and CRP measurements, because large studies show no differences. The trend is not so clear for the reported specificities. If there is publication bias, meta-analysis may not be appropriate, as it can lead to skewed conclusions.

We greatly appreciate the vast efforts that Simon et al. [1] put into producing their review, and we recognize the importance of the question it seeks to answer. However, before suggesting that PCT should be considered for widespread use in clinical practice, we hope that Simon and colleagues will address the issues raised here. In conclusion, we agree that the next step is for the true impact of use of PCT markers on outcomes to be evaluated in large prospective studies.

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Reply to Knudsen and Kristiansen

Sir—We thank Knudsen and Kristiansen [1] for critically evaluating our review article [2] and highlighting certain discrepancies they have noted with regard to the data abstraction. We have now systematically reexamined the data abstraction process and analysis, and the resulting findings are being published in an erratum in this issue (pp. 1386–8). By and large, the overall conclusions from the corrected analysis do not differ from those we reported in our review [2].

Knudsen and Kristiansen [1] have correctly addressed the issue of publication bias and the effect this may have on meta-analysis of published studies. We have avoided carrying out a formal investigation of this bias in our meta-analysis because the number of studies eligible was limited for many of the comparisons (10 maximum for comparison of bacterial infection versus noninfective inflammation). Funnel plots and statistical tests, such as the Begg's test and Egger's test, are sensitive to the number of studies included and can give misleading evidence for or against the existence of publication bias. The graphical analysis presented by Knudsen and Kristiansen [1] (figure 1 in their letter), plotting the differences in sensitivity and specificity against the sample size (for comparison of the ability of the markers to discriminate bacterial infection from noninfective inflammation), seems to indicate that differences between the markers are more evident among smaller studies and suggests the presence of publication bias. We have repeated the same analysis using the corrected data. Our analyses (figures 1 and 2) show that the magnitude of the differences in the measures of diagnostic accuracy (i.e., sensitivity and specificity) do not seem to be correlated with the size of the study.

There has been continuing debate on the existing tools for evaluating publication bias in meta-analysis. The conclusion that publication bias exists varies accord-

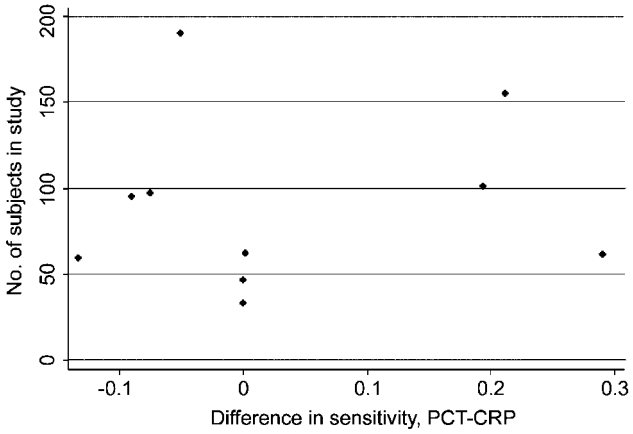

Figure 1. Differences in the sensitivities of procalcitonin (PCT) and C-reactive protein (CRP) as markers to discriminate between bacterial infection and noninfectious infammation, plotted against the number of subjects in each study (data from [2]).

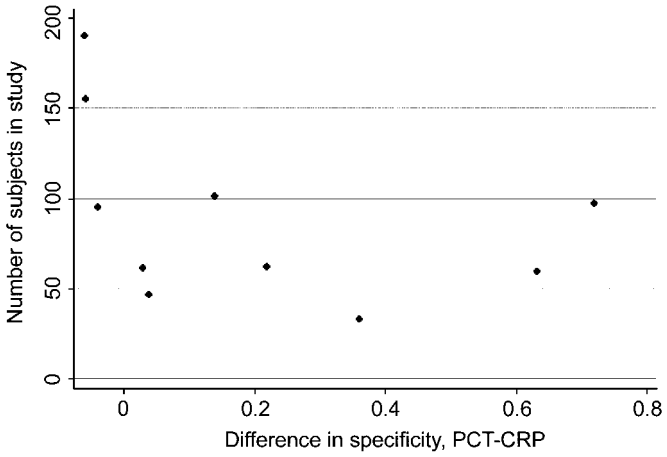

Figure 2. Difference in the specificities of procalcitonin (PCT) and C-reactive protein (CRP) as markers to discriminate between bacterial infection and noninfectious infammation, plotted against the number of subjects in each study (data from [2]).

ing to the definitions of "precision" and "effect estimate" used [3, 4]. Different measures of precision, such as SE, inverse of the SE, and sample size, can provide varying results. This was also evident when we carried out a formal in-depth analysis of our data. We created funnel plots using the inverse of the SE as the estimate of precision, which we plotted against the OR (as the effect estimate). The plot and the results of the associated Begg's test did not indicate evidence for publication bias with respect to studies reporting on the accuracy of procalcitonin (PCT) and C-reactive protein (CRP) as markers to discriminate between bacterial infection and noninfective inflammation ($P = .53$ and $P = .32$, respectively). The results of Egger's test were also not significant for both PCT and CRP.

When the SE was used as the measure of precision for PCT, the result of Egger's test was significant, indicating presence of bias, but the result of Begg's test was not. Both tests indicated there was no bias for CRP. We also used methods described by Hasselblad et al. [5] and determined the effect estimate d, estimated as $d = \sqrt{3}\,(\log \mathrm{TP} + \log \mathrm{TN} - \log \mathrm{FP} - \log \mathrm{FN})/\pi$, which we plotted against its variance, calculated as variance $(d) = 3\,(1/\mathrm{TP} + 1/\mathrm{FP} + 1/\mathrm{FN} + 1/\mathrm{TN})/\pi^2$, where TP indicates true positive results, TN indicates true negative results, FP indicates false positive results, and FN indicates false negative results. The results for PCT indicated the presence of publication bias when Egger's test was used (intercept, 1.95; $P = .007$) but not when Begg's test was used ($P = .93$). For CRP, both the tests indicated there was no publication bias. Given these discrepancies in the findings, some of which could be attributed to the limited number of studies evaluated, it would be difficult to conclude what effects, if any, publication bias had in the meta-analysis we performed [2].

The comments and issues highlighted by Knudsen and Kristiansen [1] are timely and most relevant. Meta-analysis of diagnostic studies is a growing field and has scope for improvement. We have attempted to summarize the literature on a very important clinical issue. Within the limits of existing statistical techniques, our findings show some support for the superiority of PCT over CRP as a marker for discriminating between bacterial infection and noninfective inflammation. At the same time, we agree with Knudsen and Kristiansen [1] that the limited number of available studies comparing the ability of the markers to discriminate between bacterial and viral infections precludes definitive conclusions.

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Important Factors to Consider for Patients with Community-Acquired Pneumonia

Sir—Menéndez et al. [1] provide an interesting analysis of clinical parameters that allow the identification, at admission to the hospital, of patients with community-acquired pneumonia (CAP) who have an increased probability of experiencing delay in reaching clinical stability.