World Health Organization

REGIONAL OFFICE FOR Africa

Antimicrobial Resistance in the WHO African region: Malaria resistance

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Malaria and its burden

- Malaria: life threatening parasitic disease
- Four types of human parasites: *Plasmodium falciparum, P. malariae, P ovale and P. vivax*
- P. falciparum: most deadly type of infection, most common in sub-Saharan Africa
- 2012: 207 million cases of malaria; estimated 627 000 deaths
- Most deaths occur among children living in Africa where a child dies every minute from malaria

Malaria control

Malaria control is based on the following main strategies:

- Early diagnosis (Rapid diagnostic test, microscopy)
- Effective treatment: cornerstone of malaria control. Appropriate selection of country first- and second-line antimalarial medicines is based entirely on the efficacy of the medicines against the malaria parasite
- Prevention: Insecticide-treated bednets (ITNs) / Long-lasting ITNs (LLINs); Indoor Residual Spraying; Intermittent Preventive Treatment in pregnancy (IPTp) and children (IPTc); SMC
- Surveillance and M & E: Routine HMIS, Malaria surveillance and response systems; Household surveys

Malaria medicines

BOX 1. PRINCIPLE AVAILABLE ANTIMALARIAL DRUGS

Chemical family	Drugs
4-Aminoquinolines	Chloroquine, amodiaquine, piperaquine
Amino-alcohols	Quinine, quinidine, mefloquine, halofantrine, lumefantrine
Sulfonamides and sulfones	Sulfadoxine, sulfalene, dapsone
Biguanides	Proguanil, chlorproguanil
Diaminopyrimidine	Pyrimethamine
8-Aminoquinoline	Primaquine
Sesquiterpene lactones	Artemisinin, arteether, artemether, artesunate, dihydroartemisinin
Naphthoquinone	Atovaquone
Antibiotics	Azythromycin, clindamycin, doxycycline, tetracycline

Malaria resistance

- Antimalarial Drug resistance: the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject (WHO, 1967)

- Drug resistance results in a delay in or failure to clear asexual parasites from the blood, which allows production of the gametocytes that are responsible for transmission of the resistant genotype

- Plasmodium resistance to antimalarial medicines is one of the major obstacles in the fight against Malaria (WHO, 2010)

Malaria resistance

- Drug resistance is complicated by cross-resistance, which can occur among drugs that belong to the same chemical family or which have similar modes of action
- Multidrug resistance of P. falciparum is seen when the parasite is resistant to more than two operational antimalarial compounds of different chemical classes and modes of action
- Treatment failure: Inability to clear malarial parasitaemia or resolve clinical symptoms despite administration of an antimalarial medicine

Resistance is the main cause of treatment failure and consequently of the aggravation of clinical malaria and aneamia, contributing to increase malaria morbidity and mortality

Treatment failure

Treatment failure is not, however, always due to drug resistance, and many factors can contribute, mainly by reducing drug concentrations:

- Incorrect dosage,
- Poor patient compliance in respect of either dose or duration of treatment
- Poor drug quality and drug interactions
- Individual variations in pharmacokinetics (rapid elimination, poor biotransformation of prodrugs)

Malaria resistance

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The rise of antimalarial drug resistance has changed the global epidemiology of malaria

Malaria resistance effects

BOX 2. EFFECTS OF ANTIMALARIAL DRUG RESISTANCE ON GLOBAL MALARIA CONTROL	
Disease burden	• The appearance of chloroquine resistance in Africa led to an increase in hospital admissions (Zucker et al., 1996). • Increasing mortality trends were found at community level (Trape et al., 1998; Korenromp et al., 2003). • Ineffective treatment causes anaemia and low birth weight (Björkman, 2002) and renders the health of children and adults infected with *P. falciparum* or *P. vivax* more fragile (Tjitra et al., 2008). • Resistance to antimalarial drugs was implicated, at least partially, in malaria epidemics (Warsame et al., 1990). • Resistance to antimalarial drugs is associated with increased transmission (Price & Nosten, 2001).
Economic cost	• Resistance to antimalarial drugs has increased the global cost of controlling the disease, including the cost of new drug development (Phillips & Phillips-Howard, 1996). • Therapeutic failure requires consultation at a health facility for further diagnosis and treatment, resulting in loss of working days for adults, absence from school for children and increased cost to the health system (Talisuna, Bloland & D'Alessandro, 2004).
Changes to distribution of malaria species	• The proportion of *P. falciparum* malaria has changed, such as an increase with respect to *P. vivax* (Dash et al., 2008).
Access to high-quality treatment	• Ineffective treatment in the public sector due to resistance could lead to greater reliance of patients on the unregulated private sector, which in turn could increase the use of monotherapies or substandard and counterfeit medicines and increase the risk for drug resistance.

Emergence of malaria resistance

Two phases in development of resistance:

- Initial genetic event produces a resistant mutant (de novo mutation); the event is gene mutations or changes in the number of copies of genes. The new genetic trait gives the parasite a survival advantage against the drug.
- Selection of the resistant parasites which begin to multiply, eventually resulting in a parasite population that is no longer susceptible to treatment, drug pressure-dependent.

Genetic events that confer antimalarial drug resistance are:

Spontaneous, Rare, Random, Independently of the drug

Resistance development factors

BOX 3. FACTORS THAT INFLUENCE THE DEVELOPMENT OF ANTIMALARIAL DRUG RESISTANCE

- the intrinsic frequency with which the genetic changes occur;
- the degree of resistance conferred by the genetic change;
- the 'fitness cost' of the resistance mechanism;
- the proportion of all transmissible infectious agents exposed to the drug (selection pressure);
- the number of parasites exposed to the drug;
- the concentrations of drug to which the parasites are exposed;
- the pharmacokinetics and pharmacodynamics of the antimalarial medicine;
- individual (dosing, duration, adherence) and community (quality, availability, distribution) patterns of drug use;
- the immunity profile of the community and the individual;
- the simultaneous presence of other antimalarial drugs or substances in the blood to which the parasite is not resistant; and
- the transmission intensity.

Studying malaria resistance

In vivo tests:

Based on the observation of parasite response in the patient to a fixed dose of a drug within the limits of tolerability (Wernsdorfer, 1988).

Advantages: - direct observation of drug efficacy;

- easy to perform

Weaknesses: - subject's immunity contribution unknown

- Treatment failure doesn't necessarily means drug resistance

Studying malaria resistance

In vitro tests:

Monitor drug resistance by measuring the intrinsic sensitivity of P. falciparum parasites to antimalarial drugs.

In culture, parasites are exposed to a precise concentration of drug and observed for inhibition of maturation into schizonts.

Techniques derived from the WHO schizont maturation assay and the isotopic microtest (Desjardins et al., 1979)

Advantages: - Out of immunity influence;

- Complementary of In vivo tests

Weaknesses: - Complex, costly

Studying malaria resistance

Molecular markers :

Characterization of the molecular markers of drug resistance is an important aspect of understanding resistance to antimalarial treatment.

Needs the genetic changes identified and associated with resistance

Advantages: - Practical;

Weaknesses: - Not all genes involved or potentially involved in P. falciparum antimalarial drug resistance have been identified

- Not yet for all usual antimalarial drugs

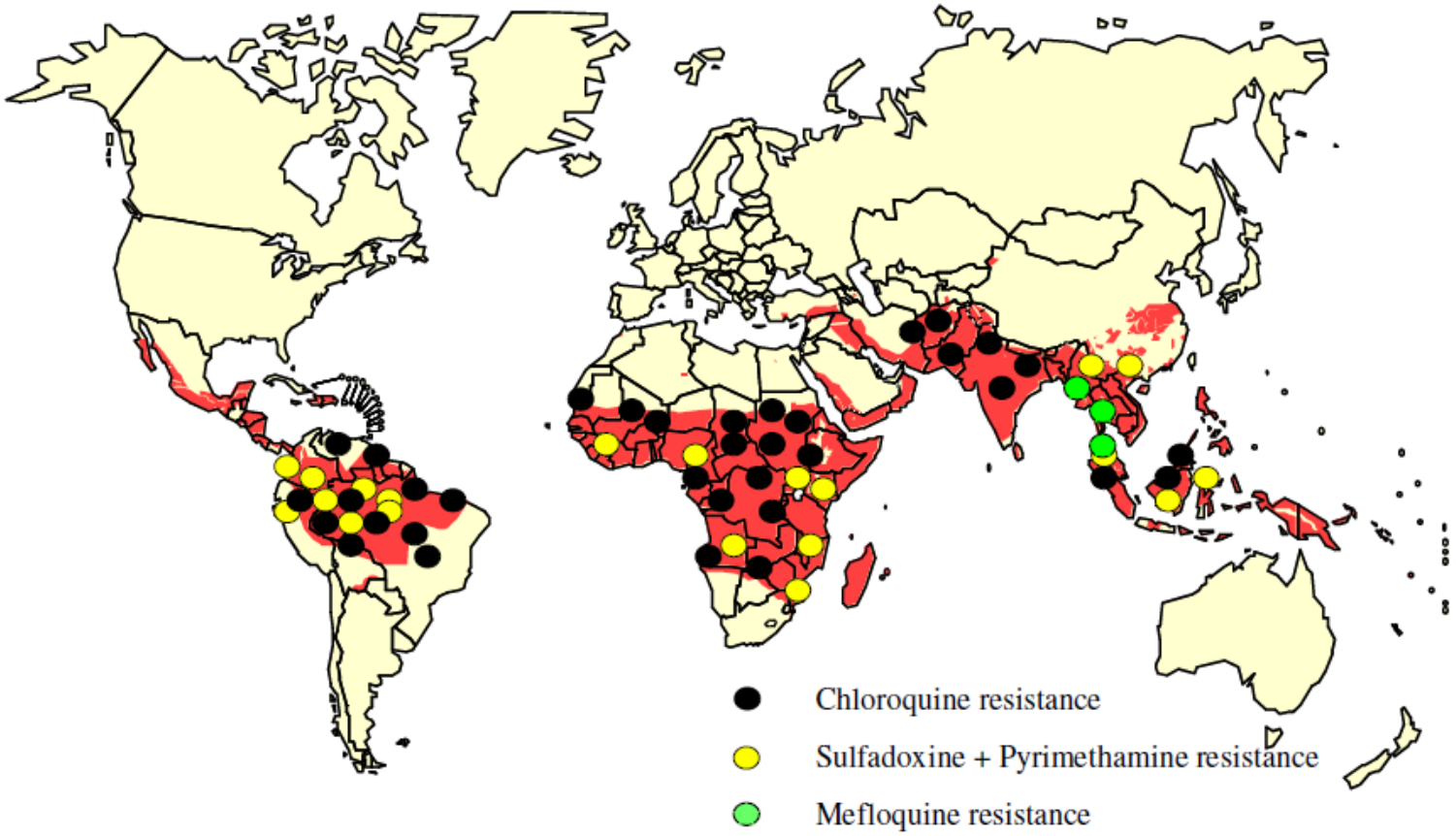
Studying malaria resistance

Molecular markers :

A limited number of genes involved or potentially involved in P. falciparum antimalarial drug resistance have been identified:

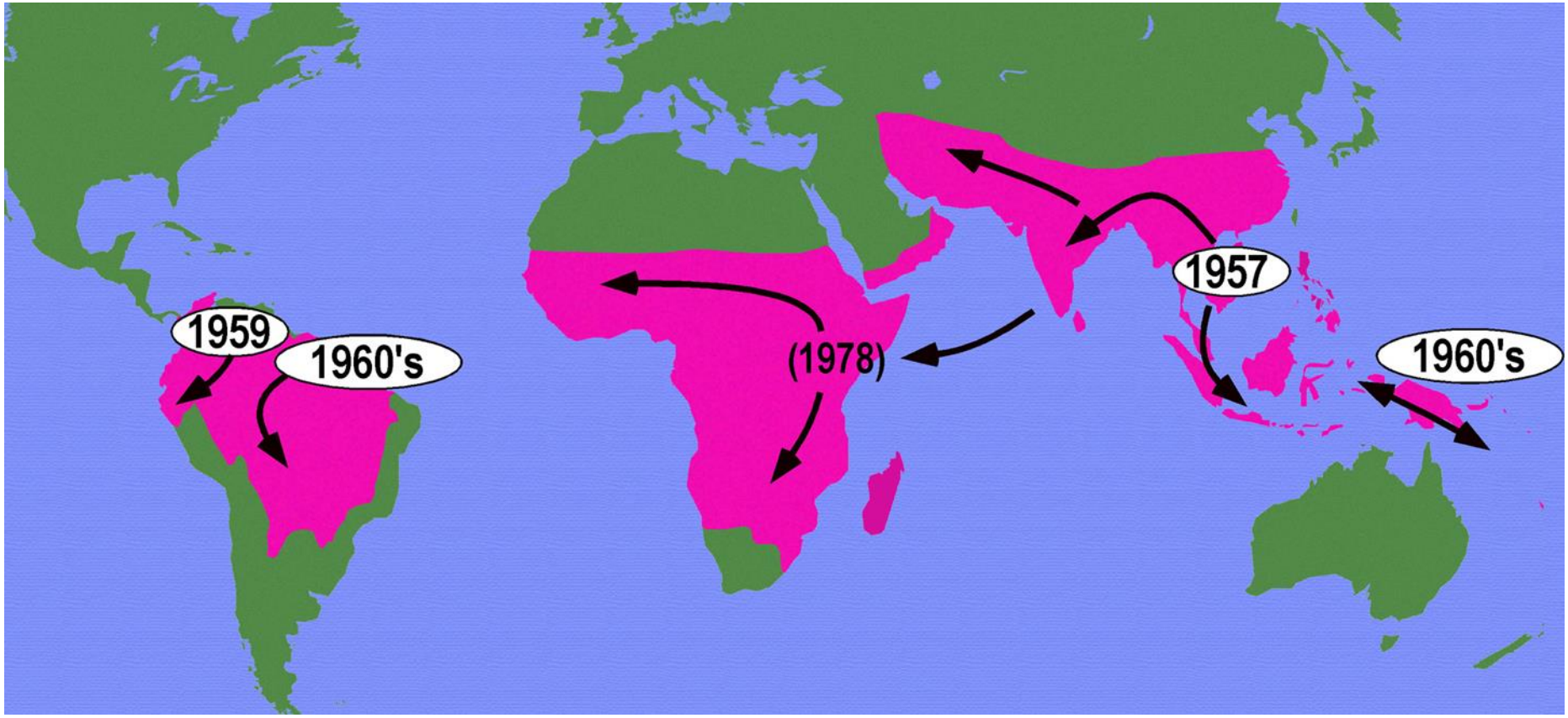
- Dihydrofolate reductase (Pfdhfr), (Pyrimethamine and cycloguanil)
- Dihydropteroate synthase (Pfdhps), (Sulfadoxine)
- Chloroquine resistance transporter (Pfcrt), (Aminoquinolines)
- Multidrug resistance 1 protein (Pfmdr1), (Aminoquinolines)
- Na+/H+ exchanger (Pfnhe-1)
- Cytochrome b
- K13-propeller SNPs (Artemisinin)

Current malaria resistance status in Africa



Chloroquine

Chloroquine is ineffective on P. falciparum in almost all malaria endemic countries.



Quinine

- Quinine efficacy reduction was first observed at the Thai-Cambodian border at the mid-1960s
- Quinine is still active in Africa
- It is however less and less used because of ACTs better efficacy and rapid action
- Many countries still have Quinine as reference medicine for severe cases

Sulfadoxine-Pyrimethamine

- Resistance to Sulfadoxine-Pyrimethamine (SP) was first described from the Thai-Cambodian border at the 1960s
- SP is ineffective in South-East Asia and the Amazon Basin for several years
- In Africa, SP resistance was detected in the late-1980s
- It is ineffective in some African regions (Southern and Eastern) and still effective in others (Western)
- SP is now reserved to prevention (IPT) in pregnant women, infancy and childhood (SMC) and treatment only when associated with Artemisinin derivatives.

ACTs resistance

Definition:

The working definition of partial artemisinin resistance was developed based on observations from routine therapeutic efficacy studies of ACTs, clinical trials of artesunate monotherapy, and K13 sequencing.

Suspected endemic artemisinin resistance is defined as:

≥ 5% of patients carrying K13 resistance-associated mutations; or

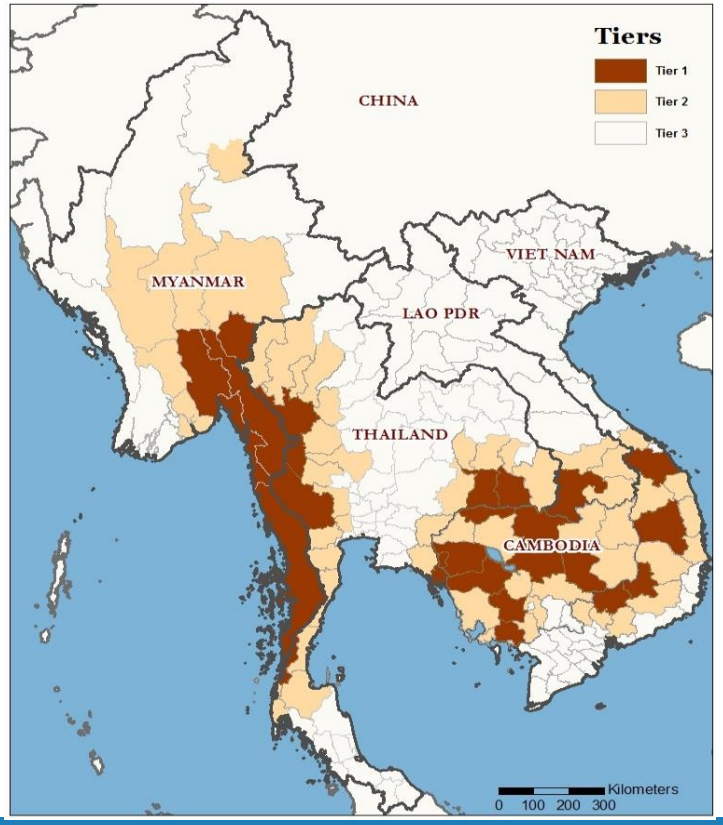
≥ 10% of patients with persistent parasitemia by microscopy on day 3 after treatment with ACT or artesunate monotherapy; or

≥ 10% of patients with a parasite clearance half-life of ≥ 5 hours after treatment with ACT or artesunate monotherapy.

ACTs resistance

Confirmed endemic artemisinin resistance is defined as:

≥ 5% of patients carrying K13 resistance-associated mutations, all of whom have been found, after treatment with ACT or artesunate monotherapy, to have either persistent parasitaemia by microscopy on day 3, or a parasite clearance half-life of ≥ 5 hours.



P. falciparum resistance to artemisinins has not been documented outside of the Greater Mekong subregion

Combatting Malaria AMR

Strategies to mitigate AMR

1. Avoid emergence of drug resistance

- **Halt the manufacture, marketing and use of oral artemisinin monotherapies**

To date All the malaria endemic countries have withdrawn Artemisinin monotherapies from their therapeutic arsenal, but nine countries still allow such marketing.

- **Improve access to quality diagnosis and combination medicines**

Use of RDTs, microscopy, ACTs, Strengthening health systems and services

- **Reduce malaria transmission**

Combine use of vector control strategies: ITNs, LLINs, IRS, Environment

Combatting Malaria AMR

Strategies to mitigate AMR

1. **Avoid emergence of drug resistance**

2. **Contain the spread of drug resistance**

- **Remove drug pressure**

Implementing antimalarial drugs quality control at national or sub-regional levels, Fighting Fake drugs manufacture, traffic and use, training clinicians and sensitizing communities on rational use of medicines, technical leadership and support for containment and elimination of artemisinin resistance

- **Eliminate malaria from areas with resistant parasites**

Real efforts at all levels (countries, organisations, communities) should be done towards Malaria elimination

Combatting Malaria AMR

Strategies to mitigate AMR

1. **Avoid emergence of drug resistance**
2. **Contain the spread of drug resistance**
3. **Monitor drug efficacy**
   - **Routine surveillance of therapeutic efficacy**

Multiply at national level used antimalarial drugs therapeutic efficacy studies, strengthen networks for information sharing, improve collaboration

   - **Develop new tools for early detection of drug resistance**

Combatting Malaria AMR

Strategies to mitigate AMR

1. Avoid emergence of drug resistance
2. Contain the spread of drug resistance
3. Monitor drug efficacy
4. Develop new medicines

- **Continue research to develop new alternative medicines to artemisinins,**

Increase research and collaboration between research and control programme

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THANK YOU