SUMMARY OF TB DIAGNOSTICS ARTICLE[1] FOR MSF WEBSITE

Introduction

A workshop proposed by the Diagnostics Working Group of the Federal Tuberculosis Taskforce was convened in Silver Spring, Maryland, in June 2011 to review the state of tuberculosis diagnostics development in adult and paediatric populations.

The objectives of the workshop were to initiate discussion and facilitate the identification and evaluation of diagnostic tools for tuberculosis and tuberculosis/human immunodeficiency virus (HIV) co-infection.

This article, which provides a summary of the key points discussed in the Clinical Research and Development of Tuberculosis Diagnostics track of the workshop, is divided by technologies and platforms currently under development or optimization, including (1) culture-based technologies, (2) molecular-based technologies, and (3) non-molecular, novel technologies for diagnosis.

The objective of the Clinical Research and Development Track was to bring together principal groups and researchers in the field of tuberculosis diagnostics to (1) identify and prioritize critical and important clinical research studies for the evaluation of current and future tuberculosis diagnostics, (2) identify and disseminate information regarding resources available to researchers, and (3) coordinate research efforts to ensure expediency of research critical to this field and to maximize efficient use of available resources.

The main topics of discussion included: improving diagnostic tests; moving from silos to synergy; current barriers and challenges with existing platforms; increasing productivity; and collaboration. In the nearly 3 days of presentations and discussions, 2 primary themes emerged: building and maintaining momentum and moving from silos to synergy.

Key messages from the article may be summarized as such:

- Collaboration is needed between Clinical Research Networks, Implementing Organisations, Fundamental Scientists and Research Organisations, and Product Development Organisations to create the synergy required to improve upon existing TB diagnostics tests.
- All current diagnostic tests for TB are laboratory-based and are only suited to regional laboratories, with the exception of smear microscopy and some nucleic acid amplification tests (NAATs), such as the GeneXpert platform and LAMP technique, which can be implemented

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[1] Nahid P, Kim P, Evans C et al. Clinical Research and Development of Tuberculosis Diagnostics: Moving From Silos to Synergy. J Infect Dis. 2012 Apr 3

at local laboratories. The LAM test has potential as a simple, inexpensive test but is too insensitive to be used as a screening test, especially in HIV negative patients.

- The limitations of laboratory-based methods and lack of capacity in resource-limited and highly endemic countries have resulted in a situation where globally around one-third of TB cases go undetected, detection in children remains poor, as many as 20% of TB cases in HIV infection are culture negative, and only a small proportion of multi drug resistant (MDR) TB is recognized at the time of initial TB diagnosis.
- NAATs are much more rapid than culture-based techniques but genotypic drug resistance testing (beyond mutations for rifampicin and isoniazid) has uncertain clinical implications and sensitivity can be lower in smear-negative samples. Further research on which mutations cause clinical resistance to which drugs should be prioritised (drugs identified as high priority for future research and incorporation into rapid diagnostics include pyrazinamide, the fluoroquinolones, and ethambutol).
- The cost and cost–benefit of the Xpert MTB/RIF test (run on the GeneXpert platform) and other potential NAATs need to be studied, with recognition of the fact that actual test costs extend beyond the cost of the cartridges and reagents and include costs for transport, personnel training, maintenance, waste disposal, mechanisms for assuring quality, and secure locations for storage. Similarly, when comparing these expenses to the use of the broadly available and inexpensive AFB smear, the costs of repeat testing as well as the societal costs of delayed and missed diagnoses, given the low sensitivity of this method for diagnosis, also need to be considered.
- Given the limitations of sputum as a diagnostic specimen, for example, in children or in extrapulmonary disease, the availability of a non-sputum-based, non-culture-based diagnostic in high-burden settings would represent a significant advancement in TB control e.g. a biomarker that could be used on a lateral flow device. LAM, detected in urine, is currently the only antigen biomarker available but lacks sufficient sensitivity (its use in the diagnosis of HIV-associated TB is under investigation). The discovery of a biomarker, or biomarker signature, which is both sensitive and specific enough for the confirmation of all versions of active TB in TB suspects should therefore be prioritized.
- Two exciting developments include: (1) The use of reporter enzyme fluorescence imaging, with MTB-specific beta-lactamase and substrate, has high potential as a sputum-smear replacement test and (2) The use of a “TB breath test”, which makes use of specific volatile organic compounds that are exhaled during TB disease and detected using “nose-based” technologies.
- Biomarker or surrogate marker research is needed not only for the development of TB diagnostic tools but also of easy treatment monitoring tools. The validation of biomarkers is highly dependent on well-preserved sample banks where samples are linked to well-documented clinical and socio-demographic data.
- Clinical trials and field studies should adhere to design and reporting

standards such as STARD (standards for the reporting of diagnostic accuracy studies).

Conclusions

- Although there is significant work under way to develop new diagnostic assays and devices for TB, a rapid, accurate, point-of-care, low-cost diagnostic has yet to be realized.
- Because TB principally affects people in limited resource settings, for any new TB diagnostic to have major public health impact, simplicity and low cost will be as important as analytical accuracy.
- TB diagnostics should also be assessed in terms of clinical impact beyond assessments of microbiological performance. Unfortunately, the current TB diagnostic research literature largely neglects the impact of diagnostic tests on patient-important diagnoses and outcomes.
- Through international input and consensus, the Stop TB Partnership of the WHO is developing a Global TB Research Roadmap (http://www.stoptb.org/global/research/).
- Synergy is needed from all stakeholders to drive the development of tests and to make sure that they are implemented where needed.