

Implementing Antimicrobial Drug Resistance Surveillance and Containment for HIV, Tuberculosis and Malaria

An Outline for National Programmes

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Background

HIV/AIDS, tuberculosis (TB) and malaria account for approximately half of the infectious disease mortality worldwide. These three diseases cause over 300 million illnesses and more than 5 million deaths each year. In many settings, the morbidity and mortality for the 3 diseases are directly related to resource shortages for the purchase of otherwise available high-quality antimicrobial drugs or for the widespread implementation of effective preventive interventions. In response, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) was created. The purpose of the GFATM is to attract, manage and disburse resources through a public-private partnership to make a sustainable and significant contribution to the reduction of infections, illness and death, thereby mitigating the impact of HIV/AIDS, TB and malaria.¹

The long-term success of the GFATM will be enhanced not only by resources made available to countries but also by assurance that the increased distribution of antimicrobial drugs does not unduly accelerate the emergence of resistance to drugs used to treat HIV, TB and malaria. In general terms, antimicrobial resistance (AMR) is the expression of the ability of microorganisms to resist the actions of naturally occurring or synthetically produced compounds inimical to their survival. In the clinical context, AMR refers to a reduction in clinical efficacy so that the benefits of antimicrobial drug treatment for the individual are reduced, and this may be reflected by increased morbidity and mortality. In the public health context, AMR reduces the efficacy of standard drug treatments, which can result in increased disease burden (because the duration of infectiousness is prolonged) and increased costs (because of prolonged duration of treatment and the need for often more costly, more toxic second-line therapies).

The fact that increasing access to drugs for HIV, TB, and malaria might cause an increase in AMR should not be taken in any way as an excuse for not making every effort to make drugs available, but rather should serve as an argument for increasing access in such a way as to minimize the emergence and spread of AMR. The World Health Organization (WHO) recommends that countries intending to increase access to treatment programmes for HIV/AIDS, TB and malaria also concurrently introduce or strengthen systems for AMR surveillance and containment. Within its guidelines for country applications, the GFATM also strongly recommends that some portion of funds received is used to monitor and contain AMR in HIV, TB and malaria.

In September 2001, WHO issued a comprehensive strategy for AMR surveillance and containment for application at the country level.² The principles contained in the global strategy are applicable to HIV, TB and malaria, and have been endorsed and further developed by specific disease interest groups (e.g. the Stop TB Partnership).

Objectives

The purpose of this document is to assist countries to prepare GFATM applications that reflect an appropriate commitment to AMR surveillance and containment activities for HIV, TB and malaria, and that are consistent with the Global Strategy. The Global Strategy addresses AMR in general, but is particularly focused on resistance to antimicrobial drugs. Therefore, this document serves to define and describe the activities for AMR surveillance and aspects of containment stemming from and directly related to AMR surveillance in HIV, TB and malaria.

¹ <http://www.theglobalfund.org/en/>

² *WHO Global Strategy for Containment of Antimicrobial Resistance*. Geneva, World Health Organization, 2001 (WHO/CDS/CSR/DRS/2001.2)

It also proposes principles and guidelines for AMR surveillance, where the primary purpose is to provide an indication of the appropriateness of currently recommended standardized treatment regimens and the effectiveness of the containment activities. Surveys of drug use, quality and accessibility should also be conducted in areas selected for sentinel site monitoring, but guidelines for these activities are beyond the scope of this document.

Containment of antimicrobial resistance in HIV, TB and malaria

Containment of antimicrobial resistance is the continuous application of a package of interventions to slow the rate of emergence and spread of AMR and to limit its public health consequences. The interventions recommended in the Global Strategy produce effects that are believed, on the basis of evidence or consensus, to collectively influence positively the various factors that contribute to AMR. Those factors that influence the development of AMR range from the immediate and obvious to the remote and indirect, meaning that the practical application of AMR containment usually involves the prioritization of interventions, from those with the greatest impact and ease of application to those with less demonstrable benefits and/or difficulties in implementation.

The Global Strategy describes six broad areas for a national AMR containment framework:³

- reduce the disease burden and the spread of infection
- improve access to appropriate antimicrobial drugs
- improve the use of antimicrobial drugs
- enforce regulations and legislation
- encourage development of appropriate new drugs and vaccines (focused research)
- strengthen health systems and their resistance surveillance capacity.

These areas are also relevant for AMR containment for HIV, TB and malaria, and can be used to categorize the most appropriate interventions to be considered within a GFATM application. As described in greater detail in the Global Strategy, there are a number of settings where these interventions should be applied: among patients and the general community; among prescribers and dispensers; in hospitals; for national governments and health systems; for drug and vaccine development; and within pharmaceutical promotion.

The antimicrobial resistance containment and surveillance (ARCS) approach, a schematic representation of the Global Strategy (see Figure 1), highlights the fundamental premise of the framework: improving antimicrobial use is the priority action for AMR containment. Some of the more relevant interventions that can have a positive effect on antimicrobial use are shown in Figure 1, and these generally fall within one of the six broad areas shown above. These interventions should be considered for inclusion in any national AMR containment strategy and may be appropriate for funding by the GFATM. Further details of these broad areas and how they relate to HIV, TB and malaria are provided below.

³ WHO Global Strategy for the Containment of Antimicrobial Resistance: Executive Summary. Geneva, World Health Organization, 2011. (WHO/CDS/CSR/DRS/2001.2a)

Reducing the disease burden and the spread of infection

The interventions for drug resistance containment are not shown in Figure 1 according to the priority of their implementation. However, prevention of disease must be considered foremost for controlling AMR, since measures that reduce the incidence of disease will reduce the need to use antimicrobials and thus help to delay the emergence of AMR. There are many interventions to reduce disease burden, such as methods to prevent transmission, early and effective diagnosis, and improved access to appropriate treatment (see also Table 1). These interventions are within the range of activities detailed within GFATM applications but beyond the scope of this document.

Improving access to appropriate antimicrobials

Insecure financing and shortages of drugs are frequent in many settings. They hamper disease control, lead to incomplete or inappropriate therapy, and can fuel the emergence of AMR. To improve access, drugs must be affordable both for governments and for consumers who purchase drugs from either the public markets or private sector sources. Countries must ensure that drug delivery systems are sufficiently well managed to avoid drug stock-outs at all levels of the health system.

HIV/AIDS

Until recently, few people in countries with limited resources had access to HIV antiretroviral (ARV) drugs. With the creation of the UNAIDS Accelerating Access Initiative, the GFATM, the World Bank Multi-Sectoral AIDS Project (MAP), the WHO “3 by 5” global target, and other drug access initiatives, affordability of and access to ARV treatment will increase. Improved access to ARV drugs also requires expanding efforts for HIV counselling and testing, increasing access to ARV drugs earlier in the course of disease, and decreasing drug costs, usually by a mixed mechanism for price reduction combining negotiations and competition.

Tuberculosis

The Global Drug Facility, hosted by WHO and managed by the Stop TB Partnership, is a mechanism aimed at expanding access to high-quality first-line antituberculosis drugs and improving their availability within countries. Countries that apply to the Global Drug Facility must meet several requirements, including adherence to the DOTS strategy.⁴

Multidrug-resistant TB (MDR-TB), i.e. tuberculosis strains resistant to at least isoniazid and rifampicin, is a global problem that threatens TB control. The Green Light Committee provides a mechanism to increase access to, and rational use of, high-quality second-line antituberculosis drugs. Via a multi-faceted procurement strategy, concessional prices have been negotiated for quality assured drugs. Countries planning MDR-TB treatment projects (DOTS-Plus) apply to the Green Light Committee for procurement of these reduced-cost drugs.⁵

⁴ <http://www.stoptb.org/GDF>

⁵ <http://www.who.int/gtb/policyrd/dotsplus.htm>

Malaria

Community-based management of malaria is an approach that trains community members to diagnose malaria and administer drugs within the community. The aim is to circumvent the problem of poor access to health services in remote areas. Implementation on a large scale will become more difficult when it is necessary to use more expensive combination treatment. Efforts to identify best practices through operational research are currently being undertaken by WHO, Centers for Disease Control and Prevention (CDC), and other partners under the coordination of a working group on case management established by the Roll Back Malaria Partnership. Issues under consideration include identifying mechanisms to make the drugs affordable at the community level, engaging the private sector, and defining the role of laboratory-based diagnosis.

Improving the use of antimicrobials

The WHO Global Strategy defines appropriate use as the cost-effective use of antimicrobials that maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of AMR. Inconsistent, partial, or incorrect treatment does not achieve the desired therapeutic outcome, and contributes to the development of AMR.

Antimicrobial use is driven by disease burden and diagnosis, prescriber behaviour, consumer expectations, and drug system characteristics (see Figure 1). Interventions to improve drug use include:

- identifying measures to promote patients' adherence to treatment;
- improving disease diagnosis through the supply of diagnostic tools and clinical training to increase the rational use of antimicrobials;
- promoting combination treatments as appropriate treatment regimens, because they may help to contain AMR;
- providing information, education and communication for both prescribers (including those in the private sector) and consumers to ensure that policies and treatment guidelines are accepted and applied in practice;
- developing and enforcing legislation and regulation governing drug cost, availability, selection and quality;
- selecting antimicrobials on the basis of essential drug lists;
- developing, maintaining and facilitating use of national guidelines and algorithms for standardized treatment, based on international recommendations (see Table 1);
- monitoring drug use to inform drug use policy.

Focused research

Although research should not distract from disease control efforts and funding basic research is not the intention of the GFATM, operational research is vital to build the evidence base that dictates sound public health practice for AMR containment. Improved methods for the surveillance of drug use and resistance need development and testing, and the utility of resistance data as a measure of programme performance should be determined.

Surveillance for antimicrobial resistance in HIV, TB and malaria

The practice of AMR surveillance for HIV, TB and malaria differs considerably, because of differences in pathogen, disease and treatment characteristics. However, the first step toward instituting drug resistance surveillance is similar for the three diseases. A national coordination team (NCT) should be strongly endorsed and firmly established within the ministry of health's respective disease control programmes. The members should include at least an epidemiologist, a practising clinician, a laboratory expert, a person representing programmatic issues from the participating clinical site or sites, and, optionally, nationally recognized disease experts from universities or research institutes. The NCT should: conduct an AMR surveillance needs assessment; be responsible for development and implementation of the surveillance protocol; supervise and assure quality control; collect the final results and report them to the national authorities responsible for drug policy; ensure that all AMR surveillance activities are conducted according to international and national ethical codes; and establish partnerships with laboratories for quality control activities and, for HIV and TB, resistance testing.

General approaches to AMR surveillance

General approaches to AMR surveillance involve preliminary consideration of four areas:

- proper epidemiological planning, examining issues of sample size and source;
- proper laboratory procedures, which include the quality-controlled use of fully documented and recognized test methods and participation in an external quality assurance programme;
- outcome measures, which include a mechanism of data analysis, production and dissemination of information for action;
- a means of implementing any required action.

The AMR surveillance proposal may then be organized by major operational issues: epidemiological considerations; laboratory management; and data management. Within epidemiological considerations, the number of patients or samples required should be calculated according to the desired confidence level (usually 95%) and precision (5% or 10%) for establishing the baseline resistance prevalence, and then the trend in resistance prevalence. Any sample size must be inflated to account for estimated losses, such as lost patients or specimens, inadequate specimens, or uninterpretable results.

Primary and acquired resistance

Primary and acquired resistance are defined as follows:

- Resistance among untreated patients ("primary resistance") is the presence of a resistant strain in a patient who, in response to direct questioning, denies having had any prior treatment (for TB, <1 month; for HIV, none) and, in countries where adequate documentation is available, in whom there is no evidence of such a history. Resistance among previously treated patients ("acquired resistance") is the presence of a resistant strain in a patient who, in response to direct questioning, admits having received treatment (for TB, ≥ 1 month) and, in countries where adequate documentation is available, in whom there is evidence of such history.

Specific summary guidelines for each disease are provided below, with references to more detailed guidelines. A comparison of the three diseases and an example budget are provided in Tables 1 and 2, respectively.

HIV

WHO, in collaboration with the International AIDS Society (IAS) and other partners, has developed the Global HIV Drug Resistance Surveillance Programme. Objectives of the Programme are to:

- assess geographical and temporal trends in ARV resistance in untreated patients and, eventually, in selected groups of treated patients, through a collaborative network of institutions, laboratories, and investigators called the HIVResNet;
- provide information to enable public health bodies to target education and intervention programmes to limit the spread and evolution of resistance.

The detailed guidelines and operations manual will be available at the WHO drug resistance web site.⁶

⁶ http://www.who.int/csr/drugresist/HIV_AIDS

Table 1. Characteristics of HIV/AIDS, TB and malaria, relevant to AMR surveillance and containment for GFATM applications

Characteristic	HIV/AIDS		TB		Malaria	
	Reduction of disease burden	Education, prevention measures, effective treatment	Education, prevention measures, effective treatment	DOTS Strategy	Education, prevention methods, vector control	
Guidelines for appropriate drug use	Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach (http://www.who.int/hiv_aids)	Combination	Treatment of tuberculosis: Guidelines for national programmes (WHO/CDS/TB/2003.313) Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis (WHO/CDS/TB/2000.279)		<i>The Use of Antimalarial Drugs</i> (WHO/CDS/RBM/2001.33) and <i>Antimalarial drug combination therapy</i> (WHO/CDS/RBM/2001.35)	
Treatment		Combination	Combination		Combination, especially including artemisinin compounds	
AMR surveillance guidelines	To be made available at www.who.int/drugresist/hiv_aids		<i>Guidelines on Anti-tuberculosis Drug Resistance Surveillance</i> (WHO/TB/96.216)		<i>Monitoring antimalarial drug resistance</i> (WHO/CDS/CSR/EPH/2002.17)	
AMR surveillance method	Sentinel sites		100% diagnostic units or weighted cluster among new cases		Sentinel sites	
AMR surveillance frequency	Every 2–3 years		Frequency dependent on needs and resources (see text)		Every 2 years	
Method to measure AMR	Genotypic testing		Antibiogram		Therapeutic efficacy	
Policy change	To be defined		MDR treatment with DOTS-Plus strategy		>25% treatment failure	
Laboratory quality control	Ongoing		National Reference Laboratories and 20 Supranational Reference Laboratories			
Estimated cost of survey*	US\$ 200 000 to 500 000 per survey		US\$ 40 000 to 80 000 per initial survey including infrastructure costs; US\$ 20 000 to 40 000 per routine survey		US\$ 5000 to 10 000 per sentinel site	

*It should be noted that the first drug resistance survey will build national capacity and therefore may require additional resources for personnel and equipment. Drug resistance surveillance should be considered routine activities for the National Programmes and thus resources should be sufficiently allocated.

Table 2. Budget template for surveillance for HIV, TB or malaria antimicrobial drug resistance

	Number	Cost	Duration	TOTAL
Personnel (contracted services)				
Principal investigator				
Laboratory principal investigator				
Information technology specialist				
Laboratory technician(s)				
Logistics staff (e.g. drivers, data entry, secretarial)				
	Subtotal			
Supplies				
General (e.g. computers, stationery, printing, etc)				
General clinical (e.g. blood drawing)				
General laboratory (e.g. safety cabinets, centrifuges, freezer)				
Specialized laboratory (e.g. reagents and equipment)				
Materials for quality control activities				
	Subtotal			
Meetings (include facility costs, transport and <i>per diem</i> allowances)				
Initial planning meeting				
Evaluation/analysis meeting				
	Subtotal			
Training (include facility costs, transport and <i>per diem</i> allowances)				
Principal investigator				
Peripheral laboratory technicians				
	Subtotal			
Collection and transport of specimens to central laboratory^a				
Transport costs, including fuel and maintenance				
Secure storage capacity				
Transport containers, other packaging				
Postage				
	Subtotal			
	TOTAL ^b			

^a National and international regulations regarding the shipment of biological materials should be taken into consideration.

^b Depending on the personnel already available and the existing laboratory capacity, the estimated survey cost may vary from US\$ 100 000 to 500 000 for HIV, US\$ 20 000 to 80 000 for TB, and US\$ 5000 to 10 000 per sentinel site for malaria. If surveys are integrated as a routine programme activity, costs are expected to decrease.

Epidemiological considerations

Surveys are recommended every 2–3 years at sentinel sites. Sentinel sites will be selected according to access to patients representative of those who have (or will have) access to well-established ARV or prevention of mother-to-child transmission (PMTCT) programmes. Although most sentinel sites should have high volume, consideration should also be given to randomly selecting additional sites to achieve better representation of the newly diagnosed population than is possible using high-volume sites only.

The ideal population for AMR surveillance is newly diagnosed patients, where possible with recent HIV infection, who have never received ARV therapy. In generalized epidemics,

newly diagnosed patients could be conveniently identified among pregnant women being tested for HIV as part of PMTCT programmes or voluntary counselling and testing (VCT) clinic attendees. Approximately 500 sequences will be required to detect, with 95% confidence and 80% power, an increase in resistance prevalence from 5% to 10%. However, actual sample size should be calculated on a site-by-site basis. Consecutive patients who meet inclusion criteria at sentinel sites should be enrolled until the sample size is met.

The following essential information should be collected with all samples: unique subject and clinic site identifier, date of blood sample collection, ARV treatment history (confirm yes or no), previous HIV tests (positive or negative result), age group, and, for pregnant women, whether first pregnancy. There may be a need for additional information, such as sex, area of residence, date of previous negative HIV test, any laboratory or clinical evidence of recent HIV infection, clinical stage of HIV, most recent CD4 cell count, and reported HIV risk factors.

Laboratory management

There are two possible ways of acquiring blood specimens for sequencing: collecting specimens specifically for AMR surveillance or using specimens that were collected for other purposes (e.g. HIV testing) can be tested. The simplest possible specimen collection and storage mechanisms should be used.

Currently, the recommended method for detecting ARV resistance is genotypic testing of plasma specimens to identify mutations that confer phenotypic resistance. Several commercially available genotypic assays are now available, offering standardization and automation of the process. Genotyping the HIV *pol* reverse transcriptase and protease regions also allows the identification of clade clustering and the correlation of resistance patterns with HIV subtype circulating in a given geographic region.

WHO is supporting the development of a system of quality assurance whereby samples of different mutation profiles, subtypes and viral load are distributed to each testing centre.

Data management

A database with safeguards for patient confidentiality has been designed and the HIVResNet has identified a data management centre within the Global HIV Drug Resistance Surveillance Programme. Data analysis will conform to internationally accepted standards. Software has been developed that will allow laboratories to transmit sequences and contextual data and to receive interpreted data. Uniformly analysed national data will be sent to the NCTs, and global summary data will then be disseminated through the WHO web site.

Tuberculosis

Detailed guidelines exist to assist national TB control programmes to develop anti-tuberculosis drug resistance surveillance systems (Table 1).

Epidemiological considerations

Surveys should be conducted in areas that have at least one functioning central culture laboratory linked by mail or messenger with the majority of its TB diagnostic centres. Surveys should be conducted at least every 3-5 years, but may be more frequent depending on the drug

resistance situation and the resources available. All newly registered sputum-smear-positive TB patients in the country should be sampled.

Calculation of the sample size should be based on the following:

- 1) the total number of new sputum-smear-positive cases detected in the previous year in the setting to be studied;
- 2) the expected prevalence of resistance to rifampicin or to the drug with the lowest known prevalence of resistance from available data; in the absence of previous surveys, the NCT should make an educated estimate;
- 3) precision should be as accurate as possible (1 or 2%).

Sampling methods may be:

- 100% sampling of diagnostic centres, wherein all eligible patients are included in each diagnostic centre with the same limited intake period, which ensures survey representativeness;
- cluster sampling: diagnostic centres are randomly selected and all sputum-smear-positive patients newly registered during a defined period of time at these selected centres are included in the survey;
- population proportionate cluster sampling, which can be used to avoid the risk of missing the largest diagnostic centres during simple cluster sampling.

The following essential information should be collected for all patients: age, sex, area of residence, facility, date of sputum collection, and whether new or re-treatment patient. For treated patients, the classification (relapse, failure, return after default, or chronic) and the date of last TB treatment should also be collected.

Laboratory management

To minimize variability due to the disruption of routine, laboratories should use the internationally accepted method with which they are most familiar: the proportion method, absolute concentration, resistance ratio or the BACTEC method. Resistance testing should be conducted for isoniazid, rifampicin, streptomycin and ethambutol.

To ensure that results are comparable between countries, susceptibility testing should undergo quality control at three levels: internally, nationally and internationally. The WHO/IUATLD Supranational Reference Laboratory (SRL) Network comprises 20 laboratories whose role is to guide and advise the NCT and the national reference laboratory (NRL) during the preparation, implementation and evaluation of a drug resistance survey. The SRL performs laboratory assessments before the start of the survey, ascertains the accuracy of the susceptibility test methods used in the NRL through proficiency testing before the start of the survey by sending a panel of coded strains of *M. tuberculosis* to the NRL, and performs quality assurance of survey results.

Data management

WHO has produced a simple and flexible software programme, Surveillance of Drug Resistance in Tuberculosis (SDRTB), for entering and analysing data from drug resistance surveys. The software is available from WHO's web site.⁷ A programmed analysis can be run easily and summary tables with the prevalence of resistance for each drug and cumulative drugs can be produced. Interpretation of the results of a survey depends on local programmatic and epidemiological circumstances.

⁷ <http://www.who.int/csr/drugresist/TB/software>

Malaria

Countries should institute the WHO standard system for monitoring antimalarial drug resistance, which is described below and elsewhere in further detail (Table 1). Guidelines were developed on how to monitor the therapeutic efficacy of standard treatment for uncomplicated falciparum malaria in high transmission areas, but have been updated and validated for use in low-to-moderate transmission areas. The methods described in the guidelines cannot 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. A number of regional networks for monitoring antimalarial drug resistance have been established (e.g. EANMAT in East Africa; RAVREDA in South America Amazon countries).

Epidemiological considerations

Surveys for drug resistance should be conducted at least once every 24 months at carefully selected sentinel sites. 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. The site can be at the periphery (community-based) or at a health facility at district level; however, patients attending hospitals in urban settings may have more complex clinical presentations, may have been referred because of previous drug failures, and may be more difficult to follow up. Thus, monitoring should be done at the periphery whenever possible. In addition, the following characteristics should be considered in the selection of sentinel sites: population density in the catchment area; feasibility of supervision; epidemiology of malaria (especially intensity and seasonality of transmission); population mobility and migration (especially in border areas); and distribution of malaria treatment failures reported by the health information system.

Although no definitive scientific evidence 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 geographical size, population distribution and density, differing malaria epidemiology or ecology, and other factors deemed important by the programme. Most programmes find it easiest to alternate test sites (e.g. four sites tested per year with each site being assessed every other year). For comparability, surveys should be conducted during the same time of year.

Population inclusion criteria include:

- age 6–59 months (<5 years in areas of high transmission and >6 months in areas of low/moderate transmission);
- absence of severe malnutrition;
- parasitaemia: 2000 to 200 000/ μ l in areas of high transmission and 1000 to 100 000/ μ l in areas of low/moderate transmission;
- absence of danger signs or signs of severe or complicated falciparum malaria;
- presence of an axillary temperature of 37.5°C in areas of high transmission or history of fever in areas of low/moderate transmission areas;
- absence of febrile conditions caused by diseases other than malaria;

- ability to comply with follow-up visits, and easy access to health facility;
- informed consent of parent or guardian.

Unlike HIV and TB, there are no exclusions based on prior treatment.

The sample size should be based on an expected proportion of treatment failures. If the expected failure rate is lower than 15%, to be representative a minimum of 50 patients should be included. Consecutive patients who meet inclusion criteria at sentinel sites are selected until the sample size is met.

In areas of high transmission, the recommended minimum length of follow-up is 14 days. Longer follow-up must be accompanied by molecular assessment (e.g. PCR) to assist in distinguishing recrudescence from reinfection. Because 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, 28, 63, and 42 days, respectively.

In areas of low/moderate transmission, the recommended length of follow-up is 28 days. However, in some circumstances, assessments of shorter duration (14 days minimum) can still provide useful results. Molecular assessment to assist in distinguishing recrudescence from reinfection is still recommended for follow-up of more than 14 days, but is not strictly essential.

The national malaria control programme should monitor the use of first-line and second-line drugs recommended in their national treatment guidelines. Combination therapies that are not currently first-line or second-line therapies might also be monitored to obtain background information on new treatments that may become necessary. Only the efficacy of drugs intended for use for ≤ 3 days should be assessed, including combinations of chloroquine, amodiaquine, and sulfadoxine–pyrimethamine with artemisin derivatives.

Response to treatment is classified as early treatment failure, late treatment failure and adequate clinical and parasitological response, definitions of which are available in the document *Monitoring antimalarial drug resistance*.⁸

Laboratory management

Monitoring antimalarial drug efficacy necessitates parasitological follow-up at Day 0, D1, D2, D3, D7, and D14 (D21 and D28 in low/moderate transmission areas). It is recommended that microscopical results be assessed with the standardized procedure recommended by WHO, including quality control. Because the validity of the assessment and the safety of the patients depend on the laboratory results, the competence of survey personnel should be ensured, including microscopists and principal medical staff. Sufficient time and resources should be allocated to training before initiating the assessment. Many staff can be trained adequately with minimal supervision. In an ideal situation, all slides should be assessed by two qualified microscopists. If this is not feasible, slides from a 10% random selection of enrolled patients or a minimum of 10 randomly selected patients (whichever is greater) should be re-read.

Data management

The life-table method is preferred for analysing therapeutic efficacy data. 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

⁸ WHO/CDS/CSR/EPH/2002.17

of intention-to-treat analysis with few of that method's drawbacks. Although life-table analyses can be conducted by hand, use of a computer will greatly facilitate analysis and reduce calculation errors.

A traditional "per protocol" method for analysis should also be used in parallel. This method removes all patients that cannot be evaluated. Results from both methods of analysis should be reported.

WHO has produced simple computer-based applications to assist in all aspects of data management and analysis. These are accessible from the WHO web site.⁹ After validation of the data, the NCT should forward recommendations to the drug policy-makers for action. Generally the level of treatment failure currently recommended for changing drug policy in areas of high transmission is 25% but countries should be in an alert phase when treatment failure of between 5 to 14% is detected, and in an action period when the failure rate is between 15 and 24%.

Conclusions

This implementation guide is intended to assist countries applying to the GFATM to comply with the recommendation to include AMR surveillance and containment. It is intended only as a guide. Differences in national circumstances, health care systems, updated guidelines, and prevalent diseases may influence the approaches taken by governments. WHO will continue to cooperate with countries to build health sector capacity and provide technical assistance. Further information can be found on the WHO drug resistance web site.¹⁰

⁹ <http://www.who.int/csr/drugresist/malaria>

¹⁰ www.who.int/csr/drugresist

Figure 1. Antimicrobial Resistance Containment and Surveillance (ARCS)

