Reviewer's report

Title: Molecular detection of rifampin and isoniazid resistance to guide TB chronic patients’ management: a feasibility study in Burkina Faso

Version: 1 Date: 28 March 2009

Reviewer: joshua fierer

Reviewer's report:

This paper by Miotto et al concerns a very important issue: the rapid detection of MDR Mycobacterium tuberculosis in a resource poor nation. In this study they tested a new commercial method for detecting the mutations responsible for INH and rifampin resistance using sputums that were collected in Burkina Faso and shipped to Italy for testing. In Burkina Faso there are no facilities for doing Mycobacterial culture, let alone sensitivity, so patients are assumed to have resistant organisms if they do not respond to anti-tuberculous treatment. It was this group of patients that were the source of the sputa that were assayed, but unfortunately more than 40% of the samples were obtained after the patients had been started on a new treatment regimen. In one laboratory (in Milano) they did the PCR and did the hybridizations using GenoType MTBDRplus (Hain Life Science), and in another lab (in Brescia) they cultured the sputa in the MGIT system and did INH and rifampin sensitivities. The group in Milano also sequenced the rpoB, inhA, and katG genes and identified the resistance mutations.

In general, the results with were quite positive and revealing, but the samples were less than ideal. For instance 1/3 of the samples taken before a new regimen was started and about half of the sample taken after therapy were smear-negative when re-examined in Italy. Thus, either the original assignments were in error, or there were relatively few organisms in the sputa because different samples were examined in Africa and Italy. However, even the smear negative sputa were useful in that 19/51 yielded a PCR result and of these 15/19 were not resistant mutants, showing the cases were clinically misclassified and those patients potentially were going to receive less than optimal therapy for their TB. Only 4/19 grew bacteria and 2 of those were MAC, not TB. One that was shown to be INH resistant by GenoType MTBDRplus assay did not grow, and another grew Nocardia, presumably a dually infected patient. The overall performance of the GenoType MTBDRplus was excellent with nearly all specimens yielding a result and there was concordance between the genotype results and sensitivity tests in nearly all cases; only 1 INH resistant strain was missed by genotyping. Where there were discrepancies that authors were able to define the mutations and explain them.

I have several suggestions for minor revisions that I think will strengthen the paper.

1. Make a figure with a flow diagram showing how many specimens were
collected before treatment, how many after treatment and divide them into smear + and smear – specimens and then show the results of analysis in the two labs.

2. In table 1 include the culture and sensitivity results.

3. In the discussion they should include much of what is in the conclusions about the usefulness of the test. This study strongly suggests that clinical criteria, promoted by the WHO and in widespread use, for diagnosing MDR Tb are inadequate because of too many false positives.

4. They say the study was designed to test the feasibility of using GenoType MTBDRplus as a more accurate test for managing patients in Burkina Faso. I think this study clearly shows the need for a more accurate and rapid test, but not necessarily the feasibility, as this study was really done in Italy and it is not feasible to ship specimens from Africa to Italy on a routine basis.

5. Unless they are sure that the strains they tested are not genetically related because of nosocomial spread, I do not think it is justified to make the statement that the genetic basis of RIF resistance is different in Burkina Faso than elsewhere. It may only be different because a resistant strain is spreading in the institutions they are studying.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interest.