Author's response to reviews

Title: An outpatient antibiotic stewardship intervention during the journey to JCI accreditation

Authors:

- Ping Song (spfcckc@126.com)
- Wei Li (liwei660501@yahoo.com)
- Quan Zhou (zhouquan142602@zju.edu.cn)

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Author's response to reviews: see over
Dear Dr Catherine MT Sherwin

Associate Editor

BMC Pharmacology and Toxicology

Thank you very much for giving us an opportunity of manuscript revision. The comments from reviewers are very pertinent. We thank them for their professional work. Response to the comments and revised points are as follows.

Our response to Referee 2

(http://www.biomedcentral.com/imedia/6537305651124223_comment.pdf)

Referee 2 EVALUATION ----Major Compulsory Revisions

Background
- There is a discrepancy between the objective of the paper “summarizing the relevant experiences in intervention programs” and the writing structure of the paper that is more like a research article (methods, results & discussion). If it is not a research article, the paper structure should be reorganized.
- Or, if this is a research article, the paper should clearly define the objective.
- There is insufficient information to demonstrate or convince the audience about the importance or rationale of this study. This background section is overcrowded with ideas but did not clearly frame the study’s question. The problem statement is also unclear. Need literature review to support arguments as well.

Author response:

Dr. Nithima Sumpradit gave us very good suggestions toward the background section. This is a research article, so we have revised according to these suggestions. We have clearly defined the objective “The aim of this article was to investigate the effectiveness of such stewardship intervention in the outpatient setting and provide some reference for international counterparts”. Also, we have added more literature, demonstrated the importance and rationale of this study and clearly made the problem statement. Especially we found Dr. Sumpradit’s findings (Bull World Health Organ 2012;90:905-913) were very helpful for us, so we cited it.

----“Sumpradit et al reported that prescription behavior could be influenced by knowledge, attitudes, subjective norms, peer pressure, patient expectations, drug promotion, physician’s diagnostic skill and exposure to hospital formularies and standard therapeutic guidelines [2]. Inappropriate prescribing of antibacterials may lead to considerable expense to health care system. The benefits of antimicrobial stewardship have been well described and implemented in the inpatient setting [3-5]. Although studies of antimicrobial consumption in outpatient services have been conducted in countries like France, Jordan and the United States [6-8], there are very few intervention programs specially targeting the outpatient antibacterial use. Gerber et al evaluated the effect of an antimicrobial stewardship intervention on broad-spectrum antibacterial prescribing for pediatric outpatients [9]. To our knowledge, there is currently no PubMed-based literature on evaluating the effects of quality improvement strategies on reducing inappropriate prescribing of all antibacterial classes (not specific to a certain category) in outpatient setting”.
Referee 2 EVALUATION ----Major Compulsory Revisions

Methods
• Details in the method session are insufficient to repeat the results. For example, in the result session (Paragraph 1, line 11-12) mentioned about “...moxifloxacin, levofloxacin, ... and clarithromycin” – this is the first time the reader learn about the list of observed antibiotics and may have questions about what kinds of antibiotics are observed in this study, what kinds of antibiotics are classified as “first line” “second line” and “third line.” There are others (e.g., types of departments included in this study – internal medicine, surgical and what else) to be identified and revised.

Author response:
Dr. Nithima Sumpradit’s comments are very reasonable. We have added Table 1 (Formulary adjustment & classification management), table 2 (Approach of i.v. to oral antibacterial switch therapy) and table 4 (Comparison in relative percentage of DDDs of oral antibacterials before and after intervention). We hope that the relevant revision meets the requirements. Also, types of departments have added in this study.

Referee 2 EVALUATION ----Major Compulsory Revisions

Methods
• Are there any inclusion and exclusion criteria for this study? How many prescriptions are included? How were the rates of DRPs identified? Information about methodological justification should be described.

Author response:
Dr. Nithima Sumpradit’s comments are very valuable. We have added some contents related to inclusion and exclusion criteria. Also, table 3 and table 5 will present relevant information. The calculation method for occurrence rate of DRPs, as well as other indicators were clearly presented in the revised manuscript.

Referee 2 EVALUATION ----Major Compulsory Revisions

Methods
• In the ‘process of intervention’ session, it lacks of focus as the interventions were presented as a checklist. What are the key interventions in this study? The interventions should be grouped by their functions (e.g., educational, motivational etc) or else defined by researchers.

Author response:
Dr. Nithima Sumpradit’s comments are very important. The interventions have been grouped by their functions, e.g., formulary adjustment & classification management, motivational measures, information technological measures, educational measures and organizational measures. We hope such revision will meet the kind requirements.

Referee 2 EVALUATION ----Major Compulsory Revisions

Methods
• Among all interventions, perhaps the most interesting intervention is “(7) Retrospective appropriateness evaluation of antibacterial-containing prescriptions were performed monthly by clinical pharmacists and the results were discussed in the meeting of Drug & Therapy Committee (DTC) and published on the hospital local area network. “Dear doctor” letters were sent from DTC to physicians. Fines would be imposed on physicians who wrote seriously inappropriate prescriptions. If there is an error for the second time for the same physician, the prescribing privilege will be deprived.” It is the audit-feedback measure and with a
penalty for doctors. Please explain more on how this works, how much for the fines, how doctors respond to this measure and how many doctors are subjected to this penalty?

Author response:
We sincerely thank Dr. Nithima Sumpradit’s encouragement and very professional suggestions. We have explain more on this respect.

-----page 6-7: " Retrospective appropriateness evaluation of antibacterial-containing prescriptions was performed monthly by clinical pharmacists and the results were discussed in the meeting of DTC and published on the hospital local area network. “Dear doctor” letters were sent from DTC to physicians. DTC allowed physicians to present evidence and argument to the results of audit-feedback during a seven-day public notice period. Fines would be imposed on physicians who wrote inappropriate prescriptions. Generally, the physician who wrote an inappropriate prescription sheet would face a fine according to the severity of DRPs. Fine punishment strength was divided into three grades [low-grade: 100 Chinese Yuan Renminbi (CNY); medium-grade: 200 CNY; high-grade: 300 CNY]. Prescribing privilege of the physician would be deprived if there was a high-grade error made by him for the second time.”

-----page 9: “During this study period, sixty-one physicians were fined due to inappropriate prescribing. A surgeon received a fine of 13000 CNY at a monthly DTC meeting for audit-feedback.”

-----page 12-13: “Suboptimal prescribing habit of antibiotics in China is partly associated with economic incentives-driven nonstandardized drug-promotion procedure by pharmaceutical companies. However, many medical disputes between patients and hospital are associated with irrational drug use. Therefore, education is an essential element of intervention program designed to influence prescribing behavior and can provide a basis of knowledge that will enhance the acceptance of stewardship strategies. Communication is also important among physicians, pharmacist and administrators before initiating the intervention program. Respects should be fully considered towards role of each staff (i.e., values, personality, perceptions, emotions and ability). The working mode of DTC on outpatient antibacterial stewardship intervention, especially allowing physicians to present evidence and argument to the results of audit-feedback during a seven-day public notice period, was pivotal to the willing acceptance of punishment by physicians who made severe DRPs. Rational antibiotic use, to a certain extent, is a health administration issue more than a professional issue.”

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Methods
•Please clearly state a list of outcome measures for this study. Outcome measures stated in the method session should be corresponding to the result session.

Author response:
We sincerely thank Dr. Nithima Sumpradit’s very careful suggestions. We have explain more on this respect.

-----“Outcome measures
The outcome measures included proportion of prescriptions containing antibacterials, proportion of prescriptions containing non-restricted antibacterials, proportion of prescriptions containing restricted antibacterials, proportion of prescriptions containing special-grade antibacterials, total expenditure on antibacterials for outpatients, proportion of expenditure on antibacterials relative to all medications, proportion of expenditure on i.v. antibacterials relative to all antibacterials, sum of DDDs of antibacterials, proportion of DDDs of all oral antibacterials relative to all antibacterials, relative percentage of DDDs of each oral antibacterial, number of DRPs, occurrence rate of DRPs, occurrence rate of DRPs made by surgeons,
occurrence rate of DRPs made by internal medicine physicians, occurrence rate of each DRP subtype and number of physicians who received fines during the study period."

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**Results**

- Details about the results are not sufficient. Tables or Graphs should be used as appropriate.

Author response:

We sincerely thank Dr. Nithima Sumpradit’s very important suggestions. We have added more details about the results. Especially, three tables refer to the section of results. We hope such revision will meet the reviewer’s kind requirements.

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**Discussion**

- Study results should not be presented for their first time in this discussion session. For example, Paragraph 3 – “Our study presented 0.4% of antibiotic prescriptions were off-label.” The discussion session should refer to information in result session.
- Should include the limitations of this study

Author response:

We sincerely thank Dr. Nithima Sumpradit’s very professional suggestions. We have paid more attention to that the discussion session should refer to information in result session. Also, the limitations of the study were further added. -----“Although the study in SAHZU showed some positive outcomes, it had some limitations which were shown as follows: (1) Follow-up of outpatients’ therapeutic outcome was not conducted; (2) Patient adherence to treatment regimens were not monitored so that prescribing data may not accurately represent actual antibacterial consumption); (3) Multiple comparisons for the same dataset might increase type I error in showing the impact of interventions and for these kind of studies interrupted time-serial analysis would be more reliable method [25].”

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**Conclusion**

- Inconsistency between the conclusion (i.e., we examined the impact of intervention program •••) and the objective of the study. Additionally, a term ‘impact’ is not an appropriate term for this study. • The conclusion is not complete. The session should include important findings.

**Abstract**

- Need to revise to match with the paper contents.

Author response:

We sincerely thank Dr. Nithima Sumpradit’s kind suggestions. The conclusion and the objective of the study have been re-conciliated. In Abstract, more information was added so as to better express our findings. The conclusion has been revised and included more information. -----“The effects of an outpatient antibacterial stewardship intervention were examined in an academic medical center hospital during the journey to JCI accreditation. The intervention program reduced the expenditure on antibacterials, improved the appropriateness of antibacterial prescriptions. Quality improvements need continuous efforts, integrated multifaceted intervention measures and long-term adherence to the antibiotic stewardship. Approach of i.v. to oral antibacterial switch therapy, classification management, and motivational measures may play the most direct and efficient role in changing antibacterial prescription practices”.

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Referee 2 EVALUATION ----Major Compulsory Revisions
Quality of written English: Not suitable for publication unless extensively edited
Author response:
We sincerely thank Dr. Nithima Sumpradit’s kind suggestions. We have tried our best to polish the English writing.

Our response to Referee 1
(http://www.biomedcentral.com/imedia/1576674903112378_comment.pdf)

Referee 1 EVALUATION
The information within the manuscript is important to the antimicrobial stewardship community. However, the amount of editing needed is beyond what can be provided by a reviewer at this time. I would recommend the authors seek editorial assistance and re-submit. Some corrections are found below:

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore) Overall, recommend removing first-person writing style (i.e. we, our)

Author response: Thanks very much for Joshua Courter’s positive suggestions and encouragements. We have polished the full text completely according to the referee’ comments. First-person writing style was removed.

Referee 1 EVALUATION
• Page 2; Abstract; Results; Sentence 1: Would change to - “The variety of antibiotics available ...”
• Page 3; Paragraph 1; Sentence 2: Would change to - “The benefits of antimicrobial stewardship have been well described and implemented in the inpatient setting, but there are few programs targeting the outpatient population”. Cite JCI Accreditation Standards for Hospitals, 4th edition.
• Page 3; Paragraph 2; Sentences 4-5: Recommend combining sentences.

Author response: Thanks very much for Joshua Courter’s professional polishment. We have revised the relevant content completely according to the referee’s suggestions.

Referee 1 EVALUATION
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
• Page 2; Abstract; Background; Sentence 2: Would change to - “The Joint Commission International (JCI) accreditation standards include quality improvement and patient safety, which is exemplified by antimicrobial stewardship”. Cite JCI Accreditation Standards for Hospitals, 4th edition.

Author response: Thanks very much for Joshua Courter’s professional suggestions. We have revised the relevant content completely according to the referee’s suggestions.

Referee 1 EVALUATION
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
• Page 2; Abstract; Results; Sentence 2: Would change to - “There are currently few reports on interventions to improve the quality of outpatient antibiotic prescribing.”
antibiotics significantly decreased following the intervention (12.7% versus 9.9%, p<0.01) ”.
- Page 2; Abstract; Results; Sentence 3: Would change to - “The overall proportion of oral versus all antibiotic prescriptions also increased (94.0% to 100% p<0.01) when measured as defined daily doses ”.
- Page 2; Abstract; Results; Sentence 4: Would change to - “Occurrence of DRPs decreased from 13.6% to 4.0% (P< 0.01), with a larger decrease seen in surgical consulting rooms (surgical: 19.5% versus 5.6%; internal medicine: 8.4% versus 2.8%, P< 0.01).

Author response: Thanks very much for Joshua Courter’s professional suggestions. We have revised the relevant content completely according to the referee’s suggestions.

Referee 1 EVALUATION
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- Page 2; Keywords: Recommend adding “stewardship “
- Page 6; Paragraph 3; Sentence 1: the abbreviation, “p.o.” has not been previously defined.

Author response: Thanks very much for Joshua Courter’s professional suggestions. We have revised the relevant content completely according to the referee’s suggestions.

Other revision
1. Spelling check has been used. English polishing has been conducted.
2. “Antibiotic” has been replaced by “Antibacterial”.
3. “Comprehensive intervention measures included formulary adjustment, classification management, motivational, information technological, educational and organizational measures. A defined daily dose (DDD) methodology was applied.” was added in the method section of “Abstract”.
4. The order of references was readjusted.
5. “The authors thank Professor Xuan-Ding Wang and Dr. Hai-bin Dai for their excellent work.” was added in the section of “Acknowledgment”.

Dear Dr Catherine MT Sherwin, thank you very much for your professional arrangement of the two reviewers. These two reviewers are very professional, highly industrious, extremely responsible. The reviewing work consumed them a lot of time and energy. Please remember me to Dr. Nithima Sumpradit and Dr.Joshua Courter.

Also, we thank Ms Ma. Celine Zapanta for her kind E-mail notice.

We tried our best to revise the manuscript. We hope that our resubmitted paper has a significant improvement in quality after careful revision based on valuable suggestions from reviewers and editors. We would appreciate very much if our paper will be finally accepted.

If further revision is needed or you have any questions, please do not hesitate to contact me.

Thank you very much!

Sincerely yours
Quan Zhou, PhD, MHA, Professor, Clinical pharmacy specialist
Department of Pharmacy, the 2nd Affiliated Hospital, School of Medicine, Zhejiang University
Zhejiang 310009, China.
E-mail: zhouquan142602@zju.edu.cn