Author's response to reviews

Title: Retrospective observational study of diagnostic accuracy of the Xpert(R) MTB/RIF assay on fiberoptic bronchoscopy sampling, for early diagnosis of smear-negative or sputum-scarce patients with suspected tuberculosis

Authors:

Pierre Le Palud (lepalud-p@chu-caen.fr)
Vincent Cattoir (cattoir-v@chu-caen.fr)
Brigitte Malbruny (malbruny-b@chu-caen.fr)
Romain Magnier (magnier-r@chu-caen.fr)
Karine Campbell (campbell-k@chu-caen.fr)
Youssef Oulkhour (oulkhour-y@chu-caen.fr)
Gérard Zalcman (zalcman--g@chu-caen.fr)
Emmanuel Bergot (bergot-e@chu-caen.fr)

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Author's response to reviews:

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Ms Ma. Celine Zapanta and Dr Sanjay Chotirmall
Executive Editors
BMC Pulmonary Medicine

Subject: revised version of Manuscript

Dear Editors,

Please find enclosed our revised manuscript entitled:

Retrospective Observational study of diagnostic accuracy of the Xpert® MTB/RIF assay on fiberoptic bronchoscopy sampling for early diagnosis of smear-negative or sputum-scarce patients with suspected tuberculosis

which we are please to re-submit to the BMC Pulmonary Medicine for publication.

First, we thank the reviewers for their comments, which contributed to greatly improve the scientific value of this paper.

Please find here our answers to all questions and comments raised by the Reviewers.
We thank Reviewer 1 (Dr Teck Boon Low) for his comment on the last sentence in the section “Ethical considerations”. We therefore corrected that sentence and, in the same paragraph, as recommended by our French ethics committee (CEPRO), we specified that our study was “approved” and we added the French name of the committee. Line 158, page 7 we now precise:

All collected data from the charts of the Microbiology Department were anonymous and therefore complied with the restrictive requirements of the Commision Nationale de l’Informatique et des Libertés (CNIL), the organization that ensures the application of data privacy laws in France. Moreover, the study protocol was evaluated and approved by the institutional review board of the French Society for Respiratory Medicine (“Société de Pneumologie de Langue Française”) for observational studies (CEPRO). Finally, all patients were informed of our TB diagnostic strategy, received written information about the FOB procedure performed after and gave their there oral consent (as recommended by the French Society of Respiratory Diseases).

We agree with Reviewer 1 according to the discrepancy between the text and the table 1. So in line 182, page 8 we replaced “1:7” by “1.7”.

As suggests Reviewer 1, we agree that it could have been interesting to compare bronchoscopy’s results to sputum induction accuracy nevertheless, we don’t use that kind of sample in our practice.

Then, with reference to table 2, Reviewer 1 asks if the denominator should be 23 instead of 20. The number of 20 was used in the left part of this table because we only evaluated accuracy of the Xpert® MTB/RIF assay on bronchoscopy’s samples respect to culture (used as the “gold standard”). Three patients had a TB diagnosis thanks to sputum’s cultures and had negative cultures on bronchoscopy’s samples, that is why, it was not possible to integrate them in the denominator to calculate sensibility of the different tests. In the right part of the table 2 the accuracy of Xpert® MTB/RIF assay was evaluated respected to the final diagnosis (done on bronchoscopy’s samples or on sputum), in this part we could integrated these 3 patients in the denominator.

We thank Reviewer 2 (Dr Keshav Sharma) for his comment on the small percentage (18.5%) of pulmonary TB finally diagnosed in our population. We can initially considered the number finally diagnosis with TB (n=30) to be fairly low. However, in retrospect we think this is would be clinically intuitive given that the cohort of 175 patients being looked at could be considered difficult diagnosis (given the negative sputum to start with and others being sputum scarce, in a population with a low incidence of TB to start with). Moreover, our incidence is higher than in the Theron’s study (reference 19) where 27 pulmonary TB were diagnosed in a cohort of 154 patients (17.5%) in a higher TB prevalence area.

Concerning the lack of novelty we can noted that our study is the first evaluation
of the Xpert® MTB/RIF assay accuracy in a low prevalence area of TB where bronchoscopy is early and safety used in the diagnostic strategy of smear-negative or sputum-scarce patients.

We thank Reviewer 3 (Dr Cedric Gunaratnam) for his detailed and pertinent analysis of our study. We agree with his remark concerning the absence of a control group which is difficult to obtain in a retrospective study of daily practice. We can added that such control group was not used in the 2 other main studies on the Xpert® MTB/RIF assay accuracy on bronchoscopy’s samples (references 18 and 19). Moreover, this test has ever been evaluated in the literature (reference 31) on different kind of samples (including sputum and bronchoscopy’s samples) and we well know now that the Xpert® MTB/RIF assay is a very specific test.

As suggests Reviewer 3, it would have been interesting to know the overall number of patients who were diagnosed (by all methods) with TB in our center during the study period. Unfortunately, our study focused on bronchoscopy’s samples and therefore we don’t know this number. However, we can precise that the incidence of TB was 5.9 cases per 100,000 in “Basse-Normandie” in 2010.

Finally, the two minor suggestions of Reviewer 3 concerning Non-tuberculous mycobacteria and the use of the Xpert® MTB/RIF assay instead of smear testing are very interesting but don’t concern our study and therefore require others future works (as cost-effectiveness studies).

We think we have answered to all remarks and criticisms of both Reviewers, and we have thoroughly followed the instructions for contributors.

All named authors have approved again its content and agreed to the submission of this revised version.

We thank you for considering our paper for publication.

Yours sincerely,

Dr. Emmanuel BERGOT, MD