PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study
AUTHORS	Wang, Huaguang; Wang, Han; Yu, Xiaojia; Zhou, Hong; Li, Boyu; Chen, Gang; Ye, Zhikang; Wang, Ying; Cui, Xiangli; Zheng, Yunying; Zhao, Rui; Yang, Hui; Wang, Zihui; Wang, Peng; Yang, Chunxia; Liu, Lihong

VERSION 1 - REVIEW

REVIEWER	Hao-Yuan Lee 1. Department of Pediatrics, Wei Gong Memorial Hospital, Miaoli, Taiwan 2. Department of Nursing, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan 3. School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei, Taiwan 4. Molecular Infectious Disease Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan
REVIEW RETURNED	07-Sep-2018

GENERAL COMMENTS	In this study, multi-aspect intervention measures were implemented by clinical pharmacists, such as formulating the activity program and performance management, advising on antibacterial prescriptions, and training doctors. Please take some specific examples for these interventions. For example, change antibiotics to first generation for some infections.

REVIEWER	José M. Cisneros University Hospital Virgen del Rocío, Spain
REVIEW RETURNED	15-Sep-2018

GENERAL COMMENTS	Abstract - Change MRSA for methicillin-resistant Staphylococcus aureus Strengths and limitations of this study - This section does not describe any of the limitations of the study, and should do so. Introduction - This statement is not accurate. “To our knowledge, few studies7, 8 have analyzed the correlation between antibiotics usage (defined daily dose, DDD) and multidrug-resistant organisms (bacterial isolation rate), and these studies have mainly focused on critically ill patients, such as those in intensive care units. In this study, we sought to demonstrate the correlation between antibacterial usage and the antimicrobial resistance rate of common nosocomial pathogens, using data from all inpatients in

	our hospital". I recommend to the authors a more detailed review of the bibliography and will find recent studies that demonstrate this relationship and that should cite. Methods - Being a study of interrupted series, you must meet the ORION statement. - Bacterial resistance indicators are not explained, it is necessary to know: o Was it only in clinical samples? o Was only one patient isolated per patient? o In the hospital, surveillance cultures are carried out ?, and in that case the isolations of these crops were included in the evaluation of the resistance? - Why has this figure been chosen?: Intensity of inpatients' antibiotic consumption ≤ 40 DDD/bed days. - The international indicator of antibiotic consumption is Defined daily doses (DDDs) per 1000 occupied bed days (OBDs) The authors use in the paper DDD per 100 bed-days. But it is not the same, and it can be very different depending on the level of occupation of the hospital. And it prevents comparison with other studies, so authors should change this indicator. - The program is not really an ASM, because is based on the management, punishing or rewarding economically the prescribers according to whether or not they achieve the objectives. And it does not describe how the training is carried out, neither what is the method nor the periodicity. This point should be highlighted in the discussion. Conclusion This conclusion, "This study demonstrated that AMS managed by clinical pharmacists has an important role in reducing and optimizing antibiotic use and controlling antimicrobial resistance" is not correct, because the impact on bacterial resistance is positive and negative at the same time. It should be corrected.

REVIEWER	Ruyu Xia Beijing University of Chinese Medicine, China.
REVIEW RETURNED	01-Dec-2018

GENERAL COMMENTS	The main problem of this manuscript is that there are many factors affecting the use of antibiotics and antimicrobial resistance. It is difficult to confirm the single factor of the decline in antibiotic use and antimicrobial resistance. I don't think the results from a non-controlled retrospective observational study can show it due to clinical pharmacists. The bias can't well controlled. And there was no specific report on the number of pharmacists, doctors and patients involved in the study. The abstract and the text are suggested to rewrite for more precise and cautious conclusions.

REVIEWER	Irene Eriksson Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	02-Dec-2018

GENERAL COMMENTS	This is a well-written paper describing and assessing an antimicrobial stewardship program implemented in a tertiary

	hospital in China. The statistical analysis carried out seems appropriate but given that I am not a statistician but a pharmacist by training, I recommend the paper to be additionally reviewed by a statistician. Please see some minor comments for consideration below: 1. Page 2, Line 29 — please specify the baseline measures too. If only end results are presented it is difficult to appreciate the change in antibiotic use. 2. Page 2, Line 49 to 53 — given the study design, perhaps you could reinforce that what you observed are associations/correlations. 3. Page 3, Line 3 to 35 — I suggest you completely rewrite the 'Strengths and limitations of this study" part. As currently formulated, #2 is neither strength nor limitation, but rather one of your study objectives; #3 and #4 also are rather ambiguous; #5 in my opinion also is neither strength nor limitation. 4. Throughout the entire text — while the manuscript overall is well written and easy to read, some minor language errors are still remaining. Please very carefully proofread the entire text to address those. 5. Page 3, Line 49 — cannot see what this sentence adds given its positioning in your introduction: "Regretfully, not all medical staff knew about the Guidelines or their significance." 6. Page 3, Line 53 — somewhat ambiguous what are the four factors, I count only three: 1) inappropriate use in healthcare; 2) inappropriate use in animals/agriculture; and 3) antimicrobial resistance. Could you please clarify? 7. Page 4, Line 12-14 — "Hospital pharmacists..." this sentence is somewhat out of place in this paragraph. 8. Page 4, Line 16 — I am sure that WHO did work on antimicrobial resistance already prior to the World Health Day in 2011... Next you have a sentence "China acted immediately." Perhaps you could rewrite it saying "In response to XYZ in 2011 the NHFPC in China put forward..." 9. Page 4, Line 45-46 — "After many years of hard work,..." this sentence does not belong in the introduction. 10. Page 4, Line 52-53 — would you consider these references relevant too?: PubMed ID 28941633; 29017750. Perhaps there are more studies, could you please just double check by conducting a systematic search? 11. Page 5, Line 35 — "The patients were not involved or recruited in this study." I cannot agree with this statement. Patients were involved indirectly as you used their medical records in this study. I understand that a requirement for informed consent was waived. In general, there must be governance for accessing patients' medical records: either a broader consent in which patients allow to use their data for research purposes, or anonymization of all data prior to release to researchers, etc... Were records made anonymous prior to use in research? How was this done in your study? 12. Page 5, Line 43-46 — were data on bacterial resistance available for 2010? 13. Page 5, Line 50-54 — is there a number for the approval document? 14. Page 6, Line 18 — '...and so on.' reads a bit imprecise. perhaps revise? Also, next sentence: "As expected,.. ": not all I guess expect what you stated, perhaps revise the language here too? 15. Page 7, Line 53-54 — perhaps "penalized" instead of 'punished'?

	16. Page 7, Line 55-56 — what does RMB stand for? 17. Page 8, Line 13-15 — maybe 'inappropriate" instead of 'irrational' 18. Page 8, Line 45-49 — instead of 'points' you could perhaps just keep RMBs only. makes it easier to follow.

REVIEWER	Peter Herbison University of Otago New Zealand
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	I think the statistics in this article are fine.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Hao-Yuan Lee

Institution and Country: 1. Department of Pediatrics, Wei Gong Memorial Hospital, Miaoli, Taiwan
2. Department of Nursing, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan
3. School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei, Taiwan
4. Molecular Infectious Disease Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

In this study, multi-aspect intervention measures were implemented by clinical pharmacists, such as formulating the activity program and performance management, advising on antibacterial prescriptions, and training doctors. Please take some specific examples for these interventions. For example, change antibiotics to first generation for some infections.

Dear professor Lee:

Thanks for your good advice. Here are the contents I added.

For example, some doctors used moxifloxacin to treat urinary tract infections, which didn’t conform to the recommendation of guideline and medicine specification; the combination of imipenem/cilastatin and metronidazole was unsuitable, the latter was unnecessary. Clinical pharmacists would contact the doctors to modify the prescriptions. (Please see page8)

I hope my revison would meet your requirements. Thank you so much.

Reviewer: 2

Reviewer Name: José M. Cisneros

Institution and Country: University Hospital Virgen del Rocío, Spain

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Dear professor:

Thanks for your good advice. The following is my response to the comment.

Abstract

- Change MRSA for methicillin-resistant Staphylococcus aureus

I have changed “MRSA”for “methicillin-resistant Staphylococcus aureus(MRSA)”.(Please see page2)

Strengths and limitations of this study

- This section does not describe any of the limitations of the study, and should do so.

I have added the limitation in the section of “Strengths and limitations of this study”, as follows:

This was a retrospective observational study without simultaneous control group, the bias couldn’t be well controlled; the evaluation of prophylactic antibiotic use by different clinical pharmacists might have individual differences. (Please see page3)

Introduction

- This statement is not accurate. “To our knowledge, few studies7, 8 have analyzed the correlation between antibiotics usage (defined daily dose, DDD) and multidrug-resistant organisms (bacterial isolation rate), and these studies have mainly focused on critically ill patients, such as those in intensive care units. In this study, we sought to demonstrate the correlation between antibacterial usage and the antimicrobial resistance rate of common nosocomial pathogens, using data from all inpatients in our hospital”. I recommend to the authors a more detailed review of the bibliography and will find recent studies that demonstrate this relationship and that should cite.

Thanks for your good suggestion again. I have done a literature review carefully and found that there were some articles that demonstrated the correlation between antibacterial usage and the antimicrobial resistance rate recently. So I have cited some new literatures, as follows:

9.Horikoshi Y, Suwa J, Higuchi H, et al.Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality.Int J Infect Dis 2017;64:69-73.

10. Wushouer H, Zhang ZX, Wang JH,et al.Trends and relationship between antimicrobial resistance and antibiotic use in Xinjiang Uyghur Autonomous Region, China: Based on a 3 year surveillance data, 2014-2016.J Infect Public Health 2018;11(3):339-346.

11.Cusini A, Herren D, Bütikofer L,et al.Intra-hospital differences in antibiotic use correlate with antimicrobial resistance rate in Escherichia coli and Klebsiella pneumoniae: a retrospective observational study.Antimicrob Resist Infect Control 2018;7:89. (Please see page4 and 20)

Methods

- Being a study of interrupted series, you must meet the ORION statement (https://www.equator-network.org/reporting-guidelines/the-orion-statement-guidelines-for-transparent-reporting-of-outbreak-reports-and-intervention-studies-of-nosocomial-infection/).

I have checked the “ORION checklist for authors”(22 items), our study meets its requirements. And when I submitted my manuscript to BMJ open, I also have provided the “STROBE Statement”at the same time.

- Bacterial resistance indicators are not explained, it is necessary to know:

o Was it only in clinical samples?

Yes, bacterial resistance indicators or data were only from clinical samples of the inpatients (e.g., blood, cerebrospinal fluid, pleural effusion, ascites, urine and sputum, etc).

o Was only one patient isolated per patient?

Duplicate isolates, defined as the isolates of the same species that showed the same susceptibility results at the same site for each patient in different days, were excluded, only the first isolated strain was included in the study (excluding isolates of surveillance cultures data). (Please see page5)

o In the hospital, surveillance cultures are carried out ?, and in that case the isolations of these crops were included in the evaluation of the resistance?

The surveillance cultures are carried out in our hospital. The Infection Management Office and the Department of Infectious Diseases and Clinical Microbiology are responsible for it. But in this study, the isolates of surveillance cultures are excluded. (Please see page5)

- Why has this figure been chosen?: Intensity of inpatients’ antibiotic consumption ≤ 40 DDD/bed days.

The indicator of intensity of inpatients’ antibiotic consumption ≤ 40 DDD/100 bed-days were established by the NHFPC(the National Health and Family Planning Commission) in 2011. (Please see page7, the title of Table 1) This was mentioned in the text, too. Please see “According to the requirements of the national antibiotic stewardship program,4 the AMS group established the goals for antibiotic application in the hospital (Table 1)”.(page 7)

- The international indicator of antibiotic consumption is Defined daily doses (DDDs) per 1000 occupied bed days (OBDs) The authors use in the paper DDD per 100 bed-days. But it is not the same, and it can be very different depending on the level of occupation of the hospital. And it prevents comparison with other studies, so authors should change this indicator.

Dear professor:

Please forgive me that I have not changed the indicator of antibiotic consumption from DDD per 100 bed-days to DDDs per 1000 occupied bed days (OBDs). Please see the following reasons:

(1)In China, it was NHFPC(the National Health and Family Planning Commission) that developed the indicator of intensity of inpatients’ antibiotic consumption ≤ 40 DDD/100 bed-days, its unit was represented as “DDD per 100 bed-days”, which showed the Chinese characteristics and was used in all the Chinese hospitals.

(2)I looked up and referred to the E-BOOK named “ANTIMICROBIAL STEWARDSHIP FROM PRINCIPLES TO PRACTICE”, which has been developed by British Society for Antimicrobial Chemotherapy (BSAC) , in collaboration with European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/ European Study Group of Antibiotic Policies (ESGAP). In Chapter 2, page 29-30, below “standardized units of measure are used to compare antibiotic use”, there is a table titled “Common units of measure of antimicrobial consumption” showing that “Hospital measures” is DDD per 100 or 1000 bed days. This means DDD/100 bed-days is also the common unit on measure of antimicrobial consumption in hospital worldwide. And in this E-BOOK, some results of different studies on the antimicrobial consumption were listed with the unit “ DDD/100 bed-days”.

(3)“Guidelines for ATC classification and DDD assignment 2019” is downloaded from the WHO website. In page 36, it mentions “DDD per 100 bed days: The DDDs per 100 bed days may be applied when

drug use by inpatients is considered……This indicator is quite useful for benchmarking in and between hospitals.”

(4)There are some studies that use DDD/100 bed-days to express antimicrobial consumption. Please see examples below:

- Natsch S, Hekster YA, Jong RD , Heerdink ER,et al.Application of the ATC/DDD Methodology to Monitor Antibiotic Drug Use. Eur. J. Clin. Microbiol. Infect. Dis., 1998, 17:20-24.(In this article, it mentioned “The number of DDDs per 1000 persons per day is usually used for studies performed in the general population, whereas the number of DDDs per 100 bed-days is preferred for inpatients. These figures allow drug use to be compared in different countries, regions, hospitals, or hospital wards.”)

- Lambert ML, Bruyndonckx R, Goossens H,et al. The Belgian policy of funding antimicrobial tewardship in hospitals and trends of selected quality indicators for antimicrobial use, 1999–2010:a longitudinal study. BMJ Open 2015;5:e006916.

- Khdour MR, Hallak HO, Aldeyab MA,et al. Impact of antimicrobial stewardship programme on hospitalized patients at the intensive care unit: a prospective audit and feedback study. Br J Clin Pharmacol (2018) 84 708–715.

- Brady M, Cunney R, Murchan S,et al. Klebsiella pneumoniae bloodstream infection, antimicrobial resistance and consumption trends in Ireland: 2008 to 2013. Eur J Clin Microbiol Infect Dis (2016) 35:1777–1785.

I hope to get your understanding, thanks.

- The program is not really an ASM, because is based on the management, punishing or rewarding economically the prescribers according to whether or not they achieve the objectives. And it does not describe how the training is carried out, neither what is the method nor the periodicity. This point should be highlighted in the discussion.

Antimicrobial stewardship(AMS) included in a multifaceted approach or strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs. Guidelines recommend how such programs should be developed and implemented, including the role of hospital pharmacists. The provision by pharmacists of prospective audit and feedback, educational meetings and outreach, printed educational materials, and reminders about AMS-specific initiatives has been shown to improve antimicrobial utilization and prescribing appropriateness, and may also reduce super-infections, antibiotic resistance, and antimicrobial costs(the above is from references). During the period of AMS in our hospital, clinical pharmacists have exactly done the tasks mentioned above. At the same time,

they collaborate with infection doctors, infection control departments, doctors and nurses to improve the rational use of antibiotics. Although our hospital established the reward and punishment mechanism, its purpose is to arouse the doctor's attention to the rational use of antibiotics. So please see my revision in “Discussion” as follows: (Please see page 16)

The implementation of AMS in our hospital is managed by clinical pharmacists and supported by the DTC, while multiple sectors participate in it. AMS includes a multifaceted approach to combat the spread of AMR. Except the regular management strategy, our hospital established the reward and punishment mechanism aiming to arouse the doctor's attention to the rational use of antibiotics.

About how the training is carried out, what is the method or periodicity. I have added relative contents in method. Please see the following.(Please see page8)

Clinical pharmacists were responsible for training the medical staff on rational use of antibiotics. Training was conducted every 6 months in two forms. (1)Clinical pharmacists gave lessons to the medical staff in the lecture hall, they need to complete an exam after class. (2) Clinical pharmacists and the medical department jointly made online learning and exam, medical staff was required to finish it. If necessary, pharmacists would go to the clinical departments to give lectures.

Conclusion

This conclusion, “This study demonstrated that AMS managed by clinical pharmacists has an important role in reducing and optimizing antibiotic use and controlling antimicrobial resistance” is not correct, because the impact on bacterial resistance is positive and negative at the same time. It should be corrected.

I have revised the conclusion as follows: (Please see page18)

This study demonstrated that AMS in our hospital could reduce and optimize antibiotic use, declining bacterial resistance to FQs was associated with its reduced consumption. Clinical pharmacists played an important role in improving the rational use of antibiotics, however, hospital infection prevention and control measures, national policy guidance all contributed to it. The findings of our study indicate some directions to pursue in controlling the prevalence of CRE and MRSA. AMR is rising worldwide, so continual effort regarding AMS is critical not only in large hospitals but also in primary or community hospitals.

I hope my revison would meet your requirements. Thank you so much.

Reviewer: 3

Reviewer Name: Ruyu Xia

Institution and Country: Beijing University of Chinese Medicine, China.

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The main problem of this manuscript is that there are many factors affecting the use of antibiotics and antimicrobial resistance. It is difficult to confirm the single factor of the decline in antibiotic use and antimicrobial resistance. I don’t think the results from a non-controlled retrospective observational study can show it due to clinical pharmacists. The bias can’t well controlled. And there was no specific

report on the number of pharmacists, doctors and patients involved in the study. The abstract and the text are suggested to rewrite for more precise and cautious conclusions.

Dear professor Xia:

Thank you very much for your relevant suggestions. According to your comment, I have revised my article (including the abstract, the text and conclusion).

- I put the revised text below, please review:

Some limitations of this study should be noted. First, this was a retrospective observational study without simultaneous control group, the bias couldn't be well controlled, it was less convincing than a prospective, controlled study design. So the favorable results obtained can not be attributed solely to the pharmacist intervention, which were affected by many factors. (Please see page18)In the section of "Strengths and limitations of this study", we also mentioned the limitations as above. (Please see page3)

- The following is the revised conclusion:

This study demonstrated that AMS in our hospital could reduce and optimize antibiotic use, declining bacterial resistance to FQs was associated with its reduced consumption. Clinical pharmacists played an important role in improving the rational use of antibiotics, however, hospital infection prevention and control measures, national policy guidance all contributed to it. The findings of our study indicate some directions to pursue in controlling the prevalence of CRE and MRSA. AMR is rising worldwide, so continual effort regarding AMS is critical not only in large hospitals but also in primary or community hospitals. (Please see page18)

- The following is the revised abstract (I have added some information):

Data and participants: Antibiotic prescriptions from 820 doctors included all outpatients (N=17766637) and inpatients (N=376627) during 2010–2016. Bacterial resistance data were from all inpatients (N=350699) during 2011–2016.

Interventions: Multi-aspect intervention measures were implemented by clinical pharmacists (13persons), such as formulating the activity program and performance management, advising on antibacterial prescriptions and training doctors. (Please see page2)

I hope my revison would meet your requirements. Thank you so much.

Reviewer: 4

Reviewer Name: Irene Eriksson

Institution and Country: Karolinska Institutet, Stockholm, Sweden

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

Please leave your comments for the authors below

This is a well-written paper describing and assessing an antimicrobial stewardship program implemented in a tertiary hospital in China. The statistical analysis carried out seems appropriate but given that I am not a statistician but a pharmacist by training, I recommend the paper to be additionally reviewed by a statistician. Please see some minor comments for consideration below:

Dear professor:

First, thank you for the encouragement of our work. The followings are my revision according to your comment one by one.

1. Page 2, Line 29 — please specify the baseline measures too. If only end results are presented it is difficult to appreciate the change in antibiotic use.

Results: There was significant decrease in the proportion of antibiotic prescriptions in outpatients (from 19.38% to 13.21%) and in inpatients (from 64.34% to 34.65%), and the intensity of consumption (from 102.46 to 37.38 DDD/100 bed-days). The proportion of antibiotic prophylaxis decreased from 98.94% to 18.93%. The proportion of rational timing of the initial dose increased from 71.11% to 96.74%, and the proportion of rational duration rose from 2.84% to 42.63%. (Please see page2)

2. Page 2, Line 49 to 53 — given the study design, perhaps you could reinforce that what you observed are associations/correlations.

Conclusions: Antimicrobial stewardship had an important role in reducing antibiotic use and surgical antibiotic prophylaxis. The AMR was positively correlated with antibiotic consumption to some extent. (Please see page2-3)

3. Page 3, Line 3 to 35 — I suggest you completely rewrite the 'Strengths and limitations of this study" part. As currently formulated, #2 is neither strength nor limitation, but rather one of your study objectives; #3 and #4 also are rather ambiguous; #5 in my opinion also is neither strength nor limitation.

Strengths and limitations of this study

- Our study described the entire process of AMS, from management of antibiotic use to AMR monitoring.
- Time series analysis, a better tool, was applied to analyze the change trends in antibiotic utilization and AMR.
- By exploring the correlation between antibiotic use and AMR， this study may indicate some potential directions for controlling the prevalence of CRE and MRSA.

This was a retrospective observational study without simultaneous control group, the bias couldn’t be well controlled; the evaluation of prophylactic antibiotic use by different clinical pharmacists might have individual differences. (Please see page3)

4. Throughout the entire text — while the manuscript overall is well written and easy to read, some minor language errors are still remaining. Please very carefully proofread the entire text to address those.

I have proofread the entire text carefully once again and have corrected some grammar errors and tense errors. If there are still some language errors because of my limited capacity, would you like to tell me to correct them? Thank you so much.

5. Page 3, Line 49 — cannot see what this sentence adds given its positioning in your introduction: "Regretfully, not all medical staff knew about the Guidelines or their significance."

I put the sentence "Regretfully, not all medical staff knew about the Guidelines or their significance" here want to express two meanings. (1)That was the present situation of Chinese medical staff before 2011. Through AMS, more and more medical staff began to know and realize the importance of the Guidelines. (2) Because the medical staff don’t know the Guidelines very well, so there would be

some inappropriate prescriptions given by doctors, which will contribute to the spread of antimicrobial resistance. (Please see page3)

If you think this sentence should not be in the introduction, I can delete it.

6. Page 3, Line 53 — somewhat ambiguous what are the four factors, I count only three: 1) inappropriate use in healthcare; 2) inappropriate use in animals/agriculture; and 3) antimicrobial resistance. Could you please clarify?

I have made a little change, as follows:

There are four main factors contributing to the spread of AMR: inappropriate use of antibiotics in the community and in hospitals, misuse of antibiotics in animal production and agriculture, and the presence of resistant bacteria in the environment. (Please see page3)

(The four factors refer to:①inappropriate use of antibiotics in the community;②inappropriate use of antibiotics in hospitals;③misuse of antibiotics in animal production and agriculture;④the presence of resistant bacteria in the environment.)

7. Page 4, Line 12-14 — "Hospital pharmacists..." this sentence is somewhat out of place in this paragraph.

I have deleted the sentence “Hospital pharmacists should ……in controlling antimicrobial resistance.” (Please see page4)

8. Page 4, Line 16 — I am sure that WHO did work on antimicrobial resistance already prior to the World Health Day in 2011... Next you have a sentence "China acted immediately." Perhaps you could rewrite it saying "In response to XYZ in 2011 the NHFPC in China put forward..."

I have rewrote this content after reviewing some literatures according to your comment, please see below:

In 2001 the World Health Organization (WHO) began to take measures to combat the spread of AMR and strongly recommended governments to implement antimicrobial stewardship (AMS).3On World Health Day 2011, AMR was also selected as the theme. In response to AMR, in 2011 the NHFPC of China put forward “National Special Stewardship in the Clinical Use of Antibiotics”,4 the historically strictest management of antibiotics up to that date. (Please see page4)

9. Page 4, Line 45-46 — "After many years of hard work,..." this sentence does not belong in the introduction.

I have deleted this sentence “After many years of hard work, the status of antibiotics use has improved substantially at our hospital.” (Please see page4)

10. Page 4, Line 52-53 — would you consider these references relevant too?: PubMed ID 28941633; 29017750. Perhaps there are more studies, could you please just double check by conducting a systematic search?

Thanks for your good advice. I have done a literature review carefully and found that there were some articles that demonstrated the correlation between antibacterial usage and the antimicrobial resistance rate recently. So I have cited some new literatures (including the two articles you suggested), as follows:

9.Horikoshi Y, Suwa J, Higuchi H, et al.Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality.Int J Infect Dis 2017;64:69-73.

10. Wushouer H, Zhang ZX, Wang JH,et al.Trends and relationship between antimicrobial resistance and antibiotic use in Xinjiang Uyghur Autonomous Region, China: Based on a 3 year surveillance data, 2014-2016.J Infect Public Health 2018;11(3):339-346.

11.Cusini A, Herren D, Bütikofer L,et al.Intra-hospital differences in antibiotic use correlate with antimicrobial resistance rate in Escherichia coli and Klebsiella pneumoniae: a retrospective observational study.Antimicrob Resist Infect Control 2018;7:89. (Please see page4 and 20)

11. Page 5, Line 35 — "The patients were not involved or recruited in this study." I cannot agree with this statement. Patients were involved indirectly as you used their medical records in this study. I understand that a requirement for informed consent was waived. In general, there must be governance for accessing patients' medical records: either a broader consent in which patients allow to use their data for research purposes, or anonymization of all data prior to release to researchers, etc... Were records made anonymous prior to use in research? How was this done in your study?

Thanks for your good advice. According to your comment, I have rewrote the “Patient and public involvement”and “Ethics statement”. Please see below:

Patient and public involvement

The antibiotics utilization data was extracted directly from the Hospital Information System (HIS) and electronic medical records of all patients (2010-2016). The patient's personal information was hidden....

Ethics statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (Approval Number: 2017-11-28-3). Because the patient's privacy was not violated in the study, so the Ethics Committee agreed exemption applications of informed consent. (Please see page 5)

Before we used the data of the patients in this research, the medical records had been made anonymous, we could only see the patient’s identification number. And before we started this retrospective observational study, we submitted the “Risk Assessment and Disposal Plan” , “Quality Management Program”, “Research Plan”,etc, to the Ethics Committee to make sure that the patient's privacy would not be disclosed.

12. Page 5, Line 43-46 — were data on bacterial resistance available for 2010?

The bacterial resistance data from all inpatients (2011-2016) was provided by the Department of Infectious Diseases and Clinical Microbiology in our hospital. But unfortunately, the data for 2010 was not available, because the Infectious Diseases and Clinical Microbiology has cleared the data for 2010 due to limited computer storage space. So I could only get the bacterial resistance data from 2011-2016.

13. Page 5, Line 50-54 — is there a number for the approval document?

Yes, I have added the “approval number: 2017-11-28-3”. (Please see page 5)

14. Page 6, Line 18 — '...and so on.' reads a bit imprecise. perhaps revise? Also, next sentence: "As expected,.. ": not all I guess expect what you stated, perhaps revise the language here too?

I have revised the language, please see the following:

...whereas the expert group was responsible for technical guidance, participation in consultations, training doctors on rational use of antibiotics and implementation of AMS monitoring (such as data collection and report, prescription review and feedback, AMR monitoring, etc). Generally the medical

department led AMS in many hospitals in China, but in our hospital, the pharmacy department was the leading department, ... (Please see page 6)

15. Page 7, Line 53-54 — perhaps "penalized" instead of 'punished'?

I have changed “punished” to “penalized”. (Please see page 7)

16. Page 7, Line 55-56 — what does RMB stand for?

I have changed “RMB” to “CNY”. CNY is Chinese currency unit (Please see page 8)

17. Page 8, Line 13-15 — maybe 'inappropriate" instead of 'irrational'

I have changed “irrational” to “inappropriate”. (Please see page 8-9)

18. Page 8, Line 45-49 — instead of 'points' you could perhaps just keep RMBs only. makes it easier to follow.

Thanks for your good advice. I have revised it according to your suggestion. Please see below:

If inappropriate use was confirmed by the experts, the relevant physician would be penalized 100–200CNY fine. (Please see page9)

Reviewer: 5

Reviewer Name: Peter Herbison

Institution and Country: University of Otago, New Zealand

Please state any competing interests or state ‘None declared’: None declared

I think the statistics in this article are fine.

Dear professor:

Thank you for the encouragement of our work.

VERSION 2 – REVIEW

REVIEWER	José M. Cisneros Hospital Virgen del Rocío, Spain
REVIEW RETURNED	17-Mar-2019

GENERAL COMMENTS	The manuscript has improved, but there are still some aspects to be answered, the most important of which remains unmentioned in the discussion: - The program is not really an ASM, because is based on the management, punishing or rewarding economically the prescribers according to whether or not they achieve the objectives. And it does not describe how the training is carried out, neither what is the method nor the periodicity. This point should be highlighted in

	the discussion. This intervention is unique among the published studies of ASM and needs to be discussed.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name

José M. Cisneros

Institution and Country

Hospital Virgen del Rocío, Spain

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below

The manuscript has improved, but there are still some aspects to be answered, the most important of which remains unmentioned in the discussion:

- The program is not really an ASM, because is based on the management, punishing or rewarding economically the prescribers according to whether or not they achieve the objectives. And it does not describe how the training is carried out, neither what is the method nor the periodicity. This point should be highlighted in the discussion. This intervention is unique among the published studies of ASM and needs to be discussed.

Dear professor:

Thanks for your good advice. The following is my response to the comment.

Antimicrobial stewardship(AMS) included in a multifaceted approach or strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs. Guidelines recommend how such programs should be developed and implemented, including the role of hospital pharmacists. The provision by pharmacists of prospective audit and feedback, educational meetings and outreach, printed educational materials, and reminders about AMS-specific initiatives has been shown to improve antimicrobial utilization and prescribing appropriateness (the above is from references).

During the period of AMS in our hospital, clinical pharmacists have exactly done the tasks mentioned above, these works are similar to the existing ones in the world. At the same time, clinical pharmacists collaborate with infection doctors, infection control departments, doctors and nurses to improve the

rational use of antibiotics in their daily works. Although our hospital established the reward and punishment mechanism, its purpose is to arouse the doctor's attention to the rational use of antibiotics. According to your advice, I have added some content to the discussion section. So please see my revision in “Discussion” as follows: (Please see page 16)

“The implementation of AMS in our hospital is managed by clinical pharmacists and supported by the DTC, while multiple sectors participate in it. AMS includes a multifaceted approach to combat the spread of AMR. Except the regular management strategy (such as multidisciplinary consultation, nosocomial infection control, prescription prospective audit, prescription evaluation and feedback, publicity and education, etc), our hospital established the reward and punishment mechanism aiming to arouse the doctor's attention to the rational use of antibiotics, which is slightly different from the existing intervention model and is unique among the published studies of AMS, but it reflects the current situation of some Chinese hospitals.”

- About how the training is carried out, what is the method or periodicity. I have added relative contents in method. Please see the following.(Please see page8)

Clinical pharmacists were responsible for training the medical staff on rational use of antibiotics. Training was conducted every 6 months in two forms. (1)Clinical pharmacists gave lessons to the medical staff in the lecture hall, they need to complete an exam after class. (2) Clinical pharmacists and the medical department jointly made online learning and exam, medical staff was required to finish it. If necessary, pharmacists would go to the clinical departments to give lectures.