Dear Dr Appleford,

Thank you for the helpful review of our manuscript. In the following, we answered all the comments of the reviewers in detail (referred to as C1 and R1, etc), which allowed to considerably improve our manuscript. Please find a highlightened (in bold and yellow) and not highlightened version of the revised manuscript. We hope that it is now suitable for publication in BMC Infectious Diseases in its present form.

Reviewer 1 comments:

Major compulsory revisions:

C1: The study is very interesting and very well written, but some limitations affect the selection criteria and methods, although the authors already address them in the discussion. There is a selection bias introduced by the fact of including patients from previous studies. To establish the patient's outcome as endpoint can improve the results, but it is still not a gold standard.

R1: We are aware that taking the patient’s outcome as endpoint can still not replace an unequivocal gold-standard. However, it represents an improved approximation towards a gold standard compared to other more routinely used surrogate measures (i.e. blood cultures, laboratory or clinical parameters). We rephrased the sentence as follows in the revised manuscript: “Although not being a new “gold standard”, this strategy better circumvented the problem of the non-existent diagnostic “gold standard” to decide on the presence or absence of a clinically relevant bacterial infection based on traditional criteria” (page 13).

C2: About the etiological diagnosis, a description of the microbiological methods used (for example for the diagnosis of Mycoplasma infection) is missing. Importance is given to the culture of respiratory secretions when it has limitations regarding the possibility of colonization, especially when including patients with COPD or with previous antibiotic treatment.

R2: We now give more details about the methods used to make an etiological diagnosis, as follows. “Mycoplasma pneumoniae was detected by culture or PCR in BAL fluid. Chlamydia pneumoniae was identified by PCR in BAL fluid. We looked for Legionella pneumophila by detection of the antigen in urine and/or by culture or PCR in BAL fluid” (page 5). We did not routinely perform serology or PCR or culture in blood and respiratory secretions for Mycoplasma pneumoniae and Chlamydia pneumoniae. Moreover, search for Streptococcus pneumoniae antigen in urine was not routinely done. This was stated as a limitation on page 13.

The rate of microbiologically documented CAP in our study population appears to be low on first sight. However, using representative respiratory secretions and blood cultures the rate of documented bacterial CAPs in our study was very similar to the one in different recent studies, e.g. Carratalà et al. Ann Intern Med 142:165-72,2005 (26% microbiologically
documented without stating criteria for sputum quality, or File et al. AAC 48:3323-31, 2004 (25.3% with defined quality criteria for sputum samples).

C3: It has been largely demonstrated that the use of biomarkers may complement and improve clinical and radiological assessment, and the results of this study confirm it. However, the fact of including patients with acute bronchitis or exacerbations of asthma and COPD, and excluding hospital acquired pneumonia or severely immunocompromised patients introduces also some bias to the favour of PCT. Measurement of biomarkers is still rather expensive, and has to be performed in the situations of difficult diagnosis, not in those that are already clinically evident.

R3: One might indeed argue that to diagnose bronchitis, CAP and AECOPD should be clinically evident as should the indication for antibiotic therapy. However, despite the presence of excellent and recent guidelines, the implementation into clinical routine namely for these “evident diseases” is insufficient. Thus in our opinion, as a biomarker PCT becomes especially valuable as a powerful tool to better complement and implement these guidelines, as shown in our intervention studies. This was mentioned in the Discussion of the revised manuscript (page 11/12).

Of course, after establishing the use PCT for antibiotic stewardship in low risk settings, the assessment of the diagnostic accuracy of procalcitonin to high-risk patients where the diagnosis is unclear and difficult is a highly interesting clinical question. However, since our study was a proof of principle study, safety was of utmost importance. Therefore, although highly interesting, patients with immunosuppression or hospital-acquired pneumonia were excluded. Observational studies and in a second step intervention studies have to be performed to assess the diagnostic accuracy of procalcitonin in immunosuppressed patients or hospital-acquired pneumonia, respectively. This was mentioned in the discussion on page 12.

Minor essential revisions:

C4: In table 2 there are some typing errors in the names of microorganisms. "menigitidis" instead of "meningitidis", "pneumophilia" instead of "pneumophila"

R4: We apologize for the mistake. The respective typing errors were corrected (page 20).

Reviewer 2 comments:

General:

The idea to use PCT and CRP and other parameters of inflammation to improve the precision of clinical assessment is appealing. For determining which patients need antibiotic therapy CURB 65 may also merit consideration.

R1: We analyzed our results with regard to the CURB65 score in the revised manuscript. Thereby, the results were similar as compared to the PSI. PCT levels increased with increasing CURB65 score (p<0.001). The respective p-value was also significant for leukocyte count (p=0.002), but not for C-reactive protein, body temperature or the visual analogue scale. This was mentioned in the revised manuscript (page 5 and 10).

Major compulsory revisions:

C2: P 3, line 18, Fig 3 and corresponding parts of the Results section. Concerning the aims of the study the material may be less optimized to answer the authors first question, to reflect the situation in primary care, since in that setting the bulk of patients will have viral respiratory
infections with different presentations and pneumonia will account for only a small proportion. In the present study 72.7% had a pulmonary infiltrate by CXR. With a totally different prevalence of pneumonia than seen in primary care, sensitivity and specificity as well as ROC curves of different parameters will be different. In fact the patients included in this study did present to an ER (p 4), so this is the setting best reflected by the presented material.

R2: We agree with the reviewer. Recently we completed a study in primary care (for study protocol see Briel et al., BMC Fam Pract 2005; 6:34) including 458 patients with respiratory tract infections. In this population, community-acquired pneumonia accounted for 15% of the diagnoses. The majority had acute bronchitis (27%), rhinosinusitis (22%) and acute pharyngitis/tonsillitis (16%). We now mention this limitation of the current study in the discussion (page 13, last sentence).

C3: Pp 5 and 10. The relevance of the results obtained in the study described in reference 22 to the methodology described on the bottom of page 5 and the results on page 10, line 4 is not evident.

R3: In reference 22 (now 23) it has been proposed that a clinically relevant CAP was absent if either an alternative cause for the pulmonary infiltrate was established without bacterial growth in culture results, or if the patient completely recovered without antimicrobial therapy. This definition was also used in our study to include patients in the category “clinically relevant bacterial CAP” or “others”, respectively. The reference 23 only applies to this definition used and not to the results in reference 23. This was re-formulated in the revised manuscript (page 5 and 10).

Minor essential revisions:

C3: P 5 and Table 2. An etiology was determined in only 26.3% of the cases of CAP. It is an unusually low figure, which may deserve a comment. Established methods as PCR for M.pneumoniae and C.pneumoniae and urinary antigen test for S.pneumoniae were not used. Also 20.2% of the patients were pretreated with antibiotics – a normal percentage. These facts concerning this study may have an impact on the usefulness of the definition of bacterial pneumonia accounted for at the bottom of p 5.

R3: Indeed, the rate of microbiologically documented CAP in our study population appears to be low on first sight. We did not routinely perform serology or PCR or culture in blood and respiratory secretions for Mycoplasma pneumoniae and Chlamydia pneumoniae. Moreover, search for Streptococcus pneumoniae antigen in urine was not routinely done. This was stated as a limitation on page 13. However, using representative respiratory secretions and blood cultures the rate of documented bacterial CAPs in our study was very similar to the one in different recent studies, e.g. Carratalà et al. Ann Intern Med 142:165-72,2005 (26% microbiologically documented without stating criteria for sputum quality, or File et al. AAC 48:3323-31, 2004 (25.3% with defined quality criteria for sputum samples).