Author's response to reviews

Title: Usefulness of C-reactive protein testing in acute cough/RTI: an open cluster-randomised clinical trial with CRP testing in the intervention group

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Author's response to reviews: see over
Letter to the Editor BMC Family Practice

Dear Mr. Editor
We would like to thank the reviewers sincerely for their useful and relevant comments. We have commented on each below (in red) and made the relevant changes in the text. We believe the paper has improved and we hope our revisions are made satisfactorily according to the reviewers’ intentions.

Reviewer: Michael Moore
Thank you for asking me to check the author responses.
Many points have been addressed (sample size, imbalance between groups, better description of follow up assessment).
However I am afraid I do not think the authors have entirely addressed some of my concerns.
I still have a problem with the title-Usefulness of C-reactive protein testing in acute cough.
How can a study be described as in acute cough when 40% of those presenting did not include cough in their baseline symptoms (Table 1). It was allowable in the entry criteria however the title is misleading as it stands.

Cough (like the other symptoms) was graded on a 1 to 4 scale (no problem, mild problem, moderate problem, and severe problem). Table 1 shows percentage of symptoms reported by patient as a moderate or severe problem. Less than 20% were classified as “no problem”, but that does not mean they did not cough at all.
The majority of the patients were probably included due to acute cough, and not due to LRTI or possible LRTI, and these acute cough patients were probably diagnosed with URTI in most cases. In the large GRACE study with the same inclusion criteria, URTI was also the most frequent diagnosis suggested by the GPs. But we agree, since the GPs made a diagnosis of URTI in a great part of the patients, it will be right to title our article:
“Usefulness of C-reactive protein testing in acute cough/RTI: an open cluster-randomised clinical trial with CRP testing in the intervention group”.

There must be a problem here with my understanding. The entry criteria listed: Patients with LRTI/acute cough (including acute bronchitis, pneumonia, and infectious exacerbations of COPD or asthma) were included. Patients with LRTI could be included in the absence of cough
However the GP description of the illness the most frequent description was URTI 50% intervention and 41% control. There must be a difference in disease labelling to account for this since to my mind a patient with URTI did not meet the entry criteria.

Patients with acute cough and URTI (as the most likely condition) meet the entry criteria. The GPs have probably also included some patients with possible LRTI, finding URTI to be more likely at the end of the consultation. It will be more correct to change the order of the inclusion criteria: “Patients with acute cough or LRTI (including acute bronchitis, pneumonia, and infectious exacerbations of COPD or asthma) were included. Patients with LRTI could be included in the absence of
cough.” Since this may seem like a questionable point, it is now dealt with in the discussion.

The authors explain the high chest x-ray rate being explained by the local guidelines in which chest x-ray is mandated in cases of suspected pneumonia. Again there is a mismatch since pneumonia was present in 7% & 17% respectively of the intervention and control group yet chest radiography was performed in 55% & 76% respectively. So chest x-rays must have been requested in some patients with a clinical diagnosis of URTI. Can there be a misunderstanding about the labelling of URTI?

Yes, GPs have certainly ordered X-ray in patients and at the same time regarded URTI as the most likely condition. Since the diagnosis was uncertain they have wanted to rule out pneumonia.

I do not think having excluded the participants recruited by two GPs that they can be included again in the results.

We suppose that this is an acceptance to remove these patients from all analysis, and we decide to keep them out.

There are serious concerns about the assessment of recovery which was not blinded to treatment allocation. I do not think this result is reliable enough to include in the final line of the abstract. This was a small study and would not have been powered to detect rare complications and I think the conclusions about recovery need to be more circumspect.

This problem has been given more attention in the discussion, page 15, and in the results section of the abstract, and we have chosen a more cautious wording in the conclusion, adding “probably”:

**Conclusion.** The study showed that CRP testing in patients with acute cough/RTI may reduce antibiotic prescribing and referral to radiography, probably without compromising recovery.

The figures do not have labels or titles.

The figures have titles placed at the end of article (below the reference list).

There are imbalances at baseline which are not taken account of with the simple chi squared analysis. These may be in favour of the intervention group (higher rates of pneumonia) but other imbalances go the other way (heart disease, temperature) and an appropriate analysis should be done.

We have added a multivariable analysis, using antibiotic prescribing as outcome in logistic regression and allocation to CRP testing as one of the explanatory variables, together with upper respiratory tract infection, any comorbidity, any chest finding, and perceived patient preference for antibiotics. See page 10 under Statistical analysis and page 12 under Sensitivity analyses. Adding pneumonia on X-ray among the explanatory variables somewhat weakened the association between intervention and outcome. We found it right not to include this variable, due to a strong correlation with...
both “any chest finding” and “any comorbidity”. And even more important, significantly more x-rays were taken in the control group than in the intervention group. Due to this last point, finding pneumonia in patients who irrespective of this would be treated with antibiotics was more likely to happen in the control group than in the intervention group. This gives power to the pneumonia variable in the multivariable analysis and weakens the association between intervention and antibiotic prescribing. It could have been right to include pneumonia among the explanatory variables if chest X-ray had been taken in all patients.

The manuscript is improved but more work needs to be done
There is a new systematic review published in this months BJGP which could usefully be cited.

Thank you for this suggestion. We have cited this review in the article (in the sections Background, page 5 and Discussion page 14).

Reviewer: Matthias Briel
Reviewer’s report:

Major compulsory revisions
1) Good that the authors now mention the Chi squared test in the methods section. However, as mentioned previously there are imbalances between groups at baseline with prognostic relevance for antibiotic prescribing (specifically in the proportion of community acquired pneumonia (17% vs 7%) and the perceived preference for antibiotics by patients (10% vs 23%)).
Randomization safely achieves balance of prognostic factors with about 500 patients per group and more. Therefore it is not a surprise that there are some imbalances with a total of 179 patients randomized. I strongly recommend conducting a multivariable regression to examine the effect of the experimental intervention on antibiotic prescribing adjusting for CAP and perceived preference - at least as a sensitivity analysis. Otherwise the results will not be valid.

We have added a multivariable analysis, using antibiotic prescribing as outcome in logistic regression and allocation to CRP testing as one of the explanatory variables, together with upper respiratory tract infection, any comorbidity, any chest finding, and perceived patient preference for antibiotics. See page 10 under Statistical analysis and page 12 under Sensitivity analyses. Adding pneumonia on X-ray among the explanatory variables somewhat weakened the association between intervention and outcome. We found it right not to include this variable, due to a strong correlation with both “any chest finding” and “any comorbidity”. And even more important, significantly more x-rays were taken in the control group than in the intervention group. Due to this last point, finding pneumonia in patients who irrespective of this would be treated with antibiotics was more likely to happen in the control group than in the intervention group. This gives power to the pneumonia variable in the multivariable analysis and weakens the association between intervention and antibiotic prescribing. It could have been right to include pneumonia among the explanatory variables if chest X-ray had been taken in all patients.
Minor essential revisions

2) I think it is insufficient to say "Due to the open design this evaluation was not blinded, and the results should be interpreted with caution." - I would suggest that you explicitly say that "GPs were aware of the purpose of the trial, they recruited and treated patients, and assessed the clinical outcome together with patients in an unblinded fashion and without standardized criteria."

Thank you for your suggestion. We used this sentence in the Strengths and weaknesses of the study section.

3) To avoid misunderstandings I would add to your statement "Regretfully we miss data on the duration of illness": "...at randomization".

We agree and we have added it.