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From the author:

We thank M. Miravitlles and C. Llor for their comments. While we do, of course, agree with their statement that it is impossible to detect bacteria when no sample is obtained, this issue is addressed in our study by the subgroup analysis, which examines only those patients with sputum samples tested for bacteria. This group demonstrates identical findings to our main cohort: that C-reactive protein (CRP) levels and body temperature are strongly associated with viral detection (either alone or with bacteria) but not with bacterial detection alone, and suggests that the findings in the main cohort are not due to a lack of sputum samples. We would also like to point out that it is similarly impossible to detect viruses if one does not test for them and of the studies referenced by M. Miravitlles and C. Llor as demonstrating an association between CRP level, sputum purulence and bacterial detection [1–5], none has tested for respiratory viruses apart from that by Daniels *et al.* [5] and this was not in a standard manner. Interestingly, another study referenced by the authors [6] did systematically test patients with exacerbations for both viruses and bacteria, and demonstrated that although infective exacerbations were associated with sputum purulence compared with those where no pathogen was detected, it found no difference in sputum purulence between exacerbations with viral or bacterial detection. It is also notable that in the randomised, placebo-controlled trial of doxycycline by Daniels *et al.* [5], although there was a weak association between CRP levels >50 $mg \cdot L^{-1}$ and a favourable response to antibiotics, there was no demonstrable association between antibiotic response and bacterial detection. Viruses were not tested for in a meaningful way in this study but only by serology for selected viruses, and patients with fever were excluded, which would be likely to exclude many patients with viruses. No analysis was conducted to examine the association between the small number of viruses detected by serology and CRP, sputum purulence or response to antibiotics. Therefore, the place of viral detection within this evidence base is uncertain and any conclusion about associations between bacterial detection, sputum purulence, CRP levels and response to antibiotics must acknowledge this uncertainty.

While we understand that our study, like most others, has methodological limitations, it does remain the largest study to examine the role of both viruses and bacteria in hospitalised patients with exacerbation of COPD, and is a real-world clinical study with results generalisable to most patients presenting to emergency departments and admission units. It has demonstrated that the detection of viruses in our cohort was strongly associated with elevated CRP levels (at least up to levels of 100 $mg \cdot L^{-1}$) and temperature but that the detection of bacteria was equally common at all levels of CRP and temperature, at least by conventional culture and pneumococcal antigen testing. This, to us, strongly suggests that the

viruses detected are likely to be causally related to the patient's inflammatory response and thus their exacerbation, but the bacteria detected may not be. This comes with the caveat that these were patients early in the course of their exacerbation (median 4 days) and that bacteria may well have a different role later in the course of their exacerbation, as suggested by GEORGE *et al.* [7] and others, and also that there were few patients in out cohort with very high CRP levels (>100 $mg \cdot L^{-1}$) and it is possible that bacteria may be more important in this group. Many questions remain unanswered. If viruses are causing most exacerbations, then why is the rate of detected viruses in most studies so low? What is the cause of exacerbations with raised CRP where neither viruses nor bacteria can be detected? How do antibiotics improve outcome in some patients with exacerbation, independently of detected bacteria? Our study cannot answer these questions but does provides new insights into the role of viruses in hospitalised patients with exacerbation of COPD, adding to the groundswell of evidence supporting their importance.

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Viruses detected are likely to be causally related to patients' inflammatory responses and thus COPD exacerbation http://ow.ly/KeMPc

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