Reviewer's report

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

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Reviewer: Matthias Briel

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Andreeva & Melbye conducted an open cluster-randomised trial including 18 GPs from 2 Northern regions in Russia to evaluate CRP testing vs no CRP testing in 179 patients with LRTI/acute cough with respect to antibiotic prescriptions, referral to radiography and rate of recovery at 2 weeks following the index-consultation. The authors report a statistically significant reduction of antibiotic prescriptions and radiography referrals with CRP testing and a comparable recovery rate between groups. The topic and findings are highly relevant for GPs. The research question is well defined, however, the current manuscript has several limitations that need to be addressed by the authors:

Major:

1.) The authors need to report in the Methods section (statistics) how they derived p-values for their statistical comparisons – currently no statistical tests are reported. Due to baseline imbalances (proportion of community acquired pneumonia, perceived preference for antibiotics by patients) a multivariable regression model taking into account these and potential other confounders would be an appropriate analysis for primary and secondary outcomes. A univariable model or a chi-squared test would not be sufficient.

2.) The duration of illness at the time of the index consultation would be a relevant baseline characteristic to report (e.g. table 1) – from my experience and as referenced in the paper (page 7 para 2, REF 15), GPs prescribe antibiotics more frequently when they know that the respiratory infection is already ongoing for more than 3 days.

3.) Who assessed patient recovery – the GP, the patient, or both together? Were there any criteria/definitions for the different categories or could GPs/patients interpret the categories as they wished? It would be a strong limitation of the trial (that would have to be mentioned) if the GPs knew about the purpose of the trial, recruited & treated the patients, and subjectively assessed the outcome of their patients without any external criteria/evaluation.

Minor:

4.) The authors could include the latest study by the GRACE consortium in their discussion (van Vugt et al. BMJ 2013); van Vugt et al diagnostically evaluated CRP and concluded that “A clinical rule based on symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough performed
best in patients with mild or severe clinical presentation.”

5.) What do the authors mean by “…suggesting that the difference between antibiotic prescribing rates in cases and controls was connected with a higher frequency of chest abnormalities among controls [25].” (page 11, bottom paragraph)? Was there a baseline imbalance between the intervention and the control group with respect to opacities found on chest x-rays? I would avoid any “case-control” terminology in a RCT.

6.) Do the authors have any idea why their findings contrast with those from Gonzales et al?

7.) The authors state on page 5, bottom paragraph, that “The sample sizes were based on a hypothesis of 20% reduction in antibiotic prescribing in the intervention group compared with the control group.” What were the target sample sizes in terms of GP clusters and patients? Were the participating GPs a random or convenience sample, or chosen through application of some selection criteria?

8.) Was the trial registered? If yes, please state the registry & registration number.

9.) Are there any data on whether the patients with antibiotic prescriptions actually filled the prescriptions and took the antibiotics?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.