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Correspondence

Diagnostic tests: what is rapid and what is inexpensive?

The article by Kisa et al. represents good quality research and shows that the FAST*Plaque* technique can be as reliable as the BACTEC 460 system for rifampin susceptibility testing of cultures grown on Löwenstein-Jensen (L-J) medium.[1] At the same time, the conclusion that the FAST*Plaque* technique is 'a rapid and inexpensive test' is debatable, depending on the definitions used for 'rapid' and 'inexpensive'.

The authors' conclusion is based on findings that results were obtained within 2 days with the FAST*Plaque* technique and within 7 days in the BACTEC—after culture isolation! What is important for the physician is the total turnaround time, which is defined as the period from the moment of specimen collection to the final laboratory report, including time for culture isolation. Culture isolation on L-J medium requires 4–8 weeks. With a minimum of 28 days for isolation, the difference in the total turnaround time between two compared techniques would be 30 vs. 35 days (maximum 58 vs. 63 days). Neither of these approaches is rapid, and the difference between them is not impressive. In fact, if a comparison was made with a direct susceptibility test on L-J medium, there would be no difference at all.

The authors suggested that the FAST*Plaque* method 'would give the results in a very short length of time' if the test is performed with cultures isolated in the BACTEC system. This approach could probably have provided a mean turnaround time of 16 vs. 21 days, but such an option was not evaluated in this study, and it could have changed the conclusion about the reliability of the FAST*Plaque* test results if the broth culture was used for this test. Such an approach would not exclude the use of expensive equipment (BACTEC), and would miss the opportunity of susceptibility testing with all four to five first-line drugs in an available BACTEC system without any potential savings in cost.

How is the cost of a diagnostic test determined? In the paper by Kisa et al., the suggested cost of determining susceptibility to rifampin by the FAST*Plaque* and BACTEC methods is $8 and $15 per test, respectively. Is this cost of materials only? Is the labor cost (5 hours to set up the FAST*PLaque* test) included in this analysis? I would suggest that the calculation of cost should include the cost of materials, labor, instrumentation (depreciated at least over 5 years and divided by the number of procedures), and overheads. The cost of any diagnostic test could be quite different in different areas/countries, and would depend on the volume of work and batching opportunities.

Conclusions about the advantages of any new diagnostic test, including its rapidity and cost-effectiveness, are always based on comparison with existing methods. The conclusion may depend on the selection of the 'gold standard' chosen from among the existing methods. Obviously, comparison with a more expensive method would indicate a cost-benefit of the new method. With regard to the methods for detection of drug resistance in a bacteriology laboratory setting, an objective conclusion about the rapidity and cost-effectiveness of the new method (FAST*Plaque* technique) should have been drawn by comparison not only with the BACTEC method, but also with other less expensive techniques. It is unfortunate that in the study by Kisa et al., as well as in other reports, an important opportunity is often missed: comparison with a *direct* test for smear-positive specimens on 7H10/7H11 agar, a truly inexpensive test that may provide results on susceptibility to more than one drug within 3 weeks of the total turnaround time.

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Reference

1 Kisa O, Albay A, Bedir O, Baylan O, Doganci L. Evaluation of FAST*Plaque*TB-RIF™ for determination of rifampicin resistance in *Mycobacterium tuberculosis* complex isolates. Int J Tuberc Lung Dis 2003; 7: 284–288.

In reply

We agree that reducing the total turnaround time is of vital importance in patient management, as also mentioned in our article, which describes a means of reducing the overall turnaround time of susceptibility testing using the FAST*Plaque*TB-RIF™ method, which yields results within 2 days from culture.[1]

Incorporation of such a method will have a positive effect on the ability to report results to a clinician more quickly than using conventional methods that take between 5 days and 3 weeks longer, depending on whether a liquid or solid system is employed. Direct culture-based susceptibility testing is recommended by Dr Heifets. However, there appears to be a lack of published data on the performance of this method, particularly in high burden, low-income countries, and the

data that are available suggest that performance can be quite variable depending on the situation.[2,3] Libonati et al., in a multi-centre study in the US, report that only 62% of smear-positive, culture-positive specimens gave valid results by the direct proportion method.[2] Further evaluation of susceptibility testing by the direct proportion method is needed in high burden countries before this method can be recommended. The rapid systems are expensive, and the direct proportion method requires a well-standardised approach, good quality reagents and considerable technical skill in preparation of media, inoculation and interpretation of results if consistent results are to be obtained. This is not always possible, particularly in high burden countries. Commercially-available tests such as FAST*Plaque*TB-RIF™ have the advantage of guaranteed quality and consistent supply of reagents and technical support.

We agree that the full cost of performing any test will be attributable to a variety of factors, including the actual cost of the reagents, labour and instrumentation, and that this will vary in different locations. Other factors should be considered with respect to cost to the service, such as the additional testing required when invalid results are obtained. We use BACTEC FAST-*Plaque*TB-RIF™ and L-J medium in our laboratory. BACTEC is a well accepted gold standard method. Although the basic aim of our study was to confirm the susceptibility results of FAST*Plaque*TB-RIF™ compared with BACTEC results, our publication gave a valid comparison of the relative cost of the FAST-*Plaque*TB-RIF™ and BACTEC tests in our situation as an indication cost within the laboratory. We agree that this may differ in other settings. Direct methods (testing directly from a specimen) should have significant advantages over indirect tests, as they would not have the reliance on the time-consuming process of culture. Comparison of FAST*Plaque*TB-RIF™ with the proportion method on solid media has been reported previously, and gave results comparable with those of our study.[4] It is well known that the BACTEC system has led to a considerable shortening of the time required for the detection of mycobacteria, and the main limitations of the system are the high cost of disposal of the radioactive waste and the need for instrumentation.[5]

When examined carefully, it is very clear that we offered FAST*Plaque*TB-RIF™ test as an alternative method for susceptibility testing in developing countries where drug resistance is relatively low and where the BACTEC system is not available.

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Should pulmonary tuberculosis patients with heavy pre-treatment bacillary load be given more aggressive treatment even under the DOTS strategy?

Conventionally it is believed that in new smear-positive pulmonary tuberculosis patients, the same numbers of drugs in the same conventional doses are equally effective, irrespective of pre-treatment bacillary load.

A retrospective study (unpublished data) was performed among 2938 new smear-positive pulmonary tuberculosis patients registered in peripheral directly observed treatment (DOT) centres from January 1996 to June 2001, covering a population of 1.6 million in Delhi, India. Patients reporting to these centres with chest symptoms suggestive of pulmonary tuberculosis were asked to give three sputum samples, spot, early morning, spot, as per national guidelines mentioned elsewhere.[1]

All slides were examined for acid-fast bacilli (AFB) by the laboratory technicians in the field. To ensure quality sputum microscopy, a Senior Tuberculosis Laboratory Supervisor (STLS) cross-checked all positive smears and 20% of negative smears. The laboratory technicians and the STLS had received modular training for sputum AFB microscopy. The results were graded as 1+, 2+, and 3+, scanty or negative as per national guidelines.[1] Patients with at least two sputum samples showing positive report for AFB were declared to have smear-positive tuberculosis. The highest grading was finally recorded.

The patients received fully supervised intermittent thrice-weekly short-course chemotherapy, as per World Health Organization (WHO) guidelines.[2] The treatment outcome of the new smear-positive patients in relation to the sputum smear grading was analysed (Table). Patients with negative or scanty results were not included in the analysis. Sputum conversion rates among patients graded as sputum 3+ and the rest of

Table Sputum conversion rates and treatment outcome of patients under study

Initial sputum status	Total patients *n* (%)	Sputum conversion		Treatment outcome				
		At 2 months *n* (%)	At 3 months *n* (%)	Cured/ treatment completed *n* (%)	Failed *n* (%)	Died *n* (%)	Defaulted *n* (%)	Transfer out/others *n* (%)
Group I (1+)	793 (27.0)	643 (81.1)	726 (91.6)	689 (86.9)	29 (3.6)	11 (1.4)	44 (5.5)	20 (2.5)
Group II (2+)	736 (25.0)	532 (72.3)	637 (86.5)	612 (83.2)	40 (5.4)	13 (1.8)	54 (7.3)	17 (2.3)
Group III (3+)	1409 (48.0)	877 (62.2)	1146 (81.3)	1079 (76.6)	109 (7.7)	38 (2.7)	144 (10.2)	39 (2.8)
Group IV (1+ & 2+)	1529 (52.0)	1175 (76.8)	1369 (89.5)	1301 (85.1)	69 (4.5)	24 (1.6)	98 (6.4)	37 (2.4)
P value								
Group IV vs III		$<10^{-5}$	$<10^{-5}$	$<10^{-5}$	<0.001	<0.05	<0.001	0.55

the patients at the end of 2 months were respectively 62.2% and 76.8% ($P < 10^{-5}$), and at the end of 3 months were respectively 81.3% and 89.5% ($P < 10^{-5}$). Cure rates in the same group of patients were respectively 76.6% and 85.1% ($P < 10^{-5}$), and failure rates were 7.7% and 4.5% ($P < 0.001$).

Another field-based study from Delhi, under the same national guidelines, reported that patients with 3+ sputum smear showed lower sputum smear conversion rates at the end of 2 months of DOT than the rest of the patients.[1] They also found that patients with 3+ sputum smear had significantly higher failure and death rates. Similarly, in a refugee camp in Thailand, Rieder observed that sputum conversion at the end of 2 months of DOT among patients with initial weakly positive sputum to be 90.9%.[3] It was 77.9% and 61.7% among patients with initial moderately positive and strongly positive sputum, respectively. Under a National Tuberculosis Control Programme with DOT, Lienhardt et al. also reported sputum conversion at the end of 2 months in patients with initial sputum smear 1+, 2+, 3+ to be 96.2%, 85.8% and 81.8%, respectively.[4] They further observed that cure rates also decreased with increasing initial bacillary load.

In 1993, Mitchison reviewed the time to sputum sterilisation of subjects enrolled in published comparative tuberculosis chemotherapy trials.[5] He found that the regimen with inferior sterilising activity at 2 months had higher relapse rates, and suggested that this parameter might be used as an early indicator of the relative efficacy of various regimens.

A high pre-treatment bacillary load appears to be an important predictor for poor treatment outcome, even under the DOTS strategy. Do the current conventions of a unified chemotherapy regimen for all newly diagnosed smear-positive pulmonary tuberculosis patients, irrespective of the pre-treatment bacillary load, need review? It could be argued that in new smear-positive patients, those patients with initial high bacillary load (sputum 3+) should be given more aggressive treatment as compared to patients with lesser bacillary load. If so, to make it operationally feasible, could this be done by increasing the number of drugs and duration of chemotherapy, as is recommended in the treatment regimen (category II) for relapse or re-treatment patients under WHO guidelines?[2]

At the same time, quality control of sputum microscopy is of paramount importance to ensure that the microscopy results at the most peripheral level are reliable. Laboratory technicians at the peripheral level should receive proper training, and the results of all positive sputum smears should be cross-checked by a trained STLS. The reliability and reproducibility of sputum smear grading under field conditions needs to be evaluated by prospective studies before a different treatment option based on sputum smear grading can be considered.

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