Interim recommendations for the surveillance of drug resistance in tuberculosis

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LIST OF ACRONYMS

DRS	Drug Resistance Survey/Surveillance
DST	Drug Susceptibility Testing
EQA	External Quality Assurance
FLD	First line drugs
IUATLD	International Union Against TB and Lung Disease (UNION)
LQAS	Lot Quality Assurance Sampling
MDR-TB	Multidrug-resistant tuberculosis
NRL	National Reference Laboratory
NTP	National Tuberculosis control Programme
QA	Quality Assurance
SLD	Second line drugs
SRL	Supranational Tuberculosis Reference Laboratory
TA	Technical Assistance
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

INH	isoniazid
RMP	rifampicin
PZA	pyrazinamide
EMB	ethambutol
SM	streptomycin
FLQ	fluoroquinolone
PAS	para-aminosalycilic acid

SUMMARY

Revised drug resistance surveillance guidelines will become available later this year. In the interim, this document has been drafted to provide guidance on the areas that will be updated in the forthcoming guidelines. These interim recommendations build on guidelines that have already been published in 2003[1]. It is important to note that these recommendations are conceptual. For practical guidance please refer to the previous guidelines and/or a technical consultant that can provide assistance in designing the survey protocol and advising on specific logistics. There are three fundamental principles of the WHO/IUATLD Global project on drug resistance surveillance. These interim recommendations follow these principles:

1. Survey sample must represent the population under study.
2. TB patients must be differentiated by previous history of treatment.
3. Laboratory results must be quality controlled.
**4. Other areas of consideration (coordination, ethics, quality assurance, budget).

1. SURVEY METHODS

General

The overall goal of monitoring drug resistance in tuberculosis is to evaluate TB programme performance and provide information which can be used to guide public health action to reduce morbidity and mortality and to improve public health. Drug resistance is monitored either through continuous surveillance by provision of diagnostic culture and DST to all TB patients, or where infrastructure is not widely available, through periodic surveys. Sometimes a system employs a combination of the two[1].

Drug resistance surveys can also strengthen lab capacity, and transport and referral systems, as well as evaluate the correct classification of patients. Surveys can also provide a platform for other types of operational research. It is important that the NTP develop the survey objectives before starting and consider in advance the ways this information will be used. It is also important that expectations of survey data generated remain realistic recognizing that drug resistance surveys can determine prevalence of resistance within certain margins of error. In some cases these may preclude the ability to meaningfully determine trends. Information generated from drug resistance surveys must always be interpreted alongside other programmatic information.

Drug resistance surveys should only be undertaken when the laboratories conducting DST are safe and appropriately equipped with trained staff working with clear standard operating procedures and producing quality assured data. The data generated from surveys will be valid and useful where high quality lab data are matched by surveillance and clinical data produced by appropriately trained survey/surveillance staff with good communication between programme and laboratory staff. It is important to note that drug resistance surveys will heavily increase the workload of the reference laboratory, and should only be undertaken where capacity is sufficient.

[1] The term drug resistance surveillance in this document is defined as the ongoing and continuous assessment of drug resistance among all cases of tuberculosis. The term drug resistance survey refers to a cross-sectional survey that takes place at one point in time. Surveys are intended to be repeated at specified intervals with the aim of documenting changes in prevalence of resistance over time.

As treatment for drug resistant cases becomes more routinely available within the NTP, mechanisms for surveillance may be modified over time. It is extremely important that a National TB Programme documents the evolution of the surveillance system in order to appropriately evaluate drug resistance data over time, and interpret trends. It is also important to note that while nationwide surveys are desirable for programmatic reasons, surveys at smaller administrative levels are also acceptable provided they are designed correctly. The size and scope of the survey should be determined by ability of the NTP to ensure quality.

Each country should take a long term view of surveillance and should design a system that best fits the needs of the country, and is based on capacity that is sustainable and ideally will allow the evaluation of trends over time, which is the primary objective of surveillance. There are several models to choose from, all of which fit into the framework set out in these guidelines.

Survey models

-Some countries conduct continuous surveillance, or conduct culture and drug susceptibility testing (DST) on all suspected TB cases as a standard of routine diagnosis. This is the approach of most high income countries, and these routine diagnostic data constitute the basis for surveillance. For these countries such data usually forms the basis of the clinical management of drug resistant TB using tailored or individualized treatment regimens.
-Some countries conduct continuous surveillance (routine culture and DST) on risk populations (all retreatment cases, or specifically chronics, or failures of category 1 or category 2), supplemented with periodic surveys of drug resistance among new cases. As drug resistant treatment programmes scale up routine surveillance of retreatment cases will become a standard for case-finding.
-Other countries conduct periodic surveys for both new and retreatment populations with appropriately sized samples, and some countries will only include retreatment cases during the intake period of surveys designed for new cases.
-Several countries with well established laboratory networks have opted for a sentinel network for trend information.

Approximately half of the countries currently reporting data to the Global Project are reporting continuous surveillance data derived from laboratory diagnosis. The other

half of countries are reporting data from periodic drug resistance surveys, and a handful report data from sentinel surveillance systems.

In general WHO recommends that countries with good lab capacity and ability to provide DST to their entire TB population work to improve their system by ensuring the quality of the laboratory, the recording and reporting system and by standardizing patient classification. If the diagnostic network is not expanded widely enough, at this time, a sentinel system may be a good interim measure. In these settings, periodic surveys should only be used to compare and validate data available from routine diagnostic programmes.

For details on sampling please refer to the Guidelines for surveillance of drug resistance in tuberculosis. Geneva, World Health Organization, 2003 (document WHO/TB/2003.320).

New recommendations for survey methodologies

A. Retreatment cases

Though WHO recommends that surveys are based on evaluation of new cases and are important for epidemiological reasons, evaluation of resistance among retreatment cases is also extremely important and provides crucial information for programme management. Information on this population is also critical in regimen development and evaluation. This is a category of patients at higher risk for having strains of TB resistant to one or more drugs and is usually the group from which patients are screened for MDR-TB treatment programmes. Therefore, developing information about the size and composition of this population and the prevalence of resistance in sub-categories of the retreatment group is extremely important for programmatic reasons. Differentiation of retreatment subcategories and well as patient interviews are critical for data interpretation and are discussed in greater detail in the next section devoted to patient classification. It is important to note that as outlined in the second Global Plan to Stop TB[2], National TB Programmes should be aiming to conduct DST on all retreatment cases by 2015 as well as 20% of targeted new TB cases, with the exception of the European region which aims to provide DST to all TB cases. A revision of this plan will be available shortly outlining an even more ambitious scale up for access to DST services. In all scenarios and for

purposes of screening and treatment, programmes are suggested to start with providing DST routinely to failure cases and chronics, and symptomatic contacts of known MDR-TB patients, as this is the most important risk group, and expand from there. Therefore, conducting a survey on retreatment cases is fully in line with this plan and may assist with scaling up access to DST for this population.

If retreatment patients do not already receive diagnostic culture and DST routinely, WHO recommends devising a separate, appropriately sized sample for retreatment cases which may require extending the inclusion period for retreatment cases well past that of new cases. The size of this sample, as in new cases, will depend on the intended level of precision or level of confidence that is desired. As with new cases, it is important that **consecutive** retreatment patients should be enrolled and classified by their subcategory of retreatment (i.e. relapse, return after default, return after failure of Cat1, chronic). If capacity is problematic then retreatment cases should be included additionally in the survey for at least the duration of the intake period for new cases. In most cases it will be impossible to select clusters that are different from the clusters selected for new cases.

B. HIV testing

Inclusion of HIV testing should be considered when designing a drug resistance survey as there are potential benefits both to patients and to the programme. The specific objectives for inclusion of HIV testing should be addressed in the protocol.

If a programme aims to determine the relative risk of drug resistant TB among HIV+ TB patients compared to HIV- TB patients, a more complex study design will be required. And very often the assumptions used will yield a much larger sample size. In addition, if smear negative cases are to be included this will also increase the sample size. Few countries have conducted such studies; therefore it is important that appropriate technical support (to advise on survey design, and laboratory) is available when designing the protocol.

Incorporating HIV testing into a routine DRS may not allow for statistically significant determination of the relative risk of resistance in HIV+ compared to HIV- TB patients; however, it may yield some important information to the programme on the relationship between HIV and TB, as well as provide important individual benefits to

patients such as better access to testing, early detection, rapid placement on treatment etc.

Most countries have policies to provide HIV testing and counselling to TB patients, but availability of testing and treatment as well as referral services will vary by country[3],[4].
This will affect how surveys are designed and whether testing is linked or unlinked. Some countries have used surveys as a way of scaling up HIV testing to TB patients. It is important that if HIV testing is included in the survey that that National HIV/AIDS programme is involved in the survey from the start. Additionally, all laws regarding testing and disclosure of information should be adhered to and if an ethics board is present in the country the protocol should be submitted to this board. Additional time should be allowed in the survey for approval to be obtained fro HIV testing. Ethical issues are more specifically discussed later in this document. It is also important to note that surveys incorporating HIV testing should be aware of limitations in interpretation of data due to incomplete information as a result of testing uptake, and proportion of patients opting out. In addition some systems do not differentiate between negative test results and test not done. Incorporation of HIV testing into a drug resistance survey should be discussed with these factors in mind.

C. Smear negative cases

Surveys are usually based on smear positive pulmonary TB cases. This is done primarily for three reasons; the first is that there is no strong evidence to indicate that prevalence of drug resistance is significantly different between smear positive and smear negative TB cases (though HIV infected cases with a higher likelihood of being paucibacillary or smear negative may be exposed to different risk factors). The second reason is that the culture yield from smear negative patients is low, approximately 35.2% (but may be even lower in some settings) compared to almost 90% among smear positive cases[5]. Inclusion of cases with a low culture yield will require a significantly larger sample size, and may increase laboratory workload up to ten times. Therefore, it is recommended that countries interested in including smear negative cases strongly consider the implications for logistics and laboratory capacity. The third reason for basing surveys on smear positive patients is that the great majority of transmission results from smear positive source cases. Recently

published Guidelines for Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary cases should also be considered[6].

D. Sentinel networks

Sentinel surveys and surveillance methods have not been extensively used in the context of the Global Project; however, there may be a role for sentinel methods to better ascertain trends in selected countries. This methodology requires further exploration and field use, before wide recommendation. Countries interested should contact WHO or other technical partners for further discussion.

Most existing models for the monitoring of drug resistance in TB are laboratory or hospital based models. Such models are most useful in countries where lab infrastructure is good, or where most of TB care is hospital based. However; a more relevant approach for most countries with a high prevalence of TB will be to keep clusters, selected in population based surveys, open over consecutive years provided that changes in catchment populations are documented.

In general, the advantages of sentinel surveillance are that systems can be designed to collect information continuously (avoiding 3-5 year intervals), can be useful for documenting trends, and can offer design flexibility. The common disadvantages of sentinel methodologies are primarily they are often not population based, and can be subject to multiple biases. Such biases can also affect trend assessment. Much depends on the design of the system and appropriate selection of sites.

Sentinel surveillance may be a good methodology to explore in countries with relatively strong laboratory capacity and/or strong and sustainable transport networks. Sentinel networks may also be useful in detecting outbreaks or localized drug resistance epidemics. It is recommended that NTPs with interest in setting up a sentinel network, contact WHO or a leading partner to obtain assistance in design of an appropriate system.

E. Sampling for repeat surveys

It is important that repeat surveys are designed to detect changes in resistance over time. WHO currently recommends conducting surveys at 3-5 year intervals. Trend determination from repeat surveys can be difficult owing to wide confidence intervals.

F. Risk populations

For purposes of developing an appropriate treatment programme and monitoring localized epidemics, National TB Programmes may want to run small surveys or conduct continuous or sentinel surveillance in selected areas such as prisons, or in border areas, or even in large referral hospitals. It is important to note that as outlined in the second Global Plan to Stop TB[7], National TB Programmes should be aiming to conduct DST on all retreatment cases by 2015 as well as 20% of targeted new TB cases, with the exception of the European region which aims to provide DST to all TB cases. A revision of this plan will be available shortly outlining an even more ambitious scale up for access to DST services. In all scenarios and for purposes of screening and treatment, programmes are suggested to start with providing DST routinely to failure cases and chronics, and symptomatic contacts of known MDR-TB patients, as this is the most important risk group, and expand from there. Therefore, conducting a survey or surveillance within risk populations such as failures, chronics, or even the entire population of retreatment cases is very much in line with the Global Plan.

High risk groups will be defined by setting. Such an approach, used to complement a nationwide system, will become more relevant as treatment programmes expand and may become part of a screening programme. The design of these systems should be done in consultation with an epidemiologist or technical partner.

G. Resistance to second line drugs

In order to better understand the prevalence and distribution of second line drug resistance WHO is recommending three approaches to enhance or complement existing systems. In general WHO recommends that countries without capacity to perform DST for second line drugs do so at an SRL, and countries that have established practices for DST for SLDs, to consult a SRL to ensure quality.

1. ***Population-based surveys:*** For settings conducting population based surveys or continuous surveillance, all MDR-TB isolates detected in a survey should be rechecked by an SRL and further tested for resistance to selected second line drugs at the SRL (see below for recommended drugs).

2. ***Routine continuous surveillance:*** National TB Programmes (or National Reference Laboratories) with SLD DST capability may want to consider conducting SLD DST on all MDR-TB isolates detected in surveys or in routine diagnostic surveillance. This should be done based on workload, and relevance of certain drugs. This decision should be taken in consultation with an SRL. For example if streptomycin is no longer used in the country it could be replaced with DST for a fluoroquinolone or for an aminoglycoside, or both.

Any country conducting drug susceptibility testing should be aware that recommendations for second line DST will be revised shortly. In addition, as soon as EQA panels for proficiency testing of second line DST become available, NRLs should be encouraged to participate to ensure their second line methods are in line with international recommendations. More information on laboratory testing is detailed in the following section.

The limitations and complexity of performing SLD is not always understood outside the laboratory. The laboratory should not perform SLD unless it has proven capacity and infrastructure.

3. ***Rapid surveys of risk groups:*** Surveys of first and second line drug resistance among high risk groups will help determine the prevalence and predominant patterns of drug resistance and will useful in providing guidance on appropriate regimens for treatment of MDR-TB. Risk groups should be identified by the NTP; however, if the purpose of the survey is for regimen design the most relevant risk groups will be known MDR-TB cases, treatment failure cases, chronics, and symptomatic contacts of MDR-TB cases.

These surveys should not be nationwide, and will not be useful for epidemiological purposes or in the determination of trends. In general, these surveys should be conducted among the first cohort of patients that will go on MDR-TB treatment, or within selected centers or diagnostic units that regularly addresses high risk cases. If DST for second line drugs is not available in the country or if standards of laboratory

performance are unknown DST for second line drugs can be conducted outside of the country at a Supranational Laboratory. Sufficient resources must be obtained to cover the cost of the SRL. A generic protocol is available, but should be adapted in consultation with WHO or another technical partner and the survey should be organized in consultation with a SRL. The budget for all lab work to be done by an SRL should be agreed before the start of the survey.

Please see the laboratory chapter for guidance on which second line drugs to test for.

2. DIFFERENTIATION OF PATIENTS BY HISTORY OF PREVIOUS TREATMENT

Distinguishing between patients by their treatment history not only has implications for how drug resistance data is interpreted, but is also relevant for programmatic decisions regarding the type of treatment a patient is to receive[8,9].

Definitions should be strictly applied regardless of where the patient obtained the first treatment. Determining prevalence of drug resistance among new cases is vital in the assessment of recent transmission in the community In general; the group of previously treated cases is at higher risk for having a resistant strain of TB than the group of new cases and comprises a heterogeneous population of patients with regard to treatment history. Subcategories include patients who fail Cat 1, those who fail Cat 2, those who relapse soon after cured, those who relapse several decades after cure, patients treated in the private sector, patients that have been re-infected with another strain, those diagnosed before DOTS implementation and so on. This great variability increases the risk of misclassification and weakens the possibility of drawing comparisons between countries. Correct patient classification by treatment status is an important aspect of a good TB control programme and therefore should be integrated into any surveillance programme. It should be noted that while combining drug resistance data from both categories will reflect the overall disease burden in the community it will make the interpretation of data more difficult.

Most drug resistance treatment programmes will base case finding on risk groups, and therefore ability to correctly classify patients will become even more important. It is also important to note, that because surveys require detailed patient treatment history to be taken, it has been found that the proportion of retreatment cases is often

higher in surveys than in routine programmatic recording. This is an important finding in itself.

A. Sub-categories of retreatment cases

Surveys should routinely distinguish between the different sub-categories of retreatment cases. Patient intake forms should include several well designed questions to elicit the correct treatment history.

Treatment failure – patients failing anti-TB treatment, i.e. patients who begin treatment for smear-positive pulmonary TB and who remain smear-positive, or become smear-positive again, at 5 months or later during the course of treatment.

Relapse – patients who become smear-positive again after having been treated for TB and declared cured after the completion of their treatment.

Return after default – patients who interrupt their treatment for more than 2 months after having received a total of at least 1 month of anti-TB treatment and who then return with bacteriologically confirmed tuberculosis (return after default).

Some programmes, for instance those with considerable private sector involvement in TB diagnosis and treatment, may have a large population of patients that have had more than one month of TB treatment, but may not exactly fall into any of the re-treatment categories. These cases are commonly notified as return after default. Another option is to place them in a specially labelled category.

Chronic – patients who continue to be smear-positive after the completion of a re-treatment regimen. Patients who have failed a CatIV regimen or regimen containing second line drugs should be clearly indicated.

* Complete histories should include information about the regimen the patient failed, how many times they had been treated and with what regimen, and if they had been previously treated in the private sector. Obtaining history of hospitalization and/or imprisonment is desirable where possible.

B. Quality assurance and patient re-interview

WHO recommends that medical records are compared with patient information to ensure accuracy and that a percentage of patients are re-interviewed to quality assure patient classification. As a general rule WHO recommends 10% of patients should be reinterviewed, but feasibility must be determined by the programme. At a minimum it is recommended that all patients with MDR-TB are reinterviewed, but particularly new patients.

C. Separate sampling of retreatment cases

WHO recommends devising a separate sample for retreatment cases where possible, or extending the sampling period for retreatment cases (beyond the intake period for new cases) in order to have more robust information about this heterogeneous group of patients. In most cases it will be impossible to develop a separate sample for each sub-category of retreatment, or to select clusters different than the clusters selected for new cases; however if the sample is large enough there should be sufficient numbers of patients from sub-categories to draw meaningful conclusions.

3. LABORATORY

The laboratory is a crucial component of TB programmes but is often the rate limiting factor in the expansion of drug resistance surveys as well as programmatic management of drug resistant TB.

A. Quality Assurance

Proficiency testing

A national reference laboratory should be requesting and receiving a panel of isolates from a SRL annually for proficiency testing of drug susceptibility testing. A NRL must indicate to the SRL before the start of panel testing that appropriate biological safety facilities are available and functioning. A panel should always be completed successfully before the start of a survey. If results of panels are unsatisfactory (one error or more for INH or RMP) then the survey should be put on hold until satisfactory results are obtained. Annual panel testing is an important component of routine external quality assurance for the laboratory. When applying to

the Green Light Committee, applicants will be asked for their latest proficiency testing results[10]. SRLs, are open to discuss the results with the NRL and either the SRL or a lab consultant of another agency can provide coordinated assistance to improve culture and DST practices. If other laboratories are included in the survey then they should participate in a round of proficiency testing coordinated by the SRL (if it is the first time), but in subsequent rounds this process should be taken over by the NRL. All PT exercises should be double blinded. Current proficiency testing panels do not include isolates with second line drug resistance for evaluation. This component will be added as an option in future.

Rechecking

During the course of a survey a proportion of isolates should be rechecked by the SRL. It is recommended that between 5 to 10% of all isolates be rechecked, but this may not always be feasible and the proportion should be decided upon between the SRL and NRL before the start of survey. At a minimum all isolates with rifampicin resistance should be rechecked and the remainder of the 5-10% should be comprised of a combination of other resistance and fully susceptible isolates. In countries with low prevalence of resistance, all isolates with resistance should be rechecked. Lot Quality Assurance Sampling (LQAS) may provide a more labour efficient method for rechecking, but this has yet to be piloted in the context of drug resistance surveys.

B. DST for first line drugs

Standard practice for drug resistance surveys has been to test for four first line drugs (H,R,E,S). Some countries also routinely test for PZA. For the purposes of surveys NTPs should conduct, at a minimum, DST for INH and RMP on all cases included in the survey.

C. DST for second line drugs

A global task force meeting was held in Geneva in October 2006. During this meeting the definition of XDR-TB was revised to the following: isolates with at least resistance to isonizaid and rifampicin and further resistance to a fluoroquionlone and one second line injectable agent (aminoglycosides: amikacin, kanamycin, or the polypeptide capreomycin). The definition was revised to reflect clinical importance of this resistance pattern, as well as reliability of DST for second line drugs[11],[12].

WHO will coordinate a meeting in Q2 of 2007 to revise guidelines for the susceptibility testing of second line drugs and will develop a plan for proficiency testing for second line DST. Until this revision takes place WHO recommends that NTPs that have not started second line testing wait for these new recommendations, or start testing only for fluoroquinolones, aminoglycosides and capreomycin under the guidance of a SRL. At this time it is not recommended that NTP' conduct DST for the thioamides, cycloserine, or PAS as reproducibility of testing is poor. As soon as proficiency testing exercises are established for DST of second line drugs, WHO recommends that NTPs that are conducting SLD DST engage in quality assurance exercises with a SRL.

Recommendations for how to approach DST for second line drugs within a surveillance network, standard drug resistance surveys, or surveys of risk groups are discussed in an earlier section of this document labelled XDR-TB. If a laboratory is developing a panel for second line drugs to be tested, WHO recommends the following:

Recommendations for selection of second line drugs to conduct drug susceptibility testing for:

-fluoroquinolones: ciprofloxacin or ofloxacin as resistance between these two quinolones is generally considered to be complete. It is further recommended that the SRL test all isolates showing resistance to ciprofloxacin or ofloxacin to a later generation quinolone (moxifloxacin is the drug most commonly selected) as the proportion of cross-resistance is not completely established.
-aminoglycosides: amikacin and/or kanamycin should be tested for. Preference should be given to the drug most used in the country, if known.
-capreomycin: capreomycin should be included in all panels.

D. New methods

Standard methods for culture and DST on solid media are well described in the current guidelines. Using MGIT 960 is also standard practice for first line drugs and more recently for second line drugs[13],[14] and should follow manufacturer's instructions. Currently there is interest in exploring the use of molecular methods for routine surveillance purposes. Use of these methods may have the following advantages,

decrease costs of shipping (because live material is not required), may decrease the workload of the NRL (if conducted outside the NRL) allowing the NRL to focus on diagnostics and supervision of the network. Molecular tests for INH and RMP show very high concordance with conventional methods, tests for other drugs are not yet well established. Use of molecular methods for purposes of surveillance are currently under evaluation, and data should be available shortly. If proven to be feasible molecular based surveys may provide a relatively fast and reliable alternative to time consuming and labour intensive phenotypic based surveys. NTPs with interest in incorporating molecular methods should discuss with WHO and/or another technical counterpart about the feasibility within their country.

4. OTHER AREAS OF CONSIDERATION

A. Coordination and survey protocol

All planned surveys should have a team designated as responsible for the survey. In our experience the most successful surveys will always have a clear outline of team members and specific roles and responsibilities. This team usually includes at least the head of the NTP and the director of the NRL. A survey protocol should be developed and should take into account all aspects of the survey: team members' roles, objectives of the survey, sample size and design, logistics, ethical considerations, quality assurance, budget and timeline. WHO and other technical partners can assist in survey protocol development. If the NTP is interested in having data included in the Global Project, then the survey protocol should be reviewed by WHO before the start of the study to ensure that all requirements are met.

B. Ethical issues

Drug resistance surveys are primarily considered a tool for programme evaluation and monitoring and there are important ethical issues that must be considered when designing a survey. In particular availability and provision of appropriate treatment and management of patients identified with MDR-TB should be documented in detail in the survey protocol. If treatment for MDR-TB with second line drugs is available in the country identified patients should be provided access to this treatment. If treatment with second line drugs is either not available or believed to be sub-standard the protocol should document plans to establish a treatment programme

following international guidelines, and investigators should consider use of patient consent forms. If there is an ethical committee or review board in the country, a survey protocol should be submitted for review. If there is no ethical review board in the country, WHO and partner organizations can provide assistance in working through this component of the protocol or submitting the protocol through their respective ethical committee or review board.

C. Quality Assurance

Quality assurance is a crucial aspect of drug resistance survey, and quality should be checked at every stage: the patient interview, transport of specimens, data entry and laboratory. Actions to ensure survey quality should be written explicitly in the survey protocol.

D. Dissemination and use of survey data

Discussion of survey data within the NTP and public health sector is important for the evaluation of various aspects of the TB programme. Programmes should examine the proportion of different patterns of drug resistance in the area surveyed, among different sex and age groups and by treatment history. Survey data should be discussed in the context of programme data (i.e. proportion of failure cases, and default) and of any information on current prescribing practices within and outside of the NTP. Such discussions could also establish a better understanding of the purpose of surveillance within different components of the NTP (laboratory workers, clinicians and health workers, epidemiologists and pharmacists). Because drug resistance surveys can also provide a platform for operational research, evaluation of the process is often worthwhile, and with particular attention to what worked well, what did not work well, and how things might be done differently.

E. Budget

The current average cost of nationwide surveys falls between 40,000-100,000 USD based on an average sample size of approximately 1000 patients. The current cost of an XDR-TB survey of risk groups, if all lab work is outsourced, is between 20,000 and 60,000 USD, based on a sample of between 100 and 200 cases. If culture is conducted in the country the costs decrease considerably.

The Supranational Laboratory will play a crucial role in providing quality assurance for surveys as well as assistance to the routine functioning of NRL performance after a survey is completed. SRLs must be compensated for their work. All budgets requiring the services of SRLs should include cost for technical assistance of SRLs, cost of retesting isolates and all lab work, cost of shipments to and from SRLs for quality assurance or referral of specimens/isolates. Below are some average costs that can help in budgeting for grant applications

Average international shipment cost of specimens/isolates is 500 USD, but can reach over 1000 USD. Average cost of rechecking 5 first line drugs is 35 USD, second line drugs is 45 USD, and primary culture falls between 10 and 20 USD depending on methods used. These include consumable costs only. There may also be important costs associated with the human resources required to process additional specimens and/or lab running costs. Please ask your SRL for the specific costs for these items and ensure all survey budgets, national budgets, and/or grant budgets anticipate these costs.

Additional information to help in budgeting surveys for grant applications can be found at the following website:
http://www.who.int/tb/dots/planningframeworks/gf_tb_proposals_preparation/en/index.html

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