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 #1: Comment 1: This paper is a very comprehensive observational study of the management of fever in a large group of children of all ages at a single institution in the UK about 6 years ago. It is unusually detailed compared to many observational studies of its type, including variables such as triage category of children, time spent in their management, clinician type and level of training, and costs. While these are strengths of the paper, they are also weaknesses, as space limitations and limitations of most readers’ capacity to absorb data make it difficult to adequately discuss and understand the different comparisons that are important to inform future improvement work. Additionally, it is incorrect to group older children and adolescents with babies in an analysis of this type, as causes and appropriate management of fever differ greatly between age groups. Results are divided by age, but analyzing all groups together is not appropriate. It may be that more than one paper with greater focus on a smaller quantity of data is needed to adequately describe the results of this ambitious study.

Authors’ response: Our study aim is a representative real-life study of all febrile children treated at the ED over a one-year period, without selection, as commended by reviewer 2. This as a major strength of our study. The overall picture and the ability to draw comparisons across groups strengthen the recommendations that we make. Although we disagree with the reviewer’s point on doing a smaller study, we do agree that it is almost impossible to present conclusions on the entire rather heterogenous group. However, we believe that selective post-analysis data omission wouldn’t be proper to drop about 50% of the data. We decided to continue to present the data in subcategories for all outcomes such that the reader has an overview of the differences and is able to select the sub-population of interest to them and draw comparisons as they see fit.

We do completely agree with the comments regarding pooling all children together and now have removed the following from the results section:

‘The mean (median) cost per completed febrile illness episode was £223.55 (£51.92). Febrile management costs varied significantly by patient age, p =0.0001’

Reviewer #1: Comment 2: Moreover, the age of the data combined with recently changing epidemiology of bacterial infections due to improvements in vaccines, especially pneumococcal and meningococcal vaccines, is a significant limitation of the work.

Authors’ response: We do not accept that the age of the data is a significant limitation in answering our research questions for the following reasons:

1) We demonstrated in a paper published in 2015 (Irwin A, Pediatrics 2015), that bacteremia in children presenting to the emergency department is increasingly healthcare associated and resistant to empirical antibiotics. This was a retrospective time series analysis of bacteremia in children presenting to our hospital ED between 2001 and 2011. These infections are associated with increased length of stay. Rates of Gram-negative bacteremia have increased, and children with Gram-negative bacteremia experience delayed antibiotic administration. There was an annual reduction of 10.6% (6.6%–14.5%) in vaccine-preventable infections, and an annual increase of 6.7% (1.2%–12.5%) in Gram-negative infections. The pneumococcal conjugate vaccine was associated with a 49% (32%–74%) reduction in pneumococcal bacteremia. Only 225/525 (43%) children had a vaccine preventable bacteremia.

2) Furthermore a recent study in Lancet Infectious Diseases (Ladhani, S, Lancet Infect Dis 2018 18: 441–51, demonstrates that from 2013/4 the incidence of all types of IPD have plateaued in <2 years
and 2–4 years, and slight decreases in 5–14 year group. Invasive pneumococcal disease incidence due to non-PCV13 serotypes doubled (7.97 per 100,000; 1.97, 1.86–2.09) since the introduction of PCV7, and accelerated since 2013/14—especially serotypes 8, 12F, and 9N, which were responsible for more than 40% of invasive pneumococcal disease cases by 2016/17.

Figure 1: Corrected trends in IPD incidence in England and Wales for all ages and by age group

3) In the EUCLIDS study (2001-2016), a prospective multicenter cohort study aiming to evaluate genetic determinants of susceptibility and/or severity in sepsis, across Europe, of 428 (54%) patients with confirmed bacterial infection, Neisseria meningitidis (n = 131, 31%) and Streptococcus pneumoniae (n = 78, 18%) were the main pathogens. This is despite Meningococcal C (Men C) vaccine being introduced in 2000, PCV 7 in 2006, and PCV13 in 2010 (Boeddha N, Crit Care 2018).

4) In England, Invasive Meningococcal Disease has declined from 1.8/100,000 in 2010/2011 to 1.1/100,000 in 2013/2014, with a small increase in 2014/2015 to 1.3/100,000. Between 1st January 2011 and 30 June 2015, Men B was responsible for 73.0% (n = 2489) of 3411 laboratory-confirmed IMD cases, followed by Men W (n = 371, 10.9%), Men Y (n = 373, 10.9%) and Men C (n = 129, 3.8%); other capsular groups were rare (n = 49, 1.4%) (Parikh SR, Vaccine 2018)

Reviewer #1: Comment 3: Background. The authors assert from the start that viral, bacterial, and serious bacterial infections (SBIs) often result in similar presentations in children. This is incorrect; it is likely true among young infants, especially those under 1 month of age, but not at all true in ages older than 3 years, and controversial in those between 3 and 36 months of age.

Authors’ response: Thank you for pointing out this oversight. We have since amended as per your comments

Reviewer #1: Comment 4: The authors cite the prevalence of occult bacteremia as 1 in 400, but these data are now 10 years old and were collected in children younger than 36 months of age. These problems propagate throughout the paper. Young infants, children 3-36 months of age, and children older than 3 years have different causes of fever.

Authors’ response: We agree and have updated the reference to Irwin 2015 which gives a rate of 1.42 per 1,000 admissions (1 in 700).


Another paper published in Spain, showed a prevalence of occult bacteremia (1.1%; 95% confidence interval: 0-2.2) in well-appearing infants 3-24 months of age with fever without a source ≥40.5°C Gangoiti I, Pediatr Infect Dis J. 2018 Nov;37(11):e271-e273

Our references have a focus on infants and we hope this is now much clearer in the text. In sum, regarding the reviewer’s main point, it indeed, given the data available, to analyse the outcomes on
older children. However, the fact that older children’s data are present does not detract from the key messages for younger children, as all results are stratified by age, to allow for comparisons by age-group.

Reviewer #1: Comment 5: Background. The authors discuss how sufficient observation time, repeated blood and urine investigations and clinical judgement are needed for accurate diagnosis and treatment. While the first and third of these are true, the second (at least in the experience of this US reviewer) is no longer the case except in very special populations such as very young infants, those with immunodeficiency, or oncology patients. Other than young infants, these two groups were excluded from this study. The importance of outpatient follow-up is a topic here although it is a common problem with US /UK studies of ED populations.

Authors’ response 5: We agree that outpatient follow-up data would add significantly to the reporting of the analysis however outpatient follow-up is not routine practice in the NHS. The manuscript provides information on readmissions and 3.43% of our cohort (224 children in total) were readmitted following discharge as shown in Table 1.

Reviewer #1: Comment 6: Methods. Subject selection: It would be interesting to briefly describe characteristics of the roughly 25% who were ineligible for the study, to be able to put study subjects in context with those not included.

Authors’ response 6: We are happy to provide this data, perhaps as supplementary material, however we are willing to take the editor’s advice on whether this is necessary. This can be done for all variables except for costs, as these are derived from the data. We provide a comparison of aggregate statistics for variables that are more complete, to illustrate the similarities between patients included and those excluded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.28 (SD=3.1)</td>
<td>3.62 (SD=3.5)</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>53.5%</td>
<td>52.1%</td>
</tr>
<tr>
<td>MTS Green</td>
<td>44.8%</td>
<td>47.5%</td>
</tr>
<tr>
<td>MTS Yellow</td>
<td>8.9%</td>
<td>8%</td>
</tr>
<tr>
<td>MTS Orange</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>MTS Red</td>
<td>0.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>MTS Orange/red</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>MTS N/R</td>
<td>3%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Temperature</td>
<td>38.7 (SD=1.07)</td>
<td>38.3 (SD=1.04)</td>
</tr>
<tr>
<td>Antibiotics (Yes)</td>
<td>32.4%</td>
<td>31.7%</td>
</tr>
</tbody>
</table>

Reviewer #1: Comment 7: Methods. It would be interesting, if data are available, to know the number of children who were not febrile at presentation and compare their management and outcomes. Often they are managed less aggressively and it would be good to know how appropriate that is.

Authors’ response 7: We appreciate the request and see the value in doing so, however this would be a different study to that presented here. Data for such children were not collected on this cohort.
Reviewer #1: Comment 8: Methods. It is important for non-UK readers to understand the MTS criteria, even if they are as useless as the data seem to indicate.

Authors’ response 8: Thank you, we agree, and have added the following more in-depth explanation above and beyond that already included in the methods section outlining the role and application of the MTS classification system:

‘All patients were initially seen by a qualified ED nurse who conducted an initial evaluation using the Manchester Triage System (MTS) reference. MTS assessments follow a flow chart based on the patient’s reason for contacting the ED. The chart begins by identifying possible criteria indicating life-threatening conditions for the patient, and if none of these conditions are present, the nurse continues along the flow chart asking questions until the nurse assigns the patient an appropriate category. The nurse’s experience can contribute to the assessment, but on the other hand, the risk of the nurse missing serious conditions is reduced because the flow chart forces the nurse to ask key questions and make vital inquiries.’


Reviewer #1: Comment 9: Methods: Where any data on symptoms or physical exam signs gathered? Broad description of these as a variable would help.

Authors’ response 9: These were and currently are not available in the existing registry. These are given as non-standardized, qualitative ‘free text and analysis of such data would be very difficult for so many children and the varied ways in which all doctors included could write such information down, or not. This was not within the remit of the study.

Reviewer #1: Comment 10: Methods, table 1 (staff time). A couple of variables seem unrealistic, specifically time to insert an IV cannula and time to interpret results of lab investigations, which are quite long.

Authors’ response 10: These were provided by several staff of varying degrees of experience, from junior doctor to consultant. The average was taken of all values obtained, as explained however, the sample uncertainty, and the fact that you would expect this to be shorter for more experienced colleagues (as you have rightly pointed out), is taken account of in the sensitivity analysis (lines 308 to 314). There is a plausible distribution around this point estimate, which means that the variation in time to undertake this activity is accounted for in the sensitivity analysis, the impact of which is translated into a wider confidence interval around both the costs and the GLM co-efficients. We also ran all estimates by all respondents so that they could themselves rule out any timings they believed were implausible (lines 312 to 314).

We have added the following text to this effect, however you can also find a more thorough explanation from lines 308 to 314 as included in the previous draft of the manuscript.

‘In all such cases a number of estimates were obtained and the average time was used because taken as tasks such as inserting a cannula for example, can be expected to take varying lengths of time depending upon factors such as experience, co-operation of the child, and state of hydration or vascular filling’
Reviewer #1: Comment 11: Methods, analyses. These appear quite comprehensive generally.

Authors’ response 11: Thank you

Reviewer #1: Comment 12: Results: Half of all children were less than 3 years of age. This would make it easy and informative to conduct a stratified and perhaps comparative analysis of management, which is more appropriate than what was done given my comment above.

Authors’ response 12: We believe this is the same point as above (point 1). Our study allows for a comparison of fever management over several variables, including use of ancillary investigations, inpatient length of stay, antibiotics, consultant-led time, healthcare costs and admittance rates for all ages, not just those aged less than three years. We believe that based on this it is straightforward to focus in on one age group vs another age group and draw comparisons, without the need for excluding children from this real-world observational cohort who were aged > 3 years, as these children also make up 50% of all cases seen in practice.

Reviewer #1: Comment 13: Results: It would be helpful to know why so many children who were eventually treated as if they were not particularly ill received orange-red and red MTS classifications. The system may be terrible but we need to know why.

Authors’ response 13: This information is not available unfortunately as we did not collect these data. However, one explanation is the fact that the MTS is prone to over triaging. This as you pointed out above, is a flaw of the MTS, particularly in younger and older children. The result is that children who appear more severe following MTS at triage, once further observations, clinical acumen and specimen results are returned, are realised to be less severe. This is documented well in a number of studies and is listed in the discussion section (line 516 to 518):

‘Recent large-scale validation studies have highlighted the low reliability of the MTS in both younger,10 and older children presenting to the ED with fever,32 with an estimated 54% of children over-triaged when using the MTS.32’

Reviewer #1: Comment 14: Results: It is striking that very few children were treated by consultants. Did some who were treated by more junior clinicians receive help from a consultant? In the US, most if not all children who are admitted to hospital require a consultant's input before the decision is made. This has implications for the Discussion and may inform practice improvement greatly.

Authors’ response 14: This is the reality of the differences in US and EU/UK led emergency services. The NHS operates a different system to the US, more representative of what happens in the rest of Europe and Australia and New Zealand. As a result, consultants see far fewer patients hands on but do have a responsibility for a number of patients simultaneously, predominantly those managed by lesser experienced colleagues. We do explain this in the discussion both as a limitation of the analysis (lines 473 to 474):

‘Our time-in-motion data did not capture information regarding additional consultations and advice from senior members of staff’

Another potential explanation could be that as a proportion of overall staffing, consultants at any one
point in time make up a smaller proportion when compared to ST1-3, registrars, junior doctors and nurse practitioners. This could be another explanation. Similarly, more experienced clinicians are routinely expected to manage higher acuity children, where the benefit of expertise is greatest, and the margin for error is lowest. It is not uncommon for children with fever to be managed by ST1-3s or as our institution now works, by on site GPs or trainee GPs as a number are low acuity, leaving consultants for more complicated cases. It is also worth noting that if we are talking about admitted children as mentioned in your comment, the costs of consultant time are included as part of the reference costing approach provided by the Department of Health. As a result, any child admitted is expected to have been overseen by a consultant at some point and this time spent by the clinician is included within the reference price for inpatient stay.

Reviewer #1: Comment 15: Results: Many older children received lab testing, including roughly 15% who gave a urine sample. This is not typical of older children treated for fever in the US. Description of symptoms, if available, would help.

Authors’ response 15: As touched upon earlier, this study reflects real-life, common practice in a tertiary children’s hospital. It was not an interventional nor quality-of-care study, so information on symptoms is not standardized and not available. As with the above comment, practice in the UK differs from US practice and that is reflected here. We could not trace comparable US data, yet we make a point in the discussion on the generalisability of the findings in US emergency department settings. We have however added a section to the limitations of the manuscript suggesting that the results may not be comparable to US settings, as shown below:

‘The economic value of improving the management of febrile illness in other settings, including the United States, where a more consultant-led approach may be more common, may differ from that demonstrated here’.

Reviewer #1: Comment 16: Discussion: The huge impact of involvement of a consultant in care on decreasing costs is discussed very little. It would seem that this would be a relatively inexpensive way to improve quality and decrease cost.

Authors’ response 16: We don’t fully agree with the assertion that consultant input will lead to a huge impact on costs as there may be cost reductions also. In this analysis, consultant led episodes were the second most expensive, behind FY1/FY2 doctors, predominantly as a result of the much higher hourly salary of consultant, which is on average (mid salary band) 3-fold higher per hour than an FY1/2 (£76.11 vs. £24.24). This could however be as much as £104.50 per hour if the consultant has been awarded clinical excellence awards. As a result, only a small amount of input from such highly skilled and high-priced staff, is likely to increase the costs of care, all things being equal, rather than necessarily reducing costs. The reality is that consultants often cannot oversee all cases due to the sheer caseload in the ED. When there are 40 children or more in the ED simultaneously, it is not always possible to oversee all children, at which point the responsibility would fall to registrars or other more experienced (but not as costly) staff, such as APNPs or nurse consultants. While we agree that there is some variability in not capturing these costs, the exclusion of consultant supervisory time (if this occurred) does not change the conclusions on the absolute figures we have reached. This will merely affect the magnitude of the difference between the costs of febrile children managed by FY1/2s and other, more experienced colleagues. One of our current messages for where POC tests may be of most value is with junior doctors. Such tests may negate any lengthy discussions with more senior members.
of staff due to increased decision certainty and confidence.

Reviewer #1: Comment 17: Discussion: Again, a stratified analysis by age (and perhaps a separate paper) would be more clinically relevant and make the data easier to interpret, especially if the goal is to improve knowledge as compared with previous studies that excluded older children.

Authors’ response 17: As stated, we disagree that an analysis which excludes 50% of the children seen in routine clinical practice (those aged > 3 years) would be an improvement. All outcomes presented in this manuscript, whether diagnostic, clinical or economic, are provided for several age groups, enabling a comparison across multiple groups, and all are subject to considerable statistical analyses to highlight meaningful differences. The goal of the manuscript is to provide an overview and to highlight the extent of the variability of real-world management of febrile illness in this large, representative, and inclusive cohort. We aimed to improve upon prior studies, as highlighted in the discussion and in the text below, by providing a report on children of all ages, and all ways fever present, for all final diagnoses (excluding those of the immunocompromised), and treated by staff of all levels of experience over a one-year period.

‘Two previous studies have reported healthcare costs for managing children with SBIs, namely UTI, and meningitis. Two studies reporting costs of management for children with fever of any cause, have been performed in the USA, with data collected at least 5 years ago, in children aged <3 years and <90 days respectively, thereby limiting their generalisability. Additionally, one study conducted in Switzerland demonstrates the cost-of-illness associated with paediatric community acquired pneumonia in 2010. However, no study prior to ours has assessed the resource implications of managing fever in a broad and representative cohort of all ages, diagnoses, and types of resource use in Europe.’

The aim of our approach was to illustrate how POC testing, if available, may be of benefit, and to which groups such tests, when available, will likely be of greatest socioeconomic value. At current it is possible to compare any age group, any level of severity (MTS), any final diagnosis or any clinical grade with any other, to provide preliminary information to help guide practice, and highlight where improvements could be made, whether by the introduction of POC testing, or other means.

Reviewer #2: Comment 1: This is a well-executed study that provides important data on the management and costs of febrile illnesses in children. It supplements information about utilization of services and costs; it is an important contribution for those working in this field. Some clarifications would be helpful: Line 89 How is this a "representative" cohort. All patients, random sample, other?

Authors’ response 1: Apologies this should have been clearer. We included all children, regardless of age, presenting symptoms, treating clinician and final diagnosis to give an externally valid demonstration of the variability (and economic impact) of managing febrile illness in a real-world setting. In doing so we aimed to highlight the impact of all observable factors on the ED-based management of febrile illness. This is explained in lines 183 to 190.

Reviewer #2: Comment 2: Line 103 9.9-fold increase compared with those not receiving antibiotics?

Authors’ response 2: This is correct. Word count limits for the abstract led to the removal of this clarification. This has now been added back in however (note to editor) we are now a few words over the abstract word limit.
Reviewer #2: Comment 3: Line 138 1 in 400 from data in reference 4 addresses children 3-36 months. The proportion is higher in infants < 3 months addressed in this paper. OK to leave but explain age group referenced.

Authors’ response 3: Thank you, this paper has since been changed as the other reviewer also made a similar comment. However as suggested we have stated the age group.

Reviewer #2: Comment 4: Line 141 References are 40 years old and address only pneumococcal bacteremia

Authors’ response 4: Well spotted! We should have picked this up earlier. We have since updated to three more up-to-date references (2010, 2012, and 2015)

Reviewer #2: Comment 5: Line 152 sensitivity of 30-40% seems low and is not referenced

Authors’ response 5: We have since included the following reference:


Reviewer #2: Comment 6: Line 155 does not necessarily imply "repeated" investigations so much as more accurate or precise investigations

Authors’ response 6: The term repeated has been removed.

Reviewer #2: Comment 7: Line 183 was this any reported history of fever or history of temperature taken by thermometer with recording > 38?

Authors’ response 7: Again, we could have made this clearer. This was 38°C or higher (tympanic) during triage, or an unverified history of fever (at home) using any form of thermometer over the previous three days provided this reading was >38°C.

We have since added the following to the participants/methods section:

‘A total of 8,552 consecutive febrile children, with a temperature above 38°C at presentation, or below 38°C with an unverified parent-reported history of fever up to 3 days previous, were prospectively identified’

Reviewer #2: Comment 8: Table 1. Nice work! Thank you.

Authors’ response 8: Much appreciated, and thank you.

Reviewer #2: Comment 9: Line 249 Later in paper you provide table 4 with utilization for urine sample. As this could be urinalysis, urine culture or both, are you referring to any of those?

Authors’ response 9: A two-step process was followed, urine was taken for urinalysis in the first
instance, followed by urine culture if anything was identified.

Reviewer #2: Comment 10: Lines 262-265 Does this mean there was a single cost applied for all infants admitted for < 3 days as opposed to separate costs for <1, 1-2, 2-3 ?

Authors’ response 10: This should have been explained with greater detail. We used the reference for a total of three days maximum and divided by 72 to provide a cost per hour. This was then multiplied by the number of hours spent in hospital. We have added the following to clarify:

‘As children could be admitted for anywhere between 1 and 72 hours under the reference tariff, this figure was divided through by 72 and multiplied by the number of hours of inpatient admission. Patients who exceeded the three-day limit, incurred an excess bed day charge which was applied from the fourth day until discharge.’

Reviewer #2: Comment 11: Line 431 yes, the largest study. However because of the # of patients excluded from this study, reference 23 reports on the largest # of patients, but they are all < 90 days.

Authors’ response 11: Thank you, this has been amended and now says ‘largest study including children aged 0-16 years’:

‘This study reports the largest prospective observational study to date, assessing the economic implications of diagnostic uncertainty when managing paediatric febrile illness, in those aged 0-16 years, in an ED setting’

Reviewer #2: Comment 12: Lines 435-436 and line 486 (cautiousness) One of the things to consider incorporating is the fact that the prevalence of invasive bacterial infections, bacteremia and bacterial meningitis, are highest in the first 3 months. This is a major independent factor in driving physician behavior towards this age group.

Authors’ response 12: Thank you, we have taken this verbatim (as it summarises the reasons succinctly) and have now added this as an explanation in the discussion immediately following the discussion around caution when managing febrile infants

Reviewer #2: Comment 13: Lines 486-489. One thing possibly worth mentioning is the cost of newer diagnostics. Some of the newer multiplex PCR tests cost 50 to 100 times as much as an antibiotic and about the same as a day in the hospital. Sad but true. Of course, diagnostic test costs can be anticipated to decline whereas hospital costs will not.

Authors’ response 13: Thank you, this is a valid point and has since been included in the discussion section.

Reviewer #2: Comment 14: Line 538 As written implies causation between antibiotic prescribing and hospitalization rather than association.

Authors’ response 14: This was unintended and has since been removed.