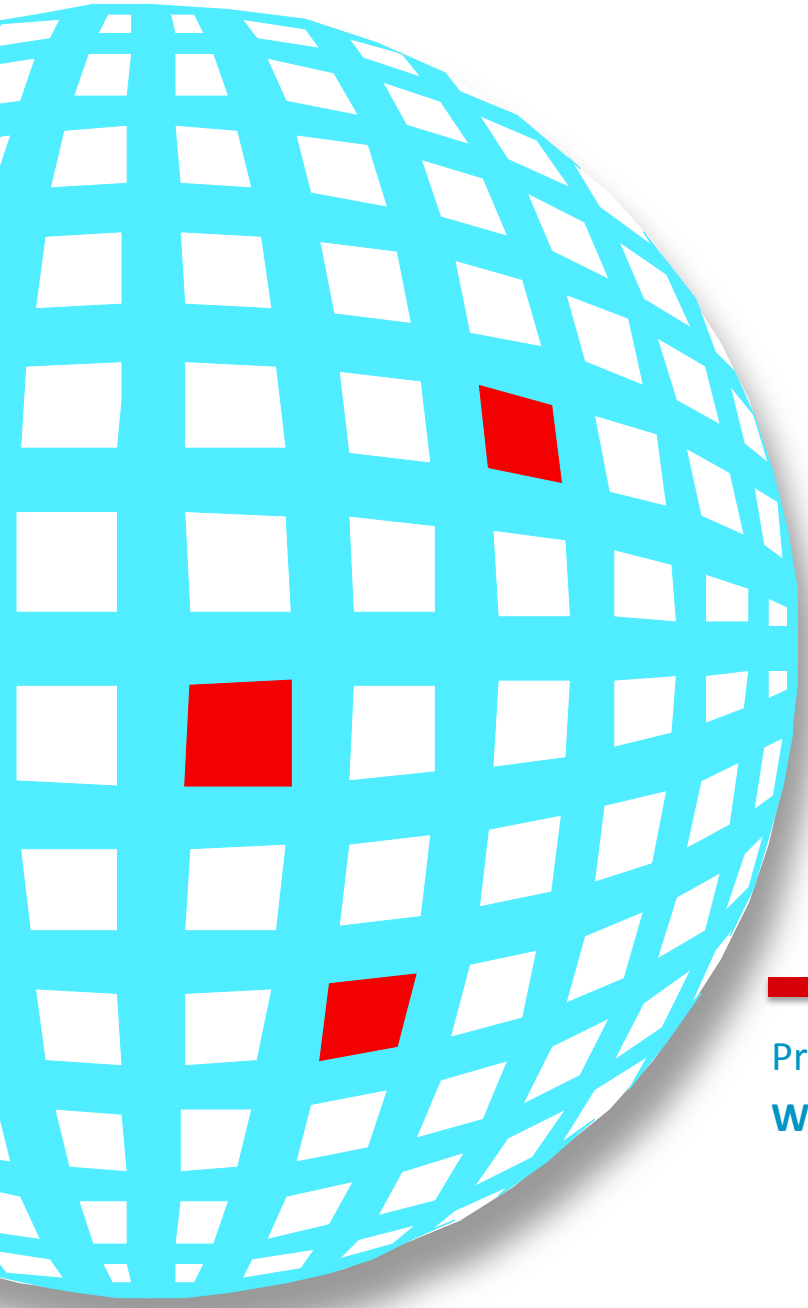


Landscape for developing a VL database

Jacob Bush
University of Oxford

Presented by **Jeffery Smith**
WorldWide Antimalarial Resistance Network (WWARN)

A Database for Kala Azar?

- **Why a clinical database for VL?**
- **Landscape of clinical data on VL?**

WWARN

Why a database?

Challenges

- VL is **underfunded** - few trials and small sample sizes
- **Few drugs** (~5) and **poorly stocked pipeline**
- Existing drugs **toxic/expensive/resistance threat**
- **Complications** - regional efficacy variation, HIV-VL
- Careful use and monitoring of drugs is required to **maximise efficacy**, **reduce toxicity** and **minimise resistance**
- Clinical trial data are **'buried'** in publications or **not published** or **delayed**

WWARN

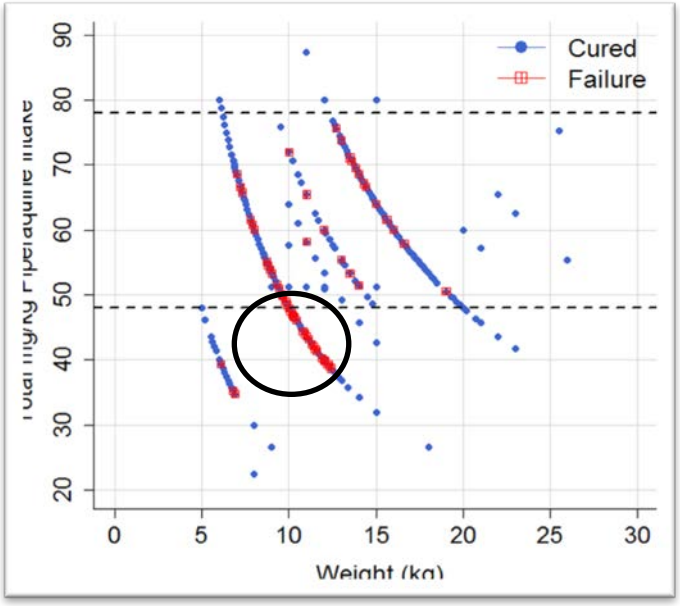
Standardised Clinical Trials Database

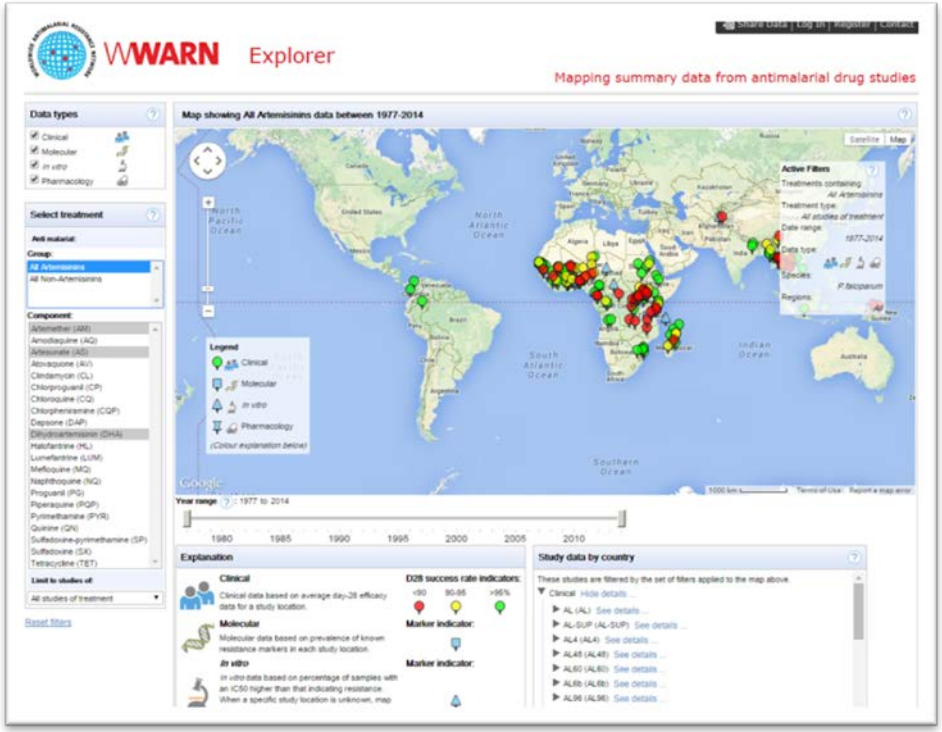
- Provides comprehensive up-to-date **clinical trial landscape**
- Allows **meta-analysis**: improved statistics, highlight subpopulation variations and resistance
- Inform **treatment allocation** and future **clinical trial design**

WWARN

WWARN Case Study

- 350 Clinical trials from 200 research institutions
- Raw data on 100,000 individuals (≈3M data points)
- WWARN Explorer
- Pooled analyses





A unique standardised database for VL?

Questions

- Are there enough trials? Are there enough data?
- Are the data from different trials comparable? Consistancy in study parameters? (e.g., dose, regimen, diagnostic tests, follow-up time and assessments?)

Assessment

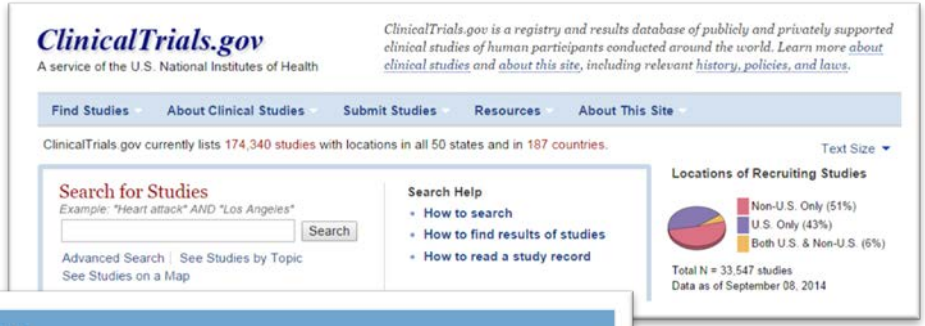
- Conduct systematic review of clinical trials landscape
- Gather key information from trials (e.g., # participants, study parameters)
- Explore the potential of a database of raw data to allow for meta-analyses

WWARN

Clinical Trials Registries

Clinical trials.gov launched in 2000

ICTRP gathers trials from all major registries



- Australian New Zealand Clinical Trials Registry
- ClinicalTrials.gov.
- EU Clinical Trials Register (EU-CTR)
- ISRCTN
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry
- Clinical Research Information Service - Republic of Korea
- Cuban Public Registry of Clinical Trials
- German Clinical Trials Register
- Iranian Registry of Clinical Trials
- Japan Primary Registries Network
- Pan African Clinical Trial Registry
- Sri Lanka Clinical Trials Registry
- The Netherlands National Trial Register
- Thai Clinical Trials Register (TCTR)

WWARN

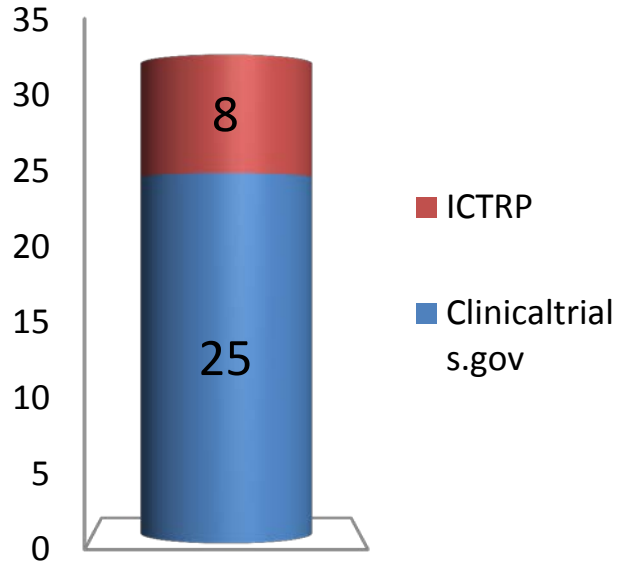
Clinical Trials Registries

Search for '**visceral leishmaniasis**' and '**kala azar**'

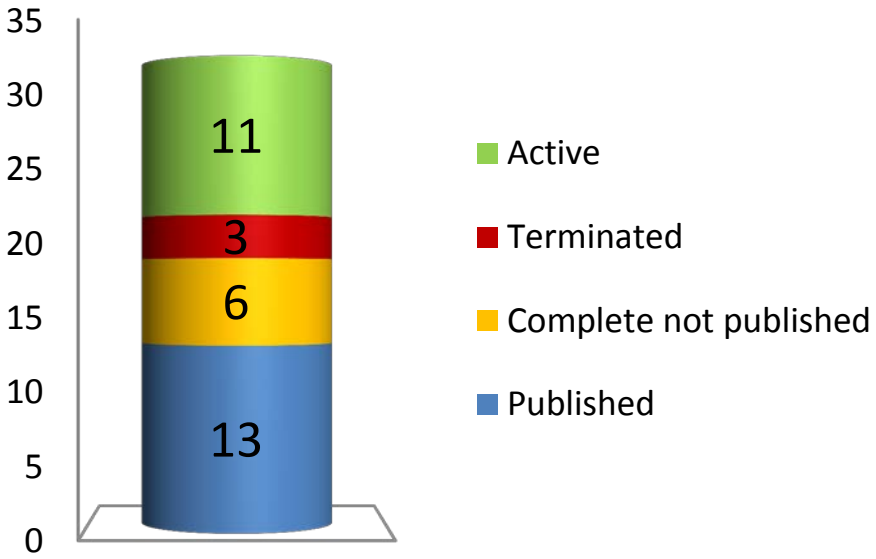
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

World Health Organization
International Clinical Trials Registry Platform
Search Portal

33 registered trials



13 of 33 registered and published



Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis

WWARN

Clinical Trials Publications

Search for '**visceral leishmaniasis**' and '**kala azar**'

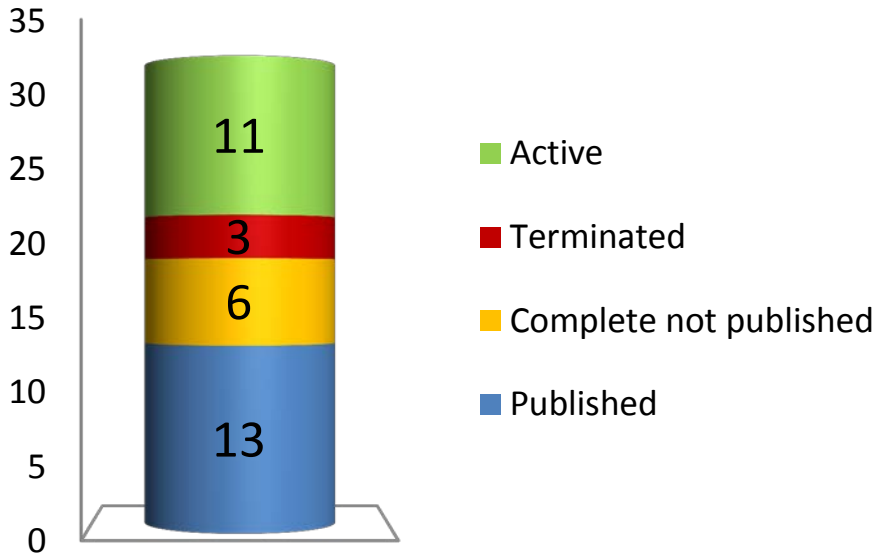
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

World Health Organization
International Clinical Trials Registry Platform
Search Portal

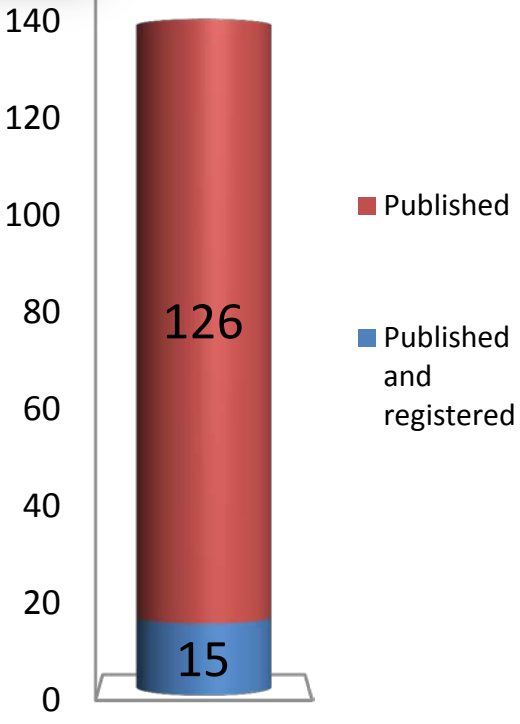
NCBI Resources
PubMed.gov

THE COCHRANE LIBRARY
Independent high-quality evidence for health care decision making

13 registered and published



141 published

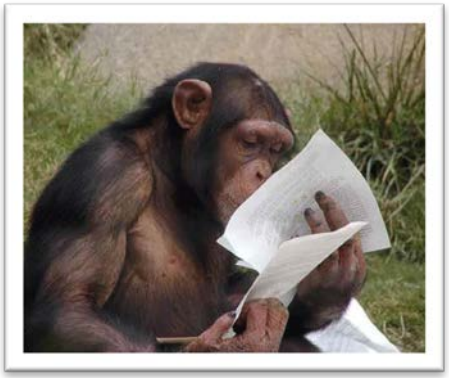


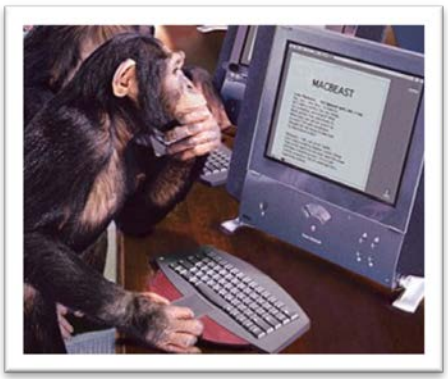
Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis

WWARN

Landscape of Clinical Trials

Find publications and extract data

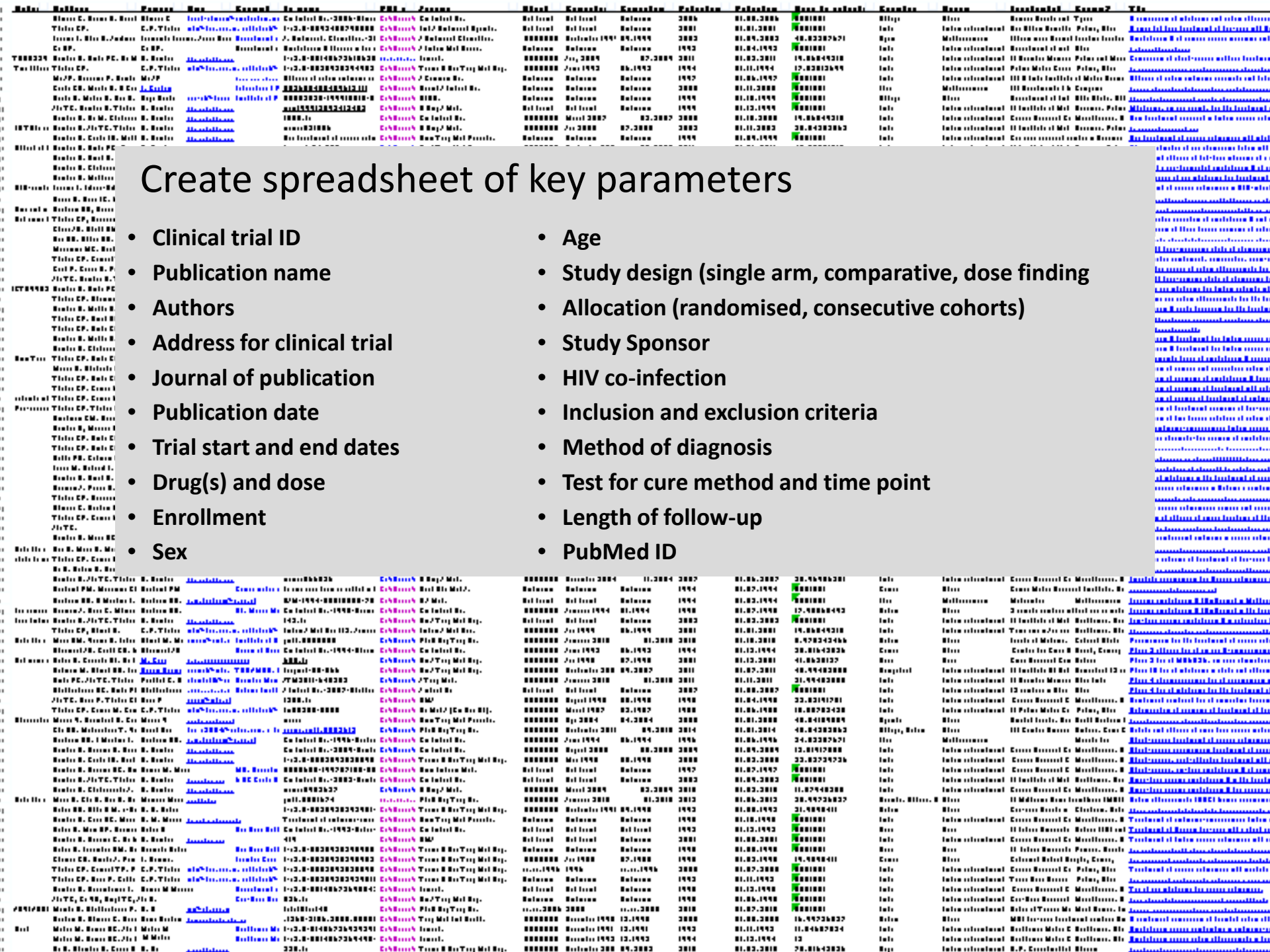




Found 138/141 original publications

- Data extracted from abstracts for other 3 publications
- Some available at online journals
- Some available only in hard copy (from WHO Library)
- Some available only through contacting author

WWARN

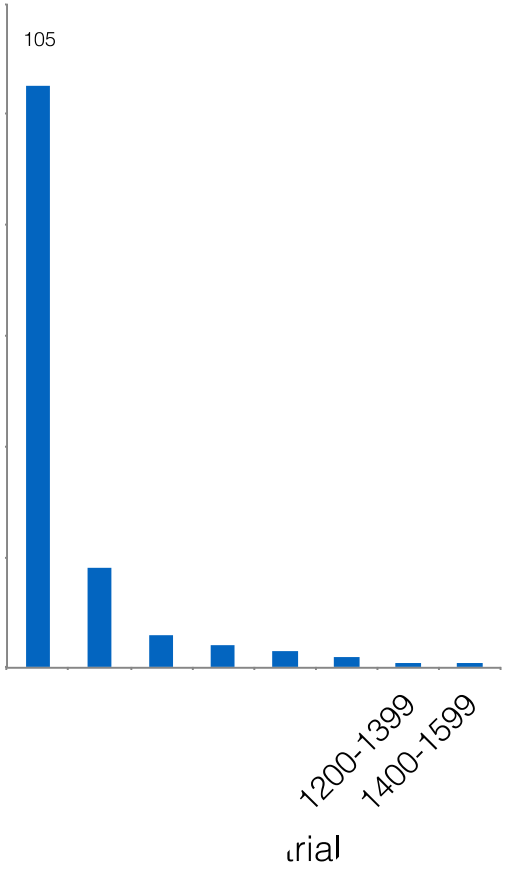


Create spreadsheet of key parameters

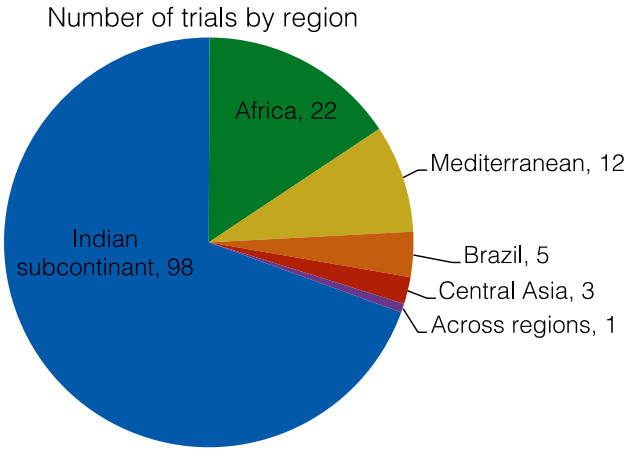
- Clinical trial ID
- Publication name
- Authors
- Address for clinical trial
- Journal of publication
- Publication date
- Trial start and end dates
- Drug(s) and dose
- Enrollment
- Sex
- Age
- Study design (single arm, comparative, dose finding
- Allocation (randomised, consecutive cohorts)
- Study Sponsor
- HIV co-infection
- Inclusion and exclusion criteria
- Method of diagnosis
- Test for cure method and time point
- Length of follow-up
- PubMed ID

Clinical Trials Landscape

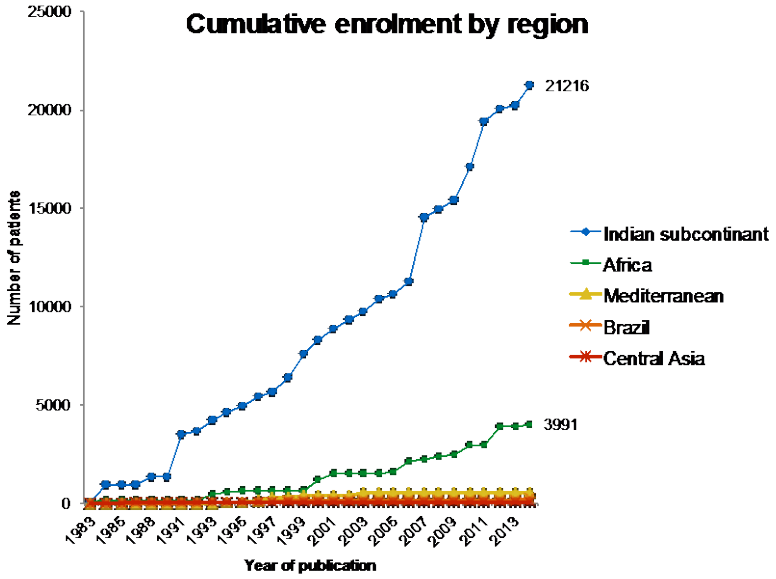
- **141 clinical studies** on VL drugs
  - **25,865 patients** (68% male)
  - Most trials enrolled less than 200
- **1,379** patients in completed, unpublished trials
- **9,802** in active trials
  - ➢ **Total of 37,046 patients**
- Earliest publication was 1983
- Since 2000: 69 published/ 35 started
- Delay to publication: average 26 months (range 8-78)



Where and When?



Most enrolment in Indian subcontinent or Africa
Gradually increasing enrolment each year



Country	Patients	Trials*
India	18192	91
Bangladesh	2250	3
Sudan	1675	10
Ethiopia	1280	6
Nepal	755	5
Kenya	667	11
Italy	290	7
Uganda	234	2
Spain	208	4
Brazil	206	6
Others	119	7

*Trials in **n** countries split into **n** trials, 1 per country

WWARN

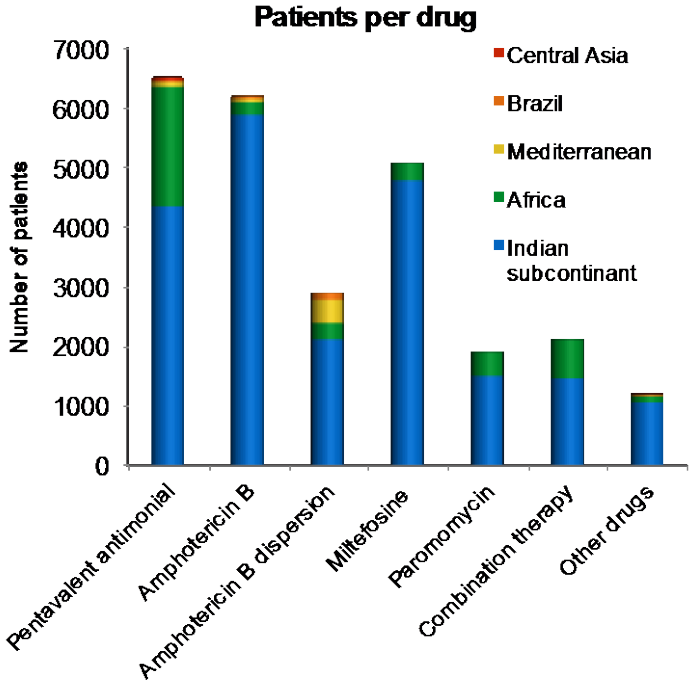
Drugs

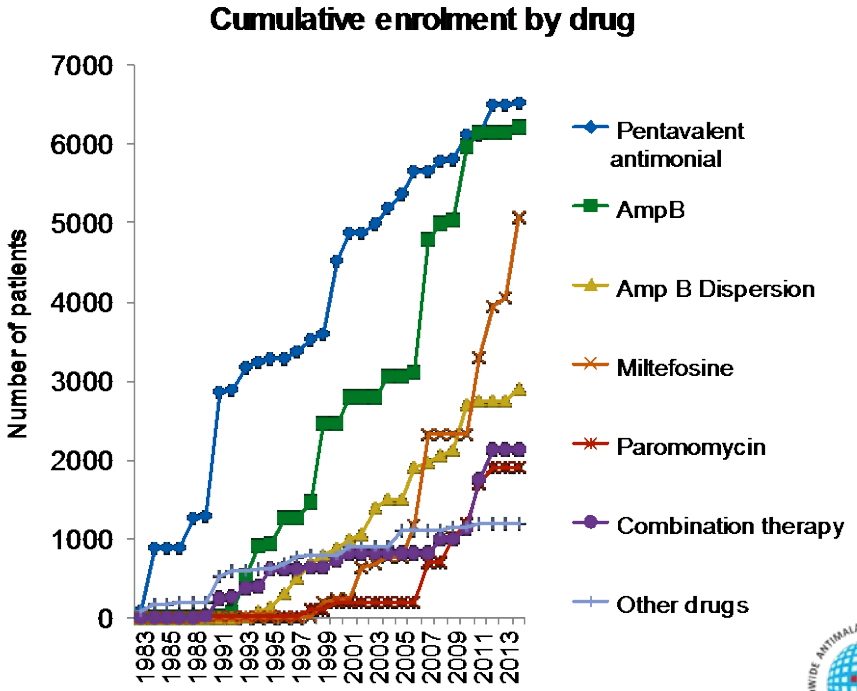
2000-6000 patients enrolled for each drug

- Mostly from India, Africa well represented for some drugs
- Suggests large scale comparisons are possible

Most enrollments for newer drugs are recent (5-10 years)

- Easier to obtain data
- Suggests more data to come





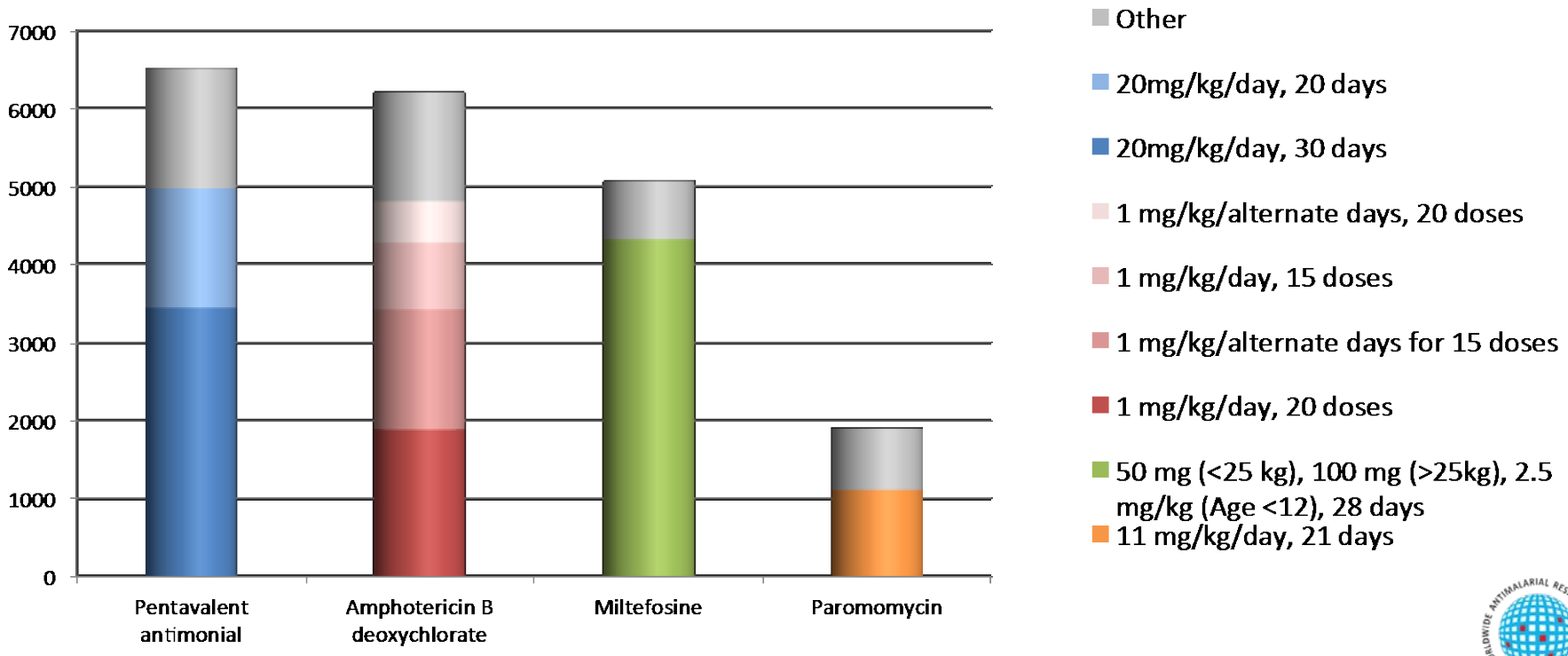
WWARN

Dose

Good consistancy in dose regimens used

1000`s of patients enrolled per dose

- Allows for pooling of data
- Allows for large scale comparisons of different dose regimens



WWARN

Trial Design

Trials evenly split between single arm, dose-finding or comparative

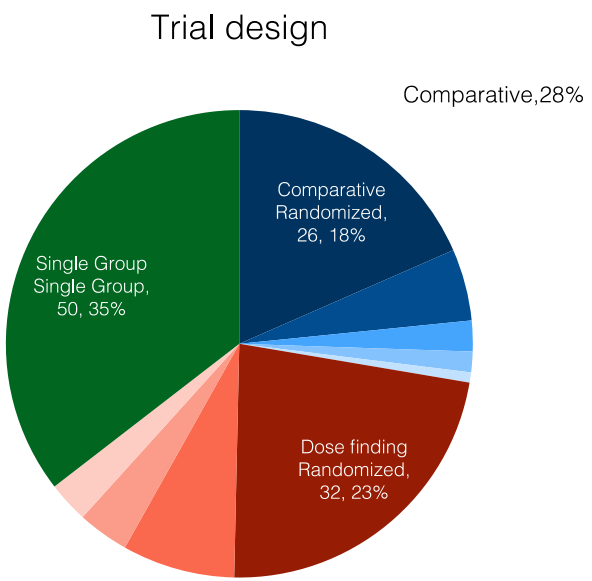
- Usually randomized

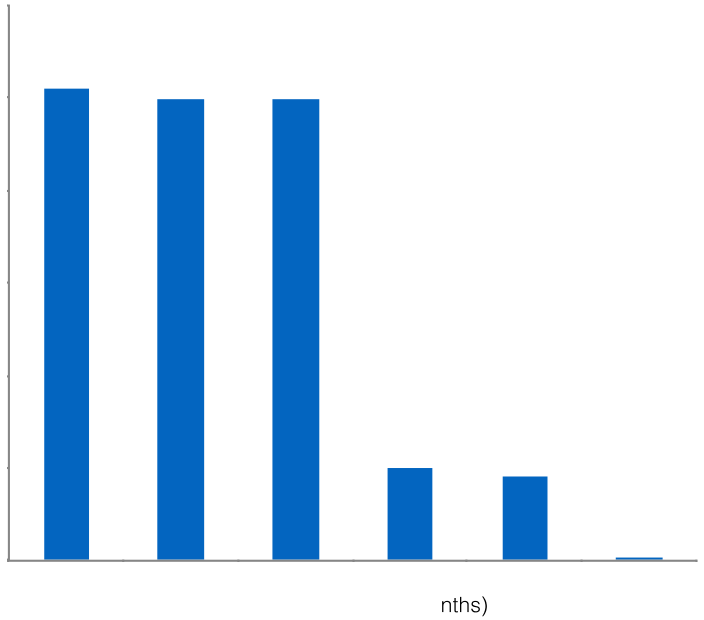
Patient follow:

- 6 months (~25,000)
- 12 months (~5000)

Allows pooling of data since end points consistant

Allows comparison of 12 and 6 months follow up on the scale of 1000`s





Diagnostics

Diagnosis by observation of parasites in an aspirate (>76%)

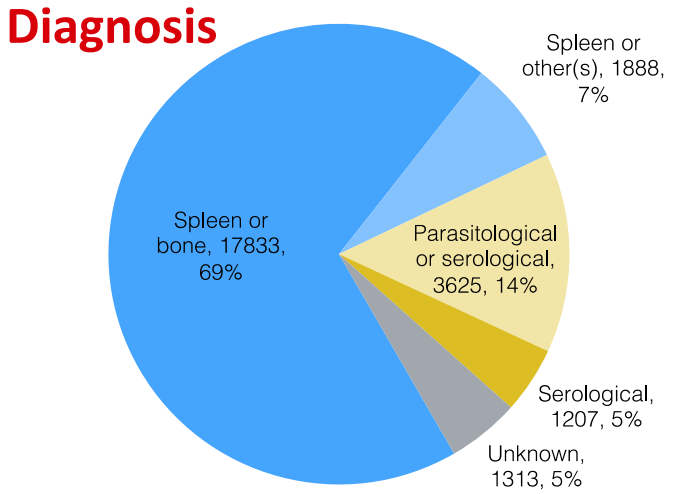
- High confidence in correct diagnosis
- Do different diagnostic tests affect outcome?

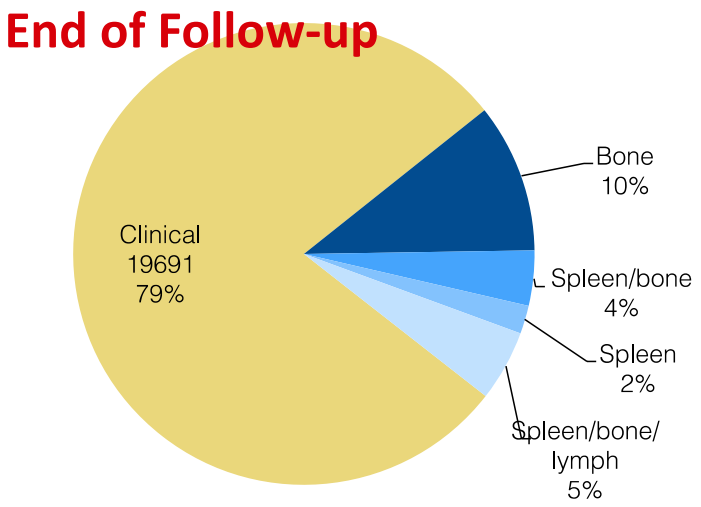
End of treatment test is generally the same as for diagnosis

- 88% patients parasitologically tested for cure after treatment

End of follow up test is usually clinical (79%) or bone (10%)

- Is there a difference in relapse with clinical vs parasitological test

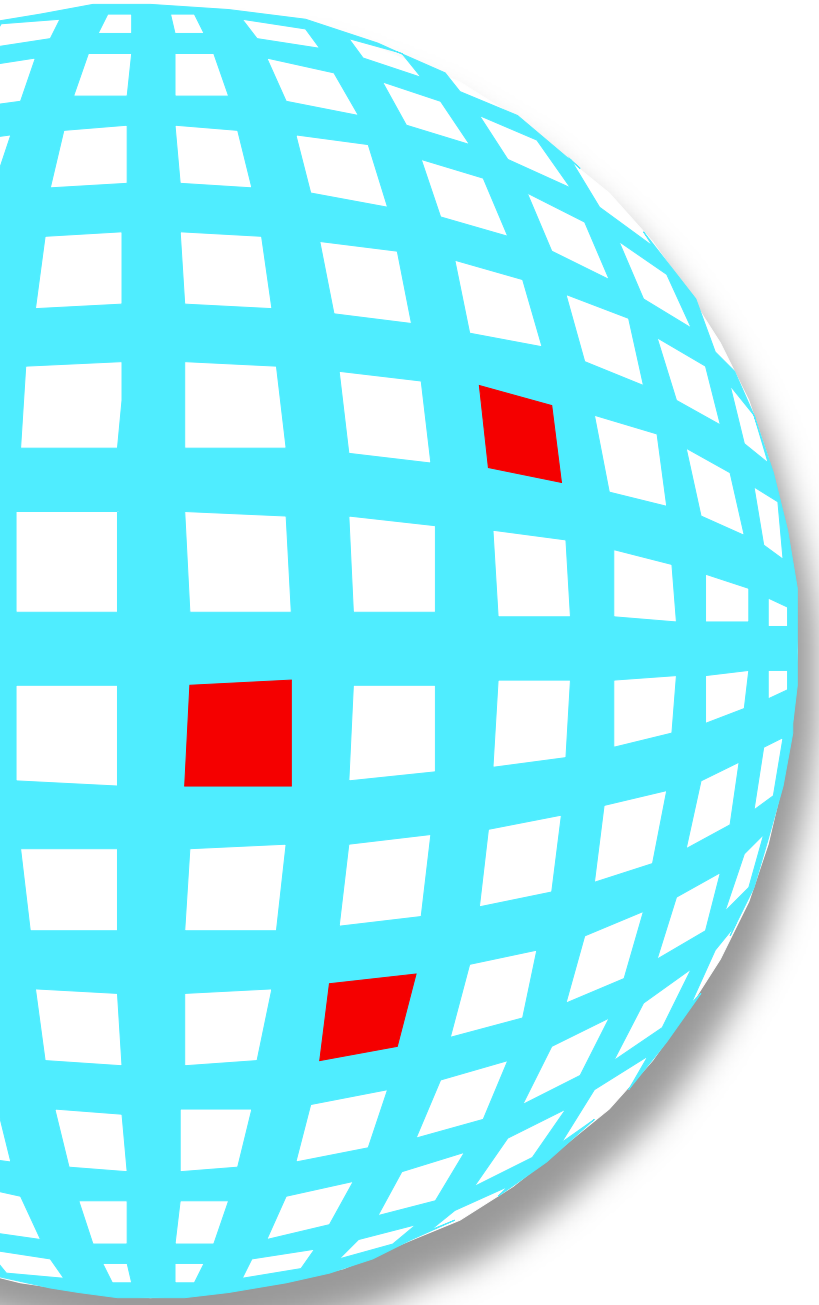




Summary

- Individual trials are small, but many trials (141) and participants (25,865, with potential for 37,046)
- Good consistency in study design and parameters
- Trial results are difficult to access, some raw data may already be lost
- A database would improve accessibility and longevity
- Develop a visualization tool for trial results
- Meta-analysis would allow comparisons on large cohorts (1000's/arm) to improve treatment efficacy and design for future studies
- Compare outcomes based on drug, dose, country, length of follow-up, diagnosis, test for cure, etc.

WWARN



WWARN's Experience

WWARN

Vision: Effective and safe malaria treatment for all

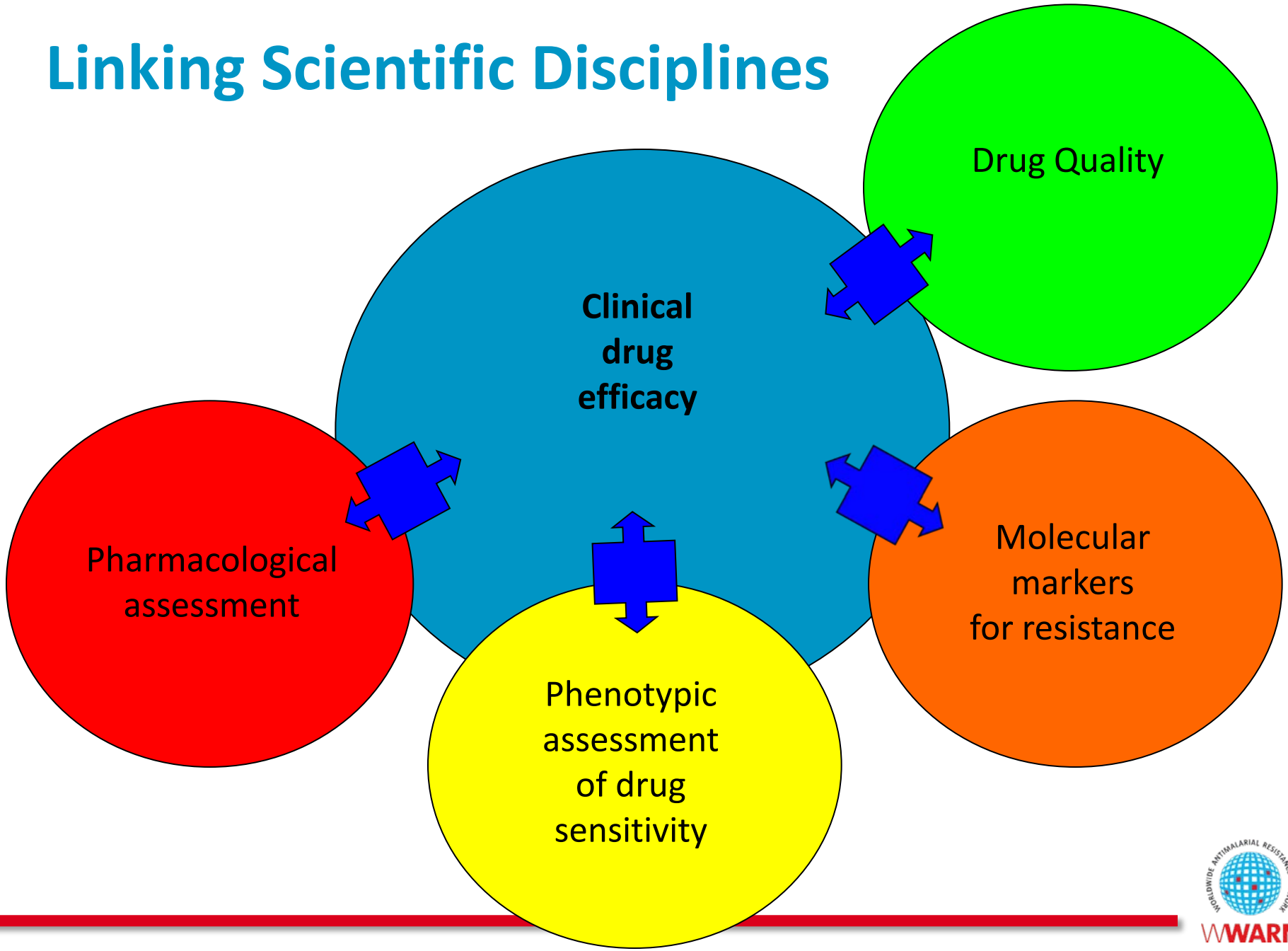
Mission: To implement a collaborative platform to assess the evolution, epidemiology and public health impact of antimalarial drug resistance, and to generate the reliable evidence necessary to inform malaria control and elimination

Goal: To inform optimal use of available and future antimalarials for malaria control and elimination

Established: 2009 as a programme of the University of Oxford Centre for Tropical Medicine and Global Health

WWARN

Linking Scientific Disciplines



Data Standardisation Process

Data submission

Access | Stata | SAS | Excel

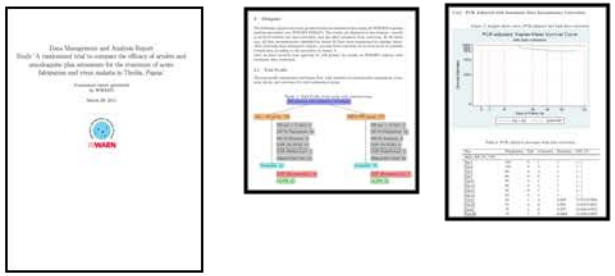
Heterogeneous data

Cleaning
Transform
Standardize
Analyse

Standardized data sets

WWARN Data Repository

Automated Reports



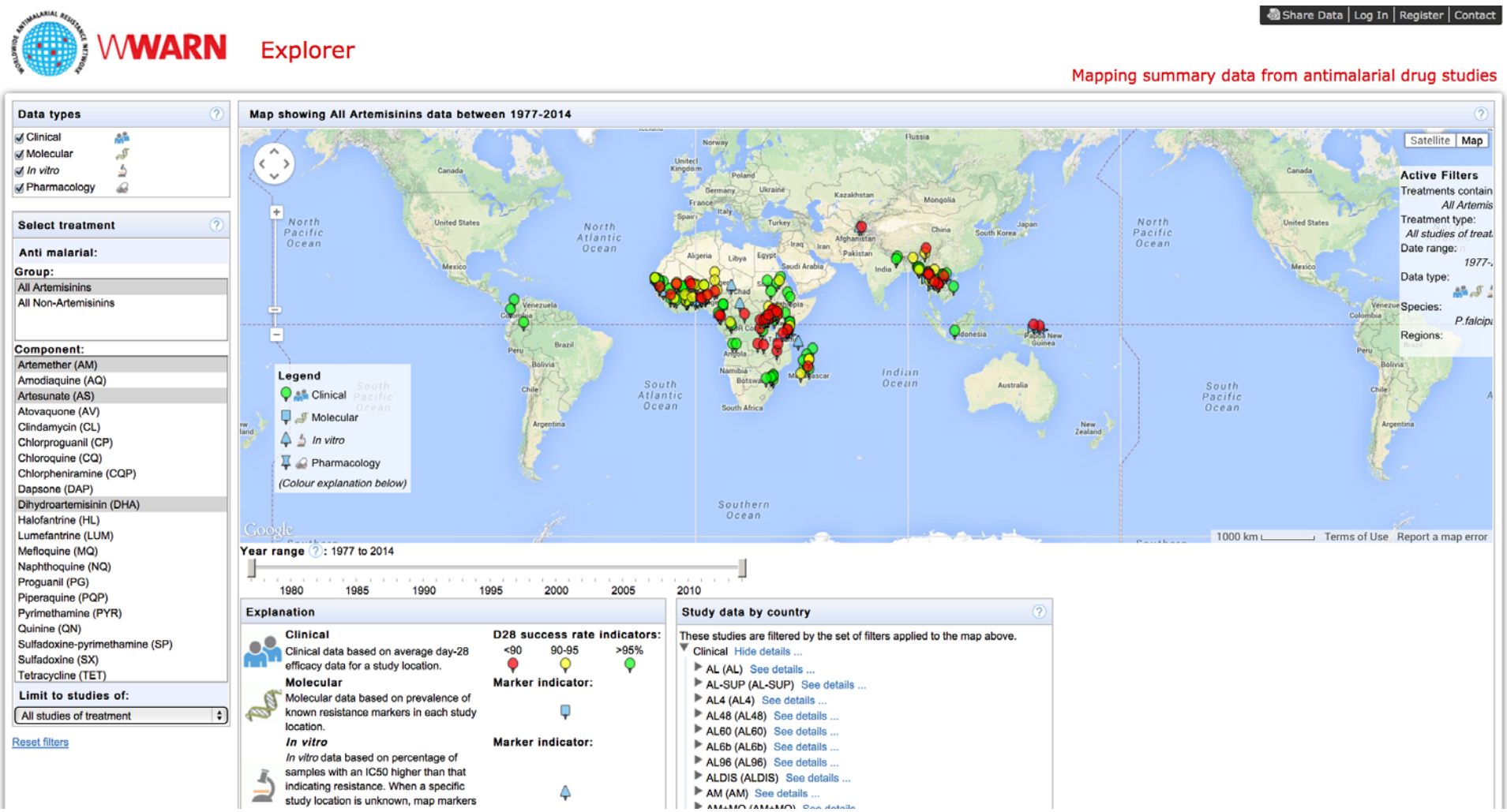
WWARN Explorer

http://www.wwarn.org/resistance/explorer

Research applications

Data sharing → Processing → Outputs

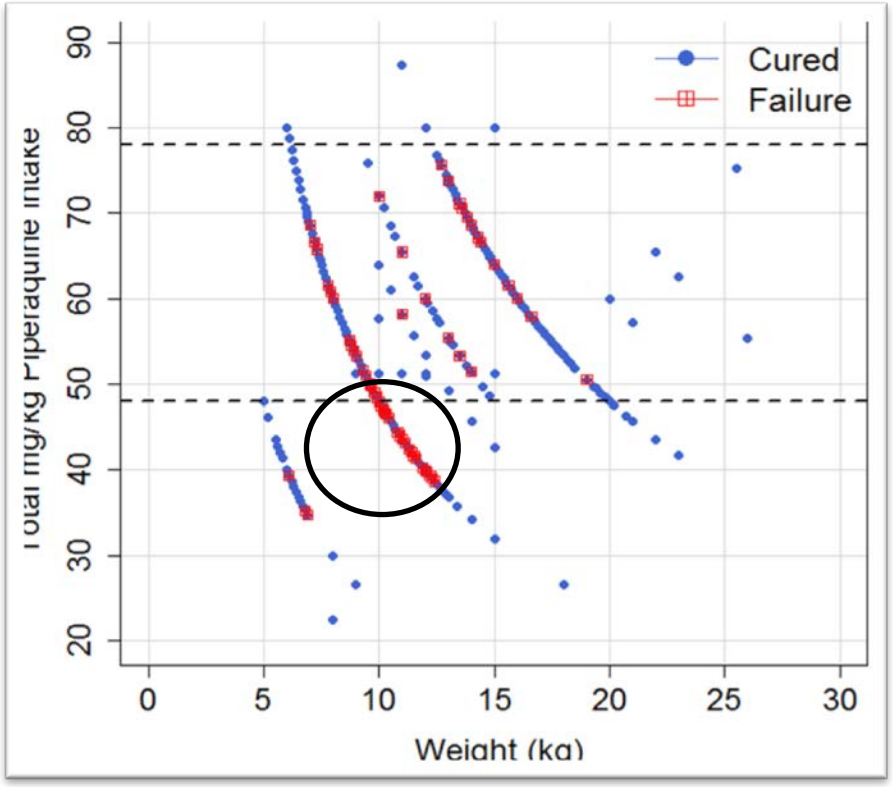
Data Visualisation

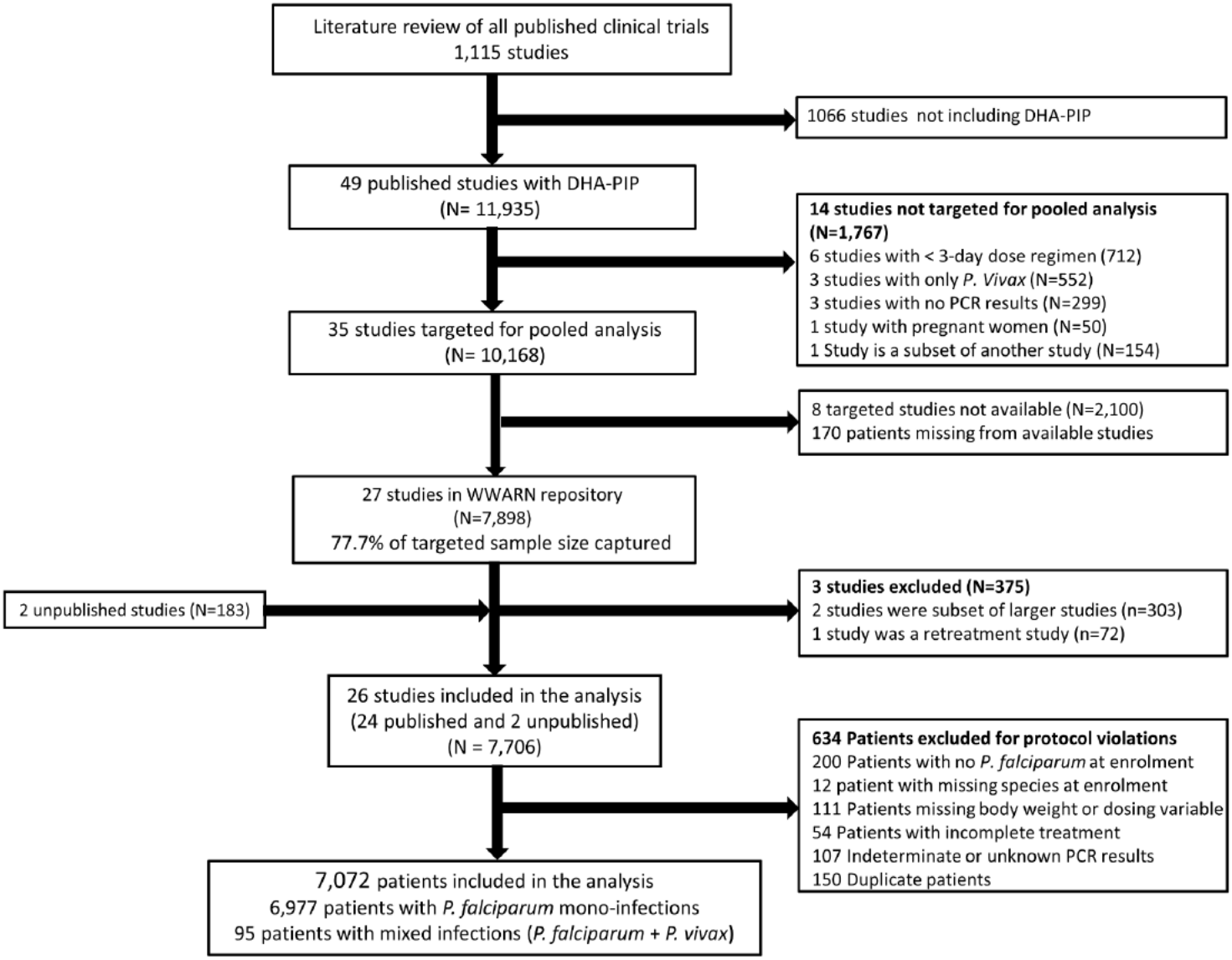


Pooling Data for more Powerful Analyses

DHA-Piperiquine mg/kg Dosing Study Group

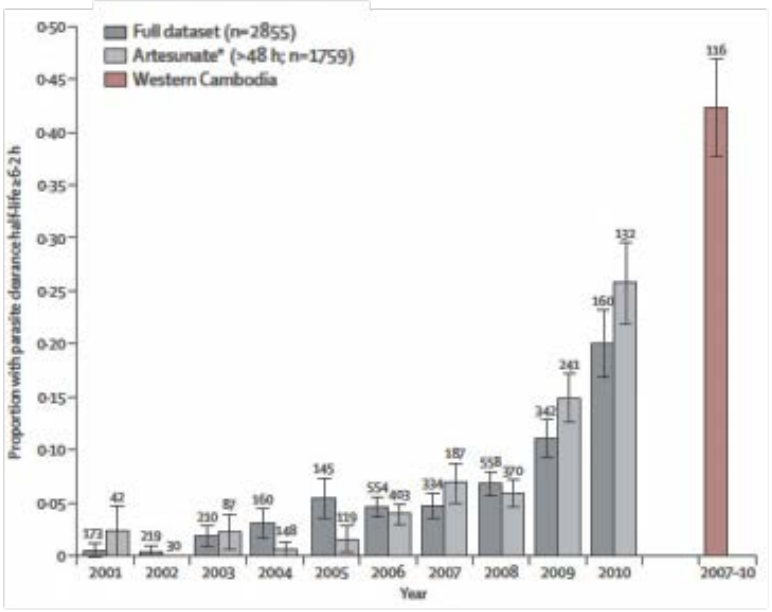
- **26 studies** (74% of 35 studies)
- **7,072 patients** between 2003–2011 (70% of 10,168)

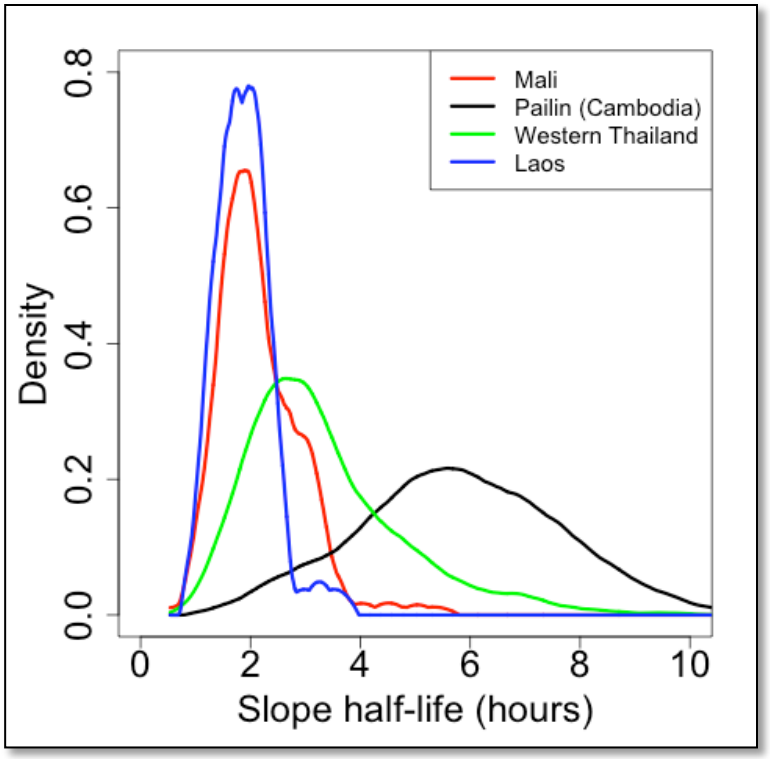



Literature review of all published clinical trials
1,115 studies
1066 studies not including DHA-PIP
49 published studies with DHA-PIP
(N= 11,935)
14 studies not targeted for pooled analysis
(N=1,767)
6 studies with < 3-day dose regimen (712)
3 studies with only P. Vivax (N=552)
3 studies with no PCR results (N=299)
1 study with pregnant women (N=50)
1 Study is a subset of another study (N=154)
35 studies targeted for pooled analysis
(N= 10,168)
8 targeted studies not available (N=2,100)
170 patients missing from available studies
27 studies in WWARN repository
(N=7,898)
77.7% of targeted sample size captured
2 unpublished studies (N=183)
3 studies excluded (N=375)
2 studies were subset of larger studies (n=303)
1 study was a retreatment study (n=72)
26 studies included in the analysis
(24 published and 2 unpublished)
(N = 7,706)
634 Patients excluded for protocol violations
200 Patients with no P. falciparum at enrolment
12 patient with missing species at enrolment
111 Patients missing body weight or dosing variable
54 Patients with incomplete treatment
107 Indeterminate or unknown PCR results
150 Duplicate patients
7,072 patients included in the analysis
6,977 patients with P. falciparum mono-infections
95 patients with mixed infections (P. falciparum + P. vivax)

WWARN

Tools for Characterizing Drug Resistance





WWARN Parasite Clearance Estimator (PCE Tool)

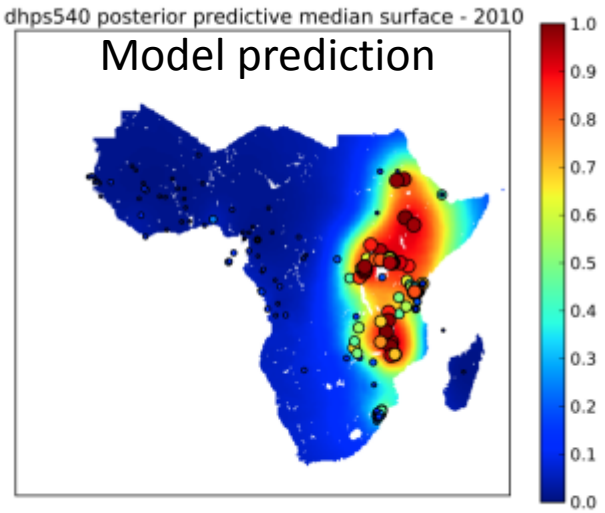
Smart Surveillance

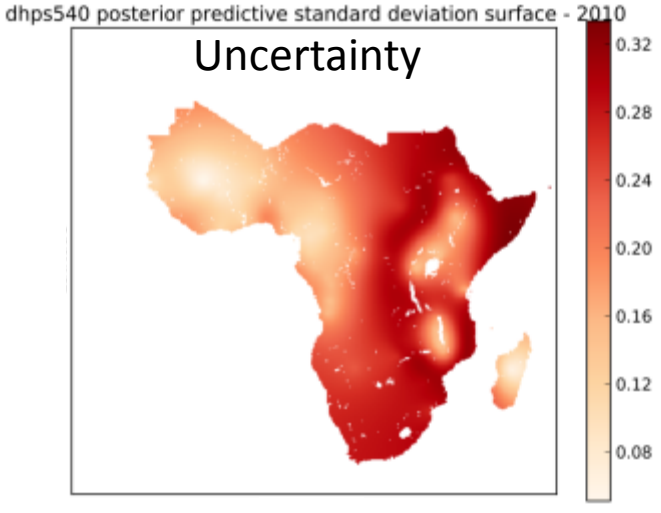
Where should we plan the next studies?

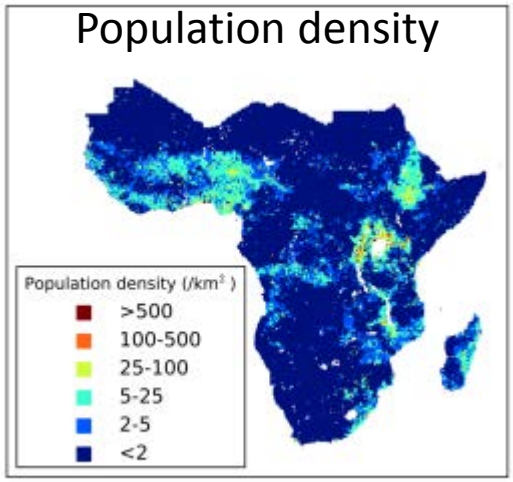
- **To optimise resources**
- **To minimise time for recruitment**
- **To target the correct populations**

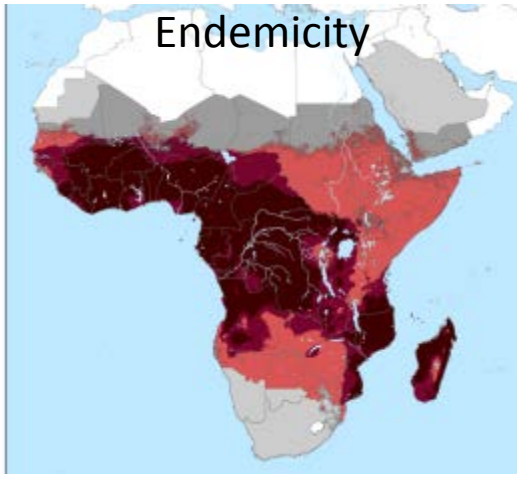
WWARN

Smart Surveillance









map
malaria atlas project

afri
pop

WWARN

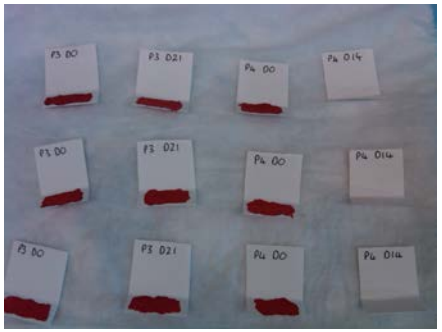
WWARN EQA Programme

Reference Material Programme

- Distribute certified antimalarial drug standards
- Pharmacology/PK labs
- In vitro/drug sensitivity testing
- Drug quality

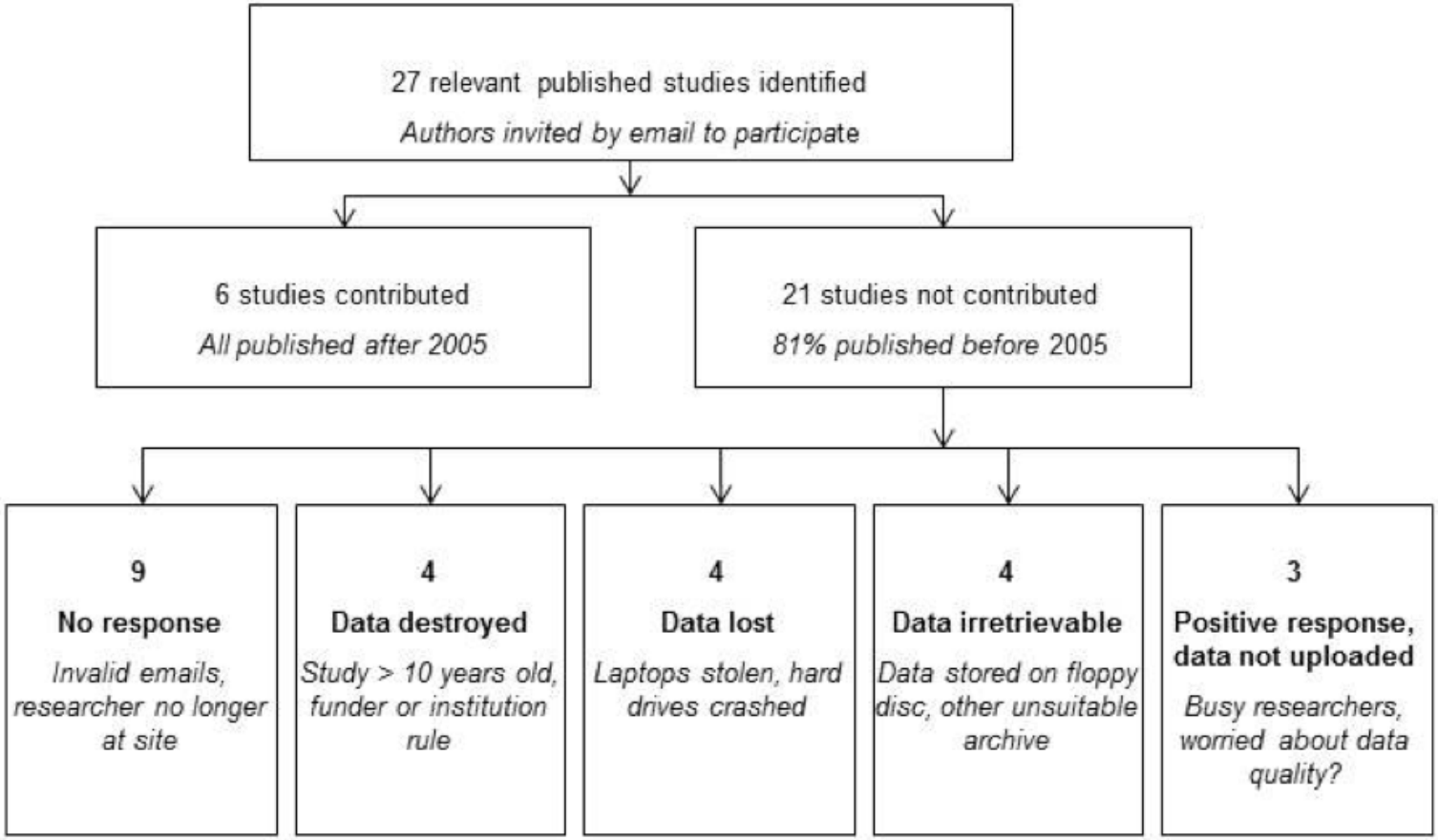
Proficiency Testing Programme

- Assess performance and provide assistance
- Pharmacology labs
- Molecular labs



Challenges to Data Sharing

Data unavailable



WWARN

WWARN Data Repository

- **350 clinical trials**
- **200 research institutions**
- **Raw data on 100,000 individuals (≈3M data points)**
- **2/3 of all published data since 2000**

WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK
WWARN

Building a VL Data Repository

- **WWARN platform exists – do not need to start from scratch**
  - **Data repository structure**
  - **Data upload systems**
  - **Data curation and harmonisation processes**
  - **Template data-sharing terms and agreements**
  - **Ethical considerations**
  - **Lessons learned from malaria**
  - **Reduces cost for establishing database**

Successful Data Sharing requires…

Collaboration, partnerships, and a lot of TRUST

WWARN

Acknowledgements

Jacob Bush

Nathalie Strub-Wourgaft

Philippe Guerin

Jorge Alvar

Fabiana Alves

Christian Nsanwabana

Piero Olliaro

All DNDi