An update from WorldWide Antimalarial Resistance Network

International Malaria Colloquium (IMC) 2010

WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK

WWARN

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2 December 2010

Bangkok, Thailand

Learning from history

- 1955: proposal for the eradication of malaria
  - house spraying with residual insecticides
  - antimalarial drug treatment
  - Surveillance
- 1969: Official announcement of the failure of the campaign
  - Global eradication policy abandoned
    - Antimalarials resistance
    - Insecticides resistance
    - Funding…

Chloroquine & SP spread of resistance

Historical data on resistance

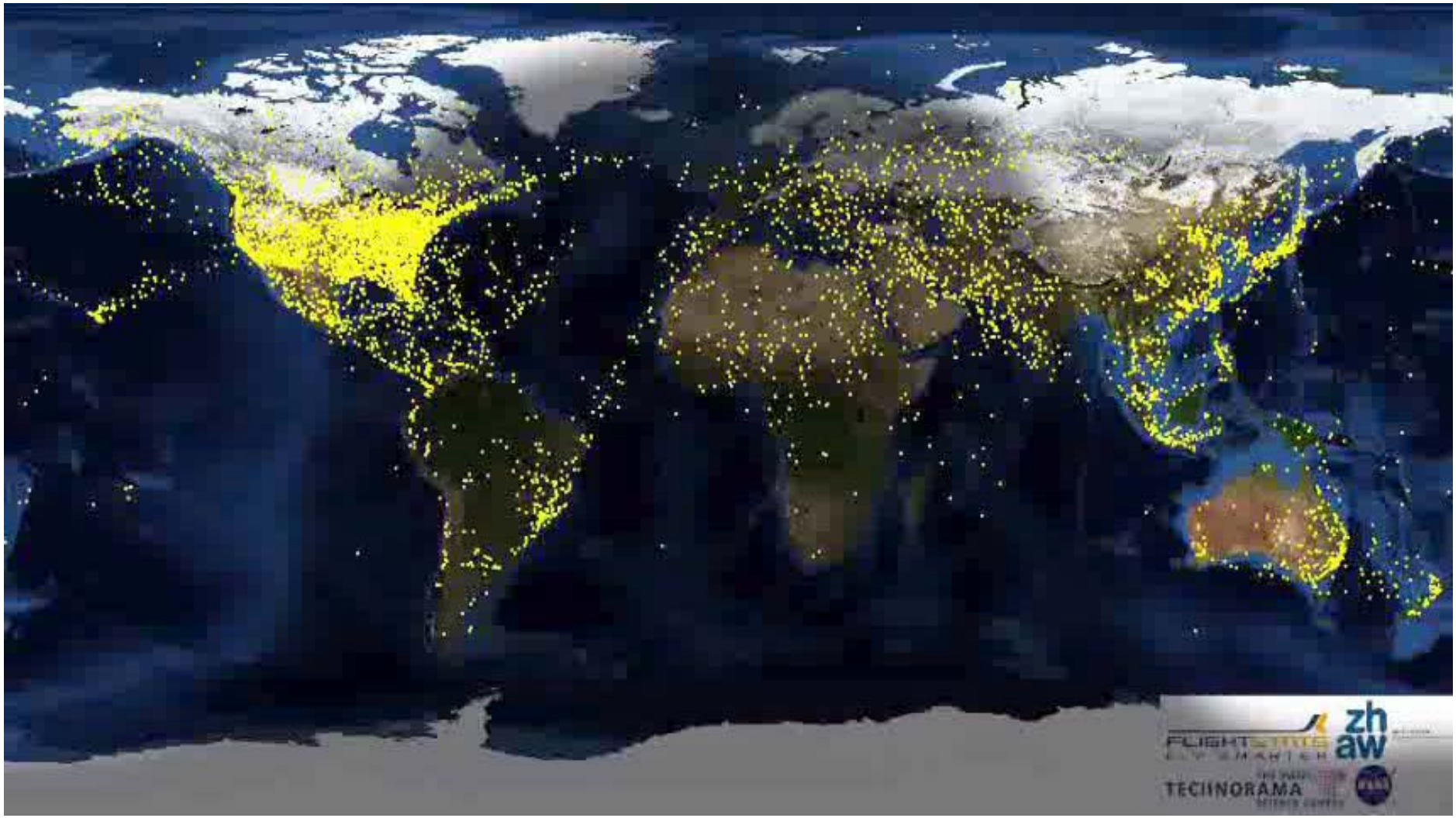
Drugs	Introduction	"First" year reported resistance	Difference (years)
Quinine	1632	1910	278
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Sulfadoxine-pyrimethamine	1967	1967	<1
Mefloquine	1977	1982	5
Atovaquone	1996	1996	<1
Artemisinin deriv.	1971	2006	35?

Adapted Wongsrichanalai et al. Lancet Infectious Diseases 2002

Why is resistance so crucial?

- Drugs
  - Most drugs currently in development are artemisinin derivatives
  - If we get a new family drug
    - Quite a long time before we get an affordable and largely available alternative
- Vaccines
  - Still under development...

Today resistance may spread differently



Resistance data status

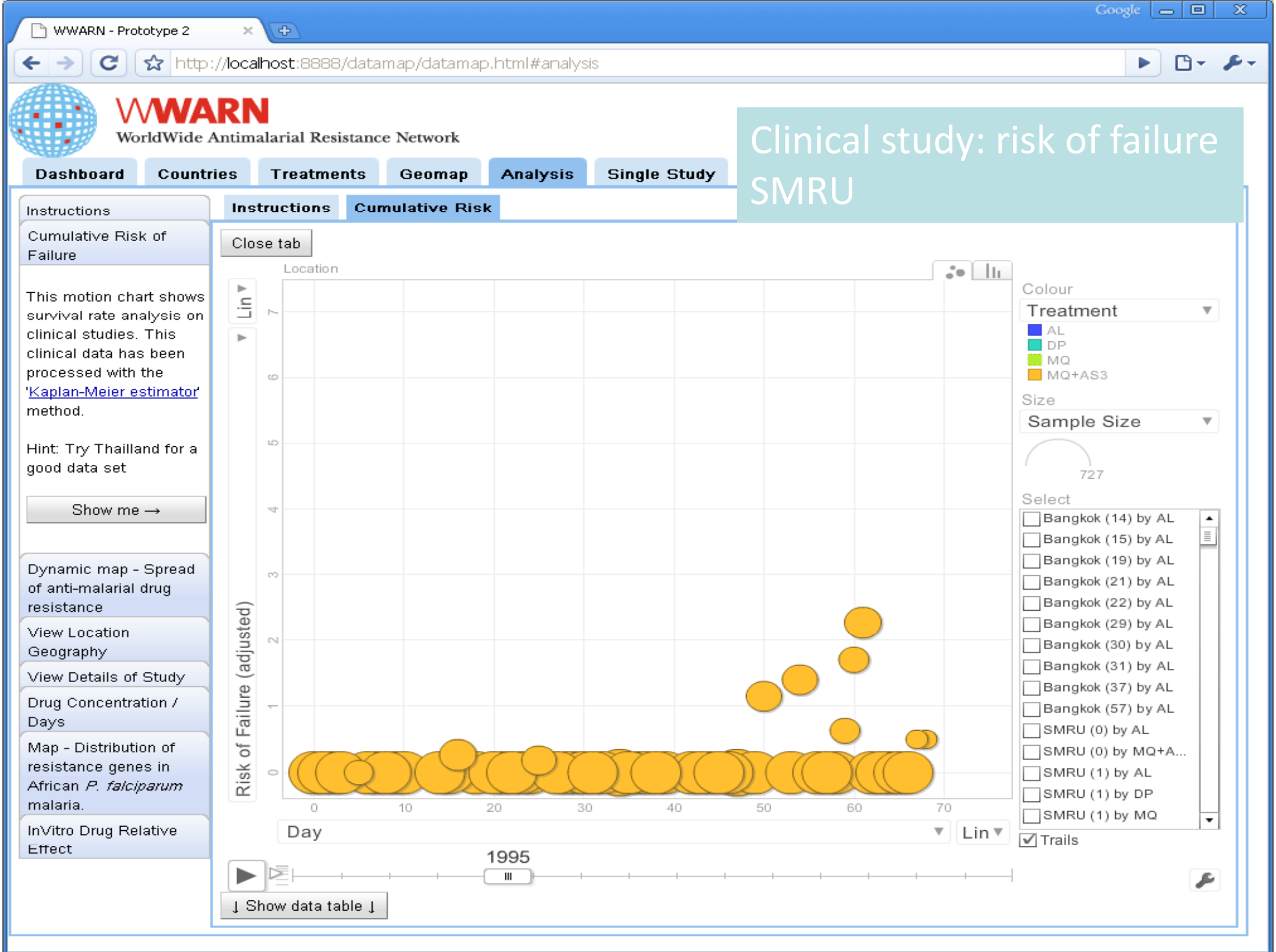
- Absence of data
  - Geographical gap – old information
- Absence of standardisation
  - Data collection, analyze
- Good quality but delay accessing data
  - Publication years after data collection
  - Unpublished data
- >30% endemic countries conduct recommended efficacy monitoring (WHO)

Overall goal of the WWARN project

- Collaborative project with WHO
- Support the collection antimalarial resistance data that are:
  - high quality, up to date, Comprehensive
  - comparable between countries and regions
- Five linked modules
  - Clinical efficacy
  - Pharmacology
  - In vitro susceptibility of isolates
  - Molecular markers
  - Drug quality

Clinical efficacy

- Analyzes anonymous *individual* patient data to overcome differences in study design and analytical methods
- Why did a properly treated patient fail to recover? Question:
  - Origin of drug
  - Dosage
  - Patient reinfection
  - WHO treatment guidelines followed


WWARN - Prototype 2
http://localhost:8888/datamap/datamap.html#analysis
WWARN
WorldWide Antimalarial Resistance Network
Clinical study: risk of failure SMRU
Dashboard
Countries
Treatments
Geomap
Analysis
Single Study
Instructions
Cumulative Risk of Failure
This motion chart shows survival rate analysis on clinical studies. This clinical data has been processed with the 'Kaplan-Meier estimator' method.
Hint: Try Thailland for a good data set
Show me →
Dynamic map - Spread of anti-malarial drug resistance
View Location Geography
View Details of Study
Drug Concentration / Days
Map - Distribution of resistance genes in African P. falciparum malaria.
InVitro Drug Relative Effect
Instructions
Cumulative Risk
Close tab
Location
Lin
Risk of Failure (adjusted)
0
1
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3
4
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0
10
20
30
40
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Day
Lin
1995
↓ Show data table ↓
Colour
Treatment
AL
DP
MQ
MQ+AS3
Size
Sample Size
727
Select
Bangkok (14) by AL
Bangkok (15) by AL
Bangkok (19) by AL
Bangkok (21) by AL
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SMRU (0) by MQ+A...
SMRU (1) by AL
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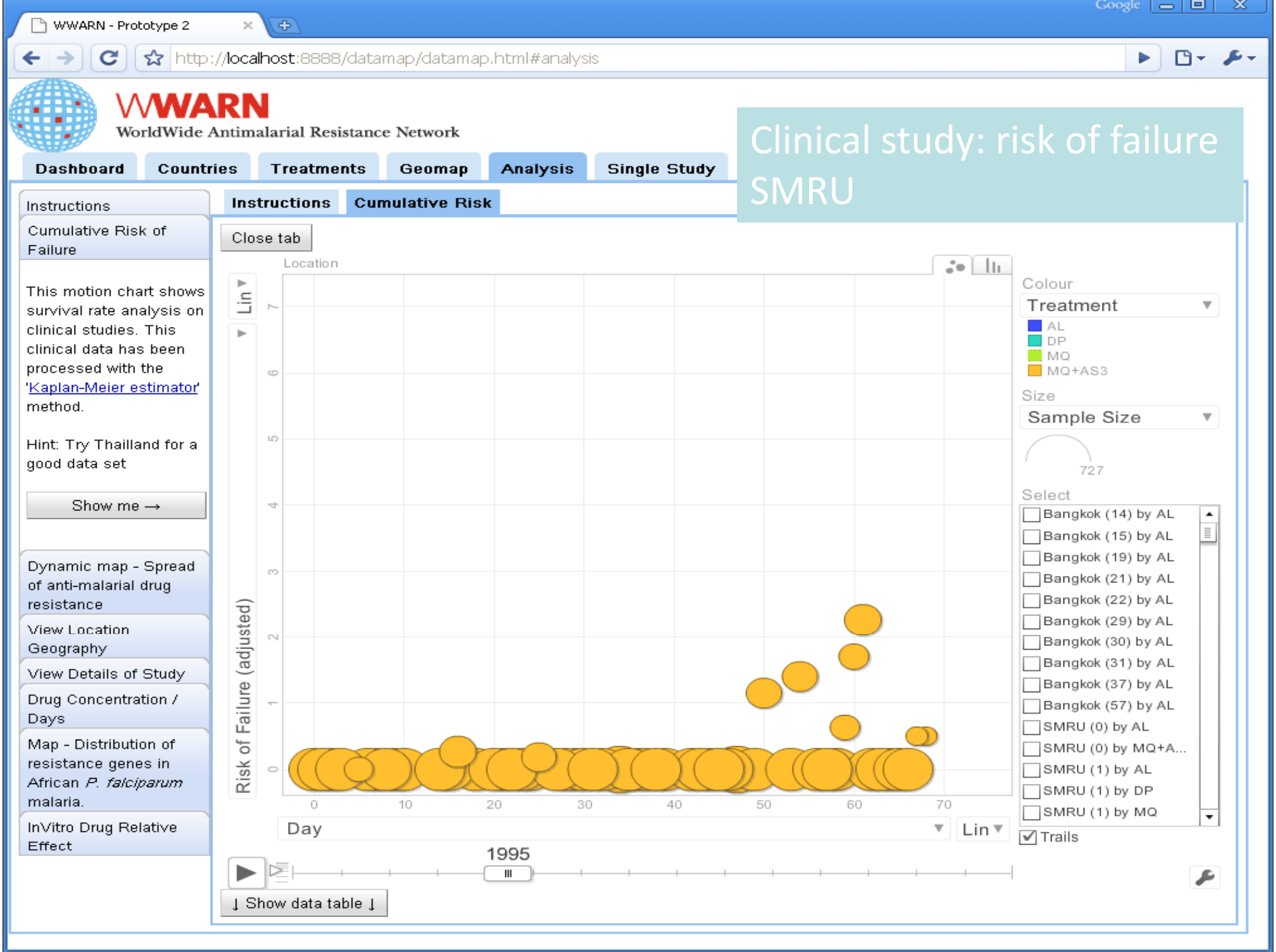
SMRU (1) by MQ
Trails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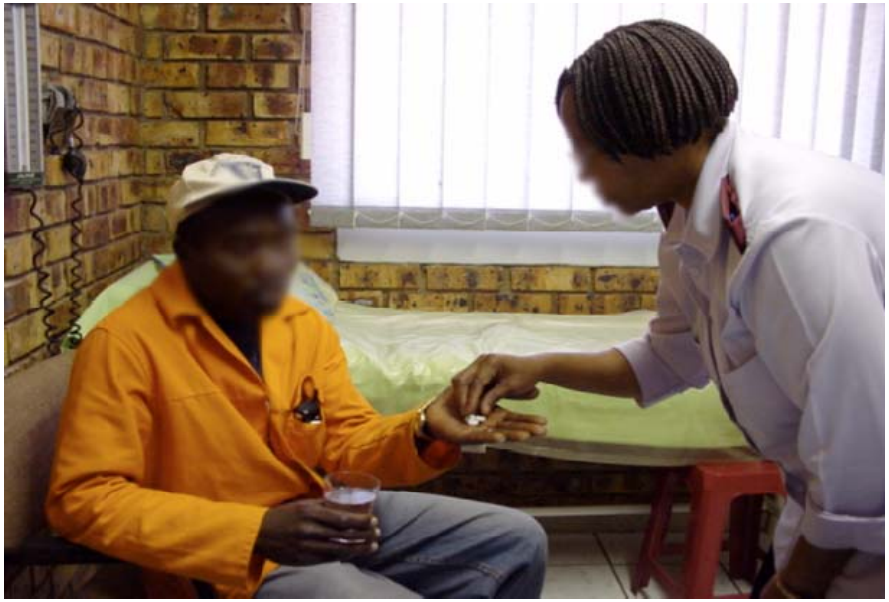
Pharmacology

- Pharmacology distinguishes insufficient drug treatment from parasite resistance
- Was the drug dosage sufficient to treat disease?
  - What was the drug concentration in the patient?
  - Was the dosage adequate for recovery?

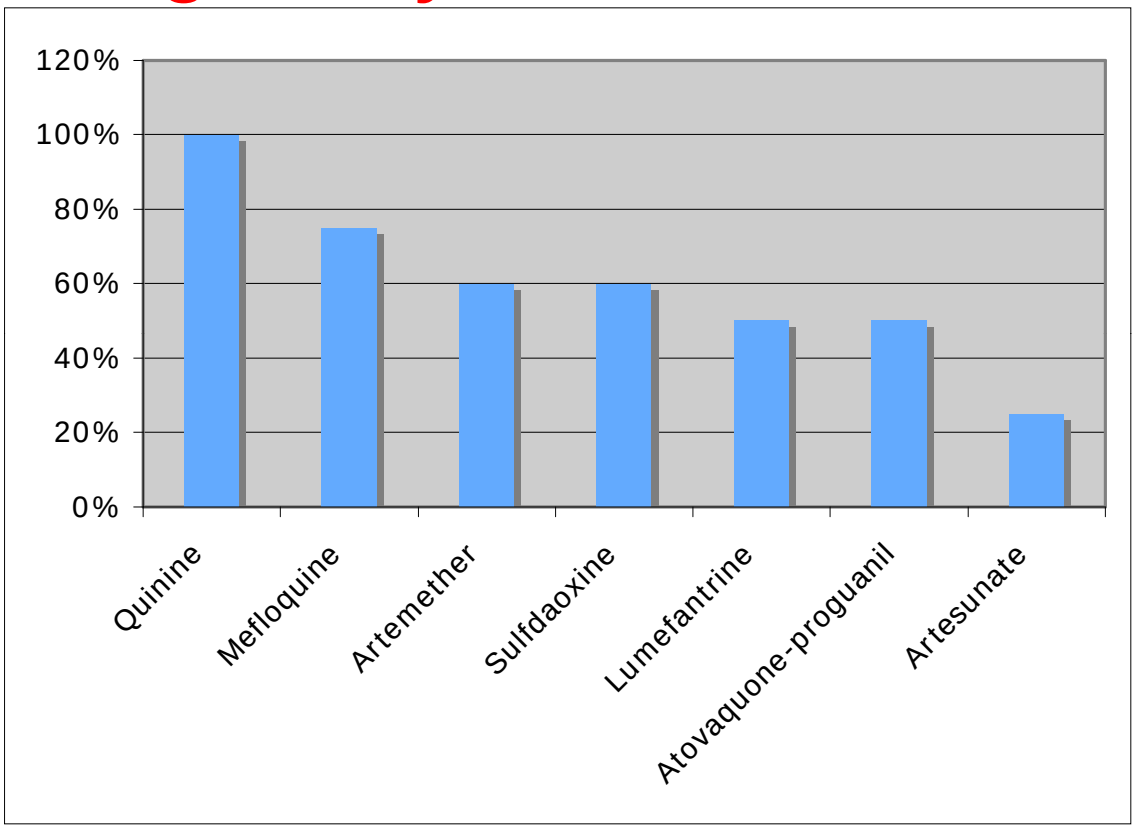


Consensus meeting 2010 – WHO/WWARN

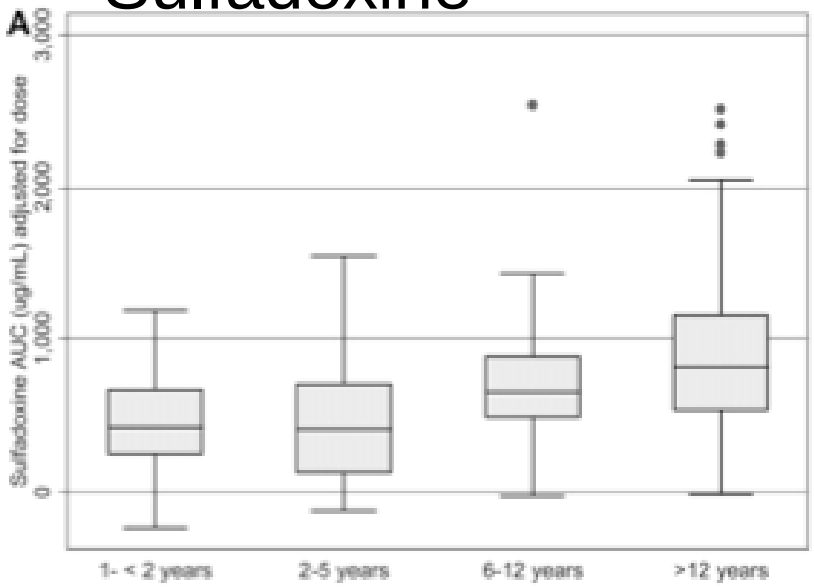
Threats - The dose is often wrong

Children

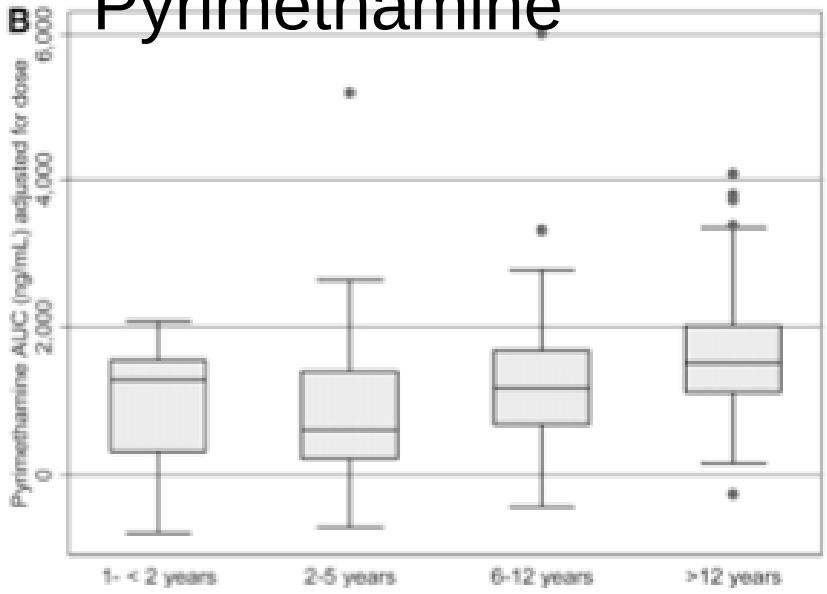
Pregnancy



Sulfadoxine

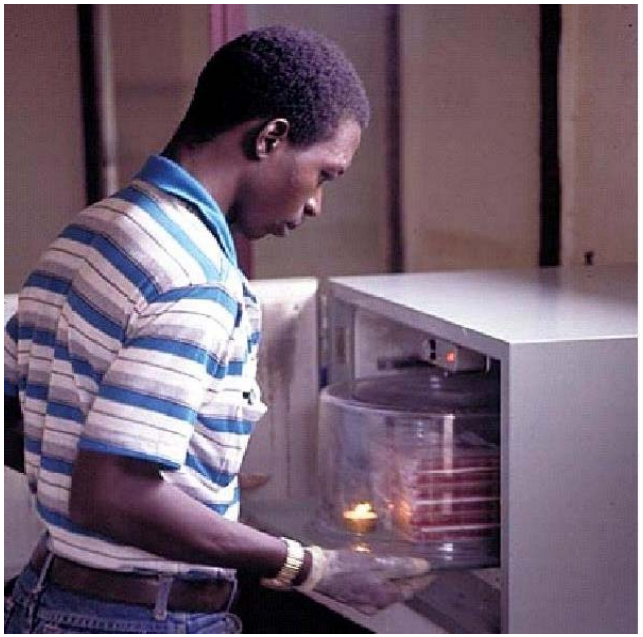


Pyrimethamine



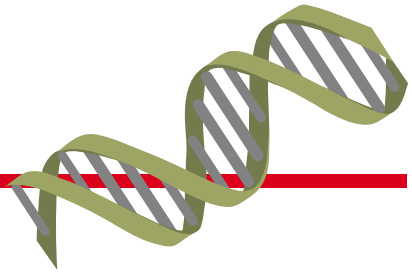
In vitro analysis

- Growing parasite outside the body eliminates confounding factors
- *In vitro* analyses:
  - Determine if patient isolate is resistant to treatment drug or other antimalarials
  - Enable comparison with reference clones



- Protocols for positive & negative controls, standard reference clones, reference drugs & metabolites

Molecular markers



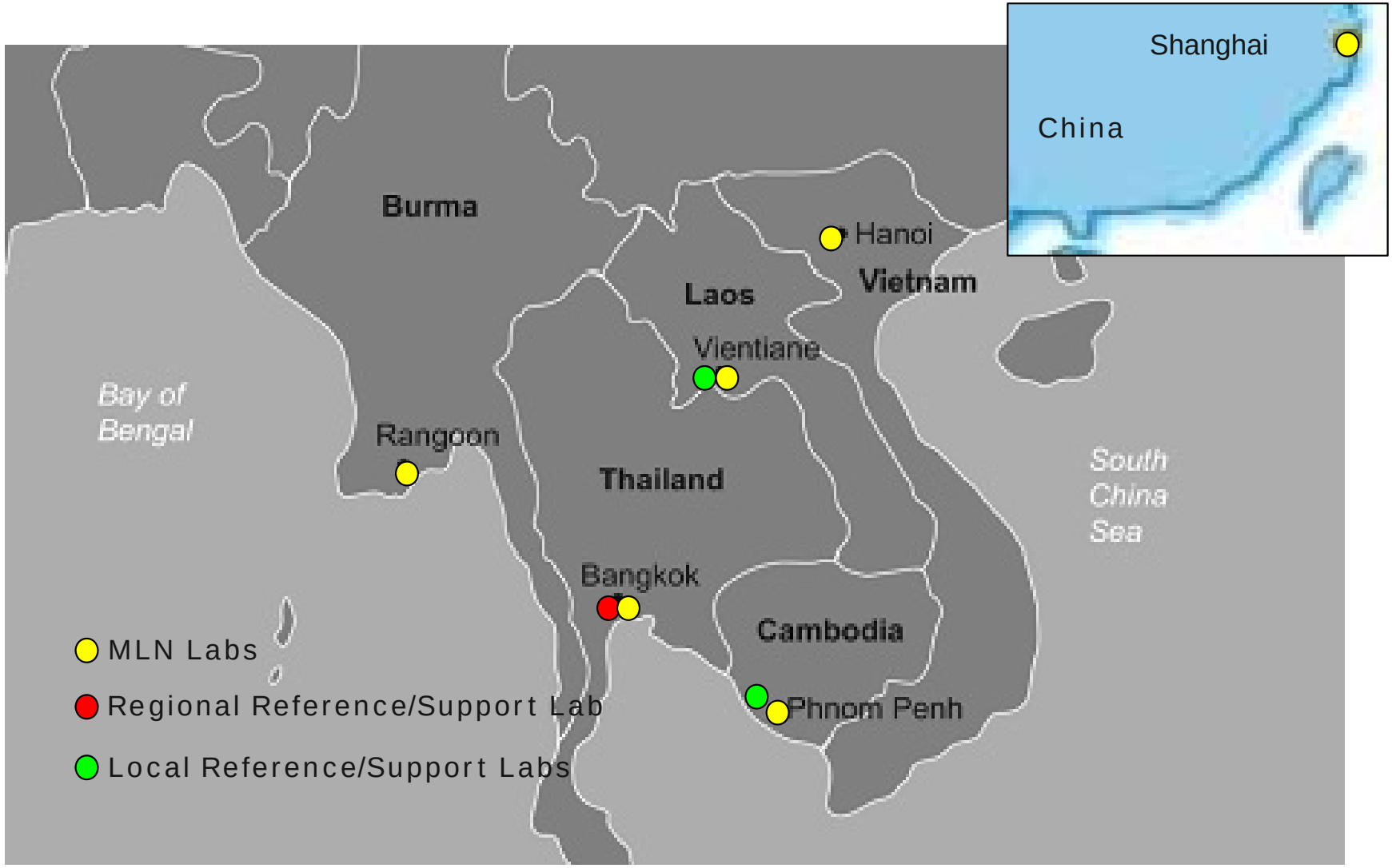
- Provide relatively rapid, simple and inexpensive way to monitor parasites for drug sensitivity
- Surrogates for more complex methods
- Database provides powerful, rapid mechanism to aid in validation of molecular markers for artemisinin resistance
  - Artemisinin Resistance Marker (ARM) platform
  - Standardization of specimen sampling

Consensus meeting 2011 – WHO/WWARN

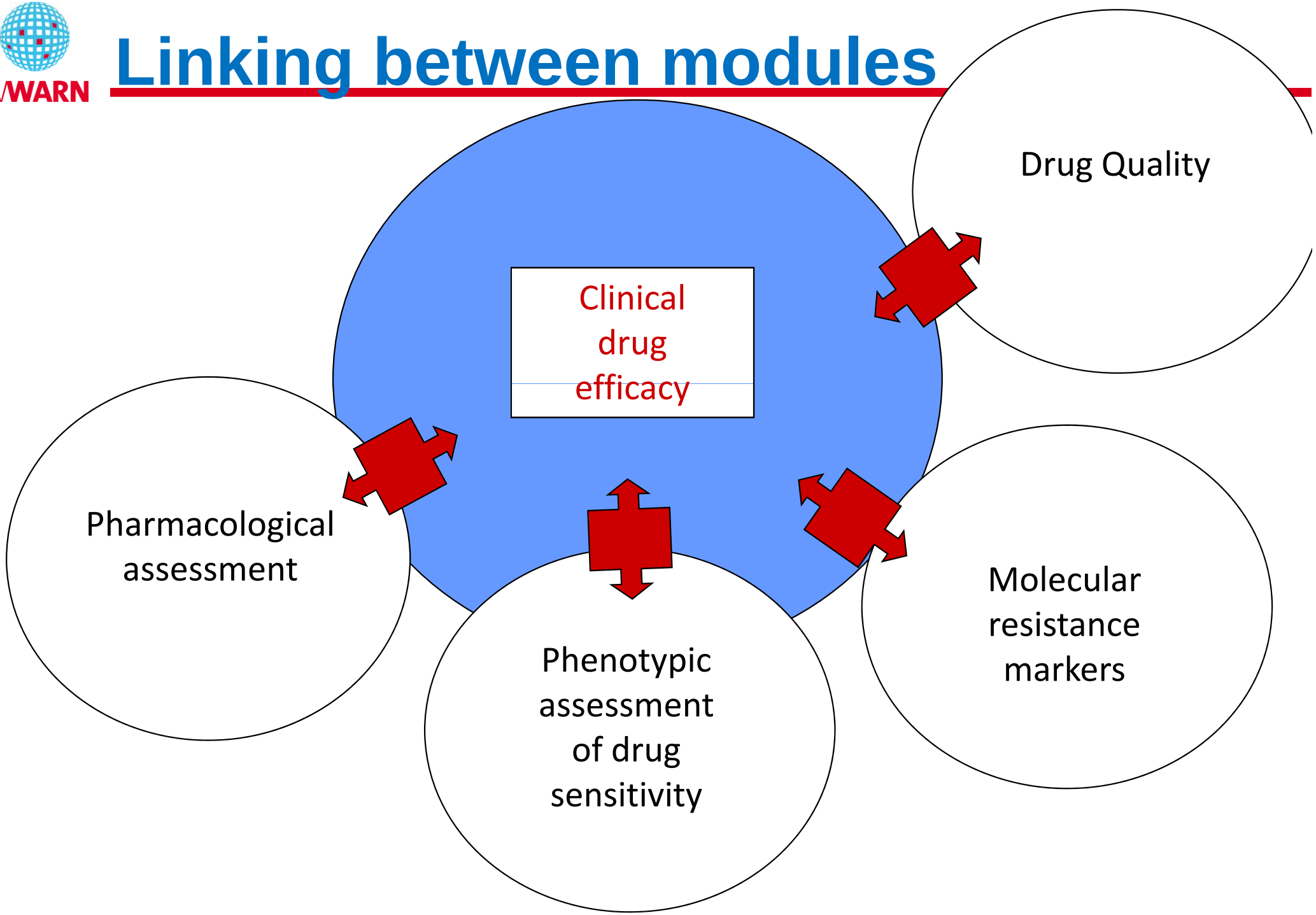
Regional efforts

- Asia Regional Centre
  - Collaboration with Mahidol University
- Several initiatives:
  - GMS Molecular Surveillance Network
  - QA/QC pharmacology and in vitro scheme
  - Capacity building activities
    - Clinical, PK, Molecular
- Centres in East and West Africa

GMS Molecular Surveillance Network



Linking between modules



Antimalarial Quality

- WHO definitions:
- Counterfeit “a pharmaceutical product that is deliberately and fraudulently mislabeled with respect to identity and/or source”
- Substandard “a pharmaceutical product with genuine packaging with incorrect quantity of ingredient (not deliberate)”

Recent Reports of Poor Quality Antimalarials

Fakes

- Chloroquine
- Quinine
- Tetracycline/Doxycycline
- Sulphadoxine-pyrimethamine
- Sulphalene-pyrimethamine
- Mefloquine
- Halofantrine
- Primaquine
- Artesunate
- Intramuscular and oral artemether
- Dihydroartemisinin
- Dihydroartemisinin-piperaquine
- Artemether-lumefantrine

Substandard

- Chloroquine
- Quinine
- Tetracycline/Doxycycline
- Sulphadoxine-pyrimethamine
- Primaquine
- Artesunate
- Intramuscular & oral artemether

Not faked ?

Atovaquone-proguanil and iv/im artesunate

Drug pressure engender artemisinin resistance

- Fake artesunate from Thai/Burma border contain 3-10 mg artesunate per tablet (genuine tablet ~ 50mg artesunate)
- Artemisinin in fake halofantrine in West Africa
- 88 % Laos shop-bought artesunate fake, in stratified random survey
  - 15% of fakes contained artemisinin … 400km from Pailin…

What is the role of WWARN?

- Support standardisation of antimalarial resistance indicators
  - Standard data formats allow analysis of data from diverse studies
  - Quality assurance schemes
- Test utility of proxy markers
- Deliver spatio-temporal evidence on drug efficacy
  - Early WWARNing System
  - Evidence base for policy makers

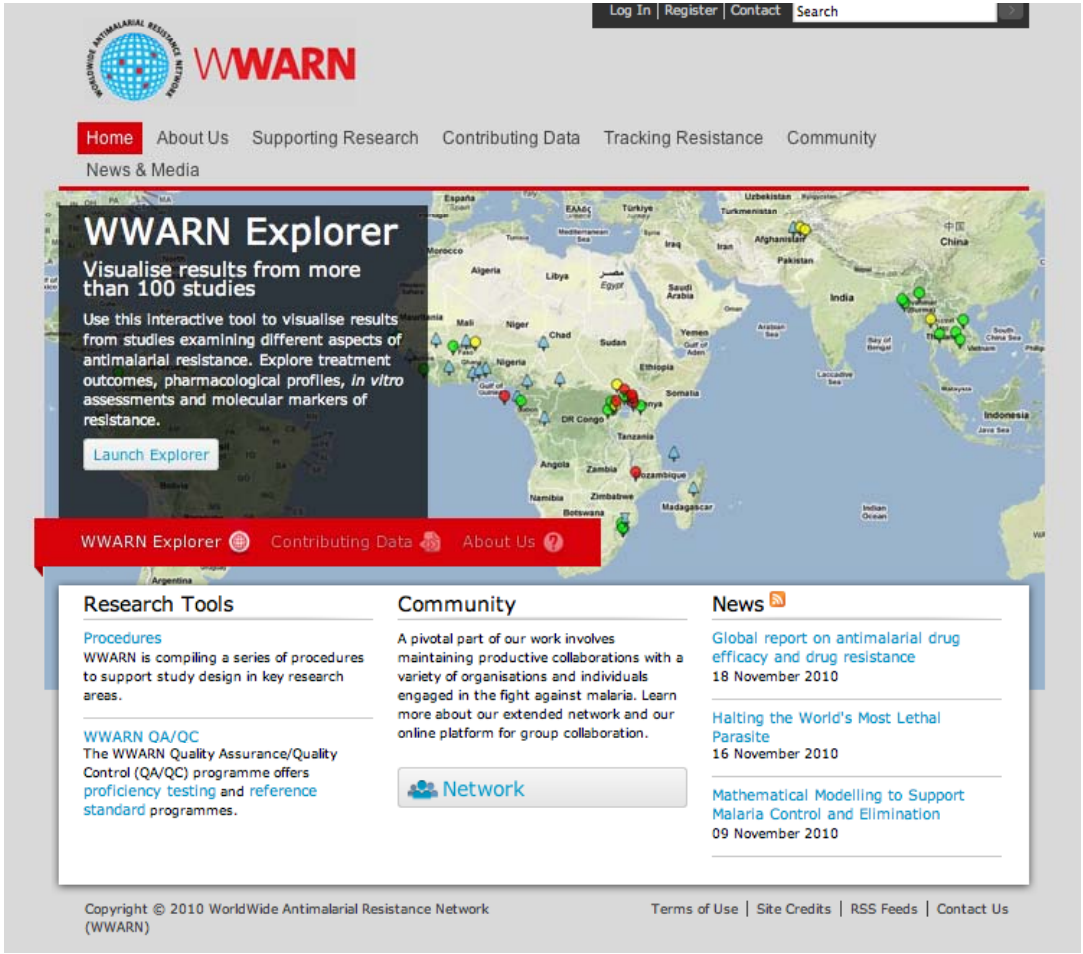
Conclusion

- Surveillance is a marginal cost but critically important
- Deliver spatio-temporal evidence on drug efficacy
  - Early WWARNing System
  - Evidence base for policy makers

- Malaria is a global problem that needs a global solution

Contact & Acknowlegments

info@wwarn.org



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