Tuberculosis Serodiagnostics: Ban and After

Have we not been shortsighted and arrogant by creating a monster out of tuberculosis (TB), by taking it out from a sanatorium cure to in-house treatment with single and multiple drugs, which lead to extensive use of drugs in resistant cases, creating a fear in the mind of our citizens, and depleting the resources of the family as well as those of the nation? The microorganism has become more powerful and resistant each day by inadequate management of control programs and a lack of understanding of a number of other factors, namely, hygiene, nutrition, environmental pollution, life style (processed food, stressful fast life), factors known to decrease the immunity and thus influencing the transmission and progression of the disease among the rich as well as the poor.

TB has been declared as global emergency in 1993. Instead of the piecemeal and half-hearted attempts made, there must be more practical, comprehensive, and all round task force approach to tackle TB to achieve successful control if not elimination. The progress in diagnostics and drugs for TB does not appear to be a heartwarming situation. I always wondered how an august body like the WHO has decided to take the unprecedented move to recommend a ban of serological tests for TB, despite the fact that it once advocated the exploration of serology to develop affordable tests for the detection of TB in resource-

limited developing countries. For HIV, serology is used as first-screening test, and the blood sample is sent to a sophisticated laboratory located elsewhere for confirmation. Serology is used for a number of infectious diseases as well as noncommunicable diseases such as cancer. What is so special about TB, that serology cannot work? Intensive diagnostic research is the need of the day in countries with high prevalence of TB. Probably one test may not answer the diagnosis of active pulmonary TB (PTB) and extrapolmonary TB (EPTB) of clinical (latent, fresh, chronic, relapse, resistant, and paucibacillary cases) and public health interests. Case history and clinical diagnosis are equally important in confirming TB. In hospital-based studies, we have used secretory protein antigens for TB screening, by detecting antibody, circulating antigen and immune complexed antigen and thus aided the physician in clinical diagnosis, in particular, childhood TB and extra PTB in our thousand bedded Kasturba Hospital.[1,2] Similarly, serology (antigen detection) was shown to be beneficial in the diagnosis of TB meningitis at the Central India Institute of Medical Sciences, a prestigious super speciality hospital at Nagpur, without commercial interests.[3] Then, may I ask, why the hurry to ban serological tests and give the impression that serology itself is not useful for TB detection? This drastic step is one of the reasons that have led to the stagnancy in TB diagnostic research.[4] There are a number of ways of regulating the import and use of commercial test kits such as (1). Allowing import of kits after verification of their registration and use in the country of the manufacturer, (2) Evaluation under Indian conditions, and (3) Educating the public on the performance of the imported test kits. None of this was done. Many serology kits were introduced and withdrawn from market by the companies when the tests were not patronized. Based on meta-analysis by Pai and associates, WHO banned serodiagnostic kits. All tests (tests introduced and withdrawn, kits extensively being used, kits just released to make fast buck and in-house assays supported by clinicians) are clubbed in meta-analysis. The announcement of blanket ban was done without seminar or discussion in different scientific forums.

There appears to be some plan, by intent or accident by commercial interests to promote the molecular assay “Xpert MTB/RIF” and remove the opposition from the use of affordable serodiagnostics in rural areas with a blanket ban of all tests, without discrimination. As far as, I am aware, the Xpert test is not approved for active TB diagnosis in the manufacturing country USA. The following events corroborate the above view.

1. WHO endorses in 2010 a new technology nucleic acid amplification test which can be done on sputum samples taking <2 h to perform for the confirmation of TB-diagnosis and also to identify drug resistance[5]
2. Codeveloper of the test The Foundation for Innovative and New Diagnostics announces that the manufacturer of the new test will offer a deep price discount[6]
3. Pai, Steingart (affiliated with Stop TB Partnership’s new diagnostics working group) and associates published the meta-analysis on commercial serological tests[6]
4. Health and economic consequences of bad diagnostics published by Pai[7]
5. Jaroslawski* and Pai (*market access and pricing manager working as Postdoctoral fellow at Bangalore Institute) reported in a joint paper that serodiagnostics are widely used in the private sector in India with a lucrative market of $45 million for 1.5 million serological tests[8]
6. Organization by Pai (sponsored by McGill University and Global Health Strategies) on August 25–26, 2011 of a seminar entitled “TB diagnostics in India: From importation and imitation to innovation” done for the indirect promotion of Xpert[9]
7. Editorial in the” National Medical Journal of India” incorporating the RNTCP advertisement banning of serological tests by Pai and Das (2013).[10]

Anderson et al. (2008) reported an elegant evaluation study comparing usefulness of In Bios Active TB Detect IgG ELISA, IBL Mycobacterium tuberculosis IgG ELISA, and Anda Biologics TB ELISA, in the detection of IgG antibody in active
TB disease. Unfortunately, it is not deliberately mentioned and discussed in the meta-analysis. The meta-analysis does tell the history of TB diagnostic tests that were explored, were introduced and were withdrawn from the market. An analysis of the sensitivity and specificity of tests predominantly used in the present times should have been discussed but was not. The crusade of Pai and Steingart and the announcement of a ban on serological tests, and the way, it was widely publicized, had a great inhibitory effect on serology research in the research laboratories. After the ban, there occurred a big boost for sales of the costly Gamma Interferon Assay, which was not recommended by the RNTCP for the detection of active TB in India. A reputed private laboratory chain charges Rs. 2550/- for gamma interferon test. Thanks to the greedy laboratories and doctors who made a big hole in the pocket of poor TB patients. In spite of this great drawback for serology research, it is heartening to see the report of five novel protein biomarkers for the rapid serodiagnosis of PTB and EPTB by Singh et al.

Now let us come to Xpert MTB/RIF test, which was aggressively marketed, demolishing the serology. It is sad to observe that it is not advantageous cost-wise, access-wise, and simplicity-wise to use in primary health centers and rural hospitals in developing countries. I just visited a district hospital catering to over 1.3 million people in the district. The costly Xpert instrument is made available with a target of 250 tests per month, each cartridge costing Rs. 2200/- for the government. The test is restricted to multidrug-resistant (MDR)/extensively drug-resistant suspects, contacts, pediatric group, EPTB, and HIV. The same test may cost double the price in private laboratories. The instrument costs more than one million in rupees with a prohibiting warranty and recurring costs for cartridges. The Xpert/rif test can detect 50–150 MTB/ml in the sample whereas 10–100/ml viable bacilli only for more sensitive culture test. The detection of rifampicin resistance by the test is considered as a surrogate marker for MDR TB.

What is the position now after 6 years of banning TB serological tests? Rufai et al. reported that MGIT-960 showed a 100% agreement with LPA while only a 64.4% agreement with Xpert MTB/RIF assay was noticed, suggesting the need for country specific probes to increase the sensitivity of the Xpert assay. Further, Rufai et al. reported that the Xpert assay for ascitic fluid samples was less sensitive than the MGIT-90 and they emphasized the need to discover new biomarkers for paucibacillary TB. Another study by Sanker et al. reported large scale “False Identification” of Rifampicin-resistant TB. Further, molecular assays are often performed sequentially or in parallel to phenotypic drug susceptibility testing. Discordances between molecular and phenotypic tests invariably occur for reasons ranging from pre-, post- and analytical errors to coexistence of non-TB mycobacteria, silent mutations, mutations outside the 81 base-pair RMP resistance – determining region and hetero resistance.

The time has come for the WHO, in the interest of successful control of TB, to review the ban on TB serological tests (in the process serology itself) and the usefulness of the costly Gene Xpert, to take corrective steps in developing countries, in particular in rural areas. WHO and the agencies working for TB control should make a serious study of in-house assays being done on nominal payment, which are being patronized by clinicians in reputed government medical colleges and hospitals and explore in developing cost-effective serodiagnostic kits for rural hospitals.

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