

from alan.johnson@hpa.org.uk  
to sandrofreddi@gmail.com  
date Wed, Sep 29, 2010 at 8:08 AM  
subject Manuscript ID: JAC-2010-1104: Decision  
mailed-by manuscriptcentral.com  
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Journal of Antimicrobial Chemotherapy  
29-Sep-2010

Manuscript ID: JAC-2010-1104

Title: Treatment of tuberculosis: challenging the World Health Organization recommendation of simultaneous oral administration at the same time of the day of rifampicin, isoniazid and pyrazinamide

Author(s): Freddi, Alessandro

Dear Dr Freddi,

Thank you for submitting the above manuscript to JAC. Your manuscript has been assigned to an Editor and reviewed, but, unfortunately, we have decided to reject the manuscript for the reasons given by the Editor, which can be found at the bottom of this e-mail.

I should mention that we currently, of necessity, have to reject about 75 percent of the manuscripts that we receive.

I am sorry to disappoint you on this occasion, but hope that you will find the comments useful and constructive.

Yours sincerely

Dr Alan Johnson

Editor-in-Chief

Journal of Antimicrobial Chemotherapy

Editor's comments:

This manuscript deals with PK/PD data on rifampicin and speculates with its putative consequences for antituberculosis drug therapy. Tuberculosis is one of the major global health concerns in our days, and hopefully, drug regimes containing rifampicin and other drugs are capable of healing individuals suffering from this dreadful disease. In recent years, the dramatic increase of drug resistant tuberculosis and the limited arsenal of drugs available for combating it, both have stimulated pharmacological wide studies on antituberculosis drugs. In such a scenario, it is difficult to understand why in a review apparently dealing with this hot topic, 84% of references are more than 10 years old, and 60% are more than 20 years old. The most recent reference dates of year 2006.

Despite some references are in fact scientific articles published in peer-review journals, many others are not. For example, transcription of discussion panels held in congresses and conferences cannot be taken as solid scientific facts (even when they were published in peer-review journals, but probably not through a peer-review process). There are many statements in the text that are not supported by any kind of publication. These are mere speculations on what could have happen but we will never know for sure.

The conclusion of the manuscript is that current antituberculosis drug recommendations are not rational because in such conditions, bioavailability of rifampicin is drastically reduced so that it reaches sub-therapeutic concentrations and produces severe toxic effects. If this were true, how can we explain the wide success of current antituberculosis treatment? Millions of people get rid of tuberculosis following the WHO and IUTLD recommended drug regimes. When treatment fails, it is often due to well-known reasons, such as poor patient compliance, inappropriate treatment or drug resistant strains; all of these have been widely documented and studied thoroughly.

In conclusion, this manuscript lacks scientific accuracy for being published in Journal of Antimicrobial Chemotherapy.

from Alessandro Freddi <sandrofreddi@gmail.com>  
to alan.johnson@hpa.org.uk  
date Sun, Oct 3, 2010 at 6:16 PM  
subject Rejection appeal of manuscript JAC-2010-1104  
mailed-by gmail.com  
10/3/10

To Dr. Alan Johnson, Editor-in-chief of the Journal of Antimicrobial Chemoteraphy.

Sir

I appeal against the rejection of the manuscript JAC-2010-1104 for the following reasons.

The paper demonstrates that the huge tuberculosis death toll is caused by the WHO recommendation which is indicated in the title. The Editor failed to confute this and failed to demonstrate that the paper is not scientifically sound.

Lack of references and peer-reviewed references are relative only to a portion of the contents, the function of which is complementary.

The Editor states that it is difficult to understand why references in the paper are not recent. Right, it is quite difficult to understand.

However, references have no expiry date.

Among total 51 references, there are 45 scientific papers, only seven of which are Congress papers (not discussions), which, therefore, could have not been subjected to the peer-reviewing process. The remaining 6 references support the number of inhabitants (ref 2) and TB cases (ref 1) in Ethiopia, indicate where a certain study has been realized (ref 21) and include also three Congress discussion, the information of which is, in part, cited just to be questioned.

Speculations, which have been proposed in the text, are quite simple to be confirmed.

The severe toxic effect, which is caused by the WHO recommendations, is expected mainly in some conditions, as explained in the text.

Therefore, the Editor's argument that many people get rid of TB following the WHO recommendation is trivial, not scientific.

Finally, the Editor lists some reasons of the treatment failure (what about the relapse?), but miss to explain why these reasons should exclude my thesis.

Here is a paper suggesting a simply way to save a large numbers of human lives, which is rejected without offering even one reference for an incorrect number or statement and without the reviewers' examination. Read the paper, please, and take the necessary actions.

Yours Faithfully

Dr. Alessandro Freddi

from Alan Johnson <alan.johnson@hpa.org.uk>  
to Alessandro Freddi <sandrofreddi@gmail.com>  
cc Colin Drummond <CDrummond@bsac.org.uk>  
date Mon, Oct 25, 2010 at 10:49 AM  
subject RE: Rejection appeal of manuscript JAC-2010-1104  
mailed-by hpa.org.uk  
10/25/10

Dear Dr. Freddi,

Further to your appeal against the decision to reject your manuscript, in liaison with the Editor, we have re-considered your original submission with special attention being paid to the specific points you raised in your email message of October 3rd.

Our considered opinion is that the manuscript does not demonstrate that current antituberculosis treatment is responsible for the high number of deaths caused by this disease. Instead, it raises a possible link between these two facts; this is the way in which the manuscript is written, for example, in the summary, line 16 'Here it is proposed...', line 19 '...death toll could simply be the consequence...', line 21 '...a proposal of explanation...'. The rest of the manuscript is written in similar terms.

Also, in your email message of October 3rd you refer to it as 'my thesis'.

For publication, your hypothesis should be fully validated experimentally using current drug formulations and current technologies. Most possibly, drugs, excipients, and techniques that were used many years ago may have changed over the years. If so, old references, although it may be true that they do not have an "expiry date", would

have lost their original accuracy and applicability. Similarly, speculations should be properly confirmed and documented. The most recent WHO report on tuberculosis indicates that on average, the treatment success for new smear-positive cases treated in the 2007 cohort was 86%. In particular, in Ethiopia, one of the high-burden countries, this rate has increased from 61% in 1995 to 84% in 2007. Such figures demonstrate that in fact a large proportion of tuberculosis patients get cured following the recommended therapy, whose composition, doses, and other details are decided upon results of clinical trials. Certainly, there is still an important percent of treatment failure, due to the reasons given by the editor, yourself (relapse, toxicity) and many others. In this context, your hypothesis could explain a proportion of such failures, once demonstrated experimentally as indicated above. For these reasons, we confirm our original decision, which is to reject the manuscript.

Yours sincerely,  
Dr Alan Johnson  
JAC Editor-in-Chief