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Letter to the Editor

'Development of diagnostic prediction tools for bacteraemia caused by 3rd generation cephalosporin-resistant Enterobacteriaceae in suspected bacterial infections' – Author's reply

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To the Editor,

Lambregts and colleagues have proposed using the number needed to treat with carbapenems to prevent one case of mismatch of empirical therapy (NNT-C-1), instead of the putative absolute reduction of carbapenem use, to determine the applicability of the recently published treatment decision tool [1,2]. In the scenario of substituting empirical cephalosporins for carbapenems in specific risk groups, the NNT-C-1 is simply the inverse of the probability of third-generation cephalosporin-resistant Enterobacteriaceae (3GCR-E) bacteraemia in a patient population. As such its value can be derived from the information provided in the manuscript.

Although it may be an attractive quantification of the need to provide empirical carbapenems, the use of NNT-C-1 also has its drawbacks. First, presenting the NNT-C-1 as fixed for a population ignores the concept of individual risk prediction. Second, carbapenems may also benefit patients infected with e.g. non-bacteraemic 3GCR-E, *Pseudomonas* or *Bacteroides*, and some infected with Gram-positive bacteria. We did not study whether these patients receive disproportionally high scores when applying our prediction rule, but these infections may in fact reduce the NNT-C-1. Third, we do not know how to interpret the NNT-C-1 for exactly the same reasons that we do not provide fixed thresholds for our scoring systems. In what cases does an NNT-C-1 of 50 justify empirical treatment with carbapenems? As stated in our paper, the downstream effects of carbapenem (over)use on resistance development are unknown, as is which patients benefit most from immediate appropriate empirical therapy. Finally, NNT-C-1 does not take into account how many patients with 3GCR-E bacteraemia are missed when applying a threshold to the prediction tool. Using a higher threshold for carbapenem treatment will always decrease the NNT-C-1 (as nicely illustrated by Lambregts and colleagues) but will also result in more 3GCR-E bacteraemia patients being empirically treated with cephalosporins. In order to convey this equilibrium, we chose to present both sensitivity and test positivity rates in our manuscript.

If patients with severe sepsis were to have considerably higher rates of 3GCR-E bacteraemia, this would have been picked up by our prediction models as predictive factors, no matter whether the underlying reason would be a higher proportion of positive blood cultures. Nevertheless, we agree with the authors that restricting empirical carbapenem use to patients with septic shock could be an attractive strategy to both curb carbapenem overuse and reduce the risks of undertreatment. Our prediction scores have not been specifically derived for this patient population. A septic-shock-specific prediction score may in fact perform better than our scores. Hence, extrapolation of the performance of our risk score to a population with septic shock, as the authors did to calculate the NNT-C-1, should be interpreted cautiously.

As the authors note, many hospitals provide initial combination therapy with aminoglycosides in cases of suspected infection. Although this will reduce inappropriate empirical therapy in cases of 3GCR-E infection, it increases unnecessary aminoglycoside usage and avoidable side effects [3]. As the primary aim of the paper was to derive improved prediction tools, we did not evaluate different treatment strategies, including risk stratification and initial aminoglycoside combination therapy. Importantly, the consequence of using our prediction model is not necessarily the prescription of carbapenems. The reported 40% carbapenem reduction using a cut-off of 120 in cases of community-onset infection should be interpreted as a 40% reduction in the

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patients classified as at risk of 3GCR-E bacteraemia compared to current risk stratification schemes. Ideally, the prediction scores provide a probability of 3GCR-E bacteraemia that assists physicians in choosing the most appropriate empirical antibiotic regimen. Hence, the results can also lead to targeted combination therapy, which may reduce the unnecessary use of aminoglycosides. As we do not know how treating physicians' decisions will be affected in real life by the results of our prediction scores, we support the idea that after external validation, experimental studies should be performed to evaluate the impact of risk prediction and stratification tools for antibiotic resistance on patient management and outcome.

Transparency declaration

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