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—authors' response

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We thank Dr Su and colleagues for their interest in our paper with reference to their pre-pandemic study.[1] We agree that procalcitonin (PCT) has the potential to improve the accuracy of both decisions to start and to de-escalate antibiotic treatment. However, our analysis, which used organisation-level data, could not reveal this level of detail. We also agree that differences in illness severity between hospitals is a potential source of bias we could not fully account for. Su *et al.* propose that more severely ill patients receive less antibiotic treatment because they may have shorter hospitals stays. We suspect there is a complicated relationship between severity of COVID-19 infection and antibiotic prescribing. These issues are being addressed in the next phase of the PEACH project (ISRCTN66682918), which will analyse individual-patient-level data and account for antibiotic durations potentially being 'truncated by death' in the most severely ill.[2]

Su *et al.* note that hospitals that adopted PCT testing had more admissions per week than those that did not. The differences in our Table S2 between hospitals that never used PCT [median 1041 (range 193–4047) admissions per week] versus PCT adopters [1295.5 (316–4948)] and PCT always-users [1182.5 (75–5764)] are small though and the overlaps large. In our sensitivity analyses we considered Trust size using estates return information collection (ERIC) data from NHS Digital but, as shown in our Table S4, this did not modify the effect of PCT introduction, nor were there any statistically significant differences between the five ERIC categories of acute Trusts (small, medium, large, multi-service, teaching). The term 'teaching hospital' is not clearly defined in the UK and smaller hospitals may be affiliated to universities so we have not attempted to look at hospital type in this way.

As regards costs, while the cost of PCT testing is high compared with C-reactive protein (CRP) in most markets it is trivial in the context of the cost of hospital treatment and we would argue unlikely to drive economic cost of antimicrobial stewardship activity. Notwithstanding the correlation between CRP and PCT, using CRP to triage patients for PCT would need to be evaluated as an intervention before concluding this as a safe and cost-effective strategy.

Su *et al.* comment that only a randomised trial can determine whether PCT testing improves antibiotic use and that the opportunity to do such a trial in the pandemic has passed. This is an important point. The rapid deployment of trials such as RECOVERY meant, in the UK at least, that very few COVID-19 patients were exposed to unlicensed treatments outside trials. In contrast, PCT testing was introduced widely in hospitals in response to COVID-19 notwithstanding NICE guidance that it should not be used.[3] Since this happened as part of clinical practice rather than research, unique opportunities for learning were missed and, more importantly, patients were exposed to this unproven intervention without consent. Retrospective interrupted time series studies cannot address these issues. Su *et al.* are correct that individual-patient randomised trials deal with issues of bias that are inherent in non-experimental designs but even outside a pandemic, they have major limitations in antibiotic stewardship research.[4] These include difficulties in achieving robust blinding, contamination across arms and infeasibility of sample sizes required to demonstrate non-inferiority for clinical outcome. Designs with cluster randomisation (e.g. hospital-level) and individual-patient-level outcome assessment may be the best approach but are logistically very challenging to set up and deliver.[5] Rather than call for trials in this field we would like to see system-wide learning platforms for the study of antimicrobial use and resistance to efficiently deliver large-scale clinical evaluation of antibiotic treatments and stewardship strategies.

Transparency declarations

References

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