

## 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>	Evaluating Antibiotic Stewardship in a Tertiary Care Hospital in Kerala, India: A Qualitative Interview Study
<b>AUTHORS</b>	Baubie, Kelsey; Shaughnessy, Catherine; Kostiuk, Lia; Joseph, Mariam; Safdar, Nasia; Singh, Sanjeev; Siraj, Dawd; Sethi, Ajay; Keating, Julie

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Maya Nadimpalli Postdoctoral Researcher, Institut Pasteur, France
<b>REVIEW RETURNED</b>	12-Oct-2018

<b>GENERAL COMMENTS</b>	<p>This manuscript describes barriers/facilitators to the implementation of an antibiotic stewardship program in a hospital in southern India, where antibiotic resistance rates are high and antibiotic stewardship is greatly needed. The authors clearly describe their methods and main findings. However, their rationale for conducting the study was confusing, and their discussion could be clearer. Specific comments are below.</p> <p><b>Abstract</b> -Some abbreviations are used without defining them first (e.g. AS, ASP)</p> <p><b>Background</b> I am confused about the emphasis on hospital-acquired infections as rationale for implementing ASPs. I think the first paragraph of the introduction (about HA infections) should be removed/significantly reduced. The second and third paragraphs provide actual context for the study + study rationale.</p> <p><b>Specific comments –</b> The authors make it seem like ASPs are specifically important for addressing ABR HA infections. Whether a person has a HA infection or community-acquired infection, they will still require antibiotic treatment at the hospital. How does the “origin” of their infection (hospital-acquired versus community-acquired) impact the need for an ASP? Page 4, Line 6-8: “..most deaths from AB take place in inpatient healthcare settings.” This citation does not support this statement and is also a webpage, rather than a published article/report. Page 4, Line 9-14: “..This discrepancy is likely due to....without prescription.” I would argue that weak hospital infection control is a major contributor to the differences in HAI rates between LMICs and</p>
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developed countries. Again, I don't think this background is necessary to provide context for your study.

Page 4, Line 27: What are ASP international programs? Please define in a few words or rephrase,

Page 4, Line 34-39: "Newly published consensus...and suitable for LMICs." I'm not sure what this sentence means. Does this checklist not account for implementation challenges in LMICs? Your next paragraph makes it seem like not.

Page 4, Line 48: "less available manpower and money" compared to who?

Page 4, Line 50: Please include a few words/a sentence explaining whether EMRs are integral to ASPs, and why.

Page 4, Line 55: You say you selected this hospital because it has recently implemented an ASP. It seems to me that you would only want to improve implementation of this ASP if you had evidence that it was effective in reducing AB use or ABR infections. Do you have any evidence of this? If not (perhaps it's too early), perhaps implementation of an ASP with a similar design/model has been successful in another LMIC, with measurable reductions in AB use or ABR infections? It's not clear to me why your study question was, "How can we better implement this ASP?" versus, "How can we modify this ASP to better achieve desired outcomes?" There must be some reason why you thought expansion of the current model would be the best way to improve AS in this hospital, but this reasoning is not described.

Page 5, line 3: Please clarify that this was a prospective qualitative study.

#### Methods

page 5, Location paragraph – Is the hospital in a rural or urban area?

Page 5, Line 29: I wasn't familiar with term "purposive" sampling. Please define it in a few words in text.

Page 5, line 39: What is "theoretical saturation" Please use another term or explain.

Page 5, line 39: What kinds of tasks related to the ASP might non English-speaking staff be involved in? Could you have missed important themes/viewpoints?

Page 5, Line 50-55: Were other frameworks evaluated? Why was SEIPS chosen, e.g. Is SEIPS better suited for low-income/low-resource settings?

Page 6: Line 11: "continuously revised to uncover novel information." I don't know what this means or how it is represented in Appendix A.

Page 6: Line 39: Include IRB approval number.

#### Results

The purpose of the "hospital antibiogramme" is unclear to me. If antibiogrammes are being performed for each infecting organism, wouldn't it better to share patient-specific results with a doctor so he/she can tailor the prescription? For example, if 70% of gram neg organisms are resistant to third-gen cephalosporins (based on the hospital antibiogramme), a physician might prescribe carbapenems to treat an infection that could actually be cephalosporin-susceptible. It seems to me that the hospital antibiogramme could actually exacerbate unnecessary use of last-resort drugs. Please comment on this possibility.

If AB are not being performed on each patients' infecting organism, this seems like a major barrier to effective ASP and should be addressed in detail.

	<p>Page 7: Line 35-36: Is email an effective way to quickly communicate this info? Did any participants mention this?</p> <p>Page 8: Line 33-34: Can you provide examples of specific suggestions from the ASP that physicians are resistant to?</p> <p>Page 11: Lines 3-8: It is interesting that staff didn't identify widespread AB pollution in India (from pharmaceutical companies) as a driver for ABR in the community. Abroad, this is a very common point for why AMR is such an issue in India. Please acknowledge in discussion.</p> <p>Discussion</p> <p>Second paragraph - Are there any external factors that could impact ASP implementation? For example, is there state-wide or federal support for ASP implementation?</p> <p>Page 12 – paragraph on EMRs. “Adoption of an EMR can improve ASP by providing micro results, radiology studies, and clinical data.” Please give a few examples (e.g. ...) of microbiology results and clinical data that the EMR can provide. Microbiology results and clinical data can be provided without an EMR – what benefit does an EMR provide? What is the relevance of radiology study results to AS?</p> <p>Page 12 – paragraph on EMRs – “These factors allow ASPs the opportunity to further curtail AB use; our data here support these findings.” What factors? You don't provide data on reductions in AB use following the hospital's adoption of an EMR, so how exactly do your data support these findings?</p> <p>Page 12 – “Our study identified high and indiscriminate community-based antibiotic use as a barrier to practicing AS at our study site.” Please clarify in a few words/one sentence exactly how this was a barrier.</p> <p>Page 12-13: “ASP in health care settings can be complemented by AS in the community...” If you found poor AS in the community was a major barrier to ASP implementation in the hospital, I would mention whether there are current initiatives in Kerala (or India) to address this issue. Is there substantial federal interest/financial support?</p> <p>Page 13- limitations paragraph. In terms of resources (staff, funding, equipment, quality of facilities...), how does your hospital compare to other hospitals in India? About average, or with exceptionally more resources than average? It will be important for readers to roughly gauge the potential to transfer your findings to low-resource hospitals.</p>
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<b>REVIEWER</b>	Elizabeth Ashley Myanmar Oxford Clinical Research Unit.
<b>REVIEW RETURNED</b>	13-Oct-2018

<b>GENERAL COMMENTS</b>	This qualitative study describes what appears to be an outstanding example of good practice in antibiotic stewardship in a large private hospital (which also provides free care to large numbers of patients) in Kerala, India. This is both a strength, in that it shows what can be achieved, and also a weakness, in terms of limiting its generalisability to other low or lower middle income country settings in particular.
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	<p>The model described is somewhat similar to that adopted in high income settings with multidisciplinary team working (microbiology/pharmacy/clinicians).</p> <p>Major comments:</p> <ol style="list-style-type: none"> <li>1. Description of ASP: A more detailed description of the hospital and the human and other resources needed to deliver the AS programme would be very useful to enable readers to gauge feasibility of implementation in their own institution e.g.       <ol style="list-style-type: none"> <li>a. What specialties are represented in the hospital</li> <li>b. Are there other consultant microbiologists and/or trainees in the hospital in addition to the one involved in ASP activities. Or if the microbiologist is single-handed how many scientists or technicians are employed to support the 24h laboratory service</li> <li>c. How many practitioners are involved in stewardship activities/ on the committee in total?</li> <li>d. How did physicians get recruited to take part, what level of seniority are they, is it a fixed-term commitment or permanent?</li> <li>e. Are any staff dedicated to antibiotic stewardship full-time or is this done in addition to other activities?</li> <li>f. Are the number of ASP consults/discussions and outcomes , e.g. whether advice is followed documented?</li> <li>g. What are the regular point-of-care stewardship activities in addition to identifying opportunities to intervene from the EPR e.g. ICU ward rounds C.difficile ward rounds</li> <li>h. Is a 24h consult service provided with out of hours antibiotic advice?</li> <li>i. How often are antibiotic prescriptions reviewed in the different areas of the hospital e.g. daily? weekly? This seems a very onerous undertaking- can the authors explain more how patients are targeted and the average no. of interventions per week. When was the electronic patient record introduced- was stewardship done before this?</li> </ol> </li> <li>2. Objectives of this research are missing from the main body of the manuscript</li> <li>3. Risk of bias: the methods state that “interested participants” were identified. Is it fair to say that the participants were more invested in the success of the programme than other potential participants. How many were ASP team members? Any reason why surgeons were not invited?</li> <li>4. Evidence of impact. The authors admit they rely on self-reporting of AMS practices. Can any assessment be made about the impact of the AMS activities on controlling or preventing AMR in the hospital e.g. comparison of AMR rates to similar institutions?</li> <li>5. Have the authors any reflections on how or if this model could be modified for more resource-constrained settings in India?</li> <li>6. Implications of findings- “Launching and sustaining a new program will be more feasible if hospital leadership is supportive and the stewardship team meets daily to discuss cases.” While daily stewardship rounds covering the whole hospital are a great idea in principle this is very demanding on stewardship teams and difficult to implement in settings of any income level. I don’t see the evidence to support this statement from the results.</li> <li>7. Access to pharmacists- it sounds as if this is valued by ASP supporters but it would not solve the problem of pharmacy advice being disregarded by other members of the hospital Consultant body which came out in the results- any suggestions as to how to overcome this?</li> <li>8. Are results of stewardship activities reported back to clinician teams?</li> </ol>
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	<p>9. The Electronic Patient Record is flagged as a key to success of the programme. Please can the authors put this into context to enable generalizability to be assessed- is EPR going to be rolled out across India or is this a hospital-led initiative?</p> <p>Minor</p> <p>1. Abstract objectives:” To conduct interviews with healthcare professionals to determine what barriers and facilitators to antibiotic stewardship existed within their facility. Isn’t the objective to determine barriers and facilitators to implementation of ASP rather than to conduct the interviews (=method)?</p> <p>2. “Our study is the first of its kind to systematically examine the key barriers and facilitators of implementing an ASP in a LMIC.” Suggest dropping or rewording this statement on the grounds that the authors are presumably only referring to published literature in the English language</p> <p>3. Description of barriers to ASP implementation- isn’t non-compliance with the ASP the barrier causing failure to de-escalate antimicrobials rather than the failure to de-escalate itself ?</p> <p>4. Clarification point- can the authors explain when the antibiogram would be used by clinicians if the antibiotic guidelines have been written to take the antibiogram findings into account. Is it consulted preferentially to using the guidelines?</p> <p>5. “The careful design of ASP with consideration to overcoming barriers and strengthening facilitators will improve antibiotic use and curb the spread of resistant organisms.” Typo- curb</p>
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<b>REVIEWER</b>	Matthew Simon Weill Cornell Medicine New York, NY USA
<b>REVIEW RETURNED</b>	05-Nov-2018

<b>GENERAL COMMENTS</b>	<p>Baubie and colleagues conducted a qualitative study of facilitators and barriers to antimicrobial stewardship in a tertiary hospital in India. The authors employed sound qualitative methods, the manuscript is well-written and the findings are novel. I think the work will be instructive to other hospitals in low-middle income countries who are attempting to implement similar programs and commend the authors for conducting this work. My main comments relate to a more thorough description of the hospital personnel, staffing, training backgrounds, leadership structure and EMR. I think the reporting of results would be improved by more clearly delineating responses/perspective from ASP team members and non-ASP team members. I have the following specific comments/questions:</p> <p>Summary Box:</p> <p>1) What is already known? Bullet 2 seems too generic. Suggest focus what is already known or recommended for ASPs in LMIC.</p> <p>2) What do the new findings imply? Bullet 1 seems bland. Based on the study findings, what are specific strategies ASPs in LMIC should implement to overcome barriers?</p> <p>Background:</p> <p>1) Paragraph 2—Sentence 1. Does the cited review by Davey et al, stratify ASP effectiveness by LMIC or high income countries? Is there any data for effectiveness in resource limited settings? If so, would reference here.</p>
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2) Paragraph 2-Sentence 3: What are the core elements for ASPs recommended by the international panel (REF18)? I think a brief description of these recommendations will be helpful for the reader who does not have background in ASP and will provide some framework for understanding the strengths/limitations of the ASP described in this study.,

Methods:

1) Location: The description of the hospital and ASP personnel is lacking. How many people comprise the ASP at the hospital?

a. What is the leadership structure of the hospital? Leadership support is identified as an important facilitator. More details regarding the hospital's leadership structure would be informative to understand what/who is meant by "leadership support".

b. Clinical pharmacists-what is the training of the clinical pharmacists involved in the ASP? Are all clinical pharmacists involved in ASP activities? Do they volunteer? What is structure of the hospital's pharmacy department? Does the ASP have a single pharmacist leader? More detail on the hospital's pharmacy resources and structure would be informative.

c. Physicians—Do the ASP physician have specialized infectious diseases training? How are they selected? Is there a single physician leader? Is the ASP part of physicians formal job responsibilities? Is the ASP distinct from the hospital infection control program or part of it?

d. Infection control nurses—They are not mentioned as part of ASP in methods section but in Results are mentioned as ASP team members who participate in the focus group. Please clarify the relationship to the hospital infection control program to the ASP.

2) Interview guide—I would recommend including the interview guide in the manuscript as a Table as it gives the reader more context for what was asked in the interviews.

3) SRQR—please define the abbreviation for readers unfamiliar with qualitative methods.

Results:

1) Reporting of results:

a. The investigators appear to have included both ASP team members and frontline healthcare workers who are not part of the ASP. In framing the results, I think these different perspectives need to be more clearly delineated. Where do the perspectives and attitudes of ASP team members and non-ASP clinicians overlap and where do they diverge?

b. Consider including some representative quotes in the manuscript text. I think it will enrich the results so readers do not have to continuously flip back to Table 1.

2) Infection control nurses—please clarify if they are part of the ASP and what is their role?

3) Organization—

a. How many people comprise the ASP in each discipline?

b. How are patients receiving antibiotics selected for evaluation? Are all patients in the hospital reviewed? Are select patients reviewed based on microbiology results? Are patients on select broad-spectrum antibiotics?

c. Email communication. This is quite interesting. What is communicated over email? Treatment recommendations or other feedback? Are other communication modalities used (e.g. in-person, text message/page, telephone, beeper)?

d. AS symposium—please describe further. What does this entail if others would like to emulate?

e. What specifically does hospital administrative leadership do to champion the ASP? Does someone in hospital leadership formally oversee the ASP and if so what is their title/role within the organization? What enabled buy-in from hospital leadership ?

f. Paragraph 2 “ Highly capable” ASP. Is this a finding/result of the study or the authors interpretation/assumption? What is the basis for describing the ASP as “highly capable.” The authors have not really presented any data yet to suggest it is effective. If it is a finding, this deserves more support/discussion.

g. Paragraph 2- “17 interviews (48.6%) regarded the microbiology labs as a key facilitator”. What is the denominator for the 48.6%? 45 people were interviewed in the study. Excluding the focus group and the 1 microbiologist 30 were interviewed. Neither percentage (17/45 or 17/30) equals 48.6%. Please clarify. Also, is the numerator 17 interviews or interviewees? Please clarify percentages throughout the results.

h. Paragraph 3—access to pharmacists. If the study participants were limited to ID and critical care teams, Was access to pharmacists a problem for only these departments or others departments/hospital wards? Which departments lacked pharmacists and which had adequate pharmacist support? Please clarify the hospital’s pharmacy resources for ASP and non-ASP activities.

i. Person—pagraph1—Does the 57.1% include AS team members? This % should probably be limited to non-ASP team members. Were the remainder of participants (42.9%) unaware of AS concepts, policies and practices? This would seem to be a high percentage of participants who are unaware of the ASP.

j. Immunity to change—were any specific services are departments more immune to change? Any other physician characteristics (older vs. younger)?

k. Tasks—Are the guidelines institutional or national guidelines? If institutional, are they based on the local antibiogram? Please clarify how a lack of knowledge of pre-admission meds lead to “antibiotic overprescription”?

l. Tools/Technology—the description of EMR is quite different than what many readers may be used to. What is included in the EMR (i.e physician notes, order entry? Laboratory results?) Did the EMR facilitate AS in any way? This is touched on in the discussion (pg 12 line 34-39) but not discussed in any meaningful way in the results.

Discussion:

Can the authors put the results in context with prior literature on AS in LMIC, particularly in India (i.e. references 19-22)? How does this study build on the prior work on AS in LMIC and in India?

Can the authors summarize the perspectives where ASP team members and front-line clinicians are aligned and where they are divergent?

Table 1: Please delineate which quotes are from AS team members and which are from non-team members.

Appendix A:

Was employee turnover a significant barrier to AS?

How are nurses involved in AS? I think this would be of interest to both LMIC and high-income countries such as the US.

## VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Maya Nadimpalli

Institution and Country: Postdoctoral Researcher, Institut Pasteur, France

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

This manuscript describes barriers/facilitators to the implementation of an antibiotic stewardship program in a hospital in southern India, where antibiotic resistance rates are high and antibiotic stewardship is greatly needed. The authors clearly describe their methods and main findings. However, their rationale for conducting the study was confusing, and their discussion could be clearer. Specific comments are below.

Abstract

-Some abbreviations are used without defining them first (e.g. AS, ASP)

Fixed.

Background

I am confused about the emphasis on hospital-acquired infections as rationale for implementing ASPs. I think the first paragraph of the introduction (about HA infections) should be removed/significantly reduced. The second and third paragraphs provide actual context for the study + study rationale.

We have reduced the first paragraph. Thank you.

Specific comments –

The authors make it seem like ASPs are specifically important for addressing ABR HA infections. Whether a person has a HA infection or community-acquired infection, they will still require antibiotic treatment at the hospital. How does the “origin” of their infection (hospital-acquired versus community-acquired) impact the need for an ASP?

This is a good point—we have removed all mentions of “hospital-acquired” since yes, infection origin does not impact need for patient care or good AS.

Page 4, Line 6-8: ..”most deaths from AB take place in inpatient healthcare settings.” This citation does not support this statement and is also a webpage, rather than a published article/report.

We have removed this sentence and its citation.

Page 4, Line 9-14: “..This discrepancy is likely due to....without prescription.”

I would argue that weak hospital infection control is a major contributor to the differences in HAI rates between LMICs and developed countries. Again, I don't think this background is necessary to provide context for your study.

Thank you, we have removed this from our paper.



Page 4, Line 27: What are ASP international programs? Please define in a few words or rephrase,

This sentence has been restructured for more clarity.

Page 4, Line 34-39: “Newly published consensus...and suitable for LMICs.” I’m not sure what this sentence means. Does this checklist not account for implementation challenges in LMICs? Your next paragraph makes it seem like not.

We have rewritten this portion in light of this suggestion, thank you.

Page 4, Line 48: “less available manpower and money” compared to who?

We have added to this sentence.

Page 4, Line 50: Please include a few words/a sentence explaining whether EMRs are integral to ASPs, and why.

We have done so by adding a sentence here.

Page 4, Line 55: You say you selected this hospital because it has recently implemented an ASP. It seems to me that you would only want to improve implementation of this ASP if you had evidence that it was effective in reducing AB use or ABR infections. Do you have any evidence of this? If not (perhaps it’s too early), perhaps implementation of an ASP with a similar design/model has been successful in another LMIC, with measurable reductions in AB use or ABR infections? It’s not clear to me why your study question was, “How can we better implement this ASP?” versus, “How can we modify this ASP to better achieve desired outcomes?” There must be some reason why you thought expansion of the current model would be the best way to improve AS in this hospital, but this reasoning is not described.

Our co-authors at the institution itself think it is too early to state whether or not this program has been effective in reducing AB use. The corresponding author believes our study question was simply “How has the implementation of an ABS at this particular hospital been going so far, and how does it work?”. I do not believe we ever had the intention of suggesting modifications as it would seem disrespectful for us to come in and make suggestions as if we truly understood the setting better than the people who actually live and work there.

Page 5, line 3: Please clarify that this was a prospective qualitative study.

This is a case study.

Methods

page 5, Location paragraph – Is the hospital in a rural or urban area?

Added detail

Page 5, Line 29: I wasn’t familiar with term “purposive” sampling. Please define it in a few words in text.

Reworded for clarity

Page 5, line 39: What is “theoretical saturation” Please use another term or explain.

Reworked this paragraph, phrase no longer used.

Page 5, line 39: What kinds of tasks related to the ASP might non English-speaking staff be involved in? Could you have missed important themes/viewpoints?

All institutions of higher learning in India use English during instruction as there are an incredible amount of local languages spoken in the country, therefore all the people we interviewed were multi-lingual. There aren't any people who don't speak English involved in the ASP itself.

Page 5, Line 50-55: Were other frameworks evaluated? Why was SEIPS chosen, e.g. Is SEIPS better suited for low-income/low-resource settings?

We used this framework to help us think through different workplace factors which influenced the overall environment the people we were interviewing work in. Researchers in the University of Wisconsin Madison group have used it before with success, as well.

Page 6: Line 11: "continuously revised to uncover novel information." I don't know what this means or how it is represented in Appendix A.

We agreed this was confusing and took out this phrase.

Page 6: Line 39: Include IRB approval number.

This is now included.

## Results

The purpose of the "hospital antibiogramme" is unclear to me. If antibiogrammes are being performed for each infecting organism, wouldn't it better to share patient-specific results with a doctor so he/she can tailor the prescription? For example, if 70% of gram neg organisms are resistant to third-gen cephalosporins (based on the hospital antibiogramme), a physician might prescribe carbapenems to treat an infection that could actually be cephalosporin-susceptible. It seems to me that the hospital antibiogramme could actually exacerbate unnecessary use of last-resort drugs. Please comment on this possibility.

Antibiogram for patient specific infecting organism is done and is reported to the clinicians for appropriate decision making. We have a state of the art Microbiology department (automated) and tests on tissues for each patients are being performed on regular basis. Lab is 24X 7 functional.

On a higher level, Hospital Antibiogram is prepared based on tissues and for each clinical department. This helps to prioritize empirical use at ER or at the time of admission (till microbiology report is available). As mentioned it may lead to over use sometimes based on antibiogram, but this was thought as most scientific guidance note to post graduates and junior faculty who start the empirical treatment at first contact. Since microbiology reports are available on Lab Information System, which is real time, de escalation is initiated. At this time, nurse also plays a critical role to inform the microbiology report to clinicians for de-escalation.

We've added some of the above detail to our paper to make it more clear.

If AB are not being performed on each patients' infecting organism, this seems like a major barrier to effective ASP and should be addressed in detail.

Antibiogram for each patient infecting organism is being done. Tests for normal flora or commensals are only not done.

Page 7: Line 35-36: Is email an effective way to quickly communicate this info? Did any participants mention this?

Email is more for having a "record" to refer back to for record keeping purposes, but bed side rounds, phone calls to the physicians, and face to face interaction also are done. E mail communication are done for immediate action and recording the details too. We've added these details to our paper.

Page 8: Line 33-34: Can you provide examples of specific suggestions from the ASP that physicians are resistant to?

We have identified certain departments to be outliers to our recommendations. Constant interaction with the consultants of those departments and presenting the proof (hardcopy of a guideline) during those interactions have brought slight changes in the long run.

Recently, the AMSP team have revised the dosing guideline for Colistin and Polymyxin. Initially, certain departments didn't comply with it but later on with constant approaching from the AMSP team have reversed the situation. The inappropriateness in dosing is still present but was brought down to a larger extent.

Page 11: Lines 3-8: It is interesting that staff didn't identify widespread AB pollution in India (from pharmaceutical companies) as a driver for ABR in the community. Abroad, this is a very common point for why AMR is such an issue in India. Please acknowledge in discussion.

Thank you, we have done so.

Discussion

Second paragraph - Are there any external factors that could impact ASP implementation? For example, is there state-wide or federal support for ASP implementation?

The state in which our institution is in is actually the only state in India out of the 29 which has a state policy on antibiotic stewardship. There have been national meetings regarding this issue as it has been recognized as a problem but no federal legislation has yet appeared to bolster awareness or support stewardship activities. It may be left up to the individual states. We felt this background information did not warrant inclusion since the vast majority of the country does not have concrete state/federal support for ASP, but given your comments below, we have added some sentences at the end of the discussion section explaining this.

Page 12 – paragraph on EMRs. “Adoption of an EMR can improve ASP by providing micro results, radiology studies, and clinical data.” Please give a few examples (e.g. ...) of microbiology results and clinical data that the EMR can provide. Microbiology results and clinical data can be provided without an EMR – what benefit does an EMR provide? What is the relevance of radiology study results to AS?

We have re-tooled this paragraph and this sentence has been changed to more accurately reflect how EMR is used for AS activities.

Page 12 – paragraph on EMRs – “These factors allow ASPs the opportunity to further curtail AB use; our data here support these findings.” What factors? You don't provide data on reductions in AB use following the hospital's adoption of an EMR, so how exactly do your data support these findings?

Good point, and our colleagues at the institution feel the program is still too much in its early days to release any data externally (although the individual clinics' data have shown a downward trend in AB use, which has encouraged the ASP their efforts are not in vain) so we have removed this sentence.

Page 12 – “Our study identified high and indiscriminate community-based antibiotic use as a barrier to practicing AS at our study site.” Please clarify in a few words/one sentence exactly how this was a barrier.

We have added a sentence as directed.

Page 12-13: “ASP in health care settings can be complemented by AS in the community....” If you found poor AS in the community was a major barrier to ASP implementation in the hospital, I would

mention whether there are current initiatives in Kerala (or India) to address this issue. Is there substantial federal interest/financial support?

Added details to end of the discussion section to address this.

Page 13- limitations paragraph. In terms of resources (staff, funding, equipment, quality of facilities...), how does your hospital compare to other hospitals in India? About average, or with exceptionally more resources than average? It will be important for readers to roughly gauge the potential to transfer your findings to low-resource hospitals.

Our hospital is a not-for profit hospital and is a faith based university teaching hospital. Our hospital, too has limited resources, but we have passionate people. The big difference is of Hospital Information System. The HIS / EPR is a home grown system which has been built with complete participation by IT and clinical team, in order to keep the cost low. Owing to limited resources, we use interns of Clinical Pharmacists. We added more details about the hospital's limited resources to give a more complete picture and allow readers to more ably compare their own situations to the one we describe.

Reviewer: 2

Reviewer Name: Elizabeth Ashley

Institution and Country: Myanmar Oxford Clinical Research Unit.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This qualitative study describes what appears to be an outstanding example of good practice in antibiotic stewardship in a large private hospital (which also provides free care to large numbers of patients) in Kerala, India. This is both a strength, in that it shows what can be achieved, and also a weakness, in terms of limiting its generalisability to other low or lower middle income country settings in particular.

The model described is somewhat similar to that adopted in high income settings with multidisciplinary team working (microbiology/pharmacy/clinicians).

Major comments:

1. Description of ASP: A more detailed description of the hospital and the human and other resources needed to deliver the AS programme would be very useful to enable readers to gauge feasibility of implementation in their own institution e.g.

a. What specialties are represented in the hospital

We've added details

b. Are there other consultant microbiologists and/or trainees in the hospital in addition to the one involved in ASP activities. Or if the microbiologist is single-handed how many scientists or technicians are employed to support the 24h laboratory service

There are 5 faculty members in the Dept of Microbiology. There are 6 trainees in the department. One faculty is engaged in Antibiotic Stewardship (full time) and Head of Microbiology is involved part time. One faculty is involved full time as Infection Prevention officer. There are 12 technicians and 8 MSc lab techs students along with the mentioned faculty members.

c. How many practitioners are involved in stewardship activities/ on the committee in total?

There are 2 internists, 1 Microbiologists and 2 Critical care physicians involved in ASP.

There are 8 clinicians (physicians and surgeons) along with microbiologists, clinical pharmacists, infection control nurses and administrator who are part of ASP Committee. We added this information already based on one of your earlier comments. Thank you.

d. How did physicians get recruited to take part, what level of seniority are they, is it a fixed-term commitment or permanent?

All physicians who are part of the ASP Team are passionate individuals with relevant experience. 2 internists are mid-level faculty (10 years of internal medicine experience), 2 critical care faculty are mid-level faculty (with 10-12 years of experience), clinical pharmacist are junior level (2 years of experience) and an administrator (with 15 years of experience).

Right now it is a fixed term commitment (2 years) and on a renewable basis. We've added relevant details to our paper.

e. Are any staff dedicated to antibiotic stewardship full-time or is this done in addition to other activities?

3 clinical pharmacists are dedicated to ASP along with 1 infection control nurse. Internists, Critical care Physicians, microbiologists and administrators are on part time basis (with defined daily schedule by hours). We've added this in so our institutions may compare their staffing abilities to our institution.

f. Are the number of ASP consults/discussions and outcomes , e.g. whether advice is followed documented?

Each case is reviewed and if appropriate prescriptions practiced, the team / individual is congratulated. If there is an inappropriate prescription practice noticed, the recommendations are discussed with the prescribing physician and a document of recommendations are attached in the medical record. The Clinical Pharmacist also reviews the compliance of the recommendations to understand the adherence to ASP team's recommendations. We've added these details to our paper.

g. What are the regular point-of-care stewardship activities in addition to identifying opportunities to intervene from the EPR e.g. ICU ward rounds C.difficile ward rounds

Each day, Clinical Pharmacist runs a report from Hospital Information System, which contains MRD (Medical Record Department) No of patients who have received reserved antibiotics (17 in no), they can also retrieve report of patients on Ventilator >48hrs and follow up the patients at each critical care locations. All Microbiology lab reports are available in Laboratory Information System (LIS), hence all positive isolates are retrieved real time and information conveyed to the treating physicians real time.

h. Is a 24h consult service provided with out of hours antibiotic advice?

Lab is working 24 X 7. Samples are accepted and tests are run. Consults service for ID is also available 24X 7 telephonically. Bed side referral and consults are not available beyond office hours. We mention the lab is a 24 hour lab, so hopefully this comes across.

i. How often are antibiotic prescriptions reviewed in the different areas of the hospital e.g. daily? weekly? This seems a very onerous undertaking- can the authors explain more how patients are targeted and the average no. of interventions per week. When was the electronic patient record introduced- was stewardship done before this?

Antibiotic prescriptions are reviewed each day. Out of 30+ prescriptions, interventions will be planned for 5-6 each day, wherein recommendations are written and follow ups are done on compliance. EPR was introduced in 2005, but stewardship was initiated in 2015. We have added these numbers to the paper so that others may see the amount of work the AS committee tackles each day.

2. Objectives of this research are missing from the main body of the manuscript

Added. Thank you.

3. Risk of bias: the methods state that “interested participants” were identified. Is it fair to say that the participants were more invested in the success of the programme than other potential participants. How many were ASP team members? Any reason why surgeons were not invited?

This is true, but it is a bias which occurs in most research. We did not want to force anyone to sit down for an interview with us. Some interviewees were ASP team members, and some were not. They were promised anonymity however, and it seemed many spoke freely about issues or problems they saw in their work. Surgeons were also invited, we categorized them as physicians instead of a separate category.

4. Evidence of impact. The authors admit they rely on self-reporting of AMS practices. Can any assessment be made about the impact of the AMS activities on controlling or preventing AMR in the hospital e.g. comparison of AMR rates to similar institutions?

This assessment can be made, but right now we have not analyzed the data. We hope to do so in the next year or two once we have been running the program for a few years. Comparison with other institutions will be challenging, since all similar institutions may not be adhering to the rigors of ASP.

5. Have the authors any reflections on how or if this model could be modified for more resource-constrained settings in India?

We mention some checklists formulated for all resource levels and would encourage any health care facility to make modifications to make their efforts the most sustainable for their situation. Our colleagues in India believe this same model can be replicated in low resource settings in India. Since trained ID physicians are not available, microbiologist or experienced internists can lead the program. Owing to accreditation, administration's responsibility and participation is improving. There are few universities who offer 6 years of Pharm D courses, they need to be explored and employed. Only big difference is presence of EPR in our institution. Manual retrieval of information will also help in designing good ASP.

6. Implications of findings- “Launching and sustaining a new program will be more feasible if hospital leadership is supportive and the stewardship team meets daily to discuss cases.” While daily stewardship rounds covering the whole hospital are a great idea in principle this is very demanding on stewardship teams and difficult to implement in settings of any income level. I don't see the evidence to support this statement from the results.

We have added more information on the impact the CMO has made on the ASP here and hope this helps strengthen our point here.

7. Access to pharmacists- it sounds as if this is valued by ASP supporters but it would not solve the problem of pharmacy advice being disregarded by other members of the hospital Consultant body which came out in the results- any suggestions as to how to overcome this?

8. Are results of stewardship activities reported back to clinician teams?

Stewardship activity is reported back to the clinicians. Line list of all Healthcare Associated Infections are sent to clinicians along with ASP dashboard and compliance. We've added more detail about this to our description of the ASP.

9. The Electronic Patient Record is flagged as a key to success of the programme. Please can the authors put this into context to enable generalizability to be assessed- is EPR going to be rolled out across India or is this a hospital-led initiative?

This is a hospital led initiative. Most tertiary care hospitals in India would be using an EPR, but this is handful of institutions (200+ out of 70,000). The data retrieved from EPR is patient information (clinical and demographics), prescription database, data on high end antibiotics being prescribed by UHID and no of days of use, Length of stay and cost of care.

We'd added some of the above as details to our description.

Minor

1. Abstract objectives:” To conduct interviews with healthcare professionals to determine what barriers and facilitators to antibiotic stewardship existed within their facility. Isn't the objective to determine barriers and facilitators to implementation of ASP rather than to conduct the interviews (=method)?

Good point, we've changed this.

2. “Our study is the first of its kind to systematically examine the key barriers and facilitators of implementing an ASP in a LMIC.” Suggest dropping or rewording this statement on the grounds that the authors are presumably only referring to published literature in the English language

Reworded to include English language suggestion

3. Description of barriers to ASP implementation- isn't non-compliance with the ASP the barrier causing failure to de-escalate antimicrobials rather than the failure to de-escalate itself ?

We're not entirely sure what this suggestion means, but we've changed the barriers description in this new version of the paper, so hopefully our new version is more lucid!

4. Clarification point- can the authors explain when the antibiogram would be used by clinicians if the antibiotic guidelines have been written to take the antibiogram findings into account. Is it consulted preferentially to using the guidelines?

Antibiograms (Tissue based and department based) are prepared by the ID department at the start of the year. Antibiotic Policy is being reviewed by each department, based on the antibiogram. Antibiograms may not be referred each time a prescription is made, though Antibiograms are made available on Intranet as a ready reckoner.

5. “The careful design of ASP with consideration to overcoming barriers and strengthening facilitators will improve antibiotic use and curb the spread of resistant organisms.” Typo- curb

Yes—thanks.

Reviewer: 3

Reviewer Name: Matthew Simon

Institution and Country: Weill Cornell Medicine, New York, NY USA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Baubie and colleagues conducted a qualitative study of facilitators and barriers to antimicrobial stewardship in a tertiary hospital in India. The authors employed sound qualitative methods, the manuscript is well-written and the findings are novel. I think the work will be instructive to other hospitals in low-middle income countries who are attempting to implement similar programs and commend the authors for conducting this work. My main comments relate to a more thorough description of the hospital personnel, staffing, training backgrounds, leadership structure and EMR. I think the reporting of results would be improved by more clearly delineating responses/perspective from ASP team members and non-ASP team members. I have the following specific comments/questions:

Summary Box:

1) What is already known? Bullet 2 seems too generic. Suggest focus what is already known or recommended for ASPs in LMIC.

Another reviewer said we did not need this summary box, so it has been deleted.

2) What do the new findings imply? Bullet 1 seems bland. Based on the study findings, what are specific strategies ASPs in LMIC should implement to overcome barriers?

See above.

Background:

1) Paragraph 2—Sentence 1. Does the cited review by Davey et al, stratify ASP effectiveness by LMIC or high income countries? Is there any data for effectiveness in resource limited settings? If so, would reference here.

Davey et al. do not stratify, unfortunately. However, other studies who are specifically in India do find ASP efforts effective, which has been drawn out better in this new version.

2) Paragraph 2-Sentence 3: What are the core elements for ASPs recommended by the international panel (REF18)? I think a brief description of these recommendations will be helpful for the reader who does not have background in ASP and will provide some framework for understanding the strengths/limitations of the ASP described in this study.,

We have added some of these checklist recommendations to the second paragraph of the Background section as suggested.

Methods:

1) Location: The description of the hospital and ASP personnel is lacking. How many people comprise the ASP at the hospital?

There are 2 internists, 1 Microbiologists and 2 Critical care physicians involved in ASP.

There are 8 clinicians (physicians and surgeons) along with microbiologists, clinical pharmacists, infection control nurses and administrator who are part of ASP Committee. We've added these details.

a. What is the leadership structure of the hospital? Leadership support is identified as an important facilitator. More details regarding the hospital's leadership structure would be informative to understand what/who is meant by "leadership support".



Chief Medical officer is the head of the institution. All clinical heads report to the Chief Medical officer functionally but administratively, they report to Medical Director too. The Chief Medical officer initiated the Antibiotic stewardship meetings, ID rounds, chart review of patients and he is Chair of ASP. CMO conducts daily review meeting of patients on VAP, verifies and validates the chart and documents and action taken. His major thrust also is on infection prevention practices compliance. We've added the most relevant of these details to the paper.

b. Clinical pharmacists-what is the training of the clinical pharmacists involved in the ASP? Are all clinical pharmacists involved in ASP activities? Do they volunteer? What is structure of the hospital's pharmacy department? Does the ASP have a single pharmacist leader? More detail on the hospital's pharmacy resources and structure would be informative.

Training: 6 years Pharm D course from a recognized University accredited by Government.

Involvement: The interns of PharmD program get undertaken into the AMSP program for a period of 2 months on a rotational basis. During this posting, they undergo a rigorous training and they work along with CP's and doctors.

Volunteer: Mandatory rotational posting of interns

Structure of Pharmacy Department: Pharmacy department has a Principal and faculty accredited by Pharmacy Council of India. During their posting in hospital, they are supervised by Professor and other supportive faculty. Each week's performance is supervised. Clinical Pharmacists are posted in clinical department where they round with clinicians.

ASP has a single pharmacist leader.

Responsibilities: Only the CP's undertaken in the AMSP programme are involved in ASP activities. They are involved in preparing dosing guidelines, therapeutic drug monitoring, monthly audit report and running other quality improvement projects in the Institution

We've added sentences with some of these most relevant details to give readers a better picture of pharmacy.

c. Physicians—Do the ASP physician have specialized infectious diseases training? How are they selected? Is there a single physician leader? Is the ASP part of physicians formal job responsibilities? Is the ASP distinct from the hospital infection control program or part of it?

No, they are internists with special interest in ID. India does not have recognized course in ID by Medical Council of India (though few institutions provide fellowship program).

Selection is on the basis of their interest and passion along with experience.

Yes, there is a single physician leader

No, ASP is not part of physicians' responsibilities. Work is under progress

ASP is a distinct program but very much part of bigger umbrella of Infection Prevention.

d. Infection control nurses—They are not mentioned as part of ASP in methods section but in Results are mentioned as ASP team members who participate in the focus group. Please clarify the relationship to the hospital infection control program to the ASP.

Infection control nurses are part of the ASP team. We have added more detail regarding their role.

Since attrition among nursing staff is very high in India, we have found great difficulty in retaining nursing staff trained in ASP. Though many have been identified but retain them. There are 2 under training with supervision of internists.

2) Interview guide—I would recommend including the interview guide in the manuscript as a Table as it gives the reader more context for what was asked in the interviews.

Thanks.

3) SRQR—please define the abbreviation for readers unfamiliar with qualitative methods.

Done, thanks for the catch!

Results:

1) Reporting of results:

a. The investigators appear to have included both ASP team members and frontline healthcare workers who are not part of the ASP. In framing the results, I think these different perspectives need to be more clearly delineated. Where do the perspectives and attitudes of ASP team members and non-ASP clinicians overlap and where do they diverge?

True, we did include both ASP team members and non-ASP team members, but there weren't radically different in their perspectives while answering our interview questions. This is why we did not delineate the differences.

b. Consider including some representative quotes in the manuscript text. I think it will enrich the results so readers do not have to continuously flip back to Table 1.

Great suggestion—we have peppered the text with quotes where appropriate.

2) Infection control nurses—please clarify if they are part of the ASP and what is their role?

Infection control nurses are part of the ASP team. We have added more detail regarding their role.

3) Organization—

a. How many people comprise the ASP in each discipline?

There are 2 internists, 1 Microbiologists and 2 Critical care physicians involved in ASP.

There are 8 clinicians (physicians and surgeons) along with microbiologists, clinical pharmacists, infection control nurses and administrator who are part of ASP Committee. We've added these details.

b. How are patients receiving antibiotics selected for evaluation? Are all patients in the hospital reviewed? Are select patients reviewed based on microbiology results? Are patients on select broad-spectrum antibiotics?

No, only those who are receiving higher antibiotics are reviewed by the ASP. This important detail was added in!

c. Email communication. This is quite interesting. What is communicated over email? Treatment recommendations or other feedback? Are other communication modalities used (e.g. in-person, text message/page, telephone, beeper)?

Both treatment recommendations, as well as feedback, are communicated over email.

Yes, other communication modalities are also used. In person during rounds, telephone calls when the clinical team is not immediately available, text message with microbiologists. We've added this information to our paper.

d. AS symposium—please describe further. What does this entail if others would like to emulate?

In reworking this section, we actually took out this sentence in order to cut down paper length.

e. What specifically does hospital administrative leadership do to champion the ASP? Does someone in hospital leadership formally oversee the ASP and if so what is their title/role within the organization? What enabled buy-in from hospital leadership ?

Hospital leadership is part of ASP team which meets on daily basis to discuss the antibiotic prescription practices. All difficult communications are done by the leadership. All defaulters are dealt by the administrative leadership. The ASP Committee is chaired by an administrator.

Oversee: Daily basis

Buy in of Hospital Leadership: Passion, Patient Safety and improving ethical and appropriate clinical care for all patients.

We've added these details to our description of the chief medical officer (CMO) and their aims.

f. Paragraph 2 “ Highly capable” ASP. Is this a finding/result of the study or the authors interpretation/assumption? What is the basis for describing the ASP as “highly capable.” The authors have not really presented any data yet to suggest it is effective. If it is a finding, this deserves more support/discussion.

We agreed this was our interpretation after hearing the praises of the staff but as we don't have numerical data to back up effectiveness claims, we took out this phrase from our paper.

g. Paragraph 2- “17 interviews (48.6%) regarded the microbiology labs as a key facilitator”. What is the denominator for the 48.6%? 45 people were interviewed in the study. Excluding the focus group and the 1 microbiologist 30 were interviewed. Neither percentage (17/45 or 17/30) equals 48.6%. Please clarify. Also, is the numerator 17 interviews or interviewees? Please clarify percentages throughout the results.

Thank you for this catch—we have clarified.

h. Paragraph 3—access to pharmacists. If the study participants were limited to ID and critical care teams, Was access to pharmacists a problem for only these departments or others departments/hospital wards? Which departments lacked pharmacists and which had adequate pharmacist support? Please clarify the hospital's pharmacy resources for ASP and non-ASP activities.

PharmD students are placed on a rotational basis of 2 months in each major department. But Clinical Pharmacist was present only in few departments – Gastrointestinal surgery, Medical ICU and stewardship programme. There was no problem with access to pharmacist but they are limited in number (employed v/s students/interns). There are only 2 dedicated Clinical Pharmacist for 1200 bed university teaching hospital, though we get support from interns posted in clinical departments.

Clinical Pharmacist are involved in Non ASP activities like Medication errors, Adverse Drug Reactions, Pharmaco-vigilance, Medication Reconciliation, Formulary preparation etc.

The leadership needs to empower Clinical pharmacists, since their exclusive training is of high value and a great contribution towards ASP. Daily rounds with clinical team will help in building the trust and recognition of value addition as a team member. Daily feedback on appropriate prescription practices

will be very beneficial, since face to face and real time correction will be essential. Clinical Pharmacist also needs to showcase the improvement which was brought in because of their recommendations which includes avoiding harm. We mentioned some of this in other parts of the piece but have added more.

i. Person—pagraph1—Does the 57.1% include AS team members? This % should probably be limited to non-ASP team members. Were the remainder of participants (42.9%) unaware of AS concepts, policies and practices? This would seem to be a high percentage of participants who are unaware of the ASP.

This was trying to show those who explicitly mentioned AS policies, but you are right in that it made it seem like many were wholly unaware of the ASP, so we have completely changed!

j. Immunity to change—were any specific services or departments more immune to change? Any other physician characteristics (older vs. younger)?

We have identified certain departments to be outliers to our recommendations. Constant interaction with the consultants of those departments and presenting the proof (hardcopy of a guideline) during those interaction have brought slight changes in the long run.

Recently, the AMSP team have revised the dosing guideline for Colistin and Polymyxin. Initially, certain departments didn't comply with it but later on with constant approaching from the AMSP team have reversed the situation. The inappropriateness in dosing is still present but was brought down to a larger extent.

k. Tasks—Are the guidelines institutional or national guidelines? If institutional, are they based on the local antibiogram? Please clarify how a lack of knowledge of pre-admission meds lead to “antibiotic overprescription”?

Institutional based on the local antibiogram. We have added details on this throughout where appropriate. As for the lack of pre-admission meds, we have clarified why this is a problem at the end of the “Tasks” section.

l. Tools/Technology—the description of EMR is quite different than what many readers may be used to. What is included in the EMR (i.e physician notes, order entry? Laboratory results?) Did the EMR facilitate AS in any way? This is touched on in the discussion (pg 12 line 34-39) but not discussed in any meaningful way in the results.

Added more detail about the EMR in the Tools section. EMR serves more as a record keeping mechanism than as an immediate AS facilitator, but will be useful should that patient have a long stay in the hospital or ever return. We hope the additional detail shows more fully the state at which this institution's EMR finds itself in.

Discussion:

Can the authors put the results in context with prior literature on AS in LMIC, particularly in India (i.e. references 19-22)? How does this study build on the prior work on AS in LMIC and in India?

Can the authors summarize the perspectives where ASP team members and front-line clinicians are aligned and where they are divergent?

Good point, we have added to the discussion section to address these points.

Again, the views weren't really so dramatically divergent.

Table 1: Please delineate which quotes are from AS team members and which are from non-team members.

As we promised interviewees anonymity, we are unfortunately unable to do this.

Appendix A:

Was employee turnover a significant barrier to AS?

Since attrition among nursing staff is very high in India, we have found great difficulty in retaining nursing staff trained in ASP. Though many have been identified but retain them. There are 2 under training with supervision of internists. Interestingly, physician turnover is not as big of a problem. Many go to the US or the UK for training or work there for a while but choose to return to Kerala and have long careers here.

As nurse turnover is a common problem, we have added this to our paper.

How are nurses involved in AS? I think this would be of interest to both LMIC and high-income countries such as the US.

Two, under supervision of internists. This has come up a few times so we've added this in.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Elizabeth Ashley Myanmar Oxford Clinical Research Unit, Yangon, Myanmar
<b>REVIEW RETURNED</b>	06-Jan-2019

<b>GENERAL COMMENTS</b>	Comments have been addressed. I would recommend acceptance.
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<b>REVIEWER</b>	Matthew Simon Weill Cornell Medicine. USA
<b>REVIEW RETURNED</b>	09-Jan-2019

<b>GENERAL COMMENTS</b>	<p>I think the authors have done an excellent job addressing the comments and incorporating the suggestions into the manuscript. I have the following minor comments:</p> <p>1) I think it is interesting and somewhat surprising the general views of ASP team members and non-team members were so similar. Was this expected or unexpected? In my opinion, the fact that there was so much overlap is a worthwhile finding in and of itself and worthwhile discussing briefly in the manuscript.</p> <p>2) immunity to change--this is a universal struggle for ASPs. I think it would be helpful to include the specific strategies this ASP used to help with behavior change. Persistent interaction and presenting physical "proof" (e.g hard-copy of guidelines) were identified as important strategies in the response. I would recommend including this in the results so that leaders of other LMIC ASPs have some concrete examples.</p>
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## **VERSION 2 – AUTHOR RESPONSE**

To our reviewers,

Thank you for your time and effort in reviewing our work. We have addressed these latest comments in our new version uploaded here.

Please see page 8 of our main document for our additions in response to Reviewer 3's second comment. Please see page 12 for our edits in regards to Reviewer 3's first comment.

Feel free to let us know if there is more information you require.

Kind Regards!