

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Randomised multi-centre effectiveness trial of rapid syndromic testing by panel assay in children presenting to European emergency departments with acute respiratory infections – trial protocol for the ADEQUATE Paediatric trial
<b>AUTHORS</b>	ADEQUATE Paediatric Trial Group, ADEQUATE Paediatric Trial Group

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Bouzid, Donia Hopital Bichat, Assitance publique hopitaux de Paris, Urgences
<b>REVIEW RETURNED</b>	15-Aug-2023

<b>GENERAL COMMENTS</b>	This seems to be a great protocol. It is very well written and the topic is certainly of interest. I would like the authors to explain their choice of days alive out of hospital at day 14 instead of day 28 in their primary endpoint. Apart from the previous remark, the manuscript is good.
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<b>REVIEWER</b>	Clark, John University of Cambridge School of Clinical Medicine, Department of Paediatrics
<b>REVIEW RETURNED</b>	20-Aug-2023

<b>GENERAL COMMENTS</b>	<p>Dear authors,</p> <p>Thank you for your protocol submission, which I read with great interest. Syndromic infection diagnostic tests are becoming more widely available and are of great interest due the global fight against AMR but also in the setting of disease outbreaks such as SARS-CoV-2. I therefore believe this trial will be of great interest to the paediatric community, particularly given the use of the BioFire diagnostic in real-time clinical decision making.</p> <p>The strengths of the proposed study are its multi-centre, randomised design; the composite data collection methods that incorporate quantitative and qualitative measures; and the integration of patient follow up into the study design.</p> <p>The limitations are the lack of protocol driven decision making based on the intervention (BioFire Respiratory Panel plus). In addition, there is no standardised procedure for microbiological cultures in the protocol – therefore bacterial co-infection is not able to be measured in most patients.</p>
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	<p>The primary outcomes of the study were changed due to a parallel trial ceasing in adults using the same BioFire diagnostic test. The reason this study was terminated is not clear in the manuscript and requires additional explanation. The third co-primary study endpoint, relating to deterioration or death was changed to become a 'key' secondary study outcome.</p> <p>Importantly, this protocol does not include an analysis plan for any of the secondary objectives for the study. It is not clear if this will be available outside the research institution. The measurement or the primary study outcomes are, however, has been more clearly defined.</p> <p>Specific comments -  Abstract  Introduction  3- Multiplex respiratory panels have also had widespread use in emergency departments in high-income countries for many years. Please include given the proposed trial is not unique in this regard.</p> <p>9 – Please name the diagnostic test in the abstract (BioFire Respiratory Panel Plus) and highlight this investigation is for viruses and atypical bacteria. In addition, state in the abstract the test is completed on nasopharyngeal swabs.</p> <p>15-18 – Suggest rewording the endpoint analysis separately for clarity E.g. The primary outcomes will be compared using a two-sample t-test. Firstly, the duration of antimicrobial treatment which will be log transformed for the analysis....Secondly the out-of-hospital survival....</p> <p>Strengths and limitations  28 – 'By design of the eligibility criteria, in the trial application of the test is targeted to a patient...' This is not clear. Perhaps 'The study intervention may influence clinical decision making at the point of care...?'</p> <p>33-34 – 'the results may therefore be sensitive to changing perceptions about current incidence of pathogens' – what do you mean by this? Are you referring to some respiratory viruses having greater pathogenicity than others?</p> <p>Introduction  40-41 – Whilst it is true that most paediatric respiratory infections do not require antimicrobial therapy, clinicians in high income settings are advised to commence treatment for pneumonia within four hours of presentation.<sup>1</sup> Clinical signs and investigations poorly discriminate between children that have lower respiratory tract infection of bacterial and non-bacterial aetiology. Identification of a virus alone cannot exclude bacterial co-infection. Please mention this in the introduction as this is an important limitation of syndromic diagnostic tests that do not incorporate common bacterial pathogens.</p> <p>50-51 – 'explains the cause of an episode of severe' – an episode of severe what?</p> <p>58 – As for comment in abstract, rapid respiratory diagnostics are very common in paediatric emergency departments</p>
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	<p>Table 1</p> <p>Parental report of fever – Does the measurement of fever at home need to have been measured with a thermometer?</p> <p>Tachypnoea for age – Please define how this was defined (was it consistent between participating institutions?)</p> <p>Reduced general state – Suggest: ‘non-specific symptoms’</p> <p>Antibiotic treatment or hospitalisation is being considered – by whom?</p> <p>Confirmed pregnancy or breastfeeding – why was this an exclusion criterion?</p> <p>Methods</p> <p>85 – ‘In most instances’ – please describe the situations in which screening will not take place as soon as possible</p> <p>88 – ‘eligibility criteria are to be re-evaluated and confirmed’...by whom?</p> <p>92-94 – Suggest rewording for clarity, perhaps ‘No diagnostic tests will be performed to determine eligibility to the study’?</p> <p>109 – ‘of the eCRF system’ – please spell out this acronym and describe the system used in the study in 1-2 sentences.</p> <p>118 – Suggest slight rewording of the first primary outcome – this reads as an inverse measure of mortality ‘days alive out of hospital’. Perhaps ‘Days free of hospital admission within 14 days of enrolment’. Then you could add the caveat that the measure included an adjustment for mortality</p> <p>Table 2</p> <p>Please consider adding some basic formatting to the table to make the hierarchy of bullet points clear</p> <p>‘Direct and indirect costs’ – please define what costs you are referring to, are they financial?</p> <p>Methods continued</p> <p>122 – Why was the adult study terminated?</p> <p>129 – ‘Based on this, the safety endpoint is considered a key secondary endpoint’. Please remove this description – if it is a key endpoint, it should have remained as one of the primary study endpoints.</p> <p>138-139 – A modified of EQ-5D, to my knowledge, can be used in children down to 3 years of age. I suspect most children in this study will be &lt;2 years old. What qualitative assessment tool will therefore be used in most of the patients in this trial?</p> <p>Sample size and power</p> <p>143-145 – Not sure what this sentence adds – one can assume ‘a reduction of one day in antibiotic treatment’...’results in a reduction in antibiotic prescribing’</p>
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	<p>145-148 – Not sure of the purpose of this sentence – all the children in the study will probably receive antibiotics?</p> <p>151 – Please reference the publication you are describing</p> <p>155 – ‘resulting in adequate power to detect a difference in one day in both endpoints. One of your endpoints is days alive out of hospital within 14 days after study enrolment. The power calculation appears to be based on the use of antimicrobial therapy alone. Please clarify.</p> <p>Analysis plan 169 – Earlier in the protocol, the upper age limit was 18, here it is 17. Please clarify.</p> <p>171 – Please define what is meant by ‘random intercept for each country (and potential emergency department in country)’ for a non-expert reader</p> <p>Monitoring 217 – ‘potential unreported events for these subject reviewed’. What is the review process and who is undertaking this?</p> <p>219 – ‘competent authorities’ – please be more specific as to the authorities you are referring to here</p> <p>Ethics and dissemination 224 – When was first approval received?</p> <p>225 – Please list the date of protocol approval and summarise the changes that have been made from the first version</p> <p>230 – Please list date of first registration</p> <p>Dissemination of results Overall - Please clarify the plans regarding data sharing</p> <p>Trial status and discussion 252 - ‘Follow up has been completed for x and x have been missed the 14d...’ Unclear if this has been an accidental omission. If this has been removed for reviewer blinding, please ignore this comment.</p> <p>259-262 – Please reword this sentence for clarity. Perhaps you mean ‘The presented protocol differs from the former control trials in two ways. Firstly, the decision to admit the patient has not yet been established at the time of randomisation. Secondly, a decision whether to commence antimicrobial therapy has not yet been determined...’ (or as you see appropriate).</p> <p>Discussion Can you discuss some of the limitations of the study?</p> <p>Issues arising from SPIRIT checklist 1- What does the ADEQUATE acronym stand for? 4 – Please clarify the role of the funders in the study. Did BioMérieux supply the equipment and consumables for the project? 7 – There is no overarching hypothesis for the trial. Please address. 9 – Were the participating centres mixed or dedicated paediatric emergency departments?</p>
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	<p>15 – Why was this criterion N/A? I imagine you must have sent emails or put up posters in the participating units, for example</p> <p>29 – Please report who can access the final study data</p> <p>31a – How will you share study findings with participants?</p> <p>32 – The consent form was not available with the materials for review, this should be included in the final published protocol</p> <p>Minor grammatical issues</p> <p>3 – signs and symptoms., (unnecessary full stop)</p> <p>12 – consists of two sets (plural)</p> <p>39 – ‘Especially Since the wide roll-out’</p> <p>49 – RSV – first use of acronym</p> <p>63- AMR – first use of acronym</p> <p>82 – (Table 1) – ARI – spell out acronym or add footnote to table</p> <p>84-85 – ‘study staff’ mentioned twice in the sentence</p> <p>98 – after a longer time than four hours</p> <p>Table 2 – Chinolone Quinolone</p> <p>124-128 – This sentence is too long. Please chunk this into smaller sentences to improve readability</p> <p>173 – We especially anticipate days</p> <p>184 – Data base database</p> <p>216 – Please define the acronyms (S)AEs, (S)ADEs and DD</p> <p>223 – Prior to study conduct, the protocol....</p> <p>226 – across a range of different settings</p> <p>I wish you the very best in completing this trial, and we look forward to hearing about your findings soon.</p> <p>Kind regards,</p> <p>Dr John A Clark University of Cambridge – UK Grampians Health – Australia</p> <ol style="list-style-type: none"> <li>1. National Institute for Health and Care Excellence. Pneumonia (community-acquired): antimicrobial prescribing. <a href="https://www.nice.org.uk/guidance/ng138/chapter/recommendations#severe-community-acquired-pneumonia-in-children-and-young-people">https://www.nice.org.uk/guidance/ng138/chapter/recommendations#severe-community-acquired-pneumonia-in-children-and-young-people</a> (2019).</li> <li>2.</li> </ol>
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<b>REVIEWER</b>	Ciccone, Emily University of North Carolina at Chapel Hill School of Medicine
<b>REVIEW RETURNED</b>	25-Aug-2023

<b>GENERAL COMMENTS</b>	<p>In this protocol paper, the authors describe an important ongoing study of rapid molecular multiplex respiratory pathogen testing in pediatric patients presenting to emergency rooms in Europe. Overall, it is clearly written and pragmatically designed. I especially appreciated the discussion of how the study differs from similar randomized control trials recently published. A few comments below regarding areas for clarification:</p> <p>Abstract</p> <p>- Consider revising the sentence in Lines 15-18 for clarity. Perhaps something along the lines of “We will perform a two-sample t-test assuming a pooled variance estimate to compare the log</p>
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	<p>transformed mean time on antibiotic treatment (in hours) and number of days alive out of the hospital within 14 days after study enrolment between the control and intervention arms.”</p> <p>Introduction  - A citation that might be worth adding to the introduction during discussion of pathogens detected in asymptomatic children – used an earlier version of the Biofire.  <a href="https://academic.oup.com/cid/article/61/8/1217/376653">https://academic.oup.com/cid/article/61/8/1217/376653</a></p> <p>Methods/Analysis  - I note that the standard of care may include "rapid diagnostic testing for specific pathogens or syndromic testing with results reported after a longer time than four hours." From the description of the participant dataset, it appears that data on this microbiologic testing will be collected. How will these data be incorporated into the analysis? Please clarify.  - Please add additional information about how the "direct and indirect costs" secondary outcome will be measured.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I would like the authors to explain their choice of days alive out of hospital at day 14 instead of day 28 in their primary endpoint.

Thank you, we now added a brief section on this (II 122-4): 14 days were selected over 30 days as time window for the primary endpoints because a potential superior effect would be expected to be more immediate, and a shorter window resulted in a small gain in power. Furthermore, delayed effects will still be captured in the secondary endpoints.

Reviewer: 2

Dr. John Clark, University of Cambridge School of Clinical Medicine

Comments to the Author:

Word document attached with comments for the authors

Abstract

Introduction

3- Multiplex respiratory panels have also had widespread use in emergency departments in high-income countries for many years. Please include given the proposed trial is not unique in this regard.

This has now been included (II59-60)

9 – Please name the diagnostic test in the abstract (BioFire Respiratory Panel Plus) and highlight this investigation is for viruses and atypical bacteria. In addition, state in the abstract the test is completed on nasopharyngeal swabs.

The assay is now named in the abstract and we specified it is used on NP swabs.

15-18 – Suggest rewording the endpoint analysis separately for clarity E.g. The primary outcomes will be compared using a two-sample t-test. Firstly, the duration of antimicrobial treatment which will be log transformed for the analysis....Secondly the out-of-hospital survival....

Thank you very much for this proposal. We appreciate this was poorly phrased as the same sentence was commented on by reviewer 3, whose kind suggestion we now incorporate in the revised manuscript.

Strengths and limitations

28 – 'By design of the eligibility criteria, in the trial application of the test is targeted to a

patient...’ This is not clear. Perhaps ‘The study intervention may influence clinical decision making at the point of care...?’

33-34 – ‘the results may therefore be sensitive to changing perceptions about current incidence of pathogens’ – what do you mean by this? Are you referring to some respiratory viruses having greater pathogenicity than others?

We have now updated the entire section in line with the editor’s request and hope that the changes also meet your concerns.

#### Introduction

40-41 – Whilst it is true that most paediatric respiratory infections do not require antimicrobial therapy, clinicians in high income settings are advised to commence treatment for pneumonia within four hours of presentation.<sup>1</sup> Clinical signs and investigations poorly discriminate between children that have lower respiratory tract infection of bacterial and non-bacterial aetiology. Identification of a virus alone cannot exclude bacterial co-infection. Please mention this in the introduction as this is an important limitation of syndromic diagnostic tests that do not incorporate common bacterial pathogens.

Has now been added (I55)

50-51 – ‘explains the cause of an episode of severe’ – an episode of severe what?

Apologies and thank you for picking this up, it has now been completed (ARI)

58 – As for comment in abstract, rapid respiratory diagnostics are very common in paediatric emergency departments

#### Table 1

Parental report of fever – Does the measurement of fever at home need to have been measured with a thermometer?

Indeed, we require a measured temperature and common observations like “they felt hot to the touch” would not fulfil this.

Tachypnoea for age – Please define how this was defined (was it consistent between participating institutions?)

We now specify that participating hospitals were not required to adhere to one single standard.

Reduced general state – Suggest: ‘non-specific symptoms’

Antibiotic treatment or hospitalisation is being considered – by whom?

Thank you, this has now been specified (the managing clinical team)

Confirmed pregnancy or breastfeeding – why was this an exclusion criterion?

We indeed thought that this was likely an unnecessary exclusion criterion but we were required to include it to facilitate approval in some countries, most prominently Spain. We are not aware of any actual exclusions because of this.

#### Methods

85 – ‘In most instances’ – please describe the situations in which screening will not take place as soon as possible

The protocol does not exclude screening at later times and some trial sites have screened patients present in the ED at intervals, when short staffed.

88 – ‘eligibility criteria are to be re-evaluated and confirmed’...by whom?

We specify this now (trained and delegated trial staff). In practice, the person randomising the patient re-checked eligibility and they were the same person obtaining consent.

92-94 – Suggest rewording for clarity, perhaps ‘No diagnostic tests will be performed to determine eligibility to the study’?

We believe the current wording expresses both that additional tests are not necessary but that the protocol does not interfere with routine management and would therefore prefer to keep it.

109 – ‘of the eCRF system’ – please spell out this acronym and describe the system used in the study in 1-2 sentences.

Thank you, we spell it out now. Some more explanation is also given in II145-6.

118 – Suggest slight rewording of the first primary outcome – this reads as an inverse

measure of mortality 'days alive out of hospital'. Perhaps 'Days free of hospital admission within 14 days of enrolment'. Then you could add the caveat that the measure included an adjustment for mortality

For the paediatric trial alone we may indeed have used length of inpatient stay, as mortality is very low in high-income settings. Days alive out of hospital integrates the state of "having died". Despite the slightly unconventional phrase, we prefer to keep it as it is to avoid incongruity between the published approved protocols in this important aspect.

Table 2

Please consider adding some basic formatting to the table to make the hierarchy of bullet points clear

Thank you for this suggestion. In our experience, BMJ journals usually use background colouring in tables that should make the hierarchy clear here.

'Direct and indirect costs' – please define what costs you are referring to, are they financial?

Thank you, a specification has now been added to table 2. This also aligns the wording of the endpoint with the trial registration. In detail, the variables collected will be

- inpatient and ICU days
- health service utilisation
- antibiotics
- antivirals and antifungals
- concomitant medication
- first day back to work
- first day all adult carers back to work

122 – Why was the adult study terminated?

The trial was discontinued for feasibility of recruitment. This is now explained in I132-4.

129 – 'Based on this, the safety endpoint is considered a key secondary endpoint'. Please remove this description – if it is a key endpoint, it should have remained as one of the primary study endpoints.

Thank you, we agree this qualifier was unnecessary.

138-139 – A modified of EQ-5D, to my knowledge, can be used in children down to 3 years of age. I suspect most children in this study will be <2 years old. What qualitative assessment tool will therefore be used in most of the patients in this trial?

This is correct. Because no validated tools exist, we are using the global rating scale on the existing EQ-5D.

Sample size and power

143-145 – Not sure what this sentence adds – one can assume 'a reduction of one day in antibiotic treatment'... 'results in a reduction in antibiotic prescribing'

Thank you for pointing this out. The sentence has now been adapted to be clearer. It was supposed to explain that "one day" was selected as the clinically relevant difference on both endpoints.

145-148 – Not sure of the purpose of this sentence – all the children in the study will probably receive antibiotics?

We included this sentence to explain, in other words, that we believe an effect may be more likely on the antibiotics endpoint. This is to explain why this endpoint was selected for the sample-size estimation.

151 – Please reference the publication you are describing

155 – 'resulting in adequate power to detect a difference in one day in both endpoints. One of your endpoints is days alive out of hospital within 14 days after study enrolment. The power calculation appears to be based on the use of antimicrobial therapy alone. Please clarify.

It has now been repeated at this point that the calculations are based on the antibiotics endpoint. Two independent significance tests are done, therefore we select an alpha of 0.025.

Analysis plan



169 – Earlier in the protocol, the upper age limit was 18, here it is 17. Please clarify.  
We stated earlier that inclusions are possible under the age of 18, we believe this is consistent.

171 – Please define what is meant by ‘random intercept for each country (and potential emergency department in country)’ for a non-expert reader

We now add that this is done to account for clustering on emergency department and country.  
Monitoring

217 – ‘potential unreported events for these subject reviewed’. What is the review process and who is undertaking this?

The monitor performs the visits (I223). The monitor for this study is a paediatric nurse who received additional training as a monitor. During SDV he compares reported events to those documented in the patients’ clinical records.

219 – ‘competent authorities’ – please be more specific as to the authorities you are referring to here

As it is a multi-country study, we would prefer not to list all authorities that may audit the trial in the respective countries.

Ethics and dissemination

224 – When was first approval received?

225 – Please list the date of protocol approval and summarise the changes that have been made from the first version

230 – Please list date of first registration

These have been added, thank you.

Dissemination of results

Overall - Please clarify the plans regarding data sharing

A sentence has been added to the end of the section.

Trial status and discussion

252 - ‘Follow up has been completed for x and x have been missed the 14d....’ Unclear if this has been an accidental omission. If this has been removed for reviewer blinding, please ignore this comment.

This has now been filled with the most recent numbers. They had been omitted before because we expected changes until the time the review is finished.

259-262 – Please reword this sentence for clarity. Perhaps you mean ‘The presented protocol differs from the former control trials in two ways. Firstly, the decision to admit the patient has not yet been established at the time of randomisation. Secondly, a decision whether to commence antimicrobial therapy has not yet been determined...’ (or as you see appropriate).

The sentence is now shortened and rephrased.

Discussion

Can you discuss some of the limitations of the study?

We included three additional paragraphs on limitations of the trial.

Issues arising from SPIRIT checklist

1- What does the ADEQUATE acronym stand for?

It has now been added in the acknowledgement section. The full title is: Advanced Diagnostics for Enhanced Quality of Antibiotic prescription in respiratory Tract infections in Emergency rooms

4 – Please clarify the role of the funders in the study. Did BioMérieux supply the equipment and consumables for the project?

That is correct. A sentence has been added (I242) and more explanation is given under the competing interests statement.

7 – There is no overarching hypothesis for the trial. Please address.

Thank you indeed for pointing this out. We did now add in I73 that the trial is designed as a superiority trial.

9 – Were the participating centres mixed or dedicated paediatric emergency departments?

At none of the trial sites, the paediatric emergency department shared rooms or staff with the respective adult department but mostly they were located in the same area of the hospital.

15 – Why was this criterion N/A? I imagine you must have sent emails or put up posters in the participating units, for example

We believe this item indeed aims at the patient-faced approaches, which are briefly outlined in the 29 – Please report who can access the final study data

The trial statistician will perform the analysis (I171). The responsible data managers will have access to the dataset until then, no other access is planned.

31a – How will you share study findings with participants?

Only as mentioned in the dissemination section, i.e., via public channels including the consortium website.

32 – The consent form was not available with the materials for review, this should be included in the final published protocol

We apologise for this, it should have been uploaded.

Minor grammatical issues

3 – signs and symptoms., (unnecessary full stop)

12 – consists of two sets (plural)

39 – 'Especially Since the wide roll-out'

49 – RSV – first use of acronym

63- AMR – first use of acronym

82 – (Table 1) – ARI – spell out acronym or add footnote to table

84-85 – 'study staff' mentioned twice in the sentence

98 – after a longer time than four hours

Table 2 – Chinolone Quinolone

124-128 – This sentence is too long. Please chunk this into smaller sentences to improve readability

173 – We especially anticipate days

184 – Data base database

216 – Please define the acronyms (S)AEs, (S)ADEs and DD

223 – Prior to study conduct, the protocol....

226 – across a range of different settings

The suggested changes have mostly been made, thank you.

Reviewer: 3

Abstract

- Consider revising the sentence in Lines 15-18 for clarity. Perhaps something along the lines of "We will perform a two-sample t-test assuming a pooled variance estimate to compare the log transformed mean time on antibiotic treatment (in hours) and number of days alive out of the hospital within 14 days after study enrolment between the control and intervention arms."

The suggested sentence does indeed read easier. We changed the manuscript accordingly.

Introduction

- A citation that might be worth adding to the introduction during discussion of pathogens detected in asymptomatic children – used an earlier version of the Biofire.

<https://academic.oup.com/cid/article/61/8/1217/376653>

Thank you, the suggested citation has now been added (ref. 8).

## Methods/Analysis

- I note that the standard of care may include "rapid diagnostic testing for specific pathogens or syndromic testing with results reported after a longer time than four hours." From the description of the participant dataset, it appears that data on this microbiologic testing will be collected. How will these data be incorporated into the analysis? Please clarify.

Because the trial specifically investigates the effectiveness of incorporating the rapid syndromic test early during management decisions, we consider patients with results available later as part of the standard of care arm for both the "treatment policy" strategy for the intercurrent event "treatment change at baseline" (akin to "intention-to-treat" principle) and the "on treatment" strategy. For the secondary endpoint "Proportion of participants with an identified respiratory pathogen in both study groups on randomisation day samples", all detected pathogens in both groups will be considered. Secondary analyses after completion of the main analysis of the trial may make use of pathogen detection data and group patients in the trial according to detected pathogens.

- Please add additional information about how the "direct and indirect costs" secondary outcome will be measured.

Thank you, a specification has now been added to table 2. This also aligns the wording of the endpoint with the trial registration. In detail, the variables collected will be

- inpatient and ICU days
- health service utilisation
- antibiotics
- antivirals and antifungals
- concomitant medication
- first day back to work
- first day all adult carers back to work

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Clark, John University of Cambridge School of Clinical Medicine, Department of Paediatrics
<b>REVIEW RETURNED</b>	20-Dec-2023

<b>GENERAL COMMENTS</b>	<p>Thank you for representing the manuscript. This has substantially improved the transparency and readability of the article.</p> <p>Minor revisions required</p> <ul style="list-style-type: none"><li>- 156-157: It is reasonable to use the modified EQ-5D in children &lt; 3 years given lack of validated qualitative assessments. However, this should be mentioned here, or in the study limitations given non-specialist readers will be unlikely to be aware of this lack of instrument validation.</li><li>- 167-168: 'From a recent publication on variations in antibiotic prescribing...the standard days on antibiotic treatment...'. Please include the relevant citation here given this underpins your power calculation.</li><li>- 187: The upper age limit for the study is 18 years, however the statistical analysis plan limits the age range to 17 years. Why are children aged 17-18 years old being enrolled to the study, without inclusion in the analysis?</li></ul>
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<b>REVIEWER</b>	Ciccione, Emily University of North Carolina at Chapel Hill School of Medicine
<b>REVIEW RETURNED</b>	26-Dec-2023

<b>GENERAL COMMENTS</b>	The authors have sufficiently addressed reviewer comments. I have no further feedback.
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## VERSION 2 – AUTHOR RESPONSE

- 156-157: It is reasonable to use the modified EQ-5D in children < 3 years given lack of validated qualitative assessments. However, this should be mentioned here, or in the study limitations given non-specialist readers will be unlikely to be aware of this lack of instrument validation.

> Thank you for pointing this out. Two brief sentences explaining the lack of a validated version and the use of the VAS (as indicated in the previous point-by-point reply) have now been entered.

- 167-168: 'From a recent publication on variations in antibiotic prescribing...the standard days on antibiotic treatment...'. Please include the relevant citation here given this underpins your power calculation.

> We apologise for this oversight. The reference has now been added (12 in the reference list).

- 187: The upper age limit for the study is 18 years, however the statistical analysis plan limits the age range to 17 years. Why are children aged 17-18 years old being enrolled to the study, without inclusion in the analysis?

> We apologise, the confusion arose from the inconsistent way we described the age boundary (including up to 17 years or below 18 years, i.e. to the day before the 18th birthday). To clarify this, the analysis plan section now uses "<18" instead of "17".