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Comment on: Impact of introducing procalcitonin testing on antibiotic usage in acute NHS hospitals during the first wave of COVID-19 in the UK: a controlled interrupted time series analysis of organization-level data

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We read with great interest the article published recently in this Journal by Llewelyn *et al.*[1] which provides an additional piece of evidence that procalcitonin (PCT) plays an important role in antimicrobial stewardship of COVID-19 patients. Besides the interrupted time series analysis, both the similarity of time series curves between PCT adopters and always users, and the dissimilarity between PCT users and never users, provide further evidence that PCT is driving usage of antibiotics in these hospitals. Our controlled study previously demonstrated that combining molecular tests in emergency departments with PCT could decrease the duration of intravenous antibiotics and hospital stays, and increase the percentage of antibiotic de-escalation.[2] The benefit of PCT in antimicrobial stewardship may have been underestimated if antibiotic de-escalation was not analysed as a major outcome. One additional potential bias that merits discussion concerns the balance of patients' illness severity between PCT-adopting and non-adopting hospitals. It has been reported that non-surviving COVID patients generally have a shorter hospital stay than surviving patients.[3,4] Hospitals that admit more severe COVID cases may have shorter average length of stay, leading to shorter antibiotic durations. These hospitals are usually teaching hospitals that also have a higher likelihood of adopting PCT testing. The relationship between the hospital level and the adoption of PCT testing is implied by Table S2 in the article by Llewelyn *et al.*,[1] which reveals that PCT adopters have more admissions per week per trust (including both total and COVID-19 admissions) than never users. Therefore, the patient severity of the hospital confounds the association between PCT adoption and antibiotic consumption. Ultimately, controlled intermittent time series analysis can provide a holistic assessment of the impact of PCT adoption on antibiotic usage, but it cannot replace a multicentre pragmatic controlled trial when it comes to causal inference. A randomized controlled trial is unlikely at this stage of the COVID-19 pandemic. However, prospective observational studies using individual patient data (such as PEACH, ISRCTN66682918), can provide some insights on the potential impact on antibiotic prescribing of PCT over and above other routinely measured biomarkers.

It is also worth mentioning that the high costs associated with PCT measurements may prevent its wide adoption. There is a high correlation between low C-reactive protein and low PCT levels, especially <0.5 ng/mL, with a negative predictive value of 97.6% on admission.[5] Prospective cohort studies can also evaluate the differential impact between PCT- and CRP-guided antimicrobial stewardship.

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Transparency declarations

None to declare.

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