Editorial

Diagnosis of Tuberculosis – Present & Future

It is estimated that 15 million people will die from tuberculosis-related deaths by 2050. [1] Even today we stand far from elimination of tuberculosis despite intensified standard measures of control. After a period of global acceleration in 2001–05, the case detection rate worldwide decelerated in 2006 and 2007, reducing the likelihood of reaching the target of a case detection rate of at least 70% by 2014. [2] Though a substantial progress has been made in treatment of TB by the directly observed therapy, short course (DOTS) strategy, difficulty in case detection remains a major obstacle to global control of tuberculosis. Unfortunately, by the time most patients are treated, they have already infected many others and this failure to interrupt transmission results in reporting of more cases of tuberculosis than in the previous year.[2, 3]

Even in 2010, national tuberculosis programmes in disease endemic countries continue to rely largely on old and inaccurate methods such as direct smear microscopy, solid culture, chest radiography, and tuberculin skin testing. Human Mycobacterium tuberculosis infection is almost always acquired by inhalation of infected aerosol droplets, which are generated by people with active pulmonary disease. Our understanding of the interaction of M tuberculosis and the human host is still incomplete. This gap of knowledge has resulted over the years in emergence of many diagnostic tools with variable reliability. Still today no single diagnostic tool has come up as a single point of care tool.

The urgency has been there to develop an accurate, cheap tuberculosis diagnostic test that is applicable in tuberculosis and also in HIV endemic areas. But until recently the industry has avoided developing and marketing products for detection for TB diagnosis as it's a disease of the poor and lack of potential of these products in terms of generating profits. The scenario has changed over the past decade, as there has been a substantial increase in investment resulting in development diagnostic tests for TB. The private sector is increasingly engaged in public-private partnerships such as the Foundation for Innovative New Diagnostics (FIND), and many others to develop and deliver a pipeline of tests that are appropriate for disease endemic countries. [4] Developed countries has now come forward because TB is no more a disease of the poor only, it is strongly associated with HIV as well.

Biomarkers have come up as potential candidate for detection of tuberculosis in areas such as in patients with active disease, to predict durable (non-relapsing) treatment success; in patients with latent M tuberculosis infection, to indicate reactivation risk; and in people other than those with active disease, Biomarkers can allow stratification of individual patients according to outcome risks, thus easing targeted interventions that might not otherwise produce overall benefit.[5]

WHO has assumed the leadership in ensuring that new tuberculosis diagnostic policies are evidence based, and in line with the grading of recommendations assessment, development and evaluation (GRADE) approach to guideline development. In 2007, they endorsed the use of liquid culture systems and rapid tests for species confirmation through antigen detection. With this policy, liquid culture systems were made affordable and feasible in countries with high HIV prevalence. [6, 7, 8] Line-probe assays, based on reverse hybridisation technology, have consistently shown excellent accuracy for rapid detection of MDR tuberculosis resulting in endorsement of the use of these assays for rapid detection of MDR tuberculosis in smear-positive patients. [9, 10]

But in a country like ours which has resource limitation, use of selected non-commercial culture and drug-susceptibility testing methods are being used as an interim solution in reference laboratories with sufficient culture capacity. The conventional fluorescence microscopy is gradually being replaced by LED microscopy in all settings and LED microscopy is to be phased in as an alternative for conventional Ziehl-Neelsen microscopy in both high-volume and low-volume laboratories. In fact, WHO recently endorsed the use of the same-day microscopy approach with the number of specimen reduced to two with the concept of a same-day diagnosis, using two sputum smears collected on the same day. [11, 12] For the diagnosis of latent M tuberculosis infection, the use of IGRAs (IGRA=interferon-γ release assays) is increasing with the two-step approach being the most common strategy (initial tuberculin skin test followed by confirmatory IGRA testing), in countries with high disease burden due to limitation of both tests individually. [13]

But the diagnostic tool that has surpassed all expectation was the automated molecular test for tuberculosis, the Xpert MTB/RIF. It avoids most of the pitfalls of conventional nucleic acid amplification tests (NAAT) (safety, contamination, ease of use, etc). It showed excellent performance in both smear-positive and smear-negative

patients, and high accuracy for determination of rifampicin resistance with the ability to detect M tuberculosis directly from sputum in less than 2 h even in a simple setting. But its applicability in a low to middle income countries an effective diagnostic tool is still in doubt due to its high cost. Some other limitations are testing only for rifampin resistance, a platform that detects a relatively small number of mutations, and inability to indicate which patients are "sputum smear–positive" for reporting purposes, infection-control intervention, and treatment monitoring. [14]

Diagnosis of tuberculosis is still a difficult task even with so many existing tools. Still many newer diagnostic tool for tuberculosis diagnosis are in the pipeline including novel serological assays, detection of volatile organic compounds in breath, handheld molecular devices, microchip technologies, and tests that exploit approaches such as microfluidics, nanotechnology, proteomics, and metabolomics and so on. But the likelihood of development of a simple dipstick like, point-of-care assay that can perform as well or better than conventional smear microscopy, and can deliver results within minutes without any sophisticated equipment, in the short term is still not a reality .

The concept of appropriate technology is vital. In a limited resource setting, discarding 125 years old smear microscopy cant be done overnight . The integration of novel diagnostic techniques is going to be a continuum. It is clear that improvements in diagnostics are driving itself in a positive cycle in care. New and improved tests attract more funding which lead to better health outcomes and ultimately, improved outcomes in health care systems.

In Bangladesh where TB is endemic, somehow it is very difficult as a clinician to have a diagnosis that does not have TB as a differential no matter how remote the possibility is. This progress in tuberculosis diagnostics after nearly a century of neglect needs to be translated into improving the lives of patients with tuberculosis, and reducing the future incidence of tuberculosis. This aim can and must be achieved, but needs strong political commitment, sustained funding, and engagement of public and private stakeholders and civil society. Health systems must be strengthened so that patients do not delay in seeking care and have prompt access to appropriate treatment once they receive a diagnosis.

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