SEROLOGICAL TESTING FOR TUBERCULOSIS SHOULD BE BANNED - W.H.O

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This editorial may be cited as: Hawthorne G, Thicket DR, Wood AM. Serological Testing for Tuberculosis should be banned - W.H.O. J Postgrad Med Inst 2012; 26(2):117-9.

Tuberculosis (TB) remains a major global healthcare issue with around 1.7 million deaths in 2009 due to TB and rising absolute number of cases each year due to the increasing global population[1]. The emergence of drug resistance, worsening malnutrition in the settings of political instability and civil unrest, and the detrimental effects of HIV coinfection has challenged TB eradication programs worldwide. The World Health Organisation (WHO) Stop TB strategy aims to reduce the global burden of TB by 2015. A key component of the Stop TB strategy is to ensure early case detection and diagnosis using appropriate quality controlled bacteriology.

The diagnosis of active TB is traditionally made using direct identification of the bacillus by smear microscopy or subsequent culture of Mycobacterium tuberculosis (M Tb). This requires appropriate specimens to examine, and time for the bacillus to grow. This can cause considerable difficulty if the infection is non-pulmonary, or if the patient does not expectorate sputum, when invasive tests are required, such as surgical biopsy or bronchoscopy. Unlike in many other infections, culture of M Tb may be prolonged or difficult, hence numerous kits for the detection of antibodies to the pathogen have been marketed, as a means for rapid identification. In commercial terms this is defined as a test which gives a result in less than an hour. At a public health level this could be beneficial if cases are identified early thus preventing spread, and at an individual level rapid diagnosis might lead to more rapid resolution of symptoms by means of early treatment. Patient distress whilst awaiting results could also be avoided. The WHO have recently released a policy statement on such tests[2], which we review here.

Serological testing can detect various classes of antibodies to the infective pathogen in the patients' serum. These antibodies are produced in response to antigenic substances or proteins on the surface of the bacterium. One of the commonest methods used clinically is to measure antibody titres in acute and convalescent sera, usually requiring a four-fold increase in the level of antibody detected. Other tests measure specific antibodies to determine the stage of infection, IgM indicating early infection and IgG indicating late or past infection.

Previous systematic reviews on this subject have found no role for the use of serological testing in suspected TB[3,4] and reported the methodological rigor of published studies was poor. However this form of testing continues to be marketed, despite these findings and despite the fact that unlike the gold standard of culturing M Tb it can give no indication about resistance of the strain involved, and therefore no guide to best therapy. This could lead to wastage of valuable healthcare resources, particularly if access to invasive tests is poor, or understanding of their utility is poor, as may be the case in developing healthcare systems. Consequently the WHO-Stop TB Group and WHO Special Programme for Research and Training in Tropical Disease (TDR) commissioned an updated review in 2011, the findings of which are detailed in a policy statement released in July 2011[2]. Evidence assessment areas targeted by the report included the use of commercial serological testing as a replacement for tests such as smear microscopy, the use of commercial serological testing as an add-on test in suspected pulmonary TB cases, the diagnostic

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accuracy of one of the most widely used kits and its accuracy in smear negative patients.

The methods used to gather evidence for the report included a systematic review and meta-analysis, a laboratory evaluation of the rapid diagnostic tests and a case study of economic and epidemiological impact of serologic testing for active TB in India. The meta-analysis found that all the commercial tests gave highly variable sensitivity and specificity and in the most commonly marketed rapid serological IgG kit (Anda-G) the sensitivity and specificity in both smear positive and smear negative groups was highly variable in pulmonary TB. The pooled sensitivity in smear positive patients was 76%, dropping to 59% in smear negative and the specificity in smear positive patients was 92% (91% in smear negative patients). The TDR then independently assessed 19 of the available commercial rapid sero-diagnostic tests using stored frozen sera and compared culture and clinical follow up with this.

The sensitivity ranged from 1-60% and specificity ranged from 53-99% with poorer performance in smear negative and HIV infected persons. Epidemiological evaluation determined that the number of false positives (2.82) for every case of TB was unacceptable, with a large proportion of the budget for treatment spent on false positive cases. The assessment concluded that as the quality of evidence was very low and the risks outweighed benefits rapid serological testing should not be used in patients with suspected TB. This is the first time that the WHO have issued an explicitly negative policy recommendation against a practice that is widely used in TB care worldwide.

In UK practice this is likely to have little effect, as current British guidance does not recommend the use of serological testing, and few are offered in the NHS. It is also important to recognise that the tests reviewed by the WHO are not the same as interferon-gamma tests (IGRAs) which have been developed using the tuberculosis antigens ESAT-6, CFP-10 and tb7.7, and are usually performed on blood. These antigens are not present in BCG, and are found in only a few species of environmental mycobacteria, so are specific to M Tb but cannot give an indication of disease activity or sensitivity to drugs, unlike culture.

IGRAs are intended for use in the same setting as Mantoux tests, predominantly for latent TB. Their utility in latent TB has recently been systematically reviewed as part of NICE guidance[5]; in general IGRAs perform better than Mantoux in immunocompromised or BCG vaccinated individuals and are recommended as an add on to Mantoux rather than sole use. The only exceptions to this in adults are (1) non-HIV immunocompromised patients (e.g. anti-TNF therapy) in whom IGRA performs better than Mantoux and (2) new entrant screening. In new entrants IGRAs may be more cost effective than Mantoux, although no firm conclusions could be drawn. Other rapid diagnostic tests considered by the NICE guideline were PCR for M Tb, which was not recommended as a sole test, since it only detects bacterial genetic material and not live organisms, and automated liquid culture. The latter is not a truly rapid test, as results may still take days or weeks, but is generally faster than use of solid culture medium and is therefore recommended. IGRAs and serological tests were not reviewed in the latest NICE guideline for diagnosis of active TB, although the use of IGRA as an adjunct to other tests in difficult cases is seen in clinical practice in the UK.

The WHO is currently reviewing IGRA usage in the setting of active TB and will produce a report on this in the near future. However in the meantime the publication of their guidance on general serological testing is a timely reminder on the use of tests that cannot guide therapy and are may simply reflect exposure rather than active disease. As Dr Karen Weyer from the WHO suggests the ongoing use of the general serology tests is unethical and should be discontinued.

ACKNOWLEDGEMENTS

GH is supported by UHB charities.

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