METHODS FOR SURVEILLANCE OF ANTIMALARIAL DRUG EFFICACY

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INTRODUCTION

Resistance to antimalarial drugs is a major public health problem, which hinders the control of malaria. In order to combat the growing resistance, a surveillance system is needed, which will facilitate monitoring and containment. In 1996, the World Health Organization (WHO) prepared a new protocol for assessing antimalarial drug efficacy in high transmission areas. Since then, WHO has regularly updated the therapeutic efficacy protocol for high transmission areas and validated the therapeutic efficacy protocol for low-to-moderate transmission areas on the basis of feedback from countries and scientific recommendations. The most recent version of the efficacy test protocol was adopted in 2001 (WHO, 2003), but adjustments are required to incorporate the changes recommended by the Technical Expert Group on Malaria Chemotherapy, which met in 2005 and 2008 to discuss the *Guidelines for the treatment of malaria* (WHO, 2006a). The most recent changes, which are incorporated into this document, are:

- applications of the same definitions of treatment responses at all levels of malaria transmission, with slight adjustment of patient inclusion criteria;
- administration of rescue treatment to patients with parasitological treatment failure at all levels of malaria transmission;
- requirement for 28 or 42 days of follow-up as a standard, depending on the medicine tested; and
- requirement for genotyping by polymerase chain reaction (PCR) to distinguish between recrudescence and reinfection.

Recommendations for monitoring the therapeutic efficacy of antimalarial medicines for uncomplicated *P. vivax* malaria are included in the WHO standard efficacy protocol (WHO, 2002). The purpose is to stimulate more routine monitoring of resistance of *P. vivax*, thereby gaining wider experience on which to base further refinement of the protocol. The standard protocol was drawn up and used mainly to test the efficacy of medicines against *P. falciparum*; however, *P. vivax* relapses, and *P. falciparum* does not. This difference requires different approaches to therapeutic evaluation.

1. *PLASMODIUM FALCIPARUM*

1.1 PROTOCOL PREPARATION

To facilitate the work of national malaria control programmes and other organizations involved in routine testing of antimalarial drug efficacy, a template protocol (see Annex 1) has been prepared, which can easily be adapted to meet local conditions and needs while maintaining standardization and interpretation of data. The template protocol translates the standard protocol into a practical format that can be used by national malaria control programmes seeking approval from ethics committees or funding from donors. To complete the protocol, the local investigator only needs to complete the highlighted sentences and paragraphs with the information specific to the study. Although this template has been reviewed by WHO Research Ethics Review Committee, the use of this template does not preclude a scientific and an ethical review.

The WHO standard therapeutic efficacy test provides the minimum essential information for deciding on a malaria treatment policy (WHO, 2005; Vestergaard, Ringwald, 2007). Studies with this basic design can form the basis of a surveillance system for monitoring changes in drug efficacy over time, when conducted periodically in a number of appropriately selected sentinel sites. Although the test does not provide all the scientific data necessary for understanding drug resistance in a given environment, it results in basic data on currently recommended first- and second-line medicines and, where necessary, possible replacement medicines, thereby allowing ministries of health to prepare rational treatment strategies and policies. It is important to stress that the standard protocol is not designed for the evaluation of new or experimental medicines. Evidence from earlier studies indicates that this protocol can also be used to assess drug regimens administered over more than 3 days, such as quinine (7 days), combinations of quinine and tetracycline or doxycycline (7 days), or artemisinin monotherapy (7 days). However, special attention must be taken to assure directly observed treatment (i.e. hospitalization or patient returns to the clinic each day over 7 days).

Considerable emphasis has been placed on maintaining simplicity and practicality. Programmes may collect any additional information that they feel is relevant; however, they are strongly encouraged to collect, at least, the data outlined in the protocol. It is only through the standardization of methods that it will be possible to compare and interpret results over time, within or between regions.

1.2 IMPLEMENTATION AND MANAGEMENT OF THE SURVEILLANCE SYSTEM

Sentinel sites

National malaria control programmes should establish sentinel sites for the surveillance of antimalarial drug efficacy. A limited number of sites is adequate to collect consistent longitudinal data and to document trends. The minimal requirements for establishing a sentinel site are: (i) trained, motivated clinical personnel; (ii) a microscopist; (iii) a laboratory for blood film examination and (iv) knowledge about the level of transmission intensity, as this influences certain protocol decisions. The facility can be community-based or located at a health facility at district level. Patients attending hospitals might have more complex clinical presentations; they may be more likely to have had previous drug failures and may be more difficult to follow up. Thus, whenever possible, monitoring should be done at or close to the community.

The following characteristics should be considered in selecting sentinel sites:

- population density;
- accessibility to and feasibility of supervision;
- epidemiology of malaria, especially intensity and seasonality of transmission; and
- population mobility and migration (especially in border areas).

The sentinel sites should represent all the epidemiological strata in the country. Monitoring can be done either by local personnel at the sentinel site or by a more specialized mobile team; the choice depends on national resources and the availability of trained staff at the sentinel sites.

Although no definitive scientific advice can be given about the number of sites needed, experience suggests that four to eight sites per country will