Diagnostic testing in the control of tuberculosis

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One of the maxims of tuberculosis (TB) control has been that bad therapy is worse than no therapy at all. Early experience with streptomycin monotherapy and later experience with poorly administered multidrug regimens taught the medical community a clear lesson. Without an uninterrupted supply of high-quality drugs and assured adherence to standard regimens, treatment was likely to result in high rates of failure and rapid creation of drug resistance. Because of this, TB control efforts have reasonably focused more on curing cases than on detecting them. But good TB control depends on a balanced equation of case detection and treatment delivery. The global expansion of DOTS as a standard TB strategy and the advent of the Global Drug Facility are two significant events in the history of TB control, and bring us closer to delivering on the promise of good access to drugs and high cure rates for the majority of the world's TB sufferers within a few years. This is a justifiable source of enthusiasm, but should also bring us to take a second look at the other side of the equation: diagnostics and case detection.

Ten years ago, DOTS treatment programmes were available to less than 5% of the world's TB patients and treatment success rates were low. In such a setting, efforts to improve case detection or develop more effective diagnostic tests, seemed to be beside the point to some. The situation is much improved today, with roughly a third of all TB patients treated under DOTS and treatment success rates in that cohort surpassing 80%. Indeed, several high-burden countries (e.g. Cambodia, China, Peru, and Viet Nam) now report cure rates at or above 90%. The dedication of a strong international partnership to expanding DOTS coverage makes it likely that these improvements will continue, or even accelerate. With the improvement in cure rates, case detection becomes the rate-limiting step in controlling TB morbidity and transmission, and here we are doing miserably.

Globally, a minority of incident TB cases is currently detected and reported, and less than a fifth of all expected cases end up on central registries as smear-positive. Of the 22 high-burden countries, 16 report treatment success rates of over 70% with DOTS implementation but, alarmingly, only 4 high-burden countries have overall smear-positive detection rates over 60%. Those cases that are detected have often been symptomatic for months and many have had prior clinic visits and diagnostic testing. Most have infected a large number of contacts, perpetuating the epidemic. How did we end up in this predicament?

There are two culprits. One is sputum microscopy itself as the case-defining diagnostic tool. Sputum microscopy is insensitive, requires multiple visits, and is technically burdensome. Moreover, it functions best in cases of more advanced disease, performs poorly in many HIV-coinfected individuals, and is wholly inadequate for paediatric and extrapulmonary TB. Clearly, simpler and more sensitive diagnostic tests are needed. The Gates-funded Tuberculosis Diagnostics Initiative at the United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, along with many commercial and academic partners, is working to develop these tests. The second culprit is the international TB community and the general medical community itself, which has always emphasized quality of treatment over quality of diagnosis. In part because of the urgent need to increase cure rates and in part because public health thinking has been dominated by clinicians and not microbiologists, drug treatment has remained higher on the global TB agenda than diagnostics.

Presently, TB diagnostic services receive little attention. The few published reviews of TB laboratory services that exist demonstrate a precarious state of affairs. Laboratories are marginalized by TB programmes, and are too often staffed with overworked, untrained and unsupervised technologists who are forced to make do with substandard reagents and inadequate or broken equipment. The poor state of laboratories leads in turn to poor performance, perpetuating a vicious cycle of laboratory mediocrity reinforcing clinical irrelevance. This is dramatically illustrated in the HIV-prevalent regions of sub-Saharan Africa. Here, the percentage of symptomatic pulmonary TB suspects who are sputum smear positive is so low that there is an inevitable drift toward syndromic management.

It is tempting to think that there will be a technical solution to this problem, and that the development of a simple, rapid, point-of-care diagnostic test will rejuvenate or even replace TB laboratory networks. However, attempting to improve case detection by dropping new technologies into the hands of poorly performing laboratories will be unsatisfying at best. The introduction of new diagnostic methods without laboratory capacity to properly evaluate and implement them will generate waste, lead to confusion in reporting as case definitions change and delay the arrival of truly useful new technologies.

New diagnostic tools are indeed coming, even if in the short term none is likely to be the desired panacea. A handful of case detection tools have already reached the market in developing countries and have predictably found first use in the private sector. Commercial and non-commercial nucleic acid amplification tests are in use in many developing world reference laboratories. The former are too expensive and

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complex for most laboratories in disease-endemic areas and the latter plagued with variable performance. Other methods, including phage replication systems, novel culture media, and sensitive colorimetric growth indicators, promise the sensitivity of culture-based detection at a speed that makes it clinically relevant. Serological tests, much improved over the past decade, cannot yet supplant sputum microscopy, but are likely to find a significant role in increased case detection due to their simplicity of use. New, rapid, susceptibility testing methods and in vitro tests for latent infection have also been developed.

Unfortunately, objective information about the performance of those tests targeting developing world markets, and not usually subject to the scrutiny of a rigorous regulatory authority, is thus far almost uniformly unavailable. In most developing country mycobacteriology laboratories, operational research capacity is non-existent and procedures as simple as comparing two sputum processing or two staining methods are beyond reach. This means that performing the kind of careful clinical trials necessary to evaluate the performance of new diagnostic tests (phase III) will not be possible in most settings. Furthermore, studies designed to determine local cost-effectiveness and to support the integration of new tools into TB control programmes (phase IV), will require the wide communication gulf commonly found between laboratories and clinics to be bridged.

How do we remedy this situation? How do we improve case detection to decrease morbidity and transmission and to maximize the impact of DOTS? The first step is to give TB laboratories the support they need, allowing them to offer high-quality services using the existing tools in settings where treatment success rates are high. This means the provision of reasonable equipment and reagents, the training and support of adequate numbers of staff, the insistence on quality control, and proficiency testing and the sponsorship of communication links between clinical and laboratory services.

The second step is to coordinate international assistance for capacity building in TB laboratories of disease endemic countries. This is needed not only to improve the performance of standard methodologies but also to support operational research. Integrating operational methodological research into routine diagnostic laboratory activities can enhance quality assurance, encourage self-improvement, make work more interesting and eventually allow disease endemic countries to perform their own meaningful evaluations of diagnostic tools or methodologies. Help, in the form of research expertise, is often surprisingly close at hand. Academic centres with strong operational research capability are often located only a few miles or kilometres from public health laboratories, but because of differing philosophies and even mutual suspicion, collaboration between academic researchers and national TB control staff is rare.

The third step is the development of new diagnostic tools that respond to the needs of high-burden countries. Funds must be mobilized to stoke the discovery pipeline, speed the development of promising candidates, and perform the necessary phased laboratory and clinical trials. This work cannot be seen as peripheral to TB control activities. Several products will emerge from the diagnostics pipeline in the coming 3–5 years, and those tests that can prove their cost-effectiveness should rapidly be put to use by the public sector and integrated into existing case-finding efforts. Here again, crosstalk between universities and disease control agencies in TB-endemic countries would be critically useful. The phase III and IV studies — needed to put new tools into appropriate use — are clinical not laboratory trials and demand a unique degree of cooperation between the laboratory and the clinic. They require clinical trial experience — something rarely available in TB control programmes.

Accurate case detection is the Achilles' heel of the DOTS strategy. The success of current concerted efforts to stop TB will ultimately depend on our ability to detect patients early enough to institute curative therapy and interrupt the cycle of transmission. The direct and indirect costs generated by the TB diagnostic process are largely borne by patients and governments. Current low case-detection rates suggest that, in many cases, they are not getting their money's worth. If we are to have a realistic hope of achieving WHO target case detection rates, funding to support laboratory capacity strengthening and to speed development of improved diagnostics must be top of the agenda. Proper use of precious health resources, including drugs, depends on it. Public satisfaction with health services depends on it. The confidence of physician and other health workers depends on it. And in the end, disease control depends on it. ■

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