Author’s response to reviews

Title: A PCR-based diagnostic testing strategy to identify carbapenemase-producing Enterobacteriaceae carriers upon admission to UK hospitals: early economic modelling to assess costs and consequences

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Reviewer reports:

Reviewer #1: This is an interesting and important analysis presenting results from a decision-analytic model on the costs and consequences of using PCR to detect CPE compared with culture-based testing. The authors clearly describe the models used and how costs were estimated. The finding that PCR testing would save costs to the NHS compared with culture testing to detect CPE remained robust for all sensitivity analyses.

I only have a few comments on this paper. Firstly, how widely is PCR testing available in UK hospitals? If this were to be widely adopted, how many hospitals would need to invest in new instrumentation and what would the costs of this be?

Author response: There is currently no published information on the availability of PCR testing for CPE in UK hospital laboratories. However, we have spoken with one of the clinical experts involved in the study about this and they have said that it is known that the vast majority of UK laboratories currently have PCR test equipment available for the detection of other conditions, and that these systems could be used for the detection of CPE through the purchase of the appropriate kit. Therefore, while the national cost of upgrading equipment to allow for universal PCR testing for CPE is unknown as information on the current availability of PCR testing
equipment for CPE is unknown, this is an interesting point and one which we have now added to the final paragraph of the discussion section.

There needs to be more background on MALDI-TOF MS and its role in the diagnostic pathway. Is this the gold standard for detection of CPE? It is unclear whether this is part of the usual care pathway for following-up positive samples.

Author response: Firstly, in order to make it clear that the section ‘Screening using culture’ in the Methods section relates to current practice, we have added ‘current practice’ in brackets at the heading of this section.

In this section, at the first mention of MALDI-TOF MS we have now indicated that this would be done on positive samples as a confirmatory test, and we have included a sentence following to explain that MALDI-TOF MS is a rapid method of microbial characterization.

There is currently no gold standard method for screening CPE, something which we have now added to the introduction, so it should now be clear that MALDI-TOF MS is one part of the diagnostic testing strategy carried out on positive samples. The use of MALDI-TOF-MS on positive samples is highlighted in both the culture and PCR testing strategy sections.

In the review of sensitivity and specificity of culture tests and PCR, which analytical methods were used as the reference standard? Were these gold standard methods and were they pre-specified before combining data in meta-analysis? If more than one method was used then please discuss the risk of bias in accurately determining the sensitivity and specificity.

Author response: As mentioned above, there is no gold standard test for screening for CPE. Therefore, the reference standard varied across studies for both the culture and PCR test papers identified. As there was variation, we have now highlighted this and added a few sentences to emphasise the fact that the RoB with regard the reference standards was low based on our quality assessment carried out using Quadas2. These changes have been made in the re-titled ‘Sensitivities and specificities of the culture and PCR screening strategies’ section.

Please provide a reference for the following sentence on page 16, line 345:

"However, with each consecutive culture test, patients with CPE who test positive have characteristics that are different from patients with CPE who test negative, and performing subsequent culture tests on patients who test negative is expected to decrease culture test performance."

Author response: We have decided to remove this section from the limitations entirely. We feel that it doesn’t add much to the paper and is unnecessary.
Reviewer #2: The authors report a study to assess the potential costs and consequences of implementing a test strategy involving a polymerase chain reaction (PCR)-based diagnosis test for CPE among high risk patients upon admission to UK hospitals to replace the current culture-based testing strategy. This study and its findings are important to clinicians, test developers and health economist who are interested in this area. I have some comments:

1. Abstract: The authors claimed that the objective of this study was to assess both potential costs and consequences of introducing the new test. However in the following methods and results sections, they seemed to only focus on costs and cost saving. It is not entirely clear what consequences they examined, e.g. test accuracy, patient's health outcome?

Author response: The consequences we were interested in was the diagnostic accuracy, and associated cost implications of the diagnostic accuracy, for each approach. We agree that the consequences side of things was not made clear in the methods and the text has now been revised to address this. We have edited text in the Methods section of the Abstract, and in the ‘Model overview’ and ‘Assessment of costs and diagnostic accuracy classifications’ sections of the Methods in the main paper to address this point. It should now be clear that the diagnostic accuracy results which we are referring to in the results section are the consequences that we are interested in.

2. Background: The authors used an estimated cost of an outbreak of CPE in a London hospital group to justify the burden of CPE and hence economic case. Can the authors provide national or/international figures on managing CPE to strengthen the case?

Author response: Unfortunately, there is no published information on the national/international cost of managing CPE. The estimated cost of an outbreak in the London Hospital group is the most relevant, published cost data available that we can cite.

I don't agree that 'early health economic models are useful predictors of the likely health outcomes and costs'. Early HE models are tools or methods used to explore/predict potential costs and outcomes of technologies under development but the models themselves are not predictors. Personally I think the early HE modelling methodologies are still an emerging area under development and currently lack a framework and guidance. It is arguable that the early modelling should 'generally involve simple analyses based on a small number of inputs' or should be comprehensive as late stage modelling. The authors may find it helpful to refer some key references here, e.g. Ijzerman 2017 on PharmacoEconomics, and Frempong 2018 on Expert review of Pharmacoconomics and outcomes research. It would be helpful if the authors provide some information of the development and adoption status of the PCR-based test strategy.

Author response: Thank you, we agree with the comment on the phrasing of this first sentence and we have now re-drafted this to clarify. We have also removed the statement that they 'generally involve simple analyses based on a small number of inputs' and have referenced Ijzerman 2017 in this paragraph.
Additionally, in response to previous reviewer comments, we have now made it clear in the Introduction of the paper that there is currently no gold standard test for screening for CPE. We have also now made it clear in the Discussion section that although it is currently unknown what percentage of UK hospitals have PCR tests available for screening CPE, it is predicted that the vast majority do have PCR equipment available for other purposes and could be used for CPE testing with the purchase of the appropriate kit. Making these two points clear, as well as stating that PCR testing is a viable alternative to the typically used culture-test strategy, is about as far as we can comment on the development and adoption status of the PCR-based testing strategy.

3. Methods - prevalence: it is not clear what population does this prevalence figure of 0.6% applies: the whole population, all patients in both primary and secondary care, or hospital patients.

- sensitivity analysis: various one-way sensitivity analysis were performed. Are there particular reasons why probabilistic sensitivity analysis have not been conducted?

Author response: The prevalence figure was based on the testing of a number of secondary care patients across the North West of England for the presence of the infection from a variety of specimen types. We have now made it clear in the ‘Prevalence of CPE’ paragraph what patient group this 0.6% figure relates to.

Regarding the sensitivity analysis, the intention was always to estimate expected values based on a deterministic analysis. We were not interested in presenting results in terms of probability of being cost-effective at various thresholds. We had a reasonable level of certainty around all cost parameters included in the model, and therefore chose not to assign distributions, and with the test performance and prevalence parameters we were always going to vary these deterministically to look at their impact on results. Therefore, we decided not to make the model probabilistic. We have carried out multiple one-way analyses to explore parameter variation and as many uncertainties as we could.

4. Results: I don't understand Table 2 on the test performance: 0.6% is the prevalence of CPE in the population, and whether and to what extent the tests could detect these CPE from the population are based on the performance of the tests. Can you explain the figures in more detail by linking with the model?

Author response: That is correct. Table 2 and the sensitivity analysis table at the end of the paper simply show the expected cost of testing with each strategy and the diagnostic accuracy, i.e. proportion of TP, FP, TN and FN patients identified with each method of testing (three rounds of testing on negative samples with culture and one round of testing for all samples with PCR) based on test performance and prevalence of the condition. The ‘Assessment of costs and diagnostic accuracy classifications’ section has been re-worded and explains that we were interested in understanding the percentage of the cohort that would be categorised into these four groups following the two testing strategies, and the method of calculation is also presented here. We feel that this section describes the model results we are presenting in sufficient detail.