Author’s response to reviews

Title: Evaluation of the impact of shigellosis exclusion policies in childcare settings upon detection of a shigellosis outbreak

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Evaluation of the impact of shigellosis exclusion policies in childcare settings upon detection of a shigellosis outbreak

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We appreciate the careful review and suggestions from the reviewers. We have sought to address all comments. Major revisions in this version include:

• An expanded version of the background, methods, and results
• A more user-friendly Appendix B
• Revised tables, and figures for clarity
The page and table numbers in our responses refer to the revised version of the manuscript. In addition to the specific responses and changes noted below, we made small additional editorial and formatting updates to the manuscript and the supplementary material.

Reviewer reports:

Varvara K Kozyreva, Ph.D. (Reviewer 1)

Dear colleagues, The manuscript addresses an important public health topic and the conclusions provided by the authors would be extremely useful for healthcare officials in defining childcare exclusion policies. The manuscript is well written and the facts are logically stated. I believe it would benefit from adding more details in the description of the methods which were used for data analysis.

Table 2/Methods section: It would be nice if more information was provided on literature sources from which the data was taken to build the estimates. E.g., what was the age range for cases from the studies used for estimations? What was n in each of the studies? Based on data for what Shigella species the estimate was made. Would the predictions for infections caused by S. sonnei vs S. flexneri be the same? Also, in the Table 2 for Attack rates, was there no range available, just a single value, considering that 4 different sources were used?

Answer: Thank you for pointing out the need for further clarification. To address your suggestion, we have now provided more information on literature sources, and the attack rate chosen on a footnote on table 2 (the footnote now reads “Hoffman et al. 10 estimated an overall attack rate of 25% in a Denver child-care servicing 18 months to 6 years old. The other references are used for suggested ranges in Appendix B.”).

In Appendix B, it is possible for the user to change the attack rate at will and a range is suggested. However, to present results for childcare-days lost, which is the only parameter where attack rates are used as input, we opted to present results for a given attack rate, which is why there is only one value in Table 2. That is, because we are evaluating different exclusion policies for a given outbreak, we chose to have the range of results express uncertainty related to inputs for the exclusion policies (such as shedding duration, and receiving the results of tests), rather than uncertainty related to the outbreak’s characteristics.
Could you please summarize in the methods section (Lines 94-101) how the assumption was made on when to consider the patient infectious upon readmission in different scenarios, not only when the antimicrobial therapy is completed but also in cases when fixed time interval-policy is used? Were the positive lab test result used as an assumption that the patient remains infectious in the source studies; is it an outbreak data documenting a transmission after the children were readmitted, etc.

Answer: The assumption of when to consider the patient infectious upon readmission was made taking into account the shedding duration for each treatment and policy. In particular, we assumed that in the beginning of the shedding period, every child was infectious; after the shedding period was over, every child was non-infectious. We assumed a linear decrease of likelihood of being infectious per day, so that if the shedding period lasts for 5 days, there would be $1 - 1/5^2 = 0.6$ or 60% of children still infectious upon return to school on day two of illness.

We have now included clarifying sentences regarding this in the methods:

Methods, 4th paragraph (added): For policies based on convalescent stool tests, the estimated likelihood that the returning patient reentered school while still infectious was calculated using the probability that the test would provide a false negative result, which was related to the test’s sensitivity (Appendix A). We opted for this conservative estimate given variability in shedding shigellae in stool, symptom duration, and time interval before receiving the test. For policies based on a fixed time interval, the estimated likelihood that the patient returned to school while still infectious was based on the duration of shedding; in particular, we assumed that the proportion of children who remained infectious decreased linearly with each day of the shedding period, from 100% in the first day to 0% in the last day. The duration of the shedding period was estimated from the literature (Table 2).

If data is available to you, could you please least the details of treatment options- particular antibiotics? (Appendix 3 or the Methods section). Also it would be great if you could add to discussion (lines 140-143) what are the current recommendations on using antimicrobial therapy for Shigella infections treatment, particularly in children?

Methods, third paragraph (added): We evaluated each policy for patients undergoing different treatment scenarios, namely: A) immediate, effective treatment; B) effective treatment after diagnosis; C) ineffective treatment; D) no treatment. We considered as effective treatment the receipt of a course of antibiotics that the particular strain of Shigella bacteria was susceptible to, as recommended in the latest guidelines 9. Ineffective treatment was defined as receiving an antibiotic that the Shigella strain was not susceptible to, or that did not have an effect in vivo based on pharmacokinetics 9.

Line 121: How do you define "Inappropriate treatment" - one where the pathogen was detected by lab test after the treatment was over or the treatment which wasn't finished, or didn't match recommendations for managing shigellosis?

Answer: As mentioned above, we defined “inappropriate treatment” as treatment to which the bacterial strain is not susceptible or that does not have an effect “in vivo” despite having an effect “in vitro” due to pharmacokinetic reasons. Again, this definition is now included in a new paragraph in the methods section:

Methods, third paragraph (added): We evaluated each policy for patients undergoing different treatment scenarios, namely: A) immediate, effective treatment; B) effective treatment after diagnosis; C) ineffective treatment; D) no treatment. We considered as effective treatment the receipt of a course of antibiotics that the particular strain of Shigella bacteria was susceptible to, as recommended in the latest guidelines 9. Ineffective treatment was defined as receiving an antibiotic that the Shigella strain was not susceptible to, or that did not have an effect in vivo based on pharmacokinetics 9.

Lines 143-147: Was the cause for ineffective therapy in the used source data known? Was it resistance of the pathogen (any known types of resistance to certain classes of antibiotics)? Or was it improper prescription?

Answer: Source data included both treatment with antibiotics that bacteria strain was not susceptible to, or which were known not to be effective for pharmacokinetic reasons. We do not know what the reason was. As mentioned before, we have tried to clarify this issue by providing a definition of ineffective therapy in a new paragraph in the methods.

It would be nice to have the point of initial diagnosis Shigellosis plotted on the Figure 1-a.
Answer: We appreciate the reviewer’s request and considered how to depict the “diagnosis” time point clearly. However, for each treatment, diagnosis can be made during a wide span of time, or in treatment D, possibly not at all. For example, in Treatment A, the child could be clinically diagnosed with shigellosis at the time of seeking care, start an appropriate antibiotic empirically, but also submit a stool specimen for culture. The culture-based diagnosis could come days after the antibiotics were started. Another child may receive clinical diagnosis only, and another, only the culture-based diagnosis. We were unable to depict this clearly on the figure. Given that the pictures already depicts several other variables, including the determining constraints for treatment success (when the treatment starts and when the child returns to school), we did not include the point of initial diagnosis.

In any case, we thank the reviewer for alerting us to this limitation. To address the reviewer’s suggestion, we have taken two actions. First, we have included a summary of the main points in this discussion as a footnote the figure 1-a. Second, we have expanded our discussion in order to consider the implications of uncertainty regarding the point of initial diagnosis:

Discussion, 4th paragraph: Our results are also limited by the lack of data regarding the prevalence of different types of treatment and uncertainty about testing parameters. However, our supplementary material allows users to evaluate policies using new data or different assumptions. Another limitation is the absence of information regarding the timing of diagnosis and prevalence of different treatment methods. In our treatment scenarios, we opted not to mention the timing of diagnosis explicitly since the determining constraints for duration of infectiousness are the start and effectiveness of treatment, and health care providers may treat empirically in the absence of a laboratory diagnosis. To note, while culture-based diagnosis is slower to obtain than PCR-based diagnosis, culture-based diagnosis allows assessment of the resistance profile of the bacteria. Therefore, the type of diagnosis could be related to the likelihood of receiving ineffective treatment, which we have not considered. If this is the case, we may overestimate the advantages of testing via PCR.

Katherine Lamba, MPH (Reviewer 2): Reviewer's Report

Title: Evaluation of the impact of shigellosis exclusion policies in childcare settings General Comments:

Thank you for the opportunity to review "Evaluation of the impact of shigellosis exclusion policies in childcare settings" by Dr. Carias and colleagues. The aim of the study was to compare shigellosis exclusion policies in childcare outbreak settings and their impact on risk of shigellosis
transmission and childcare-days lost. This study and its findings have important public health implications, and the accompanying spreadsheet tool may be valuable for guiding public health professionals' decisions when implementing outbreak control measures. One strength of the study was that the authors evaluated the impact of exclusion policies based on PCR testing; this is particularly important given the increasing use of culture-independent diagnostic tests (CIDT) for Shigella detection. Furthermore, the inclusion of the four treatment options and their effects on the exclusion policies evaluated was an important component of the study.

Overall, I think there are some points and definitions that need to be clarified in order to guide readers through the methods and findings of the study in a more logical progression. They are listed as follows: 1) It is not immediately clear to the reader that the exclusion policies were evaluated in the setting of an outbreak, as opposed to exclusion policies for sporadic cases returning to childcare settings. This needs to be clarified from the outset. 2) As a reader, there are some missing links between the results and conclusions stated in the abstract, the results section, and the data provided in the figures and appendices. The data shown in the figures and appendices should be fleshed out a bit more in the text of the results to support your statements in the abstract and make clear to the reader how these conclusions were reached. Additional detailed feedback is provided below.

Specific Comments:

Abstract

Again, it should be made clearer that these policies were evaluated in a childcare outbreak setting (vs. exclusion policies for sporadic cases). This should be addressed in the abstract, background (last paragraph, line 80), and possibly in the title of the manuscript.

Answer: Thank you for your comment. We have now revised the title, abstract, and background.

Revised title: “Evaluation of the impact of shigellosis exclusion policies in childcare settings upon detection of a shigellosis outbreak”

Revised abstract, background: In the event of a shigellosis outbreak in a childcare setting, exclusion policies are applied to afflicted children to limit shigellosis transmission. However, there is scarce evidence of their impact.

Revised Background (previous line 80): We evaluated the impact of five different child exclusion policies on the likelihood that a child returning to childcare would still be infectious, and on childcare-days lost for the afflicted children, upon the detection of a shigellosis outbreak.
See General Comments: statements in the results and conclusions sections of the abstract should be more clearly supported by your results.

Answer: We have now revised the results to make sure it more clearly supports the abstract. In particular, we have provided more detail regarding our results:

Results, after, added sentences are underlined: Figure 2 shows the probability that an infectious child returns to childcare and the number of days that the child would be excluded, by treatment type and exclusion policy. The effectiveness of policies based on negative convalescent stool tests hinged on the test’s sensitivity, with PCR-based tests leading to lower probability of the child being infectious when readmitted. If the policy required 2 consecutive PCR-negative stool samples, the probability that the child returned to school infectious was <1%, with the number of days the child spent at home ranging from 7 to 17 days (midpoint: 9 days) if the child received immediate, effective treatment. The maximum number of childcare-days lost increased to 19 days if the child received effective treatment after diagnosis; it was between 19 and 53 days if the child received ineffective treatment; and between 6 and 43 days if the child received no treatment. If only 1 Shigella-negative PCR test stool sample was required, the likelihood the child returned to school infectious was ≤ 6% and the number of days the child spent at home varied between 6 and 11 days (midpoint: 7 days) if the child received immediate, effective treatment; it was up to 13 days if the child received effective treatment after diagnosis; between 18 and 45 days for children receiving ineffective treatment; and between 5 and 35 days for children receiving no treatment.

While the specificity of PCR and stool culture tests is the same, PCR tests are almost twice as sensitive as stool cultures (Table 2). Thus, the type of diagnostic had a larger impact on readmission of infectious children than the number of tests performed. We estimated that the likelihood of reentering school while infectious after one negative PCR test was 2 to 6%, compared with 8 to 31% for two consecutive negative stool cultures. If only one negative culture was required, the likelihood that the child returned to school infectious ranged from 28 to 56%. The number of childcare-days lost for the exclusion policy involving one negative culture varied from 8 to 13 days for children receiving immediate, effective treatment, and from 17 to 29 days if the child received ineffective treatment. If two negative cultures were required, this interval ranged from 11 to 21 days if the child received immediate, effective treatment and from 22 to 46 days if the child received ineffective treatment.

The policy permitting readmission seven days after beginning antimicrobial treatment showed minimal childcare-days lost for minimum risk (0%) of infectious child readmission if the antimicrobial treatment was effective. However, all (100%) children would be readmitted while infectious if they received inappropriate treatment, because the shedding duration would be
longer than seven days after beginning antimicrobial treatment. The risk of readmitting infectious students was very variable for policies in which children returned to school 14 days after symptom onset or 24 hours after being symptom-free for patients receiving ineffective (Range: 0–88%) or no treatment (Range:0–50%).

In Appendix C, we further explored variation in the total potential childcare-days lost in a shigellosis outbreak for each exclusion policy, considering a setting of 45 children and an assumed treatment mix of affected children. Results show that the cost comparison (in childcare-days lost) hinged on treatment effectiveness. When the percent of patients receiving effective treatment increases, the estimated number of childcare-days lost decreases. Conversely, when the share of patients receiving ineffective or no treatment increases, the estimated number of childcare-days lost increases.

Lines 51-52: the phrase "policies' impact evidence is little" does not read clearly. I would suggest rewording this.

Answer: We have now reworded the sentence in question. It now reads as:

In the event of a shigellosis outbreak in a childcare setting, exclusion policies are applied to afflicted children to limit shigellosis transmission. However, there is scarce evidence of their impact.

Background

Line 69: would list incubation period as approximately 1-3 days

Answer: We have now listed the incubation period as noted by the reviewer.

Make clear what is meant by "childcare"

Answer: We have now clarified our definition of childcare. It has been defined in the beginning of the methods section (line 94) as “a facility that provides care and educational activities for around 45 children aged approximately 5 years or younger for several hours per day but not 24h per day”.

Methods

Line 93: use "data were" instead of "data was"

Answer: We have now corrected this error.

For the four treatment options, "effective" and "ineffective" treatment should be defined. Additional details were provided in Table 1, panel II, but you may want to define this up front in methods.

Answer: We have edited the Methods for clarity.

Methods, third paragraph (added): We evaluated each policy for patients undergoing different treatment scenarios, namely: A) immediate, effective treatment; B) effective treatment after diagnosis; C) ineffective treatment; D) no treatment. We considered as effective treatment the receipt of a course of antibiotics that the particular strain of Shigella bacteria was susceptible to, as recommended in the latest guidelines 9. Ineffective treatment was defined as receiving an antibiotic that the Shigella strain was not susceptible to, or that did not have an effect in vivo based on pharmacokinetics 9.

Treatment scenarios A-C are based on the assumption that the child seeks medical care on Day 2 of illness. Was this assumption based on published data or expert opinion? Consider sensitivity analyses to account for variations in this assumption (up to Day 4 would be reasonable). You may also want to include this as a parameter in your spreadsheet tool.

Answer: This assumption was meant to represent the average time to care-seeking and was based on expert opinion. If the child seeks care on a subsequent day, this would delay the return to school for children undergoing treatment A, B, and C under exclusion policies involving convalescent stool cultures, 7 days after beginning treatment, and possibly 24 hours symptom-free. Childcare-days lost for children undergoing no treatment (treatment D) would not be affected. That is, given that the interval between symptom onset and care-seeking is assumed to be the same for Treatments A-C, as seen of Figure 1a, the changes in this interval would affect childcare days lost for children under these treatments equally; it would increase childcare-days lost relative to children undergoing Treatment D. Given that we have already included a range of
sensitivity analyses to other parameters, we opted instead to add a paragraph to the discussion to reflect these concerns:

Discussion, 5th paragraph (added): Based on expert opinion, we assumed that children sought medical care on the second day of illness. Since the interval between symptom onset and care-seeking was assumed to be the same for children undergoing Treatments A-C, a delay in seeking medical care would shift the date of return to school equally forward for children undergoing treatment A-C relative to D. This would not affect the relative differences among most exclusion policies as applied to children undergoing most treatments. The only change in our estimates would be a relative increase in childcare-days lost to Treatment D, for policies requiring 24 hours symptom-free or waiting 14 days after symptom onset. […]

For the calculation of childcare-days lost, were only weekdays included, or all days of the week? This should be clarified and taken into account in calculations.

Answer: We have now clarified our calculation, as all days of the week were included.

Methods, second paragraph: We estimated the likelihood that shigellosis patients returned to childcare while still infectious as well as the number of childcare-days lost (where all days lost are assumed to be childcare-days lost as we did not account for holidays or weekends) […]

For the exclusion policies involving two negative tests (both culture and PCR), the assumption is made that the second test is not done until the results of the first test are available (per details provided in Figure 1 panel b and Table A2). I would consider the scenario where two stool specimens are collected sequentially (at least 24 hours apart), prior to waiting for results of the first test.

Answer: While this reviewer proposed strategy is reasonable, we believe the inclusion of a different treatment option would significantly increase the complexity of the results, which already involved a great number of intersections between treatment and exclusion policy options. Based on existing publications, routine collection of serial specimens 24h apart did not appear to be a standard practice during childcare-associated shigellosis outbreaks in the US. Also, and to note, the effects of this treatment can be inferred from the previously studied effects of childcare-
days lost for treatment A and B and the two consecutive test policy. Namely, reducing the time between tests would potentially reduce childcare-days lost for children undergoing treatments A and B, under the policies of two consecutive tests. Given the pertinence of the suggested policy option, we have included a paragraph about this possibility in the discussion section:

Discussion, 5th paragraph (added): […] On another note, for the exclusion policy involving two consecutive tests, we assumed that the second test would be conducted upon receipt of the results of the first test. If the second test was conducted before the results of the first test were available, the number of childcare-days lost could be marginally less than we estimated.

In Appendix B, Calculations 1, calculations for the maximum number of additional cases are provided - include this in the methods.

Answer: We have removed this calculus from Appendix B.

Results

As previously stated, I think this section can be fleshed out a bit more. The links between the results and the abstract, and the results and the figures/appendices are not immediately clear to the reader, particularly since Figure 2 is difficult to read. For example, the data stated in the abstract are buried in Appendix B and should be more explicitly addressed in the results.

Answer: We have now described our results in more detail.

Results, before: Figure 2 shows the probability that an infectious child will return to childcare and the days that the child would be excluded, by treatment type and exclusion policy. Policies based on negative convalescent stool tests hinged on the test’s sensitivity, with PCR-based tests leading to lower probability of the child being infectious when readmitted (Range: 0–6%). The type of diagnostic had a larger impact on readmission of infectious children than did the number of tests performed (we estimated that the onward transmission risk for a child returning to school after one negative PCR test was 2–6%; that risk was 8–31% for two consecutive negative stool cultures). The policy permitting readmission seven days after beginning antimicrobial treatment
showed minimal childcare-days lost for minimum risk (0%) of infectious child readmission if the antimicrobial treatment was effective, but all children would be readmitted while infectious if they received inappropriate treatment. The risk of readmitting infectious students was very variable for policies in which children return to school 14 days after symptom onset or 24 hours after being symptom-free for patients receiving ineffective (Range: 0–88%) or no treatment (Range:0–50%). In Appendix C, we further explored variation in the total potential childcare-days lost in a shigellosis outbreak for each exclusion policy, considering a setting of 45 children and an assumed treatment mix of affected children. Results show that the cost comparison (in childcare-days lost) hinges on treatment effectiveness.

Results, after, added sentences are underlined: Figure 2 shows the probability that an infectious child returns to childcare and the number of days that the child would be excluded, by treatment type and exclusion policy. The effectiveness of policies based on negative convalescent stool tests hinged on the test’s sensitivity, with PCR-based tests leading to lower probability of the child being infectious when readmitted. If the policy required 2 consecutive PCR-negative stool samples, the probability that the child returned to school infectious was <1%, with the number of days the child spent at home ranging from 7 to 17 days (midpoint: 9 days) if the child received immediate, effective treatment. The maximum number of childcare-days lost increased to 19 days if the child received effective treatment after diagnosis; it was between 19 and 53 days if the child received ineffective treatment; and between 6 and 43 days if the child received no treatment. If only 1 Shigella-negative PCR test stool sample was required, the likelihood the child returned to school infectious was ≤ 6% and the number of days the child spent at home varied between 6 and 11 days (midpoint: 7 days) if the child received immediate, effective treatment; it was up to 13 days if the child received effective treatment after diagnosis; between 18 and 45 days for children receiving ineffective treatment; and between 5 and 35 days for children receiving no treatment.

While the specificity of PCR and stool culture tests is the same, PCR tests are almost twice as sensitive as stool cultures (Table 2). Thus, the type of diagnostic had a larger impact on readmission of infectious children than the number of tests performed. We estimated that the likelihood of reentering school while infectious after one negative PCR test was 2 to 6%, compared with 8 to 31% for two consecutive negative stool cultures. If only one negative culture was required, the likelihood that the child returned to school infectious ranged from 28 to 56%. The number of childcare-days lost for the exclusion policy involving one negative culture varied from 8 to 13 days for children receiving immediate, effective treatment, and from 17 to 29 days if the child received ineffective treatment. If two negative cultures were required, this interval ranged from 11 to 21 days if the child received immediate, effective treatment and from 22 to 46 days if the child received ineffective treatment.
The policy permitting readmission seven days after beginning antimicrobial treatment showed minimal childcare-days lost for minimum risk (0%) of infectious child readmission if the antimicrobial treatment was effective. However, all (100%) children would be readmitted while infectious if they received inappropriate treatment, because the shedding duration would be longer than seven days after beginning antimicrobial treatment. The risk of readmitting infectious students was very variable for policies in which children returned to school 14 days after symptom onset or 24 hours after being symptom-free for patients receiving ineffective (Range: 0–88%) or no treatment (Range:0–50%).

In Appendix C, we further explored variation in the total potential childcare-days lost in a shigellosis outbreak for each exclusion policy, considering a setting of 45 children and an assumed treatment mix of affected children. Results show that the cost comparison (in childcare-days lost) hinged on treatment effectiveness. When the percent of patients receiving effective treatment increases, the estimated number of childcare-days lost decreases. Conversely, when the share of patients receiving ineffective or no treatment increases, the estimated number of childcare-days lost increases.

Consider including more details regarding the results from Appendix C, to support your conclusion on lines 126-127: "Results show that the cost comparison (in childcare-days lost) hinges on treatment effectiveness". Explicitly state what that means, and how those conclusions were drawn based on data provided in figures C1 and C2.

Answer: As mentioned before, we have now described our results in more detail, in specific, the results from Appendix C.

Results, last paragraph: In Appendix C, we further explored variation in the total potential childcare-days lost in a shigellosis outbreak for each exclusion policy, considering a setting of 45 children and an assumed treatment mix of affected children. Results show that the cost comparison (in childcare-days lost) hinged on treatment effectiveness. When the percent of patients receiving effective treatment increases, the estimated number of childcare-days lost decreases. Conversely, when the share of patients receiving ineffective or no treatment increases, the estimated number of childcare-days lost increases.
Discussion

Line 138-139: ineffective treatment defined here, but should be defined up front

Answer: We have now included the definition of ineffective treatment in the methods.

Methods, third paragraph (added): We evaluated each policy for patients undergoing different treatment scenarios, namely: A) immediate, effective treatment; B) effective treatment after diagnosis; C) ineffective treatment; D) no treatment. We considered as effective treatment the receipt of a course of antibiotics that the particular strain of Shigella bacteria was susceptible to, as recommended in the latest guidelines 9. Ineffective treatment was defined as receiving an antibiotic that the Shigella strain was not susceptible to, or that did not have an effect in vivo based on pharmacokinetics 9.

In the limitations you state that the "findings reflect scenarios with known shigellosis, such as during a shigellosis outbreak…" (Lines 151-152). What implications might these analyses have for known sporadic cases of shigellosis in non-outbreak settings?

Answer: The epidemiology of shigellosis is such that, given that only human to human transmission is possible, shigellosis cases are always linked to an outbreak even if unbeknownst to the patients. For this reason, while we have emphasized that the results apply to an outbreak effort, we have not focused, in the discussion to sporadic cases.

Tables

Table 2: The footnote "¶ Assumption based on the information provided…" is missing the corresponding symbol in the table

Answer: We have now included the required footnote.

Figures

Figure 1: This is a nice visual, but does not provide much additional information that is not already provided in Table 1.
Answer: After receiving feedback from different readers, we opted by including both table 1 and figure 1 as some readers prefer a tabular format and others a more graphic one. Given the variety of inputs involved and scenarios/patients involved, we find this assures that the different audiences will have a clearer understanding of the parameters involved.

Figure 2: This figure is a very important part of the results, but unfortunately the layout and overlapping text make it difficult to read. I assume this is due to the way the graph is generated in Excel. You may want to consider also including a table that shows the key results and takeaway from this figure and the Calculations in Appendix B. I think that will make more clear to the reader how you reached the conclusions stated in the abstract and results section.

Answer: We thank the reviewer for this comment. We have edited the figure and saved it in a format that with minimum overlap.

It's not immediately clear to the reader that there are data points missing because they are overlapping. Add a footnote to clarify this.

Answer: We have now edited the picture to not allow for overlap of the legends, and we have added the footnote.

Figure 2: Why is the text "7 days after beginning Tx", "24 hr symptom free", "One test: culture", etc. shown in the graph, but "one test: culture" and "14 days after symptom onset" missing? Either way I don't think this is needed since the legend is provided.

Answer: We think this may have happened because of unforeseen errors when we copied and pasted the figure from Excel. We have now edited the figure for consistency.

Figure 2 notes: policy is listed as "seven days after the end of antimicrobial treatment"- error

Answer: We thank the reviewer for this comment and have now edited the legend.
Supplementary Material

The use of "total childcare days excluded" - in some figures (in the appendices as well as the text of manuscript), this appears to refer to the number of days per child, whereas in others the "total childcare days lost" refer to total numbers in aggregate. This needs to be clarified in the methods (Line 105-106) and used consistently.

Answer: We thank the reviewer for this comment, and have now clarified the methods, as seen below. We have also clarified appendix B.

Methods, last paragraph: We further explored the impact of exclusion policies in childcare-days lost for a given childcare (in which different children receive different treatments) in a separate sensitivity analysis (Appendix C). We estimated the total number of childcare-days lost as the attack rate multiplied by the setting size and by the number of childcare-days lost for a given combination of treatments the children receive. We considered a population of 45 children (equivalent to a small childcare facility), an attack rate of 25% 10, 11 for our reference analysis, and three different combinations of treatments. We show the results for various combinations of treatment types for our reference population of children (Appendix C).

Appendix A

Table A1 and A2: wording of the third exclusion policy, "1 laboratory analysis of convalescent stool samples yields no Shigella", is unclear. This is intended to mean stool culture?

Answer: We have now clarified our expression.

Appendix B

Overall, I think this is a good tool that can be valuable for decision making by public health professionals in outbreak settings. However, you may want to consider ways that the information can be presented in a more digestible and user-friendly format for your intended audience. As a public health professional, what and where are my main take home points from using this tool?

Answer: The purpose of the tool is to assess alternative exclusion policies to stop a Shigella outbreak in childcare settings. The user can change the main parameters in the model (Table 2) to adapt them to the outbreak they are seeing or to the local conditions they need
to assess. We have revised our Appendix B to make it more user-friendly: in particular, we have added a “Title”, “Description”, “Index”. For added clarification, we have also included legends of the results in the Results worksheets.

Again, the layout of the figure in "Fig1_MS returnpat" makes it difficult to read. Hovering over the data points does help some but not completely.

There are several typos throughout this appendix where exclusion policy is written as "7 days after end of antimicrobial treatment" instead of "beginning"

Answer: We have now changed the layout of the figure and made it larger. We have also edited the appendix accordingly.

Home worksheet:

- Row 18: use "symptom onset" instead of "symptom identification" for consistency with wording in manuscript
- The listing of the worksheets (Rows 35-43) do not actually correspond with the worksheets that are there. For example, there is no "Sources" worksheet

Answer: We have edited the expression “symptom onset” in the worksheets accordingly, and have corrected the listing.

Inputs - Policies worksheet:

- Row 8: use "symptom onset" instead of "symptom identification" for consistency with wording in manuscript

Answer: We have again edited the expression “symptom onset” in the Policies worksheet.

Inputs - Treatment worksheet:

- Row 6: It is not clear what is meant by "day 1/2 of illness"
- Row 8: It is not clear what is meant by "day 1/4 of illness"

Answer: We have now clarified the expressions referenced by the reviewer.
Fig1_MS returnpat worksheet:

- Use a more descriptive title. "per patient type" is confusing, since the term "treatment type" is used in the text of the manuscript
- The same comments for Figure 2 apply here

FigB1_MS returnpat worksheet: the term "per patient mix" is inconsistent with the use of the term "treatment mix" in the text of the manuscript

Answer: We have changed the title of worksheets presenting results to Results 1- Results 3. We have also clarified the use of the expressions “patient type”, “treatment type”, and “per patient mix”. We have included legends above the results to make it clear to the reader what is shown in each picture.

Fig2_MS Days lost worksheet:

- Use a more descriptive title
- Same comment re: use of the term "patient mix" vs. "treatment mix"

Answer: As mentioned before, we have now changed the title of the worksheet; as before, we have also clarified the use of the expressions “patient type”, “treatment type”, and “per patient mix”.

Calculations 2 worksheet: provide some supplementary explanation of these data tables, since this is not addressed in the methods

Answer: We have removed from this worksheet the results that we had not alluded to in the methods. In the methods section, we included an explanation of the calculation:

Methods, last paragraph: We further explored the impact of exclusion policies in childcare-days lost for a given childcare (in which different children receive different treatments) in a separate sensitivity analysis (Appendix C). We estimated the total number of childcare-days lost as the attack rate multiplied by the setting size and by the number of childcare-days lost for a given combination of treatments the children receive. We considered a population of 45 children (equivalent to a small childcare facility), an attack rate of 25% 10, 11 for our reference analysis, and three different combinations of treatments. We show the results for various combinations of treatment types for our reference population of children (Appendix C).
Appendix C

Line 9: Table B1 is referenced- there is no table B1 (C1?)

Footnotes for Figures C1 and C2 have some errors:

- "five policies" (Lines 23 and 48) are referenced but figure title refers to 7. Make sure wording is consistent throughout

- "seven days after end of antimicrobial treatment" (Lines 25 and 50) should say beginning

- Table S2 is referenced (Lines 29 and 55)- there is no table S2

Figure C2 title: "and treatment mixes as in Table B1..."- there is no table B1 (C1?)

Figure C2, Panels a, b, and c: suggest reordering the first four rows to be consistent with the other tables in the manuscript (culture first, then PCR)

Line 58 (Figure C2 notes): "Panel A is shown in the main text"- it does not appear in the main text

Answer: We thank the reviewer for this notes. We have corrected Appendix C per the reviewers’ notes.