Discovery, Innovation, and New Frontiers in Tuberculosis Diagnostics: Reflections and Expectations

Karin Weyer
Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland

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On the evening of 24 March 1882, Robert Koch (1843–1910) announced to the Berlin Physiological Society that he had discovered the cause of tuberculosis. He had conclusively stained bacilli in lung tubercles from animals infected with tuberculosis, a discovery that proved to be a turning point for the scientific world in understanding the deadly disease that had plagued humankind for millennia.

In the audience that evening was a young Paul Ehrlich (1854–1915). A centennial paper commemorating Koch’s discovery of the tubercle bacillus [1] describes some rapid innovations following Koch’s announcement: Ehrlich (who recalled having seen, in various materials including sputum, bacilli similar to those demonstrated by Koch), obtaining from Koch a pure culture of tubercle bacilli immediately after the lecture, and on the same evening starting to experiment with various stains that he (Ehrlich) had already devised [1]. His first innovation was a shorter staining time and applying acid and alcohol for a few seconds to decolorize the surrounding tissues while the tubercle bacilli retained the primary stain and became more clear [1].

The next innovation happened overnight, by accident [1]. Apparently, Ehrlich left the stained preparations to dry on top of a cold stove in his laboratory. The next morning he was astonished to find the bacilli in clumps showing up even more clearly [1]. The benefit of heating slides had just been shown. More innovations followed rapidly; Ziehl introduced carbolic fuchsin instead of aniline as a dye, whereas Neelsen advocated the use of sulphuric instead of nitric acid, and the famous “Ziehl–Neelsen” staining technique and the “acid-alcohol fast bacillus” were born [1].

Subsequent progress in tuberculosis diagnosis and drug susceptibility testing (DST) was, however, painstakingly slow. Culture of the tubercle bacilli proved to be difficult. Koch initially used solid culture medium developed from inspissated cattle-blood serum. Several innovations by other microbiologists followed, until eventually an enriched egg-based solid medium developed by Löwenstein and Jensen in 1932 became the first “gold standard” for culture and DST. The idea of using liquid synthetic media was first introduced in 1892 [2]; however, progress was plagued by the slow growth of Mycobacterium tuberculosis, culture overgrowth by other micro-organisms, and the biohazards of manipulating suspensions containing a high number of tubercle bacilli. Innovation stagnated, and a new “gold standard” for culture and DST only emerged almost a century later, with the release of commercial liquid systems. These systems provided significant improvements over solid media (shorter turn-around time for results and an increased yield in diagnosis) but up to this day remain technically complex and costly.

The 1990s saw ground-breaking discoveries in molecular diagnostics, and the tuberculosis world started to benefit from rapid technologies to detect drug resistance. Molecular line probe assays, allowing a DST result within 24 hours for rifampicin or rifampicin plus isoniazid multidrug resistance, were approved by the
World Health Organization (WHO) in 2008 [3]. Another breakthrough came in 2010 when the first automated, closed, molecular system simultaneously detecting tuberculosis and rifampicin resistance in less than 2 hours was released: the Xpert MTB/RIF assay, running on the GeneXpert system [4], developed through an innovative collaboration between academia (University of Medicine & Dentistry of New Jersey), industry (Cepheid Inc.) and FIND, with US governmental support.

WHO approval of the Xpert MTB/RIF assay in late 2010 and rapid global uptake [5], facilitated by updated WHO policy guidance in 2013 [6] stimulated unprecedented interest in the development of “rapid followers” as can be seen from the robust pipeline of new diagnostics [7]. Most impressive is the range of molecular technologies that could potentially—and in the short term—replace smear microscopy which, despite its shortcomings, remains the cornerstone of tuberculosis diagnosis in all but the wealthiest countries.

Anticipated improvements in the Xpert MTB/RIF assay [8] and successful validation of other diagnostics in the pipeline may allow a future without (or at least much fewer) sophisticated and expensive containment laboratories for conventional culture and DST. For tuberculosis drug resistance testing, sequencing technology is increasingly playing an important role in resolving discordant results between genotypic and phenotypic tests and emerging data seem to suggest that molecular testing may become the new “gold standard” for DST in the not too distant future. This will, however, require that sequencing technology be brought closer to point-of-care and become affordable to resource-limited countries.

Less robust [7] is the pipeline for non-sputum-based diagnostic products and biomarker-based triage tests that can be used at point-of-care. This will require a breakthrough in biomarker discovery, and the conduct of well-designed trials to optimize screening and diagnostic algorithms. Urgent yet strikingly absent from the pipeline [7] are biomarker-based tests for monitoring treatment, alternatives to culture as primary endpoint for cure in clinical trials, and tests to identify people with latent tuberculosis infection who are at the highest risk of progressing to tuberculosis disease.

The WHO post-2015 End Tuberculosis strategy and its related targets adopted by the World Health Assembly in May 2014 call for early diagnosis of tuberculosis including universal DST and systematic screening of contacts and high-risk groups [9]. The initiatives outlined in this special supplement address several of the essential components necessary for accelerated discovery and innovation of new tuberculosis diagnostics: a) defining the needs for next-generation assays; b) developing target product profiles; c) collecting data on resistance-associated mutations; iv) assessing the market potential for new tuberculosis diagnostics; v) modelling cost and affordability of next-generation assays and diagnostic algorithms. In addition, well-designed validation and field trials of new diagnostics in intended settings of use will be essential to allow rapid policy development according to WHO criteria [5].

All the components outlined in this supplement are also crucial for the introduction of new tuberculosis drugs and expected new tuberculosis regimens over the next few years. For new regimens in particular, rapid identification of drug resistance in individual patients will be key to ensure optimal outcomes and prevent amplification of resistance. A major need, therefore, is to align diagnostic test development with anticipated novel tuberculosis regimens in synergised research efforts [10]. Such efforts could greatly benefit from much closer collaboration of researchers, test developers, technical agencies, funders and end-users (eg, country Ministries of Health) of sequence-based technologies, from trials that combine new diagnostics and treatment (drugs and regimens) in innovate designs, and from links with ongoing global initiatives such as the WHO drug resistance surveillance project [11]. Of crucial importance is accelerated research to evaluate the clinical prognostic value of drug resistance mutations, especially for second-line and new anti-tuberculosis drugs.

The blueprint for collective and consensus-driven tuberculosis diagnostic test development outlined in this special supplement is based on strong collaborations between industry, academia and technical/donor agencies, and end-users—which bodes well for diagnostic development in the future. These efforts deserve to be supported and the funding constraints [12] should be urgently addressed in equally innovative approaches.

Koch’s discovery of the tubercle bacillus revolutionized the management of tuberculosis in the 19th century. Pursuing new innovations with the same zeal as Ehrlich did of the humble microbiology stain by Koch in 1882, and working in collaborative partnerships such as the the one outlined in this supplement will ensure that new innovations for tuberculosis today do not take a century to reach those in need. As René and Jean Dubos wrote in 1952 [13]: “In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs.” The same holds true on World Tuberculosis Day 2015 as we prepare for a future without tuberculosis.

Notes

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References