Reviewer's report

Title: Serial counts of Mycobacterium tuberculosis in sputum as surrogate markers of the sterilising activity of rifampicin and pyrazinamide in treating pulmonary tuberculosis

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Version: 1 Date: 14 Nov 2001

Reviewer: Prof Leonid Heifets

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after revision, which I do not need to see

D.A. Mitchison is a recognized founder of a modern system for evaluation of the efficacy of individual drugs and treatment regimens in tuberculosis patients, particularly in regard to the bacteriological response to therapy. Of a special importance is the distinction between the Early Bactericidal Activity (EBA) and Sterilizing Activity (SA) suggested in a number of publications by Mitchison and his colleagues. The paper by Brindle et al. is a re-analyses of data from the previously published study, and this additional analyses is presented to meet the current needs for surrogate markers to evaluate the effectiveness of new anti-TB drugs and treatment regimens. This report makes an emphasis, that EBA, a surrogate marker of specific anti-TB activity of a drug, should be determined on a basis of decline in the number of viable bacteria in sputum during the first two or up to seven days of monotherapy in small groups of patients. On the other hand, the best surrogate marker for the sterilizing activity of treatment regimens is a series of quantitative cultures during a longer period, after the first two or seven days of therapy with a combination of drugs. In the report by Brindle et al., such an analyses is presented for days 14 and 28 of therapy to compare sterilizing effect of two treatment regimens. Based on fundamental work by the Mitchison's group, we have suggested an extended evaluation of sterilizing activity of new treatment regimens by determining the viable counts in specimens collected weekly during a period of two months or longer to create a curve of decline consisting of up to eight or more points. This suggestion has been recently supported by the Global Alliance for TB Drug Development, and I would recommend addressing this approach in the "Discussion" section of the article. My other minor recommendations for the authors' consideration are the following.

1. Page 5, lines 8 and 18. A phrase "extended early bactericidal activity" may create some confusion among the readers not involved in the field of evaluation of the TB drugs (is it still "early" activity if it is extended, and for how long?).
2. Conclusion #3, page13. Perhaps "sterilizing activities" would be more appropriate than "long term bactericidal (sterilizing) activities"
3. Page 6, lines 6-7. This text is not correlated with the data in the Table 1. On the other hand, the Table 3 is not referred in the text at all.
4. Fig.4. This figure from another publication is not necessary, since the conclusions from that study are addressed in details in the "discussion" section on page 11.
Competing interests: None declared.