Anti-tuberculosis Drug Resistance Surveillance Guidelines
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Implementing anti-tuberculosis drug resistance surveillance and containment
An outline for national programmes

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. The majority of the 34 countries that applied to receive funds to combat TB included in their proposal funding to purchase Anti-TB 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 effectiveness and the cost-effectiveness of programmes to control AIDS, TB and Malaria.

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. The framework is described below as it pertains to tuberculosis control.

1. TB prevention and infection control

Several challenges impede sustainable implementation and expansion of TB control activities. Many of these stem from weak political will that fails to elicit the required health system and societal response needed to control TB. General public health services need to enhance their capacity to sustain and expand DOTS implementation without compromising the quality of case detection and treatment. At the same time, the private sector has to be enlisted to ensure a wide, comprehensive approach to TB control.

The DOTS strategy is the most cost-effective public health measure to prevent and control TB infection. The five elements of the DOTS strategy are political commitment, case

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1 A working document prepared by WHO Departments:
÷ Communicable Diseases, Surveillance and Response (CDS/CSR/EPH): http://www.who.int/emc/
÷ Stop TB Secretariat (CDS/STB): http://www.stoptb.org
For further information please contact: azizm@who.int
detection using sputum microscopy among persons seeking care for prolonged cough, standardized short-course chemotherapy under proper case-management conditions including directly observed treatment, a regular supply of high quality drugs, and a standardized recording and reporting system that allows assessment of individual patients as well as overall programme performance.

Implementation of the DOTS strategy is thus the first priority at the country level. For further information:
http://www.who.int/gtb/dots/index.htm

2. Appropriate use of anti-TB drugs:

The mainstay of the DOTS strategy is administration of standardized short-course chemotherapy to all confirmed cases. This ought to be done under technically sound and socially supportive case-management conditions. To ensure the accountability of TB services and help TB patients adhere to first-line treatment (and thus prevent the emergence of drug-resistant forms), direct observation of therapy (DOT) is recommended whenever rifampicin is being administered. In practice, this recommendation means providing a treatment partner or supporter acceptable to the patient to reinforce motivation to continue treatment and counter the tendency of some patients to interrupt treatment. Quality-assured sputum microscopy should be accessible to monitor treatment progress, assess treatment outcomes and certify cure among patients with infectious TB.

A high prevalence of multidrug-resistant TB (MDR-TB) is a problem that some countries are facing and more are likely to encounter. In such situations, the first action – of paramount importance – is to demonstrate that the existing health system, using DOTS, is achieving high detection of all new TB cases and high cure rates. It is also essential to ensure that high detection and cure rates continue in a sustained way. This first requirement has no alternative and must be met. Secondly, management of MDR-TB cases with second-line drugs must follow clear guidelines. These guidelines allow the implementation of “DOTS-Plus” projects. These are projects that permit MDR-TB management using second-line drugs under strictly defined programme conditions in resource-limited settings. DOTS programmes achieving high detection and cure rates, possessing the capacity to manage MDR-TB cases, and having access to a sustained flow of adequate resources may consider incorporation of second-line drugs for treatment of drug-resistant cases. This must be undertaken in a systematic and standardized manner. WHO guidelines on treatment of MDR-TB within programme conditions should be followed.

For further information: tb97_Treatment Guidelines.pdf
GUIDELINESDOTS.pdf
3. Access to anti-TB drugs

The Global Drug Facility (GDF) is a mechanism aimed at facilitating global DOTS expansion by expanding access to high-quality first-line TB drugs and improving their availability within countries. The GDF enables governments and non-governmental organizations (NGOs) to implement effective TB control programmes based on the DOTS strategy. By securing the timely supply of quality TB drugs, the GDF complements other activities designed to improve both the coverage and the quality of global TB control.

Insecure financing and shortages of TB drugs are frequent and serious in many parts of the world and have hampered DOTS expansion. While poor drug supply is not unique to TB control, its impact may be especially severe. Drugs are essential to prevent and cure TB: inadequate and erratic supplies can fuel the emergence of MDR-TB. Ensuring an uninterrupted supply of quality drugs through the GDF frees human and financial resources to address problems of management, service delivery, training, supervision, and other services essential for scaling up DOTS. Countries are encouraged to apply to GDF, but must meet certain requirements, including adherence to the DOTS strategy, to qualify for assistance. The GDF is working closely with the Global Fund to ensure complementary procedures for the provision of TB drugs.

For further information: http://www.stoptb.org/GDF

The Green Light Committee (GLC) is a mechanism to increase access to, and the rational use of, high-quality second-line anti-TB drugs. Via a multi-faceted procurement strategy based on a market analysis for each of the second-line drugs on the WHO Model List of Essential Drugs, concessional prices have been achieved for quality-assured drugs. These prices are up to 99% lower than previous open market prices. However, to benefit from these concessional prices, projects must be reviewed by the GLC to ensure all essential requirements for implementing DOTS-Plus are fulfilled. The mechanism thus operates to prevent the emergence of “super MDR-TB.” In addition, projects undergoing GLC review benefit from technical assistance and a continuous external monitoring process. Patients ultimately benefit not only from having access to second-line anti-TB drugs, but also from being assured that all programmatic parameters are in place for their successful treatment.

For further information: http://www.who.int/gtb/policyrd/dotsplus.htm

4. Legislation and regulation

Because tuberculosis is a communicable disease that is hazardous to public health, all countries should have legal provisions for its control. The purpose of a communicable disease control act is to protect the population from the occurrence of the disease, to ensure that health and other authorities implement the necessary control measures, and to safeguard the rights of individuals who are affected by measures that may need to be taken. Measures needed to prevent transmission must be justifiable from the medical point of view and must not cause needless or unreasonable harm. The voluntary participation of affected citizens
should always be sought, but compulsory participation may be considered when needed to prevent spread of the disease.

Essential elements in tuberculosis control regulation include: protection against infection, detection of infectious TB cases as early as possible, insurance that persons with active TB are given adequate treatment, notification of cases, detection of TB infection and disease among close contacts of index cases, BCG vaccination to prevent disseminated TB in children, and prophylactic treatment to prevent development of the disease in certain risk groups of infected persons. Regulations can also include some exceptions to the duty of secrecy, provision of duties to report cases, restrictions relating to the performance of work and teaching, quarantine, hospital infection, transport of infectious material, and funerals. For further information: Good practice in legislation and regulations for TB control: an indicator of political will. WHO/CDS/TB 2001.290

5. Anti-TB drug resistance surveillance:

In addition to the detection and cure of patients, a major goal of effective TB management is to minimize the development of drug resistance and, in particular, the emergence of multidrug-resistant TB. Surveillance of anti-TB drug resistance is therefore an essential tool to monitor the effectiveness of TB control programmes and improve national and global efforts to reduce the burden of TB morbidity and mortality.

Guidelines are available to assist national TB control programmes to develop country-specific anti-TB drug resistance surveillance systems which determine susceptibility of *Mycobacterium tuberculosis* to first-line anti-TB drugs. The standardization of methodology and quality assurance of laboratory practices, secured through a unique system of Supranational Reference Laboratories, motivates improved laboratory practices and ensures that results of susceptibility testing are comparable both within and among countries. When establishing country-wide systems for the surveillance of drug resistance, three principles should be strictly adhered to:

- The sample of specimens should be representative of the TB patients in the country or geographical setting under investigation and the sample size should be carefully calculated to permit standard epidemiological analysis.
- Each patient's history should be carefully obtained, and available medical records reviewed, to determine clearly whether or not the patient has received prior anti-TB drugs. This step is essential in order to distinguish between drug resistance in newly diagnosed cases and drug resistance in previously treated cases.
- The laboratory methods for anti-TB drug susceptibility testing (DST) should be selected from among those that are internationally recommended and applied to four of the six anti-tuberculosis drugs used for first-line treatment, namely isoniazid, rifampicin, streptomycin, and ethambutol, should be tested by all countries adopting the guidelines.
Information gathered from any surveillance of resistance provides a critical evidence base for the evaluation of control programmes and for decisions on future treatment policies (including the use of second-line drugs) at the local and national level.

In addition, WHO has developed a plan of action to strengthen laboratory capacity at the national level not only for the surveillance of drug resistance but also for all TB-related procedures that require laboratory support. Activities aimed at strengthening laboratory capacity focus on sputum smear microscopy, internal and external quality assurance, standard operating procedures, biosafety, and training.

For further information: http://www.who.int/emc/amrtb.htm


+! SDRTB3 Drug Resistance Software
   http://www.who.int/emc/SDRTB_software/instructions.html

6. **Focused research**

Several research issues need to be addressed quickly to improve understanding of the relationship between drug resistance and treatment interventions. Urgent research needs include: i) assessment of anti-TB drug resistance levels following phased introduction of 4-drug fixed-dose combinations (4FDCs) in a field setting as a result of national policy to use 4FDCs; and ii) in collaboration with surveillance teams, assessment of the changes (if any) in levels of anti-TB drug resistance following the introduction of anti-retroviral drugs for the treatment of HIV infected patients with TB.

The DOTS-Plus strategic approach currently promoted is based on expert opinion and limited data, and is under testing and development. In order to develop final international recommendations for DOTS-Plus, five key research issues need to be addressed.

1. Identify optimal standardized protocols to treat MDR-TB
2. Identify optimal protocols for diagnostic testing
3. Identify the minimum requirements for constructing and implementing DOTS-Plus
4. Identify threshold indicators for implementing DOTS-Plus
5. Broaden the evidence base for policy development through operational research and other programmes

It is vitally important that both the international community and endemic countries follow this operational research agenda when developing research activities aimed at finding the definitive solution for MDR-TB control.
Appendix

Monitoring anti-tuberculosis drug resistance – a summary

The importance of drug resistance surveillance in the fight against tuberculosis

One of the aims of effective management of tuberculosis (TB) is to minimize the development of drug resistance and, in particular, the emergence of multidrug-resistant TB. Surveillance of anti-TB drug resistance is therefore an essential tool to monitor the effectiveness of TB control programmes and improve national and global efforts to reduce the burden of morbidity and mortality due to tuberculosis. 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 concurrently introduce or strengthen systems for the surveillance of drug resistance. Information gathered from resistance surveillance provides a critical evidence base for the evaluation of control programmes and for decisions on future treatment policies (including the use of second-line drugs) at the local and national level.

Guidelines for surveillance

In 1994, WHO joined forces with the International Union Against Tuberculosis and Lung Disease (IUATLD) and launched the Global Project on Anti-TB Drug Resistance Surveillance. The aims of this project are to measure the prevalence and monitor the trend of anti-TB drug resistance worldwide using a standardized methodology, and to study the correlation between the level of drug resistance and treatment policies in various countries. The overall goal of the project is to improve the capacity of national TB control programmes and their laboratory networks to perform drug resistance surveillance in order to inform all related policy decisions that underpin a comprehensive TB control strategy.

Guidelines summarized in this document are available to assist national TB programmes to develop country-specific anti-TB systems for drug resistance surveillance. Such systems are designed to determine susceptibility of *Mycobacterium tuberculosis* to first-line anti-TB drugs. The standardization of methodology and quality assurance of laboratory practices, through various centres worldwide which function as Supranational Reference Laboratories, ensure that results of susceptibility testing are comparable both within and among countries.

In establishing surveillance of drug resistance at the country level, three principles should be strictly adhered to:

- The sample of specimens should be representative of the TB patients in the country or geographical setting under study and the sample size should be carefully calculated to permit standard epidemiological analysis. WHO recommends that surveillance of anti-

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2 A working document prepared by Communicable Diseases, Surveillance and Response (CDS/CSR/EPH):
http://www.who.int/emc/
For further information please contact azizm@who.int
TB drug resistance cover the whole country or geographical area and that the sample size be derived from the total number of sputum-positive cases in the country.

- Each patient's history should be carefully obtained, and available medical records reviewed, to determine clearly whether or not the patient has received prior anti-TB drugs. This is essential in order to distinguish between drug resistance among newly-diagnosed cases and drug resistance among previously-treated cases.

- The laboratory methods for anti-TB DST should be selected from among those that are internationally recommended (see annex) and four of the six anti-tuberculosis drugs used in the first line treatment, namely isoniazid, rifampicin, streptomycin, and ethambutol, should be tested by all countries adopting the guidelines.

**Organization and outline of the survey**

Surveying the prevalence of anti-TB drug resistance, as for resistance to antimalarials and antiretrovirals, involves four major operational areas:

- **Implementation and management of the surveillance programme** (logistics, training, and collection of clinical information)
- **Epidemiology** (patient and population selection, patient information ascertainment, and sampling issues)
- **Laboratory management** (microscopy, culture, drug susceptibility testing, and a quality assurance programme including proficiency testing)
- **Data management** (data collection, entry, storage, analysis and dissemination)
- **Implementation and management of the surveillance programme**

**National Coordination Team**

A national coordination team including one person having expertise in each of the above areas, should be established. In general, the head of the national TB programme and the head of the national reference laboratory, or a person designated by them, will be assigned for these tasks, and an epidemiologist should be identified. The coordinating team requires strong official backing by the authority in charge of health services (Ministry of Health). The coordination team is responsible for preparation of the survey, development and implementation of the protocol, close coordination with the Supranational Reference Laboratories, supervision and quality assurance during the survey and the final collection, analysis and reporting of results. Usually a Principal Investigator is identified from within the coordination team to be the focal point for the survey.
**DEFINITIONS**

For the purpose of drug resistance surveillance, the following definitions are used:

- **Resistance among new cases (proxy of "primary resistance")** is the presence of resistant strains of *M. tuberculosis* in a patient who, in response to direct questioning, denies having had any prior anti-TB treatment (for more than one month), or in countries where adequate documentation is available, no documented evidence of such treatment exists.

- **Resistance among previously treated cases (proxy of "acquired resistance")** is the presence of resistant strains of *M. tuberculosis* in a patient who, in response to direct questioning, admits having been treated for TB for one month or more, and, in countries where adequate documentation is available, there is evidence of such history. These patients include cases classified as treatment failure, relapse, return after default, and chronic cases.

The pragmatic approach of separating patients with and without history of at least one month of anti-TB treatment has repercussions of programmatic relevance. In general, it is expected that a higher resistance rate will be detected among previously-treated cases than among new cases. Inaccurate classification of patients and/or combining drug resistance data from both categories will be misleading and will make data interpretation more difficult. It is therefore important to collect data from both new and previously-treated cases during the survey, but to stratify the results.

**Epidemiology**

**Suitable survey areas**

The country or administrative area considered as a survey area should have at least one functioning central culture laboratory linked by mail or messenger with the majority of TB diagnostic centres, for purposes of both communication and transportation of samples.

**Sample size**

Sampling for a survey of the prevalence of anti-TB drug resistance should include all newly-registered sputum-smear-positive tuberculosis patients in the country. The calculation of an appropriate 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 country or geographical 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 survey data the best guess of investigators should be used.

Precision should be as accurate as possible (1 or 2%) but calculation needs to ensure a sample that is logistically feasible to obtain. The confidence around the estimated prevalence should be 95%.
If cluster sampling is adopted, the cluster design effect needs to be taken into account, and therefore, the calculated sample size needs to be multiplied by two.

Finally, the calculated sample size needs to be increased by 5%-20% to account for expected losses. These include patients diagnosed as smear-positive who do not return to the diagnostic centres and from whom it is not possible to obtain two sputum samples; patients whose sputum cultures are contaminated or do not yield any growth of *M. tuberculosis*; and patients whose *M. tuberculosis* susceptibility testing does not give interpretable results (unreadable or too few colonies).

**Sampling strategies**

100% sampling of diagnostic centres

This sampling method is most suitable for small countries with a relatively small number of TB diagnostic units, good infrastructure and facilities for sample transportation from all diagnostic centres to the NRL. All eligible patients are included in each diagnostic centre within the same limited intake period. The representativeness of this design is ensured by the inclusion of all diagnostic centres and by the use of the same enrolment period for each. Large and small diagnostic centres are equally represented without applying a complicated sampling method. The intake period is calculated by dividing the sample size by the total number of sputum smear positive patients per year in the country.

Cluster sampling

Cluster sampling methods are best used in situations where coverage of the entire area of the country presents logistic difficulties and where the number of TB diagnostic centres is high. With this design, 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. While the main advantage of this approach is its simplicity, the main disadvantage is the risk of missing the largest diagnostic centres resulting in a non-representative assessment of resistance prevalence despite randomization.

Population proportionate cluster sampling

To avoid the risk of missing the largest diagnostic centres when drawing the sample (see above), a weighted cluster sampling technique can be used. Based on a list of all diagnostic centres with the numbers of newly registered patients per year, a cumulative population list is compiled. Assuming the minimum recommended number of 30 clusters is selected, the total number of patients registered per year in all the centres is divided by 30 to obtain the sampling interval. A random number is picked between one and the sampling interval. This random number determines the first diagnostic centre on the cumulative list to be selected. The sampling interval is sequentially added to the random number to obtain the remaining clusters from the list. If centres are large with twice or three times more patients per year then the sampling interval may well be more than one cluster per diagnostic centre.
**Laboratory management**

The laboratory capacity to perform drug susceptibility testing should be evaluated and strengthened whenever needed. The training needs of the laboratory technicians should also be evaluated and a training curriculum and agenda should be developed.

**Drug susceptibility testing**

It is recommended that participating laboratories use the drug susceptibility testing method with which they are most familiar, provided it is one of the four internationally-recommended methods: the proportion method and its variants, absolute concentration, resistance ratio, and BACTEC. This is to eliminate variability due to disruption of routine testing caused by changing to a new testing procedure.

**Quality assurance**

To ensure that DST results are reliable and comparable between different countries, a system of quality assurance is required. Susceptibility testing should be quality controlled on three levels, internally, nationally and internationally.

**Supranational Reference Laboratory**

The WHO/IUATLD Supranational Reference Laboratory (SRL) Network comprises, as of mid-2002, 20 laboratories whose role is to guide and advise the national coordinator (or coordination team) and, in particular, the national reference laboratory (NRL). Guidance is provided 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 national reference laboratory through proficiency testing before the start of survey by sending a panel of coded strains of *M. tuberculosis* to the NRL, and performs quality assurance of survey results from the survey. Through this international quality assurance scheme the SRL assures the comparability of the surveillance data gathered in countries participating in the WHO/IUATLD Global Project.

**Data management, data interpretation and policy considerations**

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 third version (SDRTB3) is based on Epi-Info, runs on DOS, and is available from WHO (http://www.who.int/emc/amrtb.htm). A programmed analysis can be run easily and summary tables with the prevalence of drug resistance for each drug and cumulative drugs can be produced. The fourth version (SDRTB4) runs on Windows and will be available from WHO in November 2002.

Interpretation of the results of a survey of the prevalence of anti-TB drug resistance depends on local programmatic and epidemiological circumstances. The key indicator of a TB control programme's performance is the prevalence of resistance among new cases and among previously-treated cases. The prevalence of resistance among newly-diagnosed cases is an indicator of the quality of a national tuberculosis programme over many years. An established national programme which implements standardized chemotherapy and an effective control
programme will see a subsequent reduction in the prevalence of primary drug resistance. A high prevalence of primary resistance may also indicate that some previously-treated patients have been misclassified as new cases.

Anti-TB drug resistance is caused by inconsistent, partial or incorrect treatment. It may also arise from an unreliable supply of drugs, treatment interruption, and use of drugs of substandard quality. The acceleration of the evolution of resistance to one or more anti-TB drugs is an obstacle to achieving TB control and undermines the effectiveness and cost-effectiveness of TB control programmes. Implementation of the DOTS strategy is a key to prevent or decrease the emergence of anti-TB drug resistance.
## Anti-TB drug resistance survey budget

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<td>bijou, glass beads, etc.</td>
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<td>Pure Antimicrobial powders</td>
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<td>Reagents for identification</td>
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<td>Containers for specimen</td>
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<td><strong>E. Collection and Transport</strong></td>
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<td>Supranational laboratory.</td>
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*Please note the first Anti-TB drug resistance survey in a country will be a capacity building exercise and therefore may require additional human resources. Drug resistance surveillance should be considered a routine activity of the National TB Programme and thus human resources should be allocated accordingly for this task for future surveillance activities.

*Please note the first Anti-TB drug resistance survey in a country will be a capacity building exercise and therefore may require additional equipment to perform a survey. Special requests may be supported, i.e. safety cabinets, centrifuges.

General Note: Excluding additional costs for equipment most survey budgets fall in between 20,000 and 40,000 USD. As it is adopted as a routine function of the National TB Programme costs are expected to decrease.
**Toolkit for Monitoring Anti-TB Drug Resistance**

**Selected resource materials**

*Updated version: 28 August 2002*

1. **General:** [http://www.who.int/emc/amrtb.htm](http://www.who.int/emc/amrtb.htm)

   WHO/CDS/TB/2000.278
   [http://www.who.int/emc-documents/antimicrobial_resistance/whocdstb2000278c.html](http://www.who.int/emc-documents/antimicrobial_resistance/whocdstb2000278c.html)

   [http://www.who.int/emc/amrtb.htm](http://www.who.int/emc/amrtb.htm)
   Part I: Definitions, Laboratories/diagnostic centres, sampling strategies.
   [http://www.who.int/emc/amrtb.htm](http://www.who.int/emc/amrtb.htm)
   Part II: Organization/Survey outline, intake of patients, national reference lab, data analysis. [http://www.who.int/emc/amrpdfs/TB_Org_outline2.PDF](http://www.who.int/emc/amrpdfs/TB_Org_outline2.PDF)
   Annexes. [http://www.who.int/emc/amrpdfs/TB_annexes.PDF](http://www.who.int/emc/amrpdfs/TB_annexes.PDF)

4. **Surveillance of Drug Resistance in Tuberculosis (SDRTB3) Software.**
   A software designed to assist the process of collection and analysis of data on drug resistance in tuberculosis. More information about this software and how to obtain it from our web site: [http://www.who.int/emc/SDRTB_software/index.html](http://www.who.int/emc/SDRTB_software/index.html)