Author's response to reviews

Title: Access to a PCR method targeting thirteen respiratory viruses can reduce antibiotics - a randomised controlled trial

Authors:

Robin Brittain-Long (brittainlong@btinternet.com)
Johan Westin (johan.westin@infect.gu.se)
Sigvard Olofsson (sigvard.olofsson@microbio.gu.se)
Magnus Lindh (magnus.lindh@microbio.gu.se)
Lars-Magnus Anderson (Lars-magnus.andersson@infect.gu.se)

Version: 2 Date: 25 February 2011

Author's response to reviews: see over
To the Editor of BMC Medicine

Gothenburg Feb 25th 2011

Thank you for the valuable comments on our manuscript “Access to a PCR method targeting thirteen respiratory viruses can reduce antibiotics – a randomised controlled trial (MS ID 6491226354579277). They have been very helpful to further improve the manuscript.

We appreciate and gratefully accept the proposal to publish our manuscript in BMC Medicine. However, if this would significantly delay the publication, we would rather like it to be published in BMC Infectious Diseases according to the original plan. The revised manuscript has now been formatted according to the BMC Medicine author’s guidelines.

As suggested by the Associate Editor of BMC Infectious Diseases, and the reviewers it has been clarified that the net effect on antibiotic prescriptions is the most important factor in order to impact antibiotic resistance, health economics, and adverse events from antibiotic therapy and that this effect was not achieved in the present study.

We have made the following revisions according to the reviewers’ suggestions:

**Reviewer 1 (Werner C. Albrich)**

**Minor revisions:**

1. The p-value has been added. After a meticulous review of the database, a minor error was corrected (number of patients receiving antibiotics at follow-up in the group randomised for delayed result was changed from 34 to 35) which does not affect the level of significance or the conclusion.

2. ”was” has been changed to “were”.

3. The definition of a Serious Adverse Event (SAE) has been added to the methods section. The fact that no SAEs were reported has been clarified in the results section and a comment has been added to the discussion.

4. Has been switched to “influenced by the randomisation in their decision to…”

5. We agree and this has been added.

6. We agree. The last part of the sentence has been deleted.
Reviewer 2 (Matthias Briel)

Major revisions:

1. We agree that an RCT aiming to reduce antibiotic prescriptions is, in general, required to show that patients are not worse off with the new strategy. We have clarified in the discussion that patient-relevant outcomes were not properly recorded due to lack of available resources.

2. We have clarified in the discussion that in order to impact antibiotic resistance and other negative effects of antibiotic therapy it is necessary to reduce the total rate of antibiotic prescriptions. The reasons for choosing antibiotic prescription at the initial visit as the primary outcome have been explained.

3. We agree that an ITT analysis provides the highest level of evidence for RCTs, in that it guards against bias and provides effect estimates for real life clinical practise. However, an ITT analysis cannot be performed if it is not possible to make reasonably accurate assumptions regarding the primary outcome for patients with missing or inadequate data. Our study evaluated the effect on antibiotic prescription rates based on the prospect of getting a rapid result of the test with an open label design. The investigators were immediately informed if samples were delayed by transport, or if patients were sampled incorrectly. Due to the nature of the primary outcome we believe that these patients should not be evaluated in the study and that making assumptions regarding the primary outcome for patients with missing data and protocol violations is impossible (or very speculative). Exclusion was performed equally in both study arms and predefined in the analysis plan in order to introduce minimal bias. We agree that this is a modification and only gives an estimate of the effect under optimal conditions for the primary outcome, but excluded patients are presented according to CONSORT guidelines in Figure 1 and the reader will have the possibility to make some judgement of the bias introduced by the chosen procedure. It has been clarified in the methods section that exclusions were made according to the pre-defined analysis plan and that results were analysed applying this modification.

Reviewer 3 (Carlos Grijalva)

No suggested changes.

Sincerely,

Robin Brittain-Long (corresponding author)