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EDITORIAL

In search of rapid diagnosis and drug-resistance detection tools: Is the *FASTPlaque*TB test the answer?

NEW, EFFECTIVE rapid diagnostic tools could help reduce the global burden of tuberculosis and the spread of multidrug-resistant tuberculosis (MDR-TB). Given the conditions of low income countries, in addition to being accurate and reliable, any new technique must also be affordable. The *FASTPlaque*TB test (FPTB) (Biotech, Ipswich, Suffolk, UK) is purported to meet these specifications. Three articles that evaluated this technique either for detecting mycobacteria in sputum,[1,2] or identifying rifampin (RMP) resistant clinical isolates,[3] have been published in the *Journal*.

To perform the FPTB test, mycobacterial phage D29 is added to decontaminated and concentrated sputum and should infect any mycobacteria present in it. A virucide is then added to destroy any remaining free phage. A suspension of *Mycobacterium smegmatis* and molten agar is added, and the mixture is poured onto a Petri dish. The phage first replicates within and lyses the mycobacteria originally present in the specimen. The amplified released phage then infects and lyses the surrounding *M. smegmatis*, resulting in small clear circles (plaques) in the agar, which are visible to the naked eye.

Two of the reports[1,2] were prospective trials comparing FPTB with microscopic examination and LJ culture for the detection of *M. tuberculosis*. The most important finding in these two studies is that the FPTB test detected mycobacteria in one-half to two-thirds of smear-negative sputum samples with 98% specificity, and a combination of the FPTB with AFB smear microscopy results confirmed the presence of *M. tuberculosis* in 80% of the culture-positive specimens in Cape Town,[1] and 90% in Karachi.[2] While these results are quite encouraging, the FPTB test has some serious problems that must be taken into account. First, the phage can be amplified by almost any mycobacteria present in the sputum, and an additional test may be needed to confirm that the sputum contains *M. tuberculosis* and not some non-tuberculous mycobacteria. Second, the FPTB plates are subject to contamination, which can be reduced by using a selective agar medium. Third, in both studies the FPTB failed to detect mycobacteria in about 13% of the smear-positive culture-positive sputum samples, many showing fairly abundant AFB on microscopy. Fourth, on smear-negative sputum there were 8% false-positives in Karachi, and 19% in Cape Town. This was presumably because the virucide failed to eliminate all free phage. The alarmingly high rate of false-positive results requires critical review of every smear-negative FPTB-positive case by taking into account the clinical picture, PPD, chest X-ray, and contact history.[4]

The effectiveness of the FPTB test for rapid detection of RMP resistance was compared with the BACTEC-460 culture method in the study from Johannesburg.[3] The technique was the same as described above for detection of mycobacteria in a sputum specimen, but the initial step required 24-hour incubation of the isolated cultures with added RMP. The sensitivity of this indirect test was 100%, and the specificity 99%, with results available in two days. A low cost screen for RMP resistance could be very valuable in low resource settings where drug susceptibility testing is too expensive to be routinely performed with all drugs and on all isolates. Because RMP resistance is a good marker for MDR-TB, the test might efficiently identify those isolates requiring full susceptibility testing and those patients who may need an alternative treatment regimen. The protocol used in this article starts with material from liquid cultures, which would entail an additional subculture step if primary isolation is on solid media.[3] However, in another previously published study, colonies from solid media were suspended directly into broth containing RMP.[5] The use of FPTB-RMP sandwiched between BACTEC for initial isolation and full drug susceptibility testing, as presented in this article,[3] is unlikely to save much time or money, but significant savings might be achieved if the test were used in conjunction with slower, traditional culture methods.

How would the FPTB fit into the flow of a laboratory with limited resources? The FPTB might be reserved for patients with a high clinical suspicion of TB and negative smear results. In such cases, culture medium would be inoculated from the same specimen processed for FPTB. Culture, along with FPTB-RMP screening, would also be performed on specimens from patients at risk of having MDR-TB, and only isolates demonstrating resistance to RMP would receive a full drug susceptibility test.

In conclusion, FPTB might improve TB diagnostic sensitivity in laboratories with limited resources, but it has problems with unexplained false-negative results—and more disturbing—false-positive results. The FPTB-RMP test appears to be a valuable cost-effective screen for MDR-TB in laboratories relying on traditional drug susceptibility testing, but it won't really be a 'rapid test' if it requires a primary isolation on solid

medium, especially with subsequent sub-cultivation in a liquid medium.

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