Roles of laboratories and laboratory systems in effective tuberculosis programmes

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Abstract Laboratories and laboratory networks are a fundamental component of tuberculosis (TB) control, providing testing for diagnosis, surveillance and treatment monitoring at every level of the health-care system. New initiatives and resources to strengthen laboratory capacity and implement rapid and new diagnostic tests for TB will require recognition that laboratories are systems that require quality standards, appropriate human resources, and attention to safety in addition to supplies and equipment. To prepare the laboratory networks for new diagnostics and expanded capacity, we need to focus efforts on strengthening quality management systems (QMS) through additional resources for external quality assessment programmes for microscopy, culture, drug susceptibility testing (DST) and molecular diagnostics. QMS should also promote development of accreditation programmes to ensure adherence to standards to improve both the quality and credibility of the laboratory system within TB programmes. Corresponding attention must be given to addressing human resources at every level of the laboratory, with special consideration being given to new programmes for laboratory management and leadership skills. Strengthening laboratory networks will also involve setting up partnerships between TB programmes and those seeking to control other diseases in order to pool resources and to promote advocacy for quality standards, to develop strategies to integrate laboratories' functions and to extend control programme activities to the private sector. Improving the laboratory system will assure that increased resources, in the form of supplies, equipment and facilities, will be invested in networks that are capable of providing effective testing to meet the goals of the Global Plan to Stop TB.

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Introduction

The laboratory has always played a critical role in diagnosing tuberculosis (TB) and monitoring its treatment. In the new millennium, the strength of the laboratory network is often a direct reflection of the success of TB control programmes. Developed countries have taken advantage of new technologies that provide rapid detection, identification and drug susceptibility testing of *Mycobacterium tuberculosis*, hastening the decline of the prevalence of the disease[1–3] when combined with good treatment programmes. In contrast, many developing countries are burdened with high rates of TB and struggle to provide good-quality microscopy, with access to culture and drug susceptibility testing (DST) being scarce to non-existent. For a long time, countries have demonstrated effective TB control using microscopy-based diagnosis and monitoring combined with well-managed treatment programmes. However, inadequate management and support of TB programmes and the laboratory networks are hindering progress against the disease. Also, the complications stemming from the HIV epidemic and multidrug-resistant TB (MDR-TB), especially in Africa and eastern Europe, prevent effective TB control that relies entirely on microscopy-based case detection and management. Effective control involves access to laboratory services at every level, which requires managing and supporting laboratory networks that provide reliable and consistent decentralized services. Although laboratory strengthening is beginning to gain higher priority on the TB agenda, as reflected in the new Stop TB Strategy, more efforts are needed to improve access to and utilization of existing diagnostics as well as to develop and implement new technologies.[4,5]

Modern techniques such as fluorescence microscopy (FM), use of liquid cultures for isolation and DST, and amplification for detection of and/or for study of drug resistance are expensive, labour-intensive or relatively slow. Increased interest has therefore emerged in developing new diagnostics and in efforts to introduce modern diagnostic methods in developing countries. The Foundation for Innovative New Diagnostics (FIND) is now applying a systematic approach to research and development for new diagnostics.[6] Focusing solely on finance, techniques and new diagnostics, however, often ignores the need for well-trained staff, quality management systems and other prerequisites that underpin the standards of practice in developed countries. Clinicians will continue to forgo existing laboratory testing services and diagnose and treat empirically in situations where there is a lack of trust and credibility concerning the quality of laboratory results.[7] Such failures to have adequate quality stan-

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dards highlight the urgent need to focus also on strengthening the laboratory system in parallel with efforts to implement new techniques and methods. The problems of MDR-TB and the recent outbreaks of extensively drug-resistant TB (XDR-TB) provide a compelling rationale for increasing capacity for culture and DST services.[8] In turn, the complexity of providing such services is driving discussion and analysis of how to build laboratory capacity that far exceeds the training, human resources and networks required for microscopy centres. For countries where TB laboratory services are integrated with general laboratory services or where there is a large private sector, there is also a question of whether national tuberculosis programmes can successfully improve the quality of and access to laboratory services in the absence of combined efforts by all health programmes to support a general initiative of laboratory capacity-building. Past efforts to provide a separate and parallel system of TB microscopy practices, records and monitoring may be insufficient to meet the demands of improving TB laboratory services in the context of changing health systems.[9] There is growing recognition that the quality of TB laboratory networks serves as either the catalyst or rate-limiting step for further progress in TB control. This paper outlines some of the key technical and organizational challenges associated with microscopy, culture, DST and the corresponding safety issues. The different components of successful laboratory services will also be examined, concentrating on human resources, research, quality management systems and laboratory network structure.

Microscopy

Microscopy remains the mainstay of rapid TB case detection, especially for those patients who are most infectious to others, with the bacterial load involved often reflecting the extent of disease requiring immediate treatment. In most countries, especially those with the highest burden of TB, the direct Ziehl–Neelsen (ZN) smear is still the most common test. However, its sensitivity depends on the diligence of the technician and on use of the appropriate technique. The co-epidemics of HIV infection and TB, especially in Africa, and concerns that the ZN smear has lower sensitivity in those with HIV infection, have stimulated interest in practical methods to improve microscopy.[10,11] Industrialized countries often use concentrated smears and FM, a combination showing high yield also in low-income, HIV high-prevalence countries, but requiring greater resources.[12] Further operational research to demonstrate the effectiveness and acceptance of this diagnostic combination under field conditions is required before it can be widely recommended.[13–15] Also, external quality assessment (EQA) programmes are needed to ensure that smears are performed and interpreted correctly and that all microscopy centres achieve an accepted level of performance.[16] Effective EQA programmes are, however, labour-intensive and complex, requiring dedicated staff for onsite supervisory visits and to recheck results for a relatively large workload of smears.[17,18] Although international guidelines recommend rechecking a blinded random sample of smears, many regions and countries have either not fully implemented rechecking or still use unblinded rechecking, the results of which are ineffective and misleading.[19,20] The implementation of EQA for microscopy has the advantage not only of strengthening laboratory networks but of improving diagnostic quality.[21] Systematic review by a laboratory expert is probably the most important component of strengthening network management, but is often limited by the cost and time involved. In integrated health systems, one solution is to broaden the scope of onsite supervision to include review and monitoring of other testing and diagnostic services, such as those for HIV, malaria, biological chemistry and haematology. Although such an integrated review would provide less attention for TB, it is a more efficient and cost-effective use of human resources, and reflects the common practice for laboratory accreditation in many high-resource countries.

Culture methods and drug sensitivity testing

The use of culture methods for TB diagnosis and of DST are standard practices in high- resource countries; however, many low-resource countries still struggle to provide culture methods for priority needs such as drug resistance surveillance (DRS), extrapulmonary and childhood TB, and MDR-TB. There is considerable debate about the feasibility and cost of providing culture for routine detection of TB cases in the high-prevalence setting, not to mention what is the most appropriate diagnostic algorithm to use.[22] However, many high-burden countries have not even developed the basic capacity for accurate and reliable culture for DRS and diagnosis of MDR-TB, as shown by the lack of data on drug resistance in most of the high-burden countries.[23] Additionally, national TB programmes need to promote appropriate use of the current limited culture capacity so that priority requests are met and TB laboratory services are made available throughout the country, and not just in selected urban areas.[24] Recent outbreaks of XDR-TB have helped to focus attention on the selection of DST for diagnosis as well as for surveillance. The use of direct specimen testing for rifampin resistance using nucleic acid amplification tests (NAAT) avoids the difficulty in providing rapid, comprehensive and accurate DST for diagnosis using culture methods. NAAT also offers the promise of centralizing testing services without the "cold chain" transport systems required for culture.[25] However, further improvements in the sensitivity, cost and robustness of NAAT must be achieved before it can be generally adopted by most laboratories.[26] For example, cross-contamination of cultures can easily lead to false positives.[27,28] Also, DST and NAAT require training, EQA and standard practices to achieve the levels of accuracy required to establish credibility and to justify the resources needed to further expand services.

Human resources

Management of microscopy networks and referral laboratories for culture and DST require highly skilled laboratory scientists, who are either in low supply or often unwilling to work in low-paid government jobs. For many countries the human resources crisis is limiting laboratory services at all levels. At the peripheral level, the shortage of laboratory technicians is forcing countries to train a new cadre of individuals with little or no formal education. For acid-fast bacilli (AFB) microscopy and HIV rapid tests, these individuals who have been trained "on the job" can perform as well as formally trained laboratory technicians, but the training programmes must be well thought out and supported at all levels, and need routine EQA to monitor performance.[18,29] The formal

training for laboratory technicians (or technologists) may vary by country, ranging from a 2- to 3-year diploma to a university degree. With the increased focus on skills for culture methods and DST, more attention will need to be given to the curriculum and requirements of laboratory technology to assure that graduates have the competencies required for increasingly specialized work. Perhaps one of the most glaring human resource deficiencies is the lack of programmes for laboratory managers and leaders. Whereas in many high-resource countries doctorates are required to direct a laboratory, in many African countries it is difficult to find laboratory staff at the national level who possess a graduate degree. Additionally, many doctorates focus on research, with little or no training in laboratory management and, unlike medical degrees, are associated with no clear career path. Laboratory management and network management are underestimated capacities that will require new mentoring and training activities in order to provide the next generation of leaders to implement new technologies and programmes.

Laboratory network structure

The challenge to developing effective laboratory networks must take into account the evolving structure of the health-care system. Most high-resource countries have large private health-care systems, including laboratories, which provide high-quality care and services. Although the quality of care correlates with resources, factors such as laboratory quality standards and regulations, mandatory reporting of cases of TB and other infectious diseases, and specific public initiatives to work with private providers have also been responsible for successful integration of disease control programmes with private health care.[30,31] However, in many countries with a high burden of TB, there is a struggle to monitor and assure the quality of testing and reporting in the growing private laboratory sector. In such settings, the national TB programmes and national reference laboratories (NRLs) must develop strategies to enrol private laboratories in EQA programmes and require reporting and referral of TB cases. However, it is unlikely that these bodies alone will be able to secure both national legislation and the resources to establish programmes that only monitor TB testing in private laboratories. This will probably require efforts to establish partnerships with other health programmes to lobby for national laboratory standards and sufficient structure to implement regulations.

A key issue is the organization of the TB laboratory services in relation to the national TB programme and the general health services. The traditional model is to have the NRL located within the national programme. An advantage of this arrangement results from the close cooperation between the two, which assures that the laboratory activities are closely aligned with the needs of the programme and receive appropriate support. The disadvantage of having a "stand-alone" TB NRL versus a TB section in an NRL facility with integrated laboratory services is that it can result in a rather small national TB laboratory with limited staff and service support. A larger integrated NRL offers many smaller countries the opportunity to share services such as support staff, equipment and supplies, and provides a greater critical mass of laboratory peers who can share technical expertise. An integrated NRL may also benefit from sharing quality assurance, information technology and specimen transportation functions. The choice may be even more pressing at the intermediate level. For individual programmes, many countries cannot raise the human and other resources required for quality assurance and other tasks at this level. The concern associated with having a TB section within an integrated NRL is to assure that the laboratory activities and support are closely aligned with the national programme. Furthermore, the laboratory requirements may be so much higher than those of the general services or other programmes that integration will be difficult. Representatives from all sectors of the health-care system should look strategically at what is the best structure for expanding and improving laboratory services.[32]

Laboratory safety

Safety is a continuing concern for laboratory staff at all levels who work with specimens and cultures containing *M. tuberculosis*. It is the responsibility of the NRL and the national TB programme to address such concerns through a combination of training and education to help promote risk assessment and safe practices, and also to support reasonable safety improvements with respect to equipment, supplies and facilities. Microscopy carries a low risk if direct smears are prepared carefully in well-ventilated areas.[33] Rather than purchase biological safety cabinets that are difficult to maintain, microscopy centres should invest in simple cabinets or "fan boxes" that are relatively inexpensive and efficiently exhaust air without filters, provided that they have sufficient extraction power.[34] When suitably installed, such cabinets can offer a level of protection that reassures technical staff. The process of culture, identification and DST has well-defined risks of causing laboratory-acquired infections. These risks present a challenge to countries in terms of supporting appropriate facility design and engineering, training and adherence to safety practices, and use and maintenance of biological safety cabinets. As countries expand their culture capacity, there will be a need for guidance and decisions on minimum safety standards that are affordable and sustainable.

Quality systems

The quality of testing services for TB remains a major barrier for microscopy, culture, DST and newer NAAT methods. Many countries are still struggling to expand effective EQA to all microscopy centres, both public and private. Effective EQA is even more important in the presence of HIV infection, with concerns that many patients will have paucibacillary specimens requiring detection of only a few AFB to make the diagnosis of TB. In the meantime, EQA may be the most practical approach to immediately improve test sensitivity, while further evidence is being obtained on the appropriateness of methods such as FM and concentration techniques, and new diagnostics are tested.[35] EQA is one component of quality and there are proven programmes for measuring performance of microscopy and DST.[36] One of the most effective is mentorship of NRLs by supranational reference laboratories and exchange of strains between them in order to measure performance in support of global drug resistance surveillance. Culture performance is often harder to measure, and existing EQA programmes do not necessarily estimate sensitivity in this respect. The low efficiency of culture methods in some settings is illustrated by surveillance for drug resistance, where some laboratories may have difficulties in isolating *M. tuberculosis* from smear-posi-

tive specimens. These quality problems cannot be solved only by EQA and must be dealt with by total quality management systems that include all the components involved: documents, records, personnel, standards, facilities and quality control. In this respect, one critical difference in many developed countries is the presence of laboratory regulations or accreditation programmes.[37] Until countries develop, implement and monitor laboratory standards by regulation, a minimum step is to develop an accreditation process for NRLs.

Research

TB laboratories also play a pivotal role in performing research, especially operational research that supports evidence-based decisions for guiding laboratory practice. Whenever possible, such research should be performed in the field in low-resource settings, where the conditions represent the situation in most countries with a high burden of TB. In contrast, research performed in academic centres that have human and material resources that differ from those in public-sector services in low-resource countries may not always provide reproducible results under programme conditions. Research carried out to improve diagnostic methods and techniques can be published in the literature and guide countries' decisions about implementing changes in technology and procedures. Many NRLs have the interest in and the capacity to perform operational research, and can be encouraged to carry it out if provided with training in research methods and by developing partnerships with research-focused institutions such as universities. It is important, however, to ensure that the NRL and other institutions balance research activities with priority initiatives to monitor and support the laboratory network. Financial and other incentives that are only available for research activities lead to misplaced priorities and neglect of the daily support that laboratory networks provide for TB control.

Conclusion

Laboratories are not just technologies, equipment and buildings; they are people and systems that manage the processes and standards required to produce accurate and timely results. Successful implementation of new diagnostic tests will still require functional networks of laboratories with trained and motivated staff, quality management systems and safe working environments. The Global Plan to Stop TB calls for 800 new culture and DST facilities at an estimated cost of US$ 700 million to reach its 2015 targets.[38] The Global Fund to Fight AIDS, Tuberculosis and Malaria can help with these costs; however, there will also have to be a corresponding requirement for attention and investment in people, organizations and systems to successfully expand services. Resources for commodities are increasing; nevertheless, currently neither funds nor efforts are directed towards addressing the human resources needed for EQA, guidance and processes to establish and enforce quality systems, practical and reasonable safety standards and steps to determine optimum organizational structures and requirements for TB laboratory services. Rather than assuming that technological developments are the only way to improve TB diagnosis, international organizations and countries should work immediately to strengthen laboratory leadership and systems through shared guidance at the global level. The solutions, in the form of technical guidance, effective quality assurance, systems and capacity building are all-attainable, but will require a new focus on the laboratory as a system. Also needed is coordination and support from organizations and countries in the Stop TB Partnership to develop the people and networks in tandem with improvements in facilities, equipment and methods. A new focus on expanding and strengthening laboratory systems for quality-assured services, that is microscopy, culture methods and DST, will help achieve the targets for global TB control. ■

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Résumé

Rôles des laboratoires et des réseaux de laboratoires dans l'efficacité des programmes de lutte antituberculeuse

Les laboratoires et les réseaux de laboratoire constituent une composante fondamentale de la lutte contre la tuberculose (TB), dans la mesure où ils assurent les tests diagnostiques, la surveillance et le suivi des traitements à tous les niveaux du système de soins de santé. Les initiatives et les moyens nouveaux destinés à renforcer la capacité des laboratoires et à mettre en place des tests diagnostiques innovants et rapides pour détecter la TB devront tenir compte de la nécessité, pour ces établissements, de disposer de normes de qualité et de ressources humaines appropriées, et aussi accorder une grande attention, non seulement aux fournitures et aux équipements, mais également à la sécurité. Pour préparer les réseaux de laboratoires à l'introduction de nouveaux outils diagnostiques et à une augmentation de leur capacité, il faut axer nos efforts sur le renforcement des systèmes de gestion de la qualité (SGQ) à travers l'apport de moyens supplémentaires aux programmes externes chargés d'évaluer la qualité des examens microscopiques, des cultures d'échantillons, des tests de pharmacosensibilité (DST) et des outils de diagnostic moléculaire. Les SGQ doivent aussi promouvoir le développement de programmes d'agrément, visant à garantir le respect des normes et à améliorer la qualité du travail et la crédibilité des réseaux de laboratoires participant aux programmes de lutte antituberculeuse. Il faut aussi veiller à prendre dûment en compte les ressources humaines à tous les niveaux des laboratoires et accorder une attention particulière aux nouveaux programmes destinés à améliorer l'administration des laboratoires et les compétences en matière d'encadrement. Le renforcement des réseaux de laboratoires supposera aussi de mettre en place des partenariats entre les programmes de lutte antituberculeuse et avec les entités s'efforçant d'endiguer d'autres maladies, afin de mettre en commun certaines ressources et de promouvoir l'application des normes de qualité, de développer des stratégies pour intégrer les fonctions des laboratoires et pour étendre les activités des programmes de lutte anti-TB au secteur privé. L'amélioration des réseaux de laboratoires permettra de garantir que les ressources supplémentaires fournies, sous forme de fournitures, de matériel ou d'installations, seront investies dans des réseaux en mesure d'effectuer des tests efficaces contribuant à la réalisation des objectifs du Plan mondial halte à la tuberculose.

Resumen

Contribución de los laboratorios y los sistemas de laboratorio a la eficacia de los programas antituberculosos

Los laboratorios y las redes de laboratorios son un componente fundamental de la lucha antituberculosa, pues realizan las pruebas de diagnóstico, vigilancia y monitoreo del tratamiento en todos los niveles del sistema asistencial. Los nuevos recursos e iniciativas requeridos para fortalecer la capacidad de laboratorio e implementar nuevas pruebas diagnósticas rápidas para la tuberculosis sólo serán posibles si se admite que los laboratorios son sistemas que requieren normas de calidad, recursos humanos apropiados y atención a los aspectos de la seguridad, además de suministros y equipo. A fin de preparar las redes de laboratorio para albergar nuevos medios de diagnóstico y una mayor capacidad, debemos centrar los esfuerzos en fortalecar los sistemas de gestión de la calidad invirtiendo más recursos en los programas de evaluación externa de la calidad de la microscopía, los cultivos, las pruebas de sensibilidad a fármacos y los medios de diagnóstico molecular. Los sistemas de gestión de la calidad deberían promover también el desarrollo de programas de acreditación para garantizar el cumplimiento de las normas destinadas a mejorar tanto la calidad como la credibilidad de los sistemas de laboratorio en los programas antituberculosos. Paralelamente hay que prestar atención asimismo a los recursos humanos en todos los niveles del laboratorio, considerando especialmente los nuevos programas respecto de la gestión de laboratorio y las aptitudes de liderazgo. El fortalecimiento de las redes de laboratorio exigirá también la creación de alianzas entre los programas antituberculosos y los que intentan controlar otras enfermedades a fin de mancomunar los recursos y de promover la adopción de normas de calidad, formular estrategias para integrar las funciones de los laboratorios y extender las actividades de los programas de control al sector privado. Mejorando los sistemas de laboratorio se logrará que se inviertan más recursos, en forma de suministros, equipo e instalaciones, en redes capaces de realizar pruebas eficaces con miras a alcanzar las metas del Plan Mundial para Detener la Tuberculosis.

ملخص

أدوار المختبرات ونُظُمها في البرامج الفعَّالة لمكافحة السل

تُعد المختبرات وشبكاتها من المقوِّمات الأساسية لمكافحة السل، لما تقدِّمه من اختبارات للتشخيص والترصُّد ومراقبة المعالجة على كل مستوى من مستويات من مستويات نظم الرعاية الصحية. إن المبادرات والموارد الجديدة لتعزيز قدرات المختبرات وتنفيذ الاختبارات السريعة والجديدة لكشف السل، تتطلَّب الاعتراف بأن المختبرات نُظُمٌ تحتاج لمعايير الجودة والموارد البشرية الملائمة والانتباه للسلامة وللمعدات والإمدادات. ومن أجل تهيئة شبكات المختبرات للتعامل مع المواد التشخيصية الجديدة ولتوسيع القُدرات فيها لابد من تركيز الجهود على تقوية نُظُم إدارة الجودة، وذلك من خلال توفير الموارد الإضافية للبرامج الخارجية لتقييم جودة الفحص المجهري، واختبار الاستجابة للأدوية والمواد التشخيصية الجزيئية، ولابد لنُظُم إدارة الجودة أن تعزز تطوير برامج الاعتماد لضمان الالتزام بالمعايير لتحسين كلٍّ من الجودة والموثوقية لنظام المختبرات ضمن برامج مكافحة السل. ولابد أيضاً من إيلاء الاهتمام لتلبية الموارد البشرية على كل مستوى من مستويات المختبرات، مع إيلاء اهتمام خاص للبرامج الجديدة لإدارة المختبرات ومهارات القيادة. وستشتمل تقوية شبكات المختبرات على إعداد الشراكات بين برامج مكافحة السل وبرامج مكافحة الأمراض الأخرى، وذلك من أجل تجميع الموارد وتعزيز الحملات الإعلامية لإعداد معايير الجودة، ولوضع الاستراتيجيات للتكامل بين وظائف المختبرات، ولمد نطاق أنشطة مكافحة السل إلى القطاع الخاص. إن تحسين نُظُم المختبرات سيضمن أن الزيادة في الموارد، بشكل إمدادات ومعدات ومرافق، ستكون استثمارات في شبكات المختبرات حتى يمكنها تقديم اختبارات فعَّالة لتحقيق المرامي للخطة العالمية لدحر السل.

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