Author’s response to reviews

Title: The cost of diagnostic uncertainty: A prospective economic analysis of febrile children attending an NHS Emergency Department

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Author’s response to reviews:
Reviewer comment 1: I would suggest revising "the precautionary use of antibiotics increases costs considerably" to "the precautionary use of antibiotics is strongly associated with increased costs"

Author response 1: This has now been completed as per your suggestion above.

Reviewer comment 2: Background. In the response to reviewers, the authors cite several studies that describe the prevalence of occult bacterial infection in children with fever (generally around 1%). This is important, but not mentioned in the revised manuscript. It would be very helpful to describe these data briefly (one sentence should be fine) somewhere in the background section to illustrate how difficult the clinician's job is to detect the "needle in the haystack" of occult bacteremia.

Author response 2: Thank you. This has now been added, and we have added two references from the response to the reviewer comments:

‘However, occurring in as few as 1% of febrile children4,5, these ‘hidden’ bacterial infections represent a needle in the haystack; and the challenge for clinicians is to accurately identify children at risk of bacterial infections. While it is possible that they may resolve spontaneously, for those in whom they do not, life-threatening and potentially life-changing complications can develop,4,7,8

Reviewer comment 3: Background, line 163. Reference citations are needed at the end of this paragraph

Author response 3: We have added in four of the studies mentioned in the discussion section, thank you for highlighting this omission.

Reviewer comment 4: Results, line 325. Here would be a good place to point out that clinical characteristics of excluded patients, as measured by age, MTS categories, temperature and antibiotic use, were not different from those included in the study. (response to my comment #6 in original critique, answered well by the authors in their response) I don't think any more than one extra sentence is needed

Author response 4: We have added a sentence to highlight the lack of a significant difference between those included/excluded in the study:

‘8,552 individual ED attendances were identified over the study period, with 2,034 excluded from the analysis due to incomplete data or failing to meet our inclusion criteria. This resulted in a complete dataset of 6,518 observations (Table 2). There was no significant difference in observable characteristics between those included and excluded; including but not limited to age, final diagnoses, MTS classification and temperature.’

Reviewer comment 5: Discussion, lines 504-506 more or less. This might be a good opportunity, if the authors feel it would help, to cite studies of clinical observational scales that are used in infants in the US to detect infants at higher risk of bacterial infection, namely the Yale and Philadelphia Observation Scales. They can be a helpful adjunct, especially for trainees, in deciding which febrile infants need further laboratory investigation.

Author response 5: Thank you, we have since added the following:

‘Additionally, the prevalence of invasive bacterial infections, bacteraemia and bacterial meningitis, are highest in the first 3 months of life, driving clinician behaviour towards a cautious approach in this
high-risk group. Clinical prediction rules, such as the Yale observation scale may be useful in these groups, particularly among those with less experience in ruling in/out serious bacterial infections; however, reliability in higher vs. lower income countries is variable, suggesting that these alone, may not be enough to fill the diagnostic gap faced by the clinician managing paediatric febrile illness.

Reviewer comment 6: Conclusions, line 562. The authors have lined out "predominantly because of increases in inpatient admissions" in their revision. I would suggest keeping it for reasons of clarity, to match the Abstract.
Author response 6: We have included as suggested.

We would like to thank the reviewers and the editor for their time and suggestions in improving the manuscript.