Drug Resistance Surveillance and Containment

Antimalarial Drug Resistance

Guidelines for Surveillance and Containment

World Health Organization

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Implementing antimalarial drug resistance surveillance and containment

An outline for national programmes [1]

Background

The first round of Global Fund grants reflects a strong commitment to a comprehensive approach to fighting HIV/AIDS, tuberculosis (TB) and malaria. Most of the approved grants include components for improved prevention and treatment. Of the 10 countries that will receive funds to combat malaria, 8 have grant proposals that are specifically related to drugs. The long-term success of the Fund will be judged not only by the products and anti-infective drugs that are made available to countries, but also by assurance that the widespread distribution of anti-infective drugs does not accelerate the evolution of antimicrobial resistance. Any accelerated development of resistance to one or more antimicrobials as a consequence of their inappropriate use is an obstacle to achieving disease control and clearly undermines the impact and cost-effectiveness of programmes to control AIDS, TB and malaria. Appropriate use of drugs must therefore be ensured.

To sustain the effectiveness of infectious diseases prevention and control programmes, WHO recommends that countries intending to increase access to treatment programmes for HIV, TB and malaria through GFATM also concurrently introduce or strengthen systems for the surveillance and containment of drug resistance. The WHO Global Strategy for Containment of Antimicrobial Resistance, issued in 2001, provides a six-point framework for doing so[1]. The framework is described below as it pertains to malaria prevention and control.

1. Reduce the disease burden and spread of infection

Measures that reduce the incidence of malaria decrease morbidity and mortality and can help prevent, or at least delay, the emergence of resistance. Reduced transmission is the best way to reduce drug use and thus lessen the opportunities for drug resistance to emerge. WHO advocates three strategies for reducing transmission.

– **Early and effective treatment**

Ensure that effective antimalarial drug policies are in place. Within countries, national drug policies must be regularly updated by the ministry of health based on results from a monitoring system set up specifically to track drug resistance. If the system detects a rate of treatment failure exceeding 25%, the national malaria programme should change its standard first- and second-line drugs. A treatment failure of 5% to 14% signals an alert phase; a failure rate of 15% to 24% signals the need for action.

[1] A working document prepared by WHO Departments:

- Communicable Disease Surveillance and Response (EPH/CSR/CDS): http://www.who.int/emc/
- Roll Back Malaria (RBM/CDS): http://www.rbm.who.int/
- Essential Drugs and Medicines Policy (PAR/EDM/HTP): http://who.int/medicines/

Base antimalaria treatment on combination therapy. The use of combination therapy is now standard practice for the management of both HIV and tuberculosis. WHO currently recommends combination therapy, especially with artemisinin derivatives, as a measure to improve treatment efficacy, delay the emergence of drug resistance, and reduce the prevalence of gametocyte carriage which could, in turn, reduce transmission[3, 4].

Implement Intermittent Preventive Treatment in pregnancy. In areas of high transmission, introduction of intermittent preventive treatment (IPT) during the second and third trimester of pregnancy as an effective way to reduce anaemia as well as parasite carriage in pregnant women. It also reduces low birth weight in newborns. WHO recommends that IPT be delivered in the context of routine services for antenatal care.

Implement community based management of malaria. A new home-based approach to treatment, which trains community members to diagnose malaria and distribute drugs within the neighbourhood, circumvents the problem of poor access to health services in remote areas. The approach is recommended to ensure that children under the age of 5 – the group most susceptible to high mortality – receive treatment within 24 hours following the onset of symptoms[5].

- **Improved coverage with insecticide treated bednets**
  Insecticide-treated materials are a safe and effective measure for reducing malaria morbidity and mortality in a range of environments throughout the African and Asian Regions [6,7].

- **Vector control**
  Integrated vector control, including indoor residual spraying, continues to play an important role in certain epidemiological settings and is of particular importance for the prevention and control of epidemics [8].

2. Improve access to appropriate antimalarials

Drug resistance may arise when an erratic drug supply forces the interruption of treatment. Several measures can help improve the drug supply.

- **Affordable drug prices**
  Medicines for the treatment of malaria must be affordable both for government (for use in the public health sector) and for consumers who may need to purchase drugs from public markets or private sector sources.

- **Adequate supply chain**
  Countries must ensure that the supply chain of drugs is sufficiently well-managed to avoid drug stock-out at all levels of the health system [9].

3. Improve the use of antimalarials

Inconsistent, partial or incorrect treatment contributes to the development of drug resistance.

– **Improve diagnosis**
When drug resistance to inexpensive first-line drugs emerges, deployment of more expensive drug combinations increases costs considerably. A more rational approach is to reduce the indiscriminate use of antimalarials, based on a presumed diagnosis of malaria, by increasing the capacity for precise diagnosis. This improvement requires investment in high quality microscopy and use of more specific diagnostic techniques, such as the rapid diagnostic dipstick[10].

– **Improve prescribing practices**

All health workers, prescribers, and dispensers should be trained to appreciate the importance of appropriate antimalarial use and given the guidance to do so. Drugs should be dispensed together with information to patients about the importance of treatment compliance.

– **Educate the public**
Public health campaigns should be used to communicate information about the appropriate use of antimalarials, personal and community measures to prevent infection, and the importance of seeking prompt health care[11, 12].

– **Establish national treatment guidelines and algorithms**
In line with national treatment policy, malaria control programmes should establish and maintain up-to-date national guidelines and algorithms for standardized malaria treatment and facilitate their implementation [13].

– **Develop appropriate pre-packaging of antimalarial products**
Pre-packaging greatly improves patient compliance. In addition, many of the newer combination therapies for malaria are not available in fixed-dose formulation. In such cases, combination treatments should be co-packaged for use in both the public and private sectors[14].

4. Strengthening the surveillance capacity of health systems

– **Institute the WHO standard system for monitoring antimalarial drug resistance**
Countries should develop, at the national level, a network of sentinel sites for monitoring the efficacy of first- and second-line drugs. They should also institute the WHO standard system for monitoring antimalarial drug resistance, which is described in detail in the attached appendix. In addition, the national malaria control programme must ensure that data flow directly to the ministry of health for use in updating drug policies. The development of regional networks facilitates data

sharing and provides an alert to changes in drug policies among neighbouring countries[15, 16].

- **Establish systems for monitoring antimalarial use at multiple levels**
  Evidence suggests a link between THE use of antimalarials in communities and the development of resistance. Monitoring of drug use needs to extend to communities as well as to dispensaries, district hospitals, and reference hospitals to ensure that drugs are being used only when indicated[17].

5. Enforce regulations and legislation

Legislation and regulations governing drug quality must be enforced for all drugs, including antimalarials. Such enforcement does much to ensure that good quality drugs are available within countries.

- **Legislation**
  Countries need to have adequate legislation to ensure that antimalarial drugs on the market are of the desired quality standards [18].

- **Quality control**
  Countries are encouraged to develop national facilities of quality control to assess and monitor the quality antimalarial drugs on the market[19].

6. Encourage research

It is in the best interest of endemic countries to encourage clinical trials of new antimalarials, combination therapies, and vaccines. Such trials should follow international guidelines for good clinical practice and international ethical guidelines for biomedical research involving human subjects. Approved products must be produced in compliance with internationally accepted good manufacturing practices.

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Selected resource materials available from WHO

Drug policy

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5. Community involvement in rolling back malaria. WHO/CDS/RBM/2002.42

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Appendix

Monitoring antimalarial drug resistance – a summary[2]

The importance of drug resistance surveillance in the fight against malaria

Antimalarial drug resistance is a major public health problem, which hinders the control of malaria. Faced with this growing burden, the establishment of a system for international surveillance is urgently needed to allow better containment. In view of the creation of Global Fund to Fight AIDS, TB, and malaria (GFATM), the World Health Organization recommends that countries aiming to increase access to treatment programmes for these diseases should simultaneously implement new, or strengthen existing, drug resistance surveillance systems.

Guidelines for surveillance

In 1996, WHO developed a new protocol for assessing antimalarial drug resistance for high transmission areas. This protocol has recently been updated and the protocol for low to moderate transmission areas has been validated. The fundamental design of these protocols for surveillance is intended to provide essential information for monitoring the therapeutic efficacy of a range of antimalarial drugs against uncomplicated falciparum malaria as needed for programmatic purposes. It is recognized that these methods cannot, nor should be expected to, provide all possible scientific information necessary for understanding drug efficacy and resistance in a given environment. Rather, they are intended to ensure a minimal evidence base from which ministries of health can develop informed treatment policies and guidelines. The use of a standardized protocol will allow the comparison of the results in country and among countries in the same region.

Organization and survey outline

Surveying the prevalence of antimalarial drug resistance, as for resistance to anti-tuberculosis and antiretroviral drugs, involves four major operational issues:

1. **Implementation and management of the surveillance programme**

÷! National Coordination team

At the initial stage, a national core group of experts (national malaria control programme, ministry of health, universities, institutes of research, national reference laboratory) should be established to coordinate all activities. The coordinating team requires strong official backing by the authority in charge of health services. The coordination team is responsible for the preparation of the survey, development and implementation of the protocol, supervision and quality assurance during the survey and the final collection, analysis and reporting of results to the National Authorities responsible for drug policy.

[2] A working document prepared by Communicable Diseases, Surveillance and Response (EPH/CSR/CDS): http://www.who.int/emc/

2. Epidemiology

÷! Sentinel site surveillance system

Malaria control programmes should establish sentinel site surveillance to monitor antimalarial drug efficacy. A system of well-selected sentinel sites will enable the collection of consistent longitudinal data and documentation of trends. The minimal requirements for establishing a sentinel site are the availability of trained and motivated clinical personnel and microscopists, with a laboratory for blood film examination. This can be at the periphery (community-based), or based at a health facility at district level. Patients attending hospitals in urban settings may have more complex clinical presentations, are more likely to have been referred because of previous drug failures and may be more difficult to follow up. Thus, whenever possible, monitoring should be done at the periphery.

Although no definitive scientific advice can be given regarding the number of sites needed, experience suggests that between four and eight sites achieve a balance between representativeness and practicality. Programmes should increase or decrease this number as needed to account for geographic size, population distribution and density, differing malaria epidemiology or ecology and other factors deemed important to the programme. When making such decisions, emphasis must be placed on the need for a "manageable" number of sites to ensure proper monitoring and supervision.

Again, based on experience rather than definitive science, it is recommended that assessments be conducted at least once every 24 months. For comparability, assessments should be conducted during the same time of year. Most programmes conducting sentinel site surveillance of therapeutic efficacy find it easiest to alternate test sites (e.g. four sites tested per year with each site being assessed every other year).

The following characteristics should be considered in the selection of sentinel sites:

- population density;
- accessibility to and feasibility of supervision;
- epidemiology of malaria, especially intensity and seasonality of transmission;
- population mobility and migration (especially in border areas);
- distribution of malaria treatment failures reported by health information system.

The sentinel sites should be selected to be representative of each major epidemiological strata into which the country can be divided.

Due to the importance of the private sector in drug procurement and distribution in many countries, and the heterogeneity of drug resistance, drug utilization and drug quality studies should be conducted, whenever feasible, in the areas selected for sentinel site monitoring.

÷! Sample size and sampling strategies

The use of classical statistical methods are recommended for determining sample size, based on an expected proportion of treatment failures, desired confidence level (95%) and precision (5% or 10%). In the case of an expected failure rate lower than 15% and in order to be representative, a minimum of 50 patients should be included.

3. Protocols for surveillance of therapeutic efficacy of antimalarial drugs

÷! Inclusion criteria

- Age: between 6 and 59 months, i.e. less than 5 years in areas of intense transmission and all patient over 6 months in for low transmission area.
- Absence of severe malnutrition
- Parasitemia: limits of parasite count for inclusion are 2 000–200 000/vl in areas of intense transmission, and 1 000–100 000/vl for low transmission area.
- Absence of general danger signs or signs of severe and complicated falciparum malaria according to definition given by WHO [Severe falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene, 2000, 94; supplement 1].
- Presence of auxiliary temperature × 37.5 °C ,or history of fever for low to moderate transmission areas
- Absence of febrile conditions caused by diseases other than malaria
- Ability to comply with the stipulated follow-up visits, and easy access to health facility
- Informed consent of parent or guardian

÷! Recommended duration of assessment

Areas of intense transmission. The recommended minimum length of follow-up is 14 days. Studies of longer duration in areas of intense transmission must be accompanied by molecular assessment (e.g. PCR) to assist in distinguishing recrudescence from re-infection. Based on several trials and experiences, it is obvious that a 14-day follow-up underestimates the true rate of failures. The most suitable duration of follow-up for chloroquine, amodiaquine, sulfadoxine-pyrimethamine, mefloquine and artemether-lumefantrine should be 28, 28, 42, 63 and 42 days respectively.

Areas of low to moderate transmission. The recommended length of follow-up for assessments conducted in areas of low to moderate transmission is 28 days. However, in some circumstances, assessments of shorter duration (14 days min.) can still provide useful results and may be utilized. Molecular assessment to assist in distinguishing recrudescence from re-infection is recommended, but not strictly essential, for studies of more than 14 days duration.

Monitoring of antimalarial drug efficacy necessitates a clinical and a parasitological follow-up at Day 0, D1, D2, D3, D7 and D14 (D21 and D28 in low to moderate transmission areas).

÷! Drugs to be tested

The WHO protocol is designed to assess drug regimens given over periods not longer than 3 days, such as chloroquine, sulfadoxine-pyrimetmine or combination therapy including chloroquine/amodiaquine/sulphadoxine-pyrimethamine, or combination therapy with artemisinin derivative. This protocol is not designed for regimens such as quinine given for 7 days, combinations of quinine and tetracycline or doxycycline given over 7 days, or artemisinin derivatives given alone for 5 to 7 days.

Each national malaria control programme should monitor the first- and second-line drugs according to their national treatment guidelines. In addition, combination therapies should be monitored in order to obtain background information of new treatments.

4. Data management

÷! Classification of response to treatment: see annex

÷! Data analysis

The life-table method is the preferred method for analyzing data derived from these assessments of therapeutic efficacy. This method allows for inclusion of data from patients who are withdrawn or lost to follow-up without requiring that assumptions be made about ultimately unknown outcomes. This provides the essential benefits of intention-to-treat analysis with fewer of the intention-to-treat method's drawbacks. Although life-table analyses can be accomplished by hand, access to computer assistance will greatly increase ease of analysis and reduce calculation errors.

It is also recommended that a traditional "per protocol" method be used in parallel (the "per protocol" method removes all patients that cannot be evaluated [i.e. those withdrawn or loss to follow-up] from the denominator). It is highly recommended that results from both types of analyses be reported.

Computer-based applications have been developed by WHO to provide assistance in all aspects of data management and analysis. These applications are accessible from the WHO web site at (http://www.who.int/emc/amrmalaria.htm).

÷! Data interpretation and policy considerations

After validation of the data, the national coordination team should forward recommendations to the drug policy-makers for action. It is likely that results will differ between sites; some sites may identify a substantial deterioration in treatment efficacy while others continue to record an acceptable response to the same drug. The programme should consider how to respond to this eventuality: can specific treatment guidelines be targeted to affected areas without changing national policy or guidelines? How many sites need to show unacceptable treatment failures before national policy or treatment guidelines are altered?

Once a site demonstrates a high level of treatment failure with the existing first-line drug and national policy or treatment guidelines are not altered, is there a need to continue to evaluate that drug or site relationship in the future? At what level of treatment failure would this occur? Generally, the level of treatment failure currently recommended for changing drug policy in areas of intense transmission is 25 %, but countries should be in an alert phase between 5% to 14% of treatment failure and in an action period when the failure rate ranges between 15% and 24%.

Annex. Classification of response to treatment

INTENSE TRANSMISSION AREA		LOW TO MODERATE TRANSMISSION AREA
	Early Treatment Failure (ETF)	
ETF • Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitemia • Parasitaemia on Day 2 higher than Day 0 count irrespective of axillary temperature • Parasitemia on Day 3 with axillary temperature × 37.5 °C • Parasitemia on Day 3 × 25 % of count on Day 0		**ETF** • Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitemia; • Parasitaemia on Day 2 higher than Day 0 count irrespective of axillary temperature; • Parasitemia on Day 3 with axillary temperature × 37.5 °C; • Parasitemia on Day 3 × 25 % of count on Day 0.
	Late Treatment Failure (LTF)	
Late Clinical Failure • Development of danger signs or severe malaria after Day 3 in the presence of parasitemia, without previously meeting any of the criteria of early treatment failure • Presence of parasitemia and axillary temperature × 37.5°C on any day from Day 4 to Day 14, without previously meeting any of the criteria of early treatment failure		**Late Clinical Failure** • Development of danger signs or severe malaria after Day 3 in the presence of parasitemia, without previously meeting any of the criteria of early treatment failure • Presence of parasitemia and axillary temperature × 37.5 °C (or history of fever) on any day from Day 4 to Day 28, without previously meeting any of the criteria of early treatment failure
Late Parasitological Failure • Presence of parasitemia on Day 14 and axillary temperature < 37.5°C, without previously meeting any of the criteria of early treatment failure or late clinical failure		**Late Parasitological Failure** • Presence of parasitemia on any day from Day 7 to Day 28 and axillary temperature < 37.5 °C, without previously meeting any of the criteria of early treatment failure or late clinical failure
	Adequate Clinical and Parasitological Response (ACPR)	
ACPR • Absence of parasitemia on Day 14 irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late clinical failure or late parasitological failure.		**ACPR** • Absence of parasitemia on Day 28 irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late clinical failure or late parasitological failure.

Antimalarial drug resistance survey budget

		Number	Cost	Duration	TOTAL
A. Personnel (contracted services)*					
Principal investigator					
Clinician					
Lab technicien					
Driver					
	Subtotal				
B. Supplies					
Clinical					
Drugs					
Laboratory					
slides, reagents, etc.					
General					
Stationary, patient forms, etc.					
Fuel and maintenance of vehicle					
	Subtotal				
C. Meeting					
Meeting of Principal investigator, Head NRL, Technician, and other concerned parties.					
Transportation for participants					
	Subtotal				
D. Training					
Peripheral staff Per Diem					
National supervisor Per Diem					
Facilitator Per Diem					
Transportation for participants					
	Subtotal				
E. Equipment					
microscope per sentinel site					
other					
	Subtotal				
	TOTAL				

***Please note the first Antimalarial drug resistance survey in a country will be a capacity building excercise and therefore may require additional human resources. Drug resistance surveillance should be considered a routine activity of the National Malaria Programme and thus human resources should be allocated accordingly for this task for future surveillance activities.**

General Note: Excluding additional costs for equipment, training and meeting, most survey budgets should require about US$ 5,000 per sentinel site.

Toolkit for Monitoring Antimalarial Drug Resistance

Selected Resource Materials

Updated version: 28 August 2002

1. General: http://www.who.int/emc/amrmalaria.htm

2. Monitoring Antimalarial Drug Resistance. Report of a WHO Consultation. Geneva, Switzerland, 3–5 December 2001. WHO/CDS/CSR/EPH/2002.17-WHO/CDS/RBM/2002.39
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