Expanding culture and drug susceptibility testing capacity in tuberculosis diagnostic services: the new challenge

LAboratories form the foundation of the national tuberculosis control programme (NTP) and are one of the first points of contact for tuberculosis (TB) suspects. Confidence or mistrust of TB patients in the health system and the NTP will be initiated at this point. As highlighted in the new World Health Organization (WHO) Stop TB Strategy launched on World TB Day 2006,1 bacteriology is vital for DOTS expansion and control of drug resistance. A network of well-performing laboratories is crucial for implementing the strategy. By responding quickly and providing quality services, including culture, the laboratory network will enable the early diagnosis of TB, hence reducing transmission of both drug-susceptible and -resistant TB, enabling appropriate treatment of disease and minimising the risk of possible complications, including death.

Early laboratory diagnosis of TB still relies on the microscopic examination of respiratory specimens for acid-fast bacilli (AFB). The technique, although old and certainly not ideal, is relatively simple, not very expensive and currently indispensable in the detection of the most infectious cases of pulmonary TB.

As culture of mycobacteria provides the definitive diagnosis of TB, it is considered the gold standard for the bacteriological confirmation of the disease. Culture on solid media, especially Löwenstein-Jensen and its modified version introduced by the International Union Against Tuberculosis and Lung Disease (The Union), is the most widely used technique. Culture is much more sensitive and specific than smear microscopy. The main disadvantage, however, of the culture technique using traditional methods is the extended time required (i.e., 4–8 weeks) for growth of mycobacteria on a solid medium and unwarranted delay in treatment due to the absence of a confirmed diagnosis. In addition, the requirements for performing culture include a suitable infrastructure (including bio-safety measures), sound technical skills and motivation of the laboratory personnel.

Despite the evident difficulties associated with utilising this technique, strengthening culture and drug susceptibility testing (DST) capacity at country level is necessary to address multidrug-resistant TB (MDR-TB), especially in Europe, and the human immunodeficiency virus (HIV) associated TB emergency in Africa, where a large proportion of cases are sputum smear-negative.

A recent publication emphasised that developing culture capacity in resource-limited countries is not a priority.2 While smear microscopy must be improved and maintained, the WHO takes the position that strengthening culture capacity to address MDR-TB, and providing the ability to confirm the diagnosis of TB, especially in HIV-infected patients, is necessary. Furthermore, the increased resources at the country level through funding mechanisms, especially the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM), provide an opportunity to implement more ambitious laboratory strengthening plans. These comprehensive efforts will contribute to achieving the World Health Assembly targets as well as the Millennium Development Goals (MDGs) related to TB control.3,4

SITUATION ANALYSIS

In most resource-limited countries, AFB smear microscopy is the primary, and often the only available technique for microbiological diagnosis of TB. However, to ensure the reliability of laboratory results, external quality assurance (EQA) systems for smear microscopy should be implemented systematically. Some countries started the process in the past; however, due to insufficient financial and human resources, such attempts remain sporadic and unsatisfactory.

Currently, only 15 of the 22 high TB burden countries (HBCs) have a fully functional national reference laboratory (NRL). In addition, four of the 22 HBCs do not have an EQA scheme, while the remaining HBCs have reported limited implementation.

It should be noted that the AFB microscopy technique has limitations for TB diagnosis in patients with HIV co-infection, paediatric TB, extra-pulmonary TB and for identification of MDR-TB. Culture techniques are used in both middle- and low-income countries as a diagnostic tool for these reasons. The outcome of the recent survey performed by Tropical Disease Research (TDR) confirmed that the number of cultures for TB diagnosis performed in the public sector exceeds 15 million yearly.5 Further, it was determined that more than 600 000 cultures are performed annually in the WHO Africa Region alone.

To guarantee reliable results, all laboratory techniques must be performed by appropriately trained staff working according to standardised operating procedures in safe, properly equipped laboratories and according to clear national and international proficiency and quality standards. Unfortunately, these requirements are not met by many NTPs, resulting in unreliable results.
Improved laboratory performance for TB control can strengthen general laboratory capacity and be beneficial for the primary health care network and key disease control programmes. One example is the collaboration between the TB and HIV control programmes, where HIV testing of TB patients is expanding significantly,* but promotion of diagnosis of TB in HIV-positive patients is still needed.

**CONSTRAINTS**

Although TB diagnosis and monitoring of treatment response rely on bacteriological examination of clinical specimens, the laboratory network remains weak in most countries. Unsatisfactory performance of TB diagnostic services is attributed to a combination of several factors:

- Problems related to the availability and accessibility of TB diagnostic services
- Underestimation of the importance of the TB laboratory network performance and quality assurance by planners
- Weak communication between the NTP and the NRL, which are often unlinked structurally within the government organisation
- A deficient quality assurance system for sputum microscopy, culture and DST
- Inadequate human resources, with low numbers and often limited capacity of laboratory staff
- Insufficient financial resources often resulting from inadequate planning and poor awareness, despite a much greater influx of external resources available
- Delay of technology transfer from industrialised to resource-limited countries
- Lack of proper coordination with non-public health laboratories.

**LABORATORY STRENGTHENING EFFORTS IN THE FRAMEWORK OF THE STOP TB STRATEGY**

To address deficiencies in laboratory performance, the DOTS Expansion Working Group (DEWG) established the Subgroup on Laboratory Capacity Strengthening (SLCS) in August 2002 to assist countries in strengthening their laboratory capacity to extend the provision of reliable, high-quality diagnostic services. The Subgroup consists of the members of the supranational TB reference laboratory network (SRLN), other laboratory experts and representatives from international and national organisations involved in strengthening and maintaining proficient TB laboratory diagnosis (e.g., The Union, KNCV Tuberculosis Foundation, the US Centers for Disease Control and Prevention, the Japan International Cooperation Agency [JICA], the Association of Public Health Laboratories, Management Sciences for Health, the German Leprosy Relief Association and PATH). The Subgroup secretariat is based at the WHO headquarters. The Laboratory Subgroup meets annually to discuss important strategic and technical issues.

In addition, the WHO developed a 4-year strategic plan 2006–2009 for the improvement of laboratory capacity and to ensure that the laboratory network will actively support the TB diagnosis procedures underlined in the new Stop TB Strategy and the Global Plan to Stop TB 2006–2015. The laboratory strategic plan focuses on the following aspects:

- improvement of AFB microscopy
- standardisation of laboratory materials, including training curricula
- assessment of the laboratory network in high-burden countries world-wide
- country support (planning, training and identification of funds)
- monitoring and evaluation of laboratory improvements
- supporting the development and testing of new diagnostic tools under field conditions
- facilitating the transfer of existing modern technology to resource-limited settings
- developing/strengthening culture and DST capacity, and
- supporting the development of operational research agendas.

The laboratory strategic plan provides the main work direction at the international, regional and country levels. It was endorsed by the SLCS during the annual Subgroup meeting in October 2005 in Paris, France, and should be the basis for the development of country and regional plans on improvement of TB diagnostic services.

During its third annual meeting, in November 2004, members of the Subgroup issued an official statement recommending that NTPs perform culture whenever needed according to national policies. The recommendation of the use of culture for diagnostic purposes is not an innovative approach. In 1998, the WHO and experts from partner organisations, including The Union and the SRLN, developed and published guidelines on Laboratory Services in Tuberculosis Control. In these guidelines, the use of culture was recommended for drug resistance surveillance, cases with clinical and radiological signs of pulmonary TB where smears are repeatedly negative, diagnosis of extra-pulmonary and childhood TB, follow-up of TB cases who fail a standardised course of treatment and who may be at risk of harbouring drug-resistant organisms, and investigation of high-risk individuals who are symptomatic, such as labo-

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* Preliminary analysis of data reported by countries for inclusion in the WHO 2007 Report on Global Tuberculosis Control.
ratory workers and health care workers looking after multidrug-resistant patients.

Careful examination of the recommendations of 1998 and those issued by the SLCS in 2004 reveal their consistency. However, in the past few years, epidemiological and programmatic conditions have significantly changed:

- In some settings, the number of sputum-negative TB cases is increasing, mainly due to the HIV epidemic.
- Many countries are implementing drug resistance surveys and are monitoring the trends of MDR prevalence at regular intervals.
- Second-line drugs are available, and the DOTS-Plus strategy for treatment of MDR cases is being mainstreamed into the DOTS programmes of an increasing number of countries.
- Increased resources are available for TB control through the GFATM, the Development Banks and bilateral mechanisms.
- Culture is widely used even in resource-limited countries. Therefore, there is already a foundation to build upon and to promote expansion of quality assured services.

In the light of the above, the WHO advocates for more extensive use of culture as an indispensable tool for effective management of MDR-TB and for definitive diagnosis of smear-negative patients, especially those who are HIV-infected.

NEXT STEPS

To address the global emergency and new challenges in TB diagnosis, all countries should develop/strengthen their capacity to perform proper smear microscopy as well as culture and DST according to national policies. The success of such an advance will depend on strict adherence to standardised operating procedures for performing culture and DST. In addition, relevant technical documents and training material to strengthen the technical capacity and increase the overall performance of laboratories should be available.

The importance of the laboratory in TB control is gradually gaining the attention it deserves. More laboratory assessment missions are taking place, and technical assistance and guidance for improvements in TB laboratory performance are being provided. Standardised training packages on sputum smear microscopy, culture and DST are under development. Related training programmes are supporting these activities. A number of technical documents and guidelines for TB laboratories are in progress, such as standard operating procedures (SOPs), quality assurance for culture and DST, and a compendium of performance indicators.

It is evident, however, that strengthening laboratory capacity to perform quality culture will require a substantial increase in human and financial resources and the development of more effective collaboration between NTPs and partner institutions. Recognising the need for expansion activities, NTPs, NRLs, the WHO and key international organisations will continue to review the country/regional epidemiological data, organisation, structure and the role of the laboratory networks to determine needs and the resource requirements for laboratory strengthening.

The WHO recommends establishing one quality assured culture facility per approximately 5 million population in middle- and low-income countries.* Expansion of culture services should be progressive. The goal, as laid out in the Global Plan, is to ensure that in 2010, 50% of the global population has access to culture and DST services and that the scale-up be completed by 2015, covering more than 5 billion people.†

The WHO is actively following the progress of the development and introduction of innovative technologies in TB diagnostics. Subsequent to the conclusion of the demonstration tests under field conditions by the New Diagnostics Working Group, the DEWG will assist countries with the implementation of these techniques as part of routine NTP operations. This will require substantial efforts in registration of new products in countries, developing new policies, procurement of equipment, training of staff, supervision and financial support to perform the tests.

In 2004, the DEWG declared laboratory strengthening its highest priority for TB control. There is increasing recognition, for example in the Stop TB Strategy and the Global Plan to Stop TB, 2006–2015, that laboratory services are often the weakest link in TB control. In a deliberate effort to address this situation the Stop TB Department provided countries with a planning framework to facilitate the process of identifying the needs of national laboratory services and to define an adequate budget that should be included in their grant applications (e.g., GFATM).

Despite these efforts, current resources are insufficient to properly support countries in the development and implementation of their workplans for laboratory strengthening. The Global Plan to Stop TB calls for 800 new culture and DST facilities† at an estimated cost of 700 million dollars to reach the 2015 targets. This cost is for infrastructure, laboratory equipment and supplies alone. Detailed budgets will be required to anticipate the cost of technical support, quality assurance, human resources and training. Unless urgent attention is focused on expanded laboratory efforts for quality-assured services, i.e., microscopy, culture and DST, the targets for global TB

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* Data from Eastern Europe and Central Asian countries not included.
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control and the TB-related Millennium Development Goal (Goal 6; Target 8) will not be reached.

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