

# World Antimalarial Resistance Network

**WARN**

**To create a global, comprehensive, and inclusive network, providing quality-assured information on antimalarial drug resistance.**

**ACTs CURRENTLY EFFECTIVE,  
BUT.....**

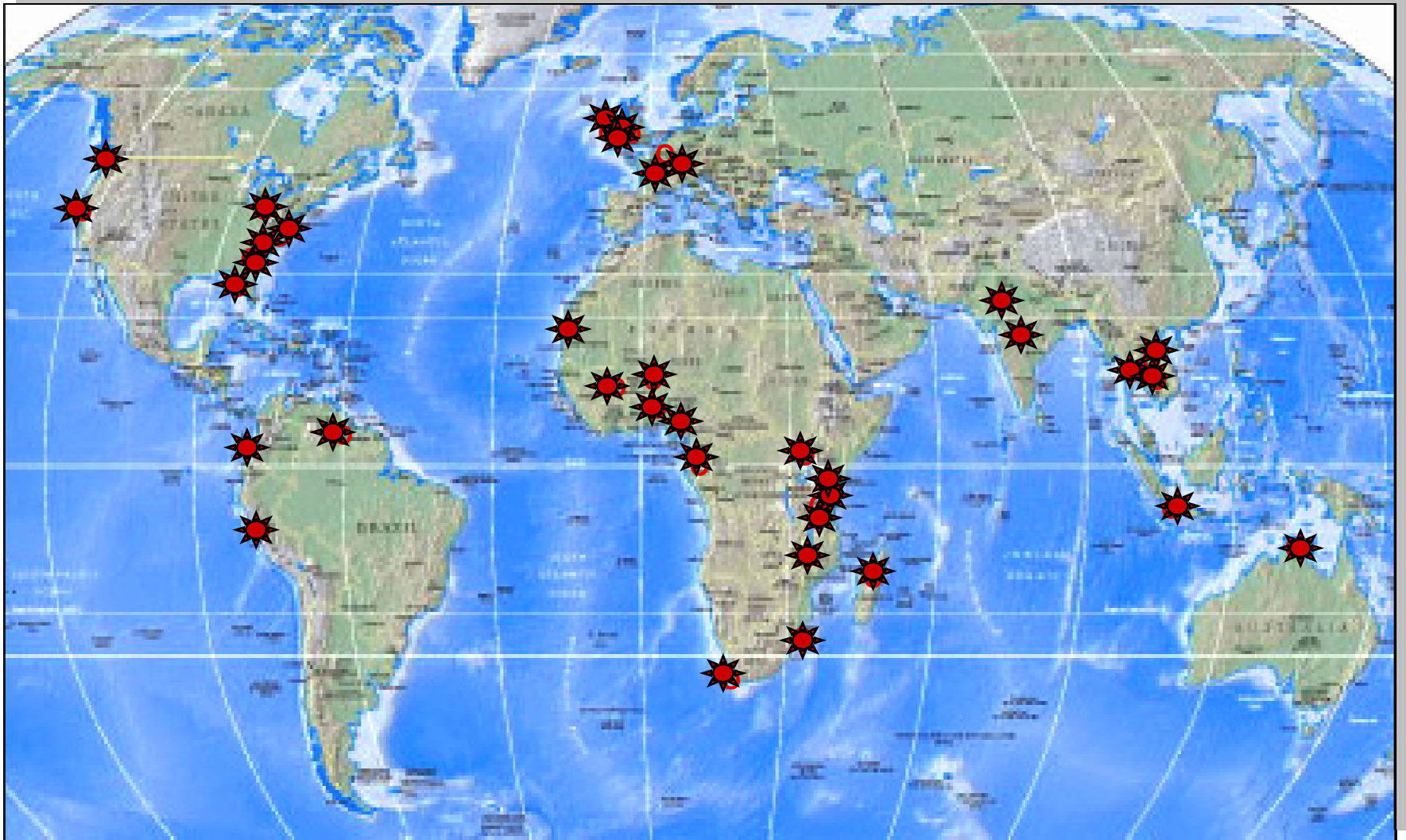
**HOW CAN WE SUSTAIN  
MAXIMUM  
USEFUL THERAPEUTIC LIFE  
OF ACTs?**

**HOW CAN WE  
STAY AHEAD OF THE  
EVOLUTIONARY CURVE?**

# HISTORY OF WARN

- **INFORMAL MEETINGS**
  - **ASTMH, 2004, 2005**
  - **MIM 2005**
- **PLANNING MEETING**
  - **BMGF, October 2006**
- **SUMMARY PAPERS PUBLISHED**
  - *Malaria Journal, SEPT 2007*
- **1 YEAR PLANNING GRANT**
  - **BMGF funded, Sept 2007**
- **IMPLEMENTATION GRANT SUBMISSION**
  - **July, 2008**

# WARN PLANNERS 2006/2008

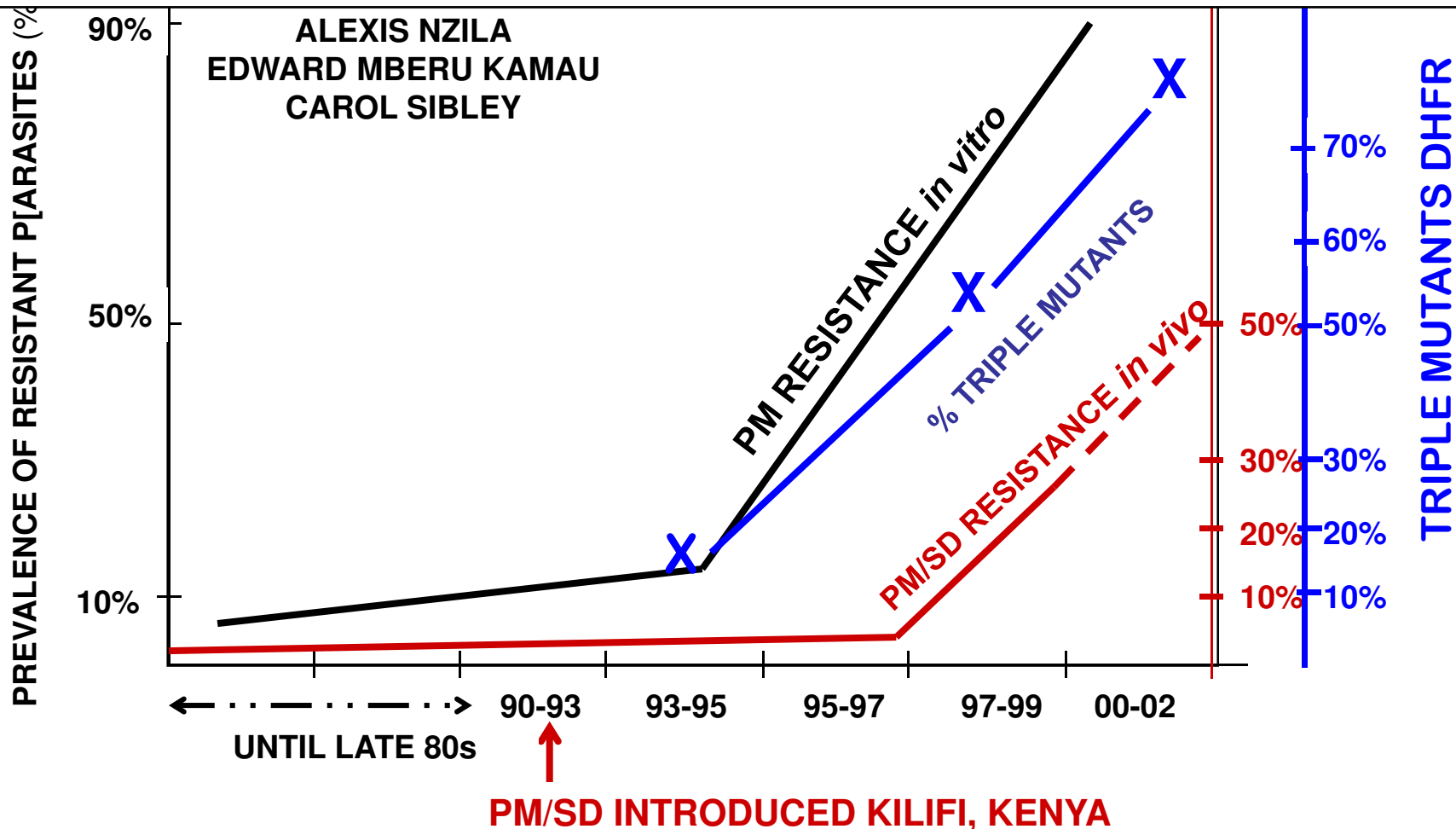


# **WHAT HAVE WE LEARNED FROM “OLD” DRUGS?**

- **RESISTANCE ARISES RARELY, BUT SPREADS RELATIVELY QUICKLY**
- **CLINICAL TREATMENT FAILURE IS THE LAST STEP IN A LONG SERIES OF CHANGES**

# HOW CAN WE FIT THIS TOGETHER?

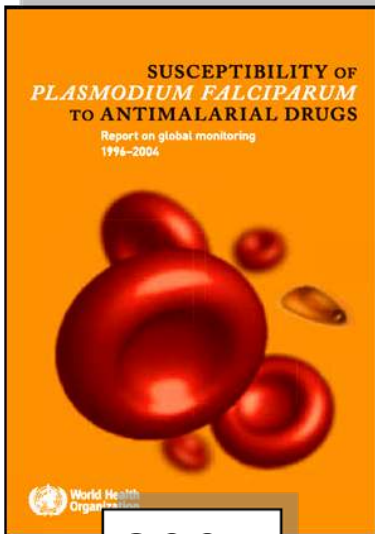
## EARLY WARNINGS OF CLINICAL FAILURE



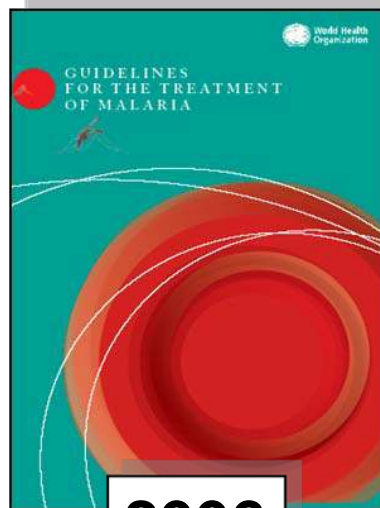
# **EARLY WARNING OF RESISTANCE**

- **SLOWER TIME TO CLEAR PARASITES**
- **IN VITRO INCREASES IN IC<sub>50</sub> VALUE**
- **INCREASING PREVALENCE OF  
“RESISTANT” ALLELES**

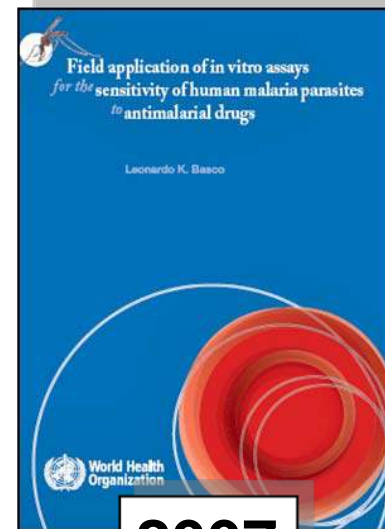
# TOOLS AND PARTNERSHIP



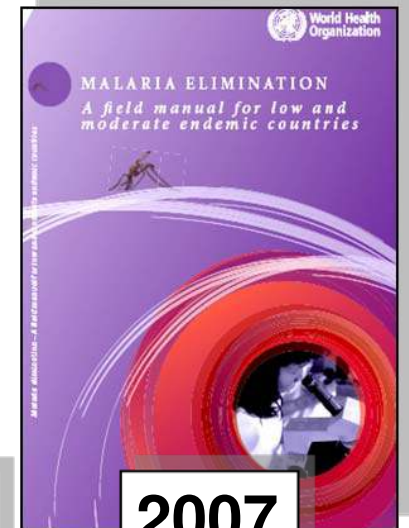
2004



2006



2007



2007

Pascal Ringwald

WHO/GMP GUIDELINES



# OVERVIEW OF PLAN

**WEB BASED, OPEN ACCESS  
(WITH REGISTRATION)**

**FREELY AVAILABLE **TOOLS** FOR DATA  
**ORGANIZATION**  
**INPUT**  
**ANALYSIS****

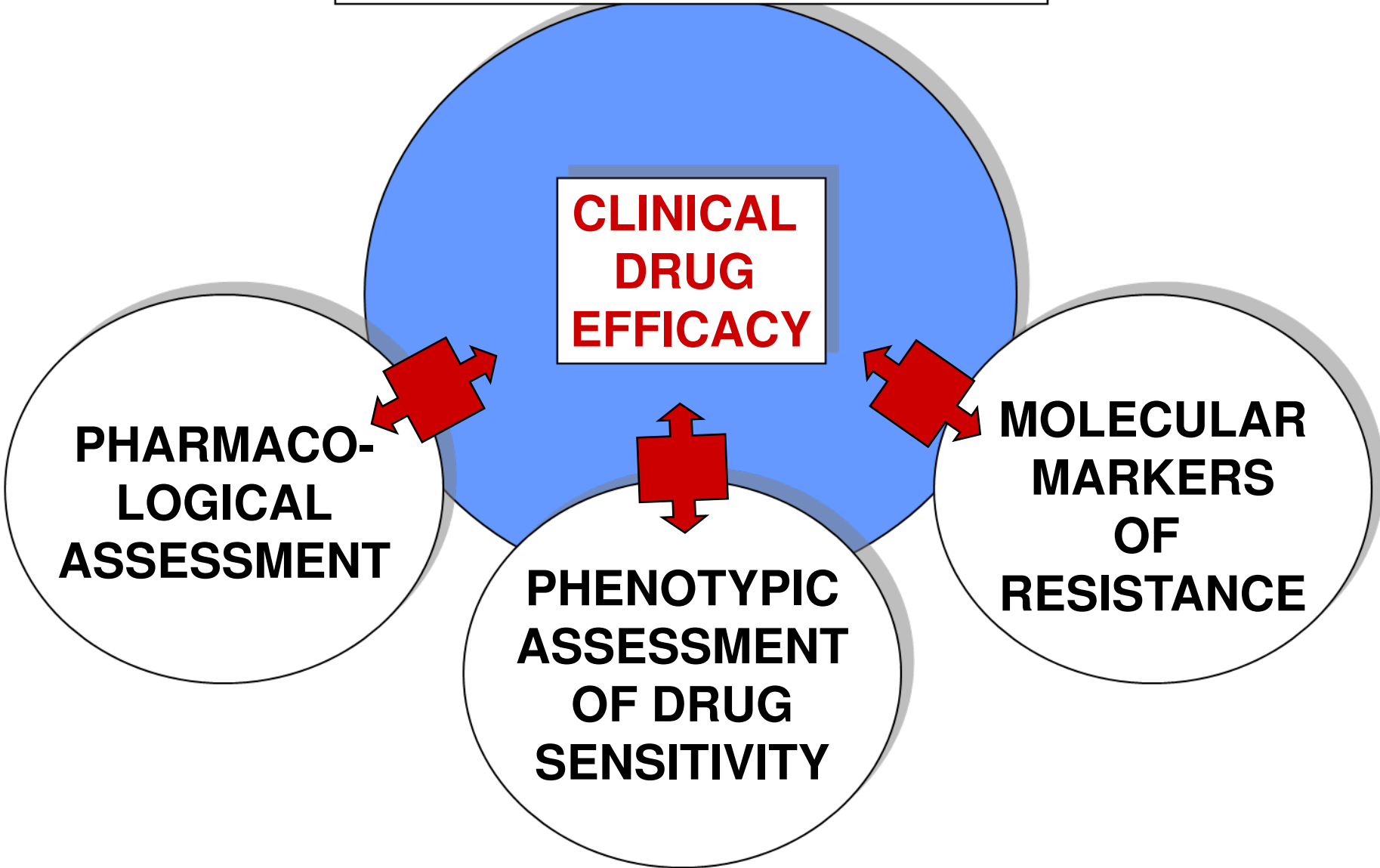
**GATEKEEPERS TO FACILITATE DATA UPLOAD (and  
assure quality)**

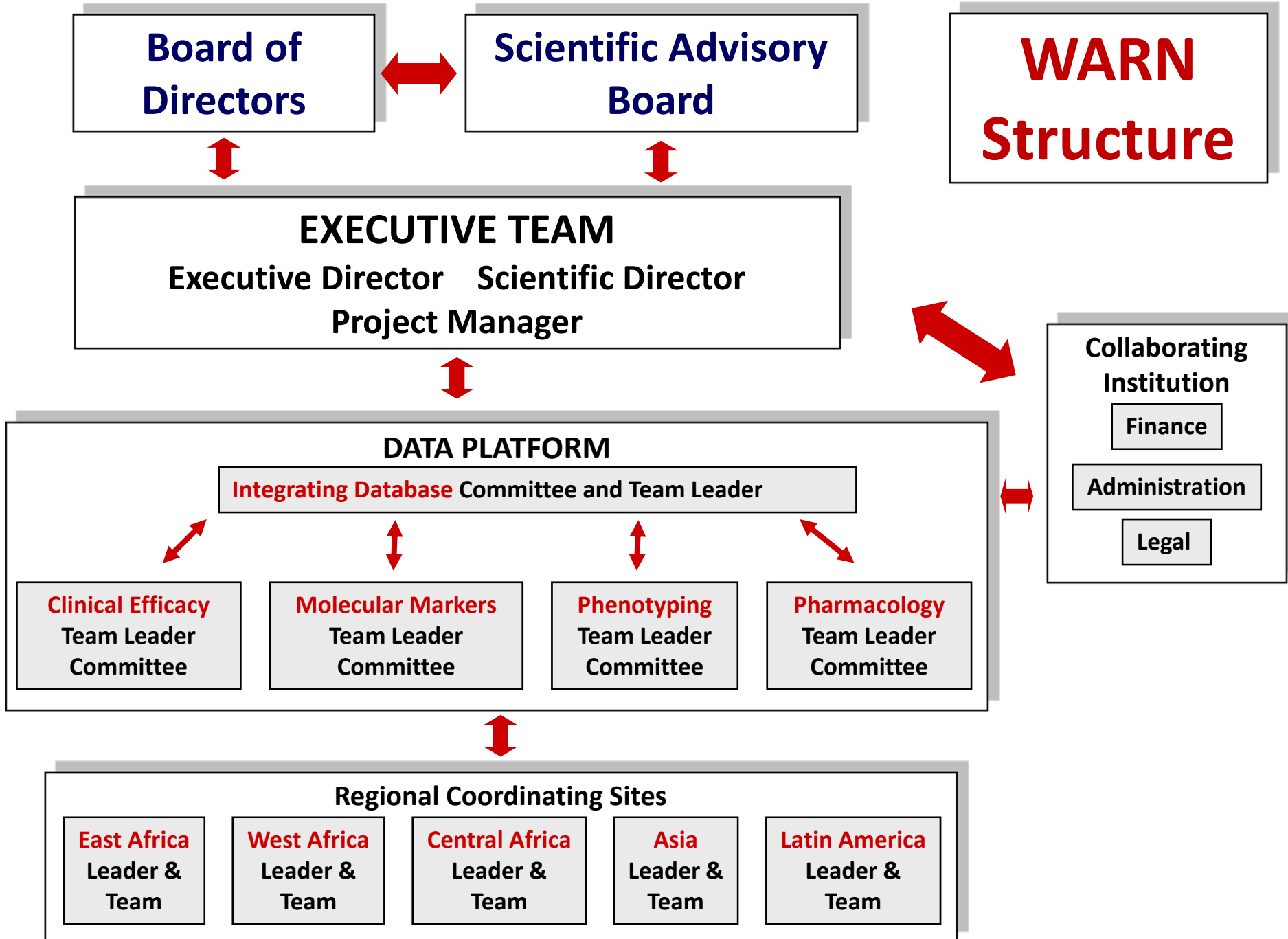
**FREELY AVAILABLE TOOLS FOR DATA **OUTPUT**  
**MAP BASED**  
**GRAPHICAL**  
**TABULAR****

# OVERVIEW OF PLAN

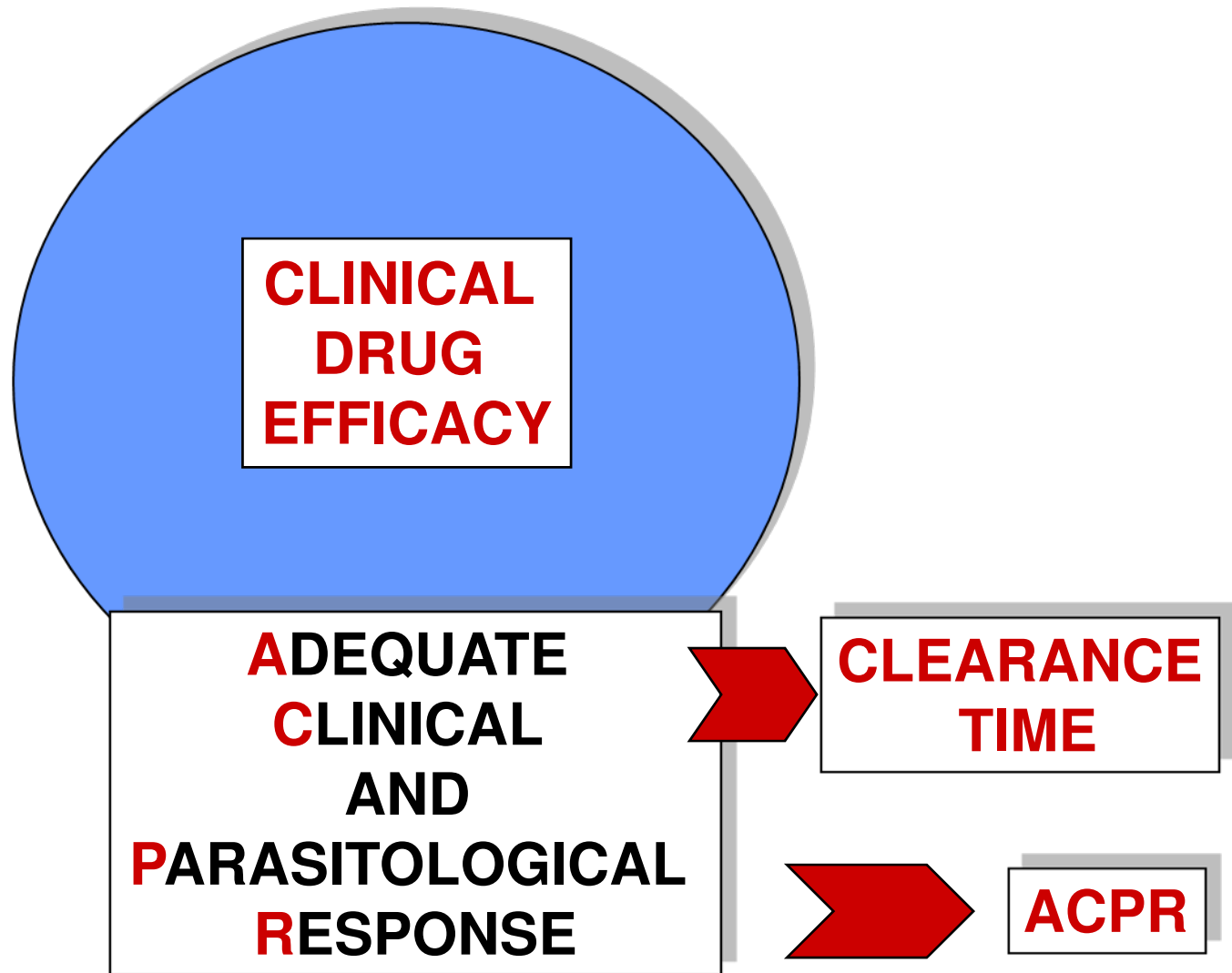
- **PROSPECTIVELY FOCUSED**
- **INDIVIDUAL** PATIENT/ISOLATES RECORDS
- **COMMON PROTOCOLS FOR QUALITY ASSURANCE**
- **STRONG LINKS WITH OTHER GROUPS INVOLVED IN SURVEILLANCE**
- **FOUR LINKED MODULES**
  - CLINICAL EFFICACY**
  - PHARMACOLOGY**
  - IN VITRO SUSCEPTIBILITY OF ISOLATES**
  - MOLECULAR MARKERS**

# WORLD ANTIMALARIAL RESISTANCE NETWORK





# THE CENTRAL OUTCOME MEASUREMENT

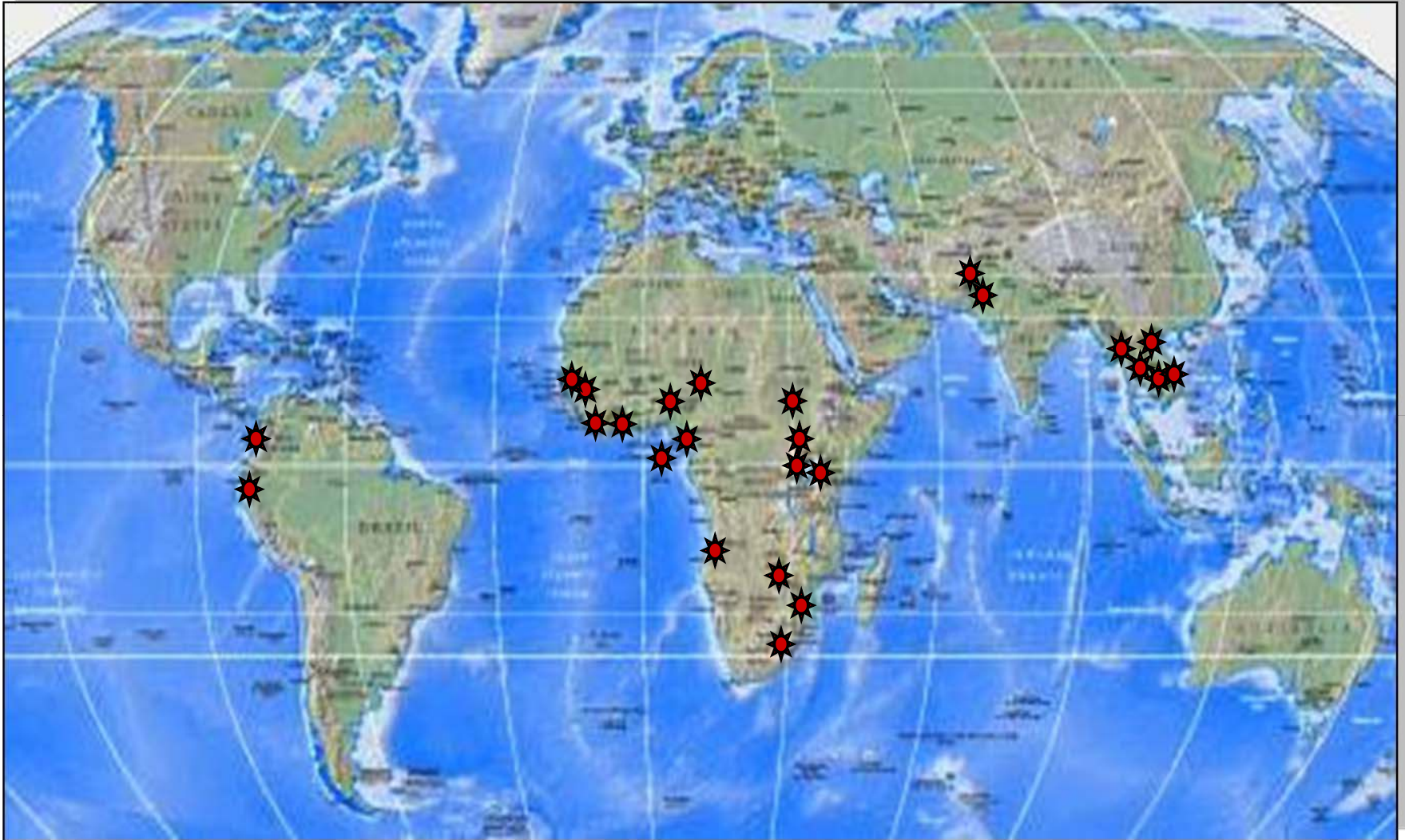


# CLINICAL EFFICACY STUDIES

- **WHO GUIDELINES**, 28 DAY+ FOLLOW UP
- PARTICIPATION OF SENTINAL SITES
- BASIC DATA ON STUDY SITE
- STANDARDIZED REPORTING OF KEY VARIABLES ON **INDIVIDUAL** PATIENTS

- **Patient and study**
- **Date**
- **Treatment received**
- **Initial species of infection**
- **Last day of follow up**
- **Outcome on last day**

# 25 COUNTRIES OF ORIGIN- CLINICAL STUDY DATA



# DEMONSTRATION OF UTILITY

<b>STUDY SITE</b>	<b># PATIENTS</b>
<b>SMRU:</b>	<b>11,399</b>
<b>Uganda and Burkino Faso</b>	<b>5,539</b>
<b>Epicentre/MSF</b>	<b>1,590</b>
<b>Other</b>	<b>10,259</b>
<b>TOTAL</b>	<b>25,214</b>

**Ric Price**  
**Grant Dorsey**  
**Liz Ashley**  
**Ambrose Talisuna**

**25 Countries**  
**Varied Study Designs**  
**Duration of follow up**  
**Pf and Pv efficacy studies**  
**Recoding of LPF and LCF**



# PHARMACOLOGICAL ASSESSMENT OF DRUGS

**WHY DID THE PATIENT FAIL TREATMENT?**

**CLINICAL DRUG EFFICACY**

**WAS THE DRUG LEVEL ADEQUATE?**

**PHARMACOLOGICAL ASSESSMENT**

**South-south network for antimicrobial pharmacology**

**SSNAP**

**Karen Barnes  
Nick White  
Bill Watkins**



# PK ASSESSMENT IN AT RISK GROUPS

**DID FAILURE RESULT FROM  
INADEQUATE DRUG LEVELS?**

- **INFANTS, UNDER 5s**
- **PREGNANT WOMEN**
- **MALNOURISHED**
- **HIV+/AIDS**
- **COINFECTION WITH OTHER PATHOGENS**

# PHARMACOLOGY NETWORK

- **5 REGIONAL ANALYSIS LABS**
  - **1 ASIA**
  - **3 AFRICA**
  - **1 LATIN AMERICA**
- **LINKED BY COMMON QC CRITERIA**
- **SHARED TEST REAGENTS**
- **COORDINATED WITH CLINICAL ASSESSMENTS**
  - **DRUG LEVELS ON DAY 7**

**CLINICAL FAILURE  
WITH ADEQUATE DRUG**



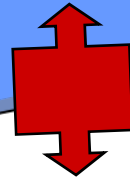
**PRESUMPTIVE  
RESISTANT PARASITES**



**ANALYSIS OF PARASITE  
DRUG SENSITIVITY  
PHENOTYPES**

# WORLD ANTIMALARIAL RESISTANCE NETWORK

**CLINICAL  
DRUG  
EFFICACY**



**PHENOTYPIC  
ASSESSMENT  
OF DRUG  
SENSITIVITY**

**ARC3**

**Jacques Le Bras  
Mark Fukuda  
David Bacon  
John Barnwell**

# PARASITE PHENOTYPING NETWORK

- REGIONAL REFERENCE LABS/ QC SOURCE
- ANALYZE CURRENT PATIENT ISOLATES
- AGREED PROTOCOL ON  
**TIME, MEDIA, PARASITEMIA, HEMATOCRIT**
- AGREED QC
  - POSITIVE AND NEGATIVE CONTROLS
  - STANDARD REFERENCE CLONES
  - STANDARD DRUGS
- VARIOUS ANALYSIS METHODS, BUT STRICT ADHERENCE TO CHOSEN PROTOCOL

**DATA COMPARABLE  
OVER TIME  
FROM ONE LAB TO NEXT!**

**PARASITE ISOLATES WITH DECREASED  
DRUG SENSITIVITY PHENOTYPE**



**PRESERVED AND SHARED  
CANDIDATES FOR  
INTENSIVE GENETIC ANALYSIS**



**IDENTIFICATION OF LOCI ASSOCIATED  
WITH RESISTANCE TO  
EACH PARTNER IN ACT**

# WORLD ANTIMALARIAL RESISTANCE NETWORK

**CLINICAL  
DRUG  
EFFICACY**



**MOLECULAR  
MARKERS  
OF  
RESISTANCE**

**Chris Plowe  
Cally Roper  
Abdoulaye Djimde  
Colin Sutherland  
Phil Rosenthal**

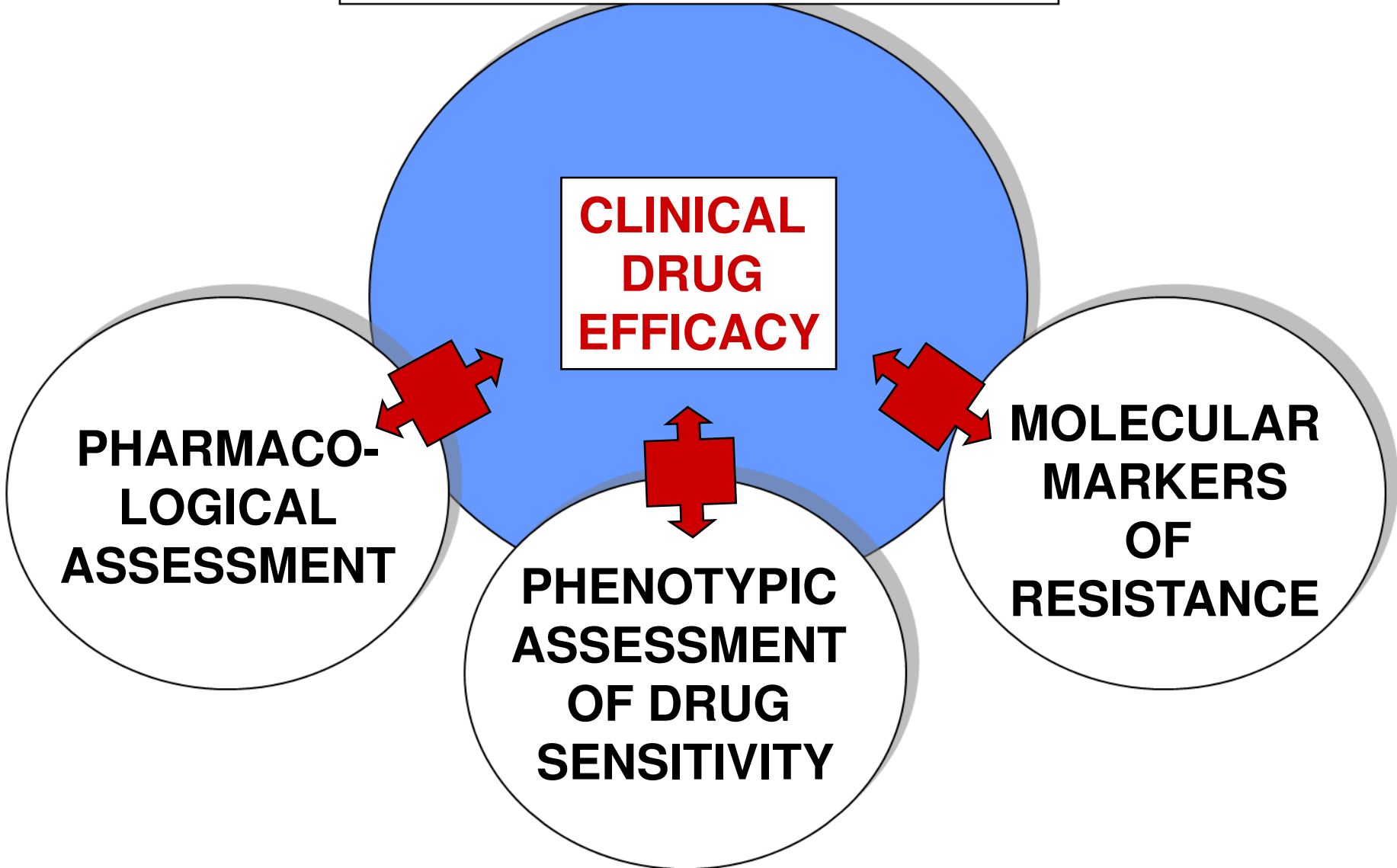
**ARC3**



# IDENTIFYING MOLECULAR MARKERS

- **VERIFIED PHENOTYPE-**  
**DECREASED DRUG SENSITIVITY**
- **GENOME/TRANSCRIPT COMPARISONS**  
**SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)**  
**COPY NUMBER VARIATION**  
**TRANSCRIPTION PROFILE?**
- **COMPARISON** AMONG STRAINS FROM DIFFERENT  
REGIONS WITH SAME PHENOTYPE
- **VERIFIED MOLECULAR MARKERS** FOR  
**COMPONENTS OF ACTs**

# WORLD ANTIMALARIAL RESISTANCE NETWORK



# WHAT CAN WE EXPECT FROM NETWORK?

## FOR NEW COMBINATION DRUGS

**GEOGRAPHIC PATTERNS  
TEMPORAL PATTERNS**

- **CLINICAL EFFECTIVENESS**
- **CORRECT DOSES FOR AT RISK GROUPS**
- **PARASITE DRUG PHENOTYPES, IN VIVO CORRELATES?**
- **MOLECULAR CORRELATES OF RESISTANCE?**

# IMPACT OF DATABASE

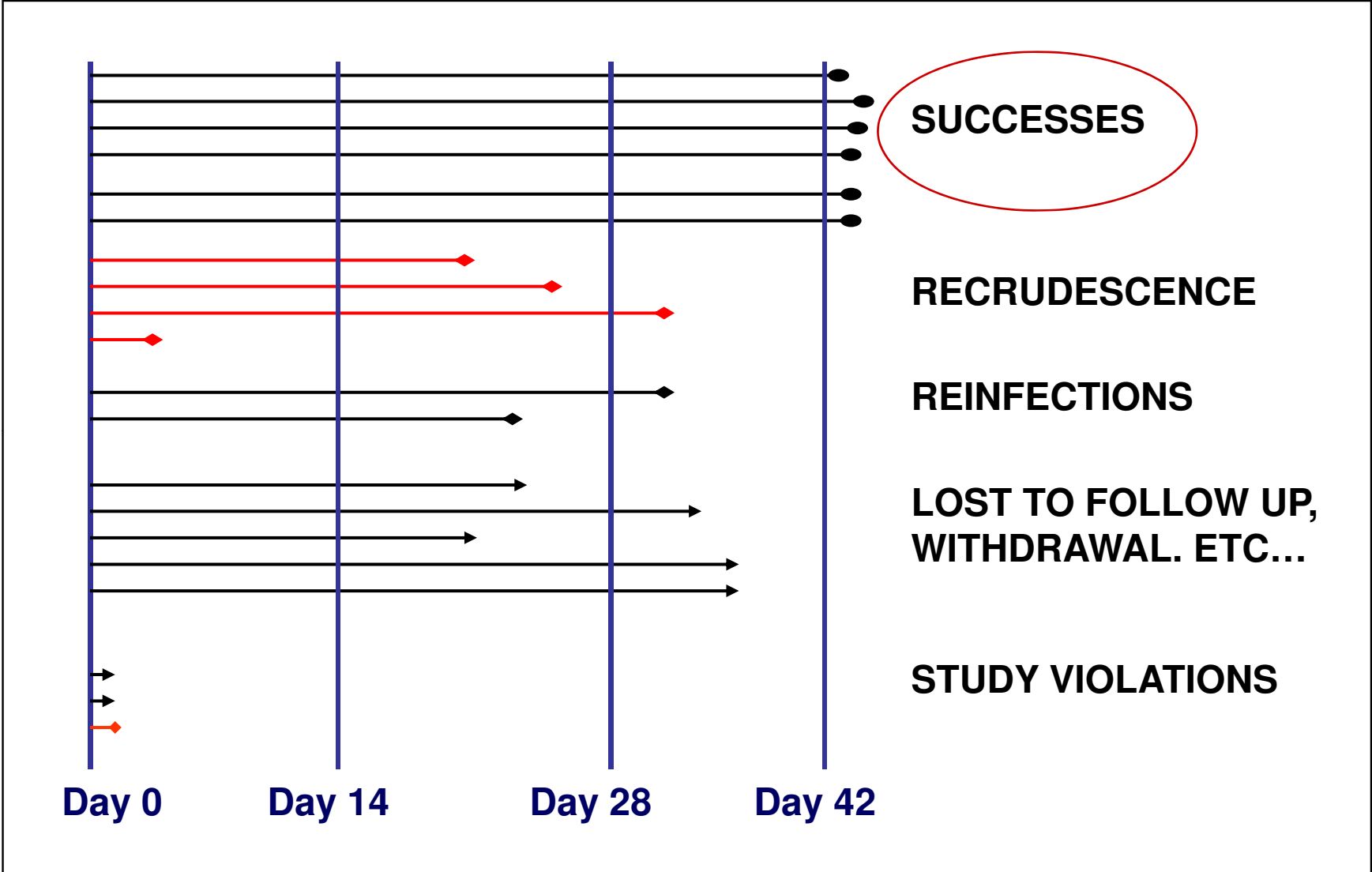
- **TIMELY EVIDENCE ON DRUG EFFICACY**
- **TOOLS FOR ANALYSIS AND OUTPUT  
INCENTIVES FOR PARTICIPATION**
- **REGIONAL OUTPUT/ANALYSIS OF DATA**
- **IMPROVED COMMUNICATION  
OF DRUG EFFICACY TO POLICY MAKERS**

# IMPLEMENTATION CHALLENGES

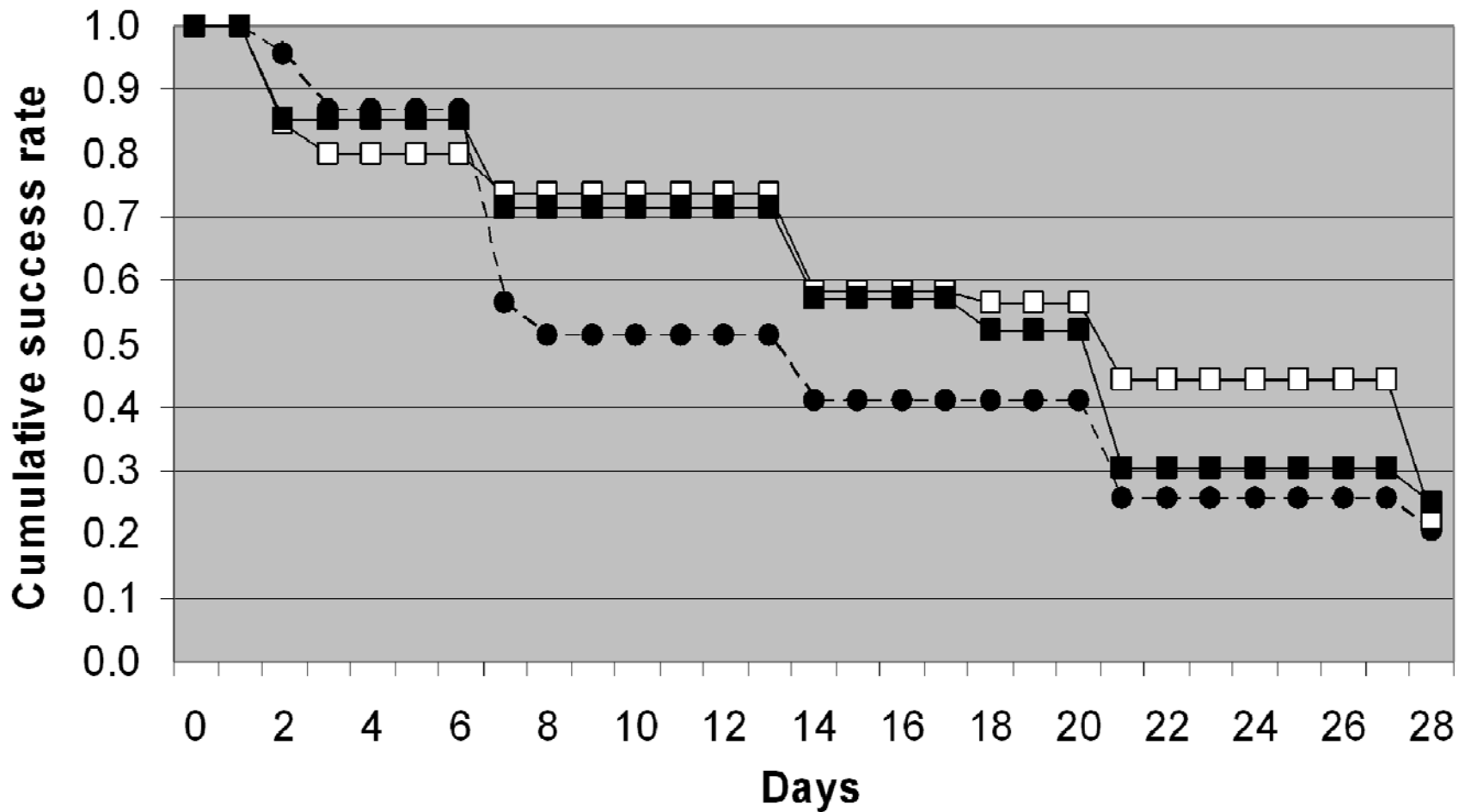
- **Integration with WHO**
- **Coordination with**
  - **Other groups engaged in malaria surveillance**
  - **MMV**
  - **Networks/regional data centers**
- **Adaptation to local/regional needs**
- **Establishing relations with MoHs**
- **Sustainable funding**



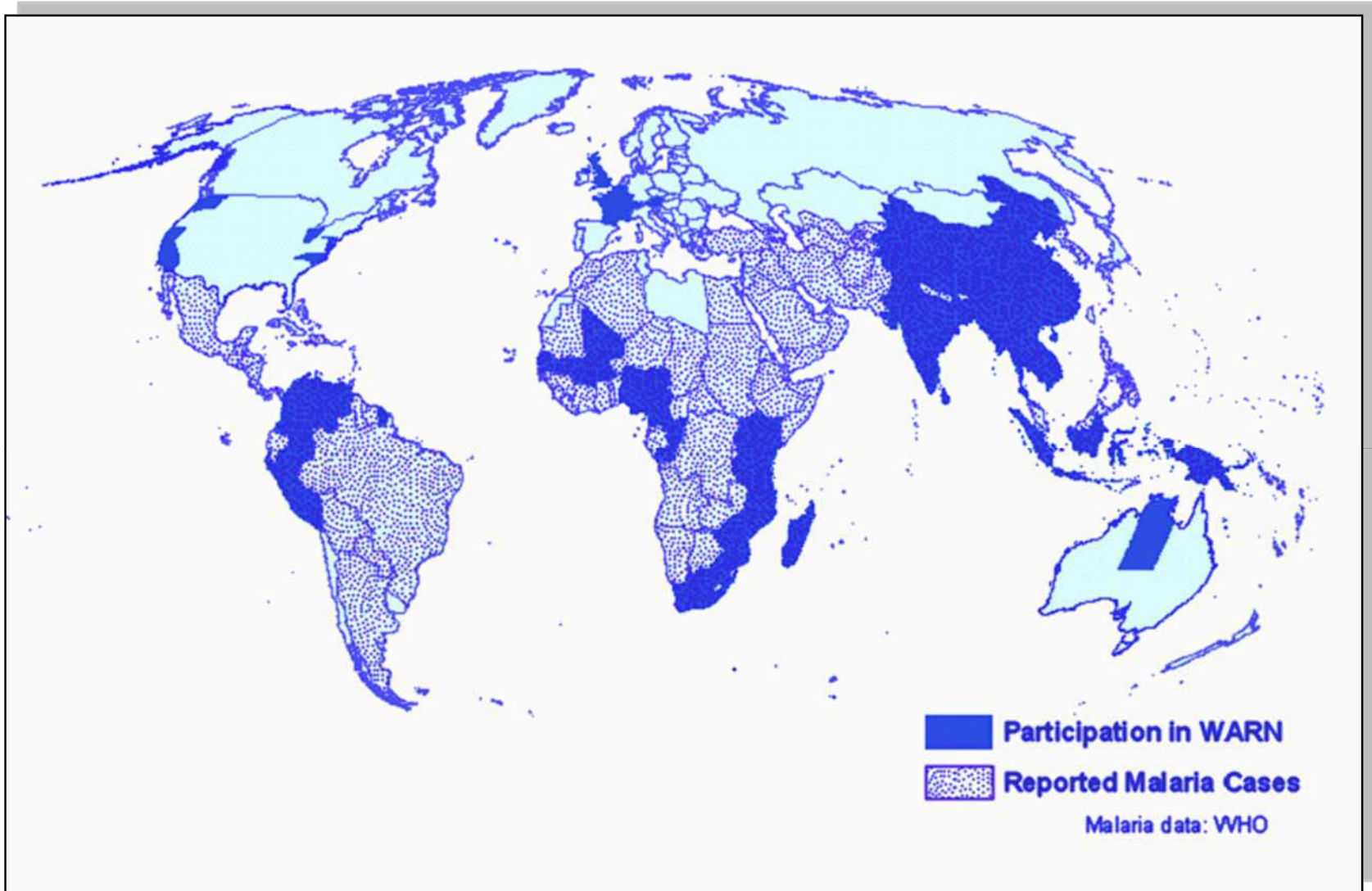
# SIMPLE ANALYSIS OF TREATMENT OUTCOME



# SURVIVAL ANALYSIS OF INDIVIDUAL PATIENT DATA







## **...BUT NEW COMBINATIONS ARE IN USE OR IN TRIALS**

- **ARTESUNATE-MEFLOQUINE**
- **ARTEMETHER-LUMEFANTRINE**
- **ARTESUNATE-AMODIAQUINE**
- **DIHYDROARTEMISININ-PIPERAQUINE**
- **ARTESUNATE- SULFADOXINE-PYRIMETHAMINE**

# PHARMACOLOGICAL ASSESSMENT

[DRUG] ADEQUATE?

NO

YES

NOT  
RESISTANCE

IN VITRO SUSCEPTIBILITY  
OF ISOLATE?

HIGHER THAN  
STANDARD?

NO

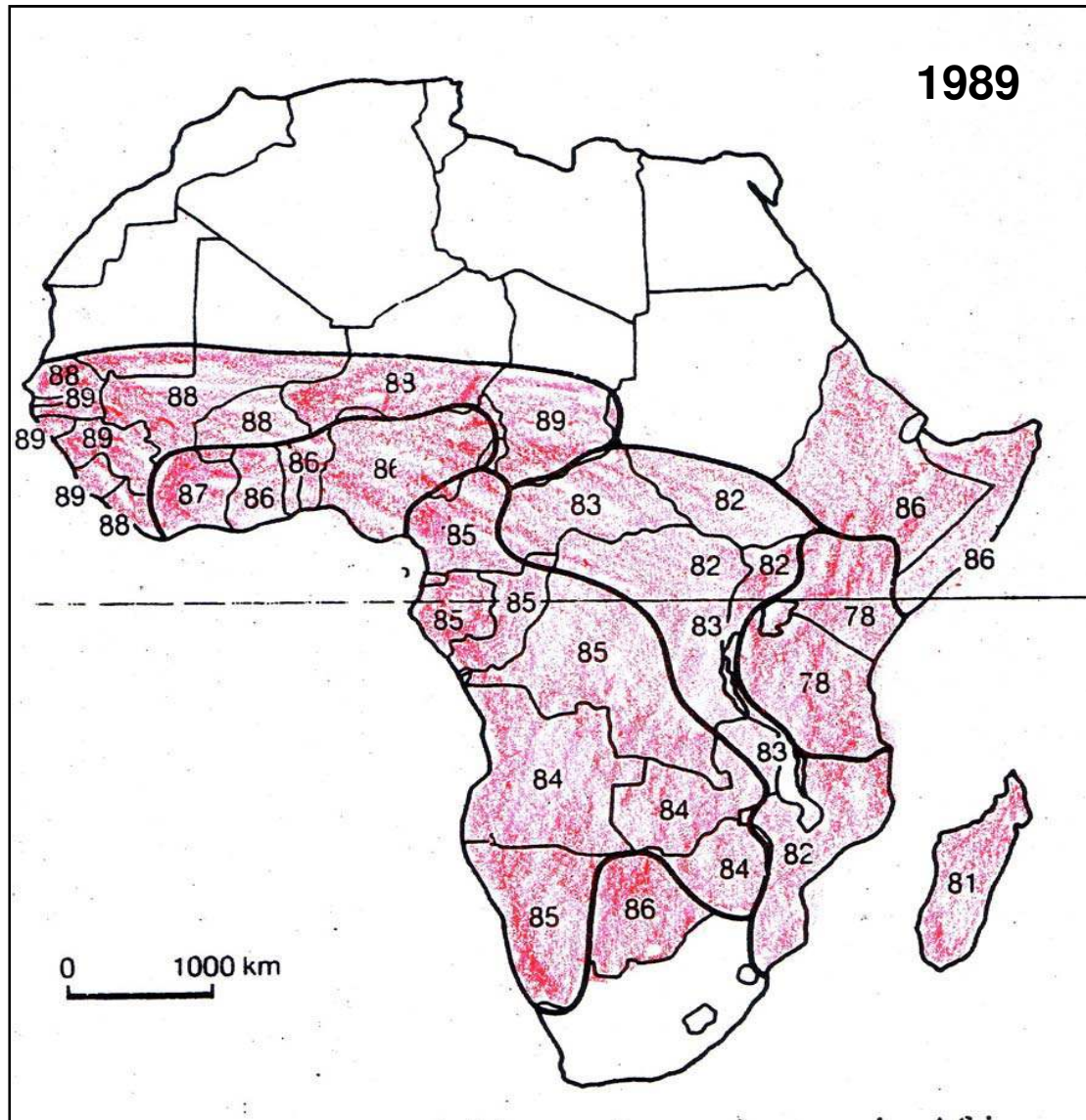
YES

NOT  
RESISTANCE

GENETIC ANALYSIS  
OF PARASITE

MARKERS  
OF DRUG  
RESISTANCE?

# FIRST REPORTS OF CHLOROQUINE RESISTANCE IN AFRICA



**HUMAN  
MIGRATION  
IS KEY  
TO  
RESISTANCE  
SPREAD**

**ADAPTED FROM  
CHARMOT ET AL, 1991**