Author's response to reviews

Title: Knowledge, Attitude and Practice of Antibiotics: A Questionnaire Study among 2500 Chinese Students

Authors:

Ying Huang (doctorhy82@gmail.com)
Jiarui Gu (jrgu@sina.com)
Mingyu Zhang (zhangmy@hrbmu.edu.cn)
Zheng Ren (poppy_ren@163.com)
Weidong Yang (yangweidong3000@yahoo.com.cn)
Yang Chen (koala19820807@126.com)
Yingmei Fu (yingmeifu@yahoo.cn)
Xiaobei Chen (chenxiaobei626@yahoo.com.cn)
Jochen W.L. Cals (j.cals@hag.unimaas.nl)
Fengmin Zhang (fengminzhang@yahoo.com.cn)

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Author's response to reviews: see over
Dear Editor,

Thank you very much for reviewing our manuscript (titled “Knowledge, Attitude and Practice of Antibiotics: A Questionnaire Study among 2500 Chinese Students”; Manuscript ID: 1438214373858216) and giving us constructive and positive comments. We have tried our best to revise the manuscript according to the reviewers’ comments. We have conducted a thorough proof-reading of the manuscript. We hope the revised manuscript may meet the requirements and provide answers to all the questions raised by the reviewers.

Thanks and best regards!

Yours sincerely,
Fengmin Zhang

Our point-to-point response to the comments:

Editors:
1. Background: I agree with the reviewers that more information is needed regarding 'medical education'. At what point do the students begin their clinical education? Are all students at the medical university studying to become physicians? How are antibiotics regulated in China? Are prescriptions required?

Answer: Thank you very much for your positive suggestions. In the manuscript, we didn’t clearly describe the medical education of China, which will not help the readers understanding our study. The medical college in China is typically divided into departments: clinical medicine, pharmacy, nursing, and dentistry among many others. But, in this study, the whole medical students mentioned major in clinical medicine. In China, the duration of undergraduate medical education is five years: the first 3-year classroom education on basics of medicine and the next 2-year hospital-based clinical training, and they will get the prescription right and become physicians after examination. In 2004, Chinese government release drug management policy and the purchase of antibiotics needs doctor's prescription. But, actually, the implementation process is not strict.

In the manuscript, we have added the content about clinical medicine education and the regulation of antibiotics in China in the partition Background as followed (paragraph 3):

“At present, China antibiotic management policy has been released, but the implementation process is not strict. Doctor prescription and self-prescription co-exist. In China, the medical students major in clinical will have prescription right in the future after examination. The clinical courses offered in medical colleges generally provide students knowledge and medicine practice of biomedical bases, diagnosis, treatment, and prevention of diseases. The duration of medical and non-medical is different. Medical profession is generally 5-year, rather than non-medical profession
4-year. In the 5-year undergraduate study, students do class work in the first three years and hospital-based practice in the final two years. The clinical medicine curriculum gives some introduction of pathogenic microorganisms and infectious diseases, but does not set up antibiotics as a separate entity. Contents related to antibiotic use and resistance is mainly imbedded in chapters of pharmacology and microbiology courses. And the practice of antibiotics prescription is supervised by clinicians during students’ clinical internship.”

2.Materials and Methods: In the first sentence of this section, the authors refer to a study conducted ‘by means of concentrated question-answer and face-to-face interview’. Was there a questionnaire used to support the interview? This was not clear. How did the authors determine that if 80% of the questions were answered, that was sufficient to consider the survey complete enough for analysis?

Answer: Thank you very much for pointing out our deficiencies. As mentioned by editor, this study was indeed based on paper-questionnaire and assembly conducted in three universities. In the strict sense, it is not a face-to-face interview. In the statistical analysis partition, we adopt the statistician’s advice that if 80% of the questions were responded to, it met the evaluation index threshold for validation in statistical analysis in cases where there is partial data loss. And we accept the hypothesis when the data loss is less than 20%, it can still be used to extract the main characteristics of the samples. In fact, all the questionnaires used in our statistical analysis, were either 100% or nearly 100% complete. The returned questionnaires that were not included in the statistical analysis were all less than 50% complete.

We have made the correction in the revised manuscript (line 109-110, page 5) as followed:

“The survey was questionnaire-based and the questionnaire is designed for two objectives: to get an overview of the students’ understanding of antibiotics, and to compare the MS’ and NS’ KAP towards antibiotic use, also consider about the differences among grades.…”

3. I understand that you could score the correct response for knowledge questions. What I could not understand was how the ‘correctness’ of their perception/attitude was done. Rather, their perceptions were compared to currently accepted practice. In a way, this overlaps with knowledge, but attitudes are not ‘wrong’. When measuring practice/utilization, are you measuring opinion or behavior? Do the students prescribe antibiotics, or are they reporting what they would do in a situation? When measuring ‘awareness of public education’ are you measuring awareness of the existence of public education or awareness of the content presented as part of public education?

Answer: Thanks for the editor’s valuable suggestion. In the manuscript, we did not accurately define knowledge, attitude, behavior and awareness of public education, which caused misunderstanding of these four concepts: 1) Attitude refers to the extent to which misuse of antibiotics has been perceived and reflected on by the students and may not necessarily overlap with knowledge. It measures whether respondents have
realized there is misuse of antibiotics or that resistance to viruses has become a problem in China or that resistance to viruses affects their health or that of their family. The higher the respondents scored on these questions, the better their attitude was towards antibiotics usage. 2) Behavior here refers to an act which has taken place or real experiences of the students in the past. In China, because of poor implementation of regulations on antibiotics use, self-medication among NS and MS has become relatively prevalent. Behavior in this study does not refer to viewpoints. 3) Awareness of public education, to some degree, falls under the category of attitude. It was listed as a separate entity to underscore its inevitability and the urgency surrounding the current situation. As a component of attitude, the necessity of public education on antibiotic use has been highlighted with our results showing significant differences in the perception on public education between MS and NS.

In the revised manuscript, we have add some content to explain the questions as followed (line 130, page 6):

“As shown in the supplementary materials, a common grading standard was used for each question in all the four categories. We graded the answers as ‘right’ or ‘wrong’ for the single-answer questions generally considering whether it corresponded with the natural situation. 2 or 0 points were assigned to the ‘right’ or ‘wrong’ answers, respectively. For the multiple-answer questions, we assigned one point for each ‘right’ answers and 0 points for the ‘wrong’ ones. A higher score in the first three categories presented better knowledge of antibiotics usage and more positive attitude and perceptions Also, the five-answer questions in the behavior section were graded with 1 point for ‘always’, 2 for ‘often’, 3 for ‘sometimes’, 4 for ‘seldom’ and 5 for ‘never’. A higher score here presented a lower dependency on antibiotics corresponds to better antibiotics usage behavior.”

4. Statistical analysis: Please report more information on how ‘grading standards’. Instead of including information on how the correct responses were determined should be in the methods and materials section. While the chi-square statistic can be statistically significant, the language typically used denotes statistically significant association rather than statistically significant differences.

Answer: Thank you for the valuable suggestions. In the materials and methods section, we didn't clearly describe the grading standard and the judgment of the responses. It may indeed puzzle the readers. In order to solve this problem, we have made a detailed description of the scoring process in the manuscript (see question 3) and added the supplementary materials. In the statistical analysis process, we have repeatedly used chi-square test to evaluate whether medical education (clinical medicine) is associated with students’ knowledge, attitude and practice/behavior regarding antibiotic use. The statement in the results implying the presence of statistically significant differences is not appropriate. We accept editor’s suggestion to revise it in the manuscript.

In the partition of the statistical analysis of the revised manuscript, we correct the descript of chi-square test as followed (line 146, page 6):

“…The statistical analyses of categorical variables (such as responses to questions
on knowledge, attitude, behavior/practice and public perceptions) were done using Chi square test to assess the association between medical education and KAP towards antibiotic use. A $p<0.05$ was considered statistically significant. Bonferroni method was employed to do multiple test correction.”

5. Results: Provide overall differences in the text, if statistical comparisons were made. For example, the authors noted 'that MS scored remarkably better than NS overall on knowledge...', but table 2 presents information for each item. The reported results were mixed with interpretations by the authors. Report the statistical results and present implications in the discussion section. For example, when reporting differences between first-year MS and NS, present the overall difference, and text such as 'medical education enhanced mastery of antibiotic knowledge' should be part of the discussion. Although four subtests were described, the results are presented as if behavior/practice and public education were scored together.

**Answer:** Thank you for pointing out our deficiencies. And we accept the suggestions of the editor.

(1) For the question “Provide overall differences ..., but table 2 presents information for each item”, We have included the statistical results along with their implications in the revised manuscript as followed.

In line 163, page 7: “The results show that overall MS scored remarkably better than NS on knowledge of antibiotic use ($\chi^2=191.8869$, $p<0.0001$) while no significant difference was found between first-year MS and first-year NS ($\chi^2 =1.2190$, $p=0.2696$).”

In line 176, page 8: “The results showed that on the questions of attitude on antibiotic use, the MS scored significantly higher than the NS ($\chi^2=90.7200$, $p<0.0001$). A similar pattern was obtained from the analyses of the students’ perception of public education ($\chi^2=40.5875$, $p<0.0001$).”

In line 190, page 8: “It is interesting to note that our data revealed that MS scored more poorly than the NS on the behavior towards the use of antibiotics. ($\chi^2=101.2526$, $p<0.0001$).”

(2) For the question “The reported results...should be part of the discussion.” We accept the editor’s suggestions and delete the interpretation and implication sentences such as “indicating that medical education enhanced medical students’ mastery of knowledge on antibiotic use.”, “Accordingly, these data reveal that MS had a better insight into...to promote and rationalize the use of antibiotics” and et al. We rewrite the Discussions partition with the order of the results and add correlated comments of in the revised manuscript as followed:

In line 228, page 10: “The result of knowledge studies show that medical students can get more information about antibiotics than other students or public, The increase of knowledge can be well presented by the relative specialized question whether antibiotics can cure viral infection which is described in result partition, whenever it is compared between MS and NS and between grades of MS(69% of year 5 and 49% of year 1). Some similarity can be drawn from the study in Jordan in 2012 by Suaifan et al that highlights existing gaps in the knowledge of MS and NS on antibiotics use[22].
The difference, however, lies in the fact that in Jordan self-medication as a result of lack of knowledge on antibiotics plays a leading role in the misuse antibiotics while in China it is the clinicians with the right to prescribe that are at the forefront of antibiotic abuse.

In line 261, page 11: “We analyze from the level of different grades to research the KAP towards antibiotics use, which is an important feature of our study. Figure 1a, b, c and d show the comparisons between MS’ and NS’ levels of knowledge, attitude, perception of public education and behavior towards antibiotic use. The MS’ knowledge, attitude and perception on antibiotic use improved as they progressed in course peaking at year 4 with a slight scale-back at the year 5. It is worth noting that the clinical medicine students are introduced antibiotics and antibiotic-related information from the second year in courses such as microbiology (year 2), pharmacology (year 2), internal medicine (year 3), and epidemiology (year 4). Although they could touch prescription of antibiotics during the years 4 and 5, MS do not prescribe any medicines until after they have completed the course. The most senior (years 4 and 5) MS’ scores on behavior towards antibiotics use were lower than those of their junior colleagues (years 1, 2 and 3) indicating that there could be some negative impact on students’ erstwhile good antibiotic practices by the hospital environment during clinical. This fluctuation of KAP could be due to inherent flaws in the medical curriculum. And it reflect that add some courses on rational antibiotic practice in the medical curriculum in China is urgently needed.”

(3) For the question “Although four subtests were described, the results are presented as if behavior/practice and public education were scored together.” In the manuscript, we set the title of the third partition of Results as “The influence on attitude and the public education of antibiotics” which lose the intention on the analogy of attitude and perception. In the revised manuscript, we correct the title as “The influence of medical curriculum on MS’ attitude and perception of public education” (line 175, page 7), and in this section, we carried out the result description of attitude and perception.

Reviewer #1:
a) The authors do not state how they recruited medical students. In general, pharmacist, dentist, nursery etc. are usually classified as medical students. The author should clarify if medical students’ stands for those registered at the faculty of medicine.

Answer: Thanks for the important suggestion from the reviewer. The medical students enrolled in this study are clinical medicine (major) students from a medical university in Northeastern China. In medical schools of China, clinical medicine is a general practice education which aims to provide students with general knowledge of medicine practice and relates it to diagnosis, treatment, and prevention of diseases. It also develops their ability to distinguish and classify the causes and pathogenesis of diseases. The clinical medicine course is separate and distinct from pharmacy, nursing and dentistry and others. We have added this description to the partition Background in the revised manuscript as followed (line 78, page 4):
“…In China, the medical students major in clinical will have prescription right in the future after examination. The clinical courses offered in medical colleges generally provide students knowledge and medicine practice of biomedical bases, diagnosis, treatment, and prevention of diseases. Contents related to antibiotic use and resistance is mainly imbedded in chapters of pharmacology and microbiology courses. And the practice of antibiotics prescription is supervised by clinicians during students’ clinical internship.”

And in line 101, page 5: “…All the clinical medicine students (1250) of one representative medical university of Chinese medical education participated in the study. Students from pharmacy, nursing and dentistry programs were not included.…”

b) In general, this paper needs to be proof read by native speaking individual. There are some grammatical mistakes and some statement are too long missing comma’s.

Answer: Thanks for reviewer pointing out our deficiency. According to the recommendation of the reviewer, we have engaged native English-speaking individuals to read through the revised manuscript to correct any discovered grammatical mistakes and change the long sentences. For example, the long sentence “These public surveys reflect the general public’s lack of understanding on proper use of antibiotics thereby reinforcing the fact that establishing certain guidelines for public education on the use of antibiotics still remains essential if their misuse and resultant resistance were to be controlled.” is rewrite as “These surveys reflect the general public’s lack of understanding on proper use of antibiotics. Thereby, it reinforces the necessity that establish certain guidelines for public education on the use of antibiotics.” (line 63, page 3)

c) Authors should enrich their discussion by comparing their study outcome with others performed recently in countries where antibiotics prescription is misused as a result of government relaxing regulation, such as the recent study performed by Suaifan et al., and Shehadeh et al., in Jordan.

Answer: Thanks for reviewer’s valuable suggestions. We have carefully read the references of Suaifan et al., 2012 and Shehadeh et al., 2011, and compared the findings of the two studies with our work. It shows that the situation of antibiotics abuse is quite similar in Jordan and China. And the study results are consistent with each other on the point of medical education will increase the student’s knowledge and attitude on antibiotics usage compared with Suaifan et al., 2012 and our work. The difference is that Suaifan et al., 2012 mainly considers the relationship of public practice on antibiotics use with the lack of antibiotic knowledge, while our research tend to think of the impact of medical education on clinical students and analyze the relationship between antibiotic courses and antibiotic abuse. These studies clarify the unique reasons of antibiotic abuse from different national conditions, respectively. And we add the corresponding discussions in the revised manuscript as followed (line 232, page 10):

“…Some similarity can be drawn from the study in Jordan in 2012 by Suaifan et al
and in 2011 by Shehadeh et al that highlights existing gaps in the knowledge of MS and NS on antibiotics use[22,23]. The difference, however, lies in the fact that in Jordan self-medication as a result of lack of knowledge on antibiotics plays a leading role in the misuse antibiotics while in China it is the clinicians with the right to prescribe that are at the forefront of antibiotic abuse.”

Reviewer #2:
Major Compulsory Revisions
1. Abstract conclusion: I think it is not possible to infer that these results ‘reflect an inherent weakness in the system of medical curriculum on proper use of antibiotics’ when earlier it has been shown that knowledge of antibiotics is higher in medical students.

**Answer:** Thanks for the reviewer’s suggestion. The conclusion about ‘reflect an inherent weakness in the system of medical curriculum on proper use of antibiotics’ is not proper. In this study, the results reveal MS were better than NS in terms of knowledge, attitude and perception on the level of education on antibiotic use, but worse on behavior. This study also reveal that the senior MS has a more positive behavior on the usage of antibiotics compared to lower grade MS and NS in general. It shows an significant association between antibiotic use practice and medical education, reflecting the deficiency of antibiotics usage instruction in the Chinese medical curriculum. So, we have revised it in the revised abstract as followed (line 51, page 3):

“…The study also shows an excessive use of antibiotics especially among the more senior medical students, signifying a deficiency of antibiotics usage instruction in their curriculum. This might explain why there are frequent abuses of antibiotics in both hospital and community settings from a certain angle.”

2. Background: Whilst interesting to read, this should be considerably more focused: it is only on paragraph three that medical students are introduced. Furthermore, there is no introduction to the pathway medical students take at these universities in their studies; this is important in order to interpret a number of the findings. Do the students have lectures in the first two years and then clinical work in the final three years? When do students typically receive education on antibiotics? When do students start to get practice at prescribing antibiotics? Most of these points can be addressed in the discussion section, but some form of introduction is required here.

**Answer:** Thanks for the reviewer’s important suggestions. As the reviewer pointing out, we did not provide enough introduction to the pathway medical students take., which will puzzle readers. In the five-year undergraduate program, the students have lectures in the first three years followed by hospital-based clinical work in the final two years. Throughout the clinical medicine course, general knowledge and information on antibiotics has not been set apart as a separate entity in the curriculum but the information related to antibiotic use and resistance is embedded in chapters in
the broad areas of pharmacology and microbiology. Furthermore, the practice of antibiotic prescription is usually supervised by practitioners in internal medicine and surgery during internship. We added these information to the partition Background as followed (line 79, page 4):

“In China, the medical students major in clinical will have prescription right in the future after examination. The clinical courses offered in medical colleges generally provide students knowledge and medicine practice of biomedical bases, diagnosis, treatment, and prevention of diseases. The duration of medical and non-medical is different. Medical profession is generally 5-year, rather than non-medical profession 4-year. In the 5-year undergraduate study, students do class work in the first three years and hospital-based practice in the final two years. The clinical medicine curriculum gives some introduction of pathogenic microorganisms and infectious diseases, but does not set up antibiotics as a separate entity. Contents related to antibiotic use and resistance is mainly imbedded in chapters of pharmacology and microbiology courses. And the practice of antibiotics prescription is supervised by clinicians during students’ clinical internship.”

We also add comments on courses, attitude, and behavior of students to the partition of Discussions under the suggestion of the reviewer as followed (line 266, page 11):

“It is worth noting that the clinical medicine students are introduced antibiotics and antibiotic-related information from the second year in courses such as microbiology (year 2), pharmacology (year 2), internal medicine (year 3), and epidemiology (year 4). Although they could touch prescription of antibiotics during the years 4 and 5, MS do not prescribe any medicines until after they have completed the course. The most senior (years 4 and 5) MS’ scores on behavior towards antibiotics use were lower than those of their junior colleagues (years 1, 2 and 3) indicating that there could be some negative impact on students’ erstwhile good antibiotic practices by the hospital environment during clinical. This fluctuation of KAP could be due to inherent flaws in the medical curriculum. And it reflect that add some courses on rational antibiotic practice in the medical curriculum in China is urgently needed.”

3. Materials and methods, background of respondents: the first paragraph needs to be considerably clearer as to how the questionnaire was conducted. ‘Face to face interviews’ are mentioned but in the results section it is stated that 2470 questionnaires were returned. Were interviews used, and if so, who conducted them? Or was this a paper-based or online questionnaire sent to students to conduct alone? If a mixture of methods were used, this needs to be very clear, and a breakdown of response rates by questionnaire type should be included in the results.

Answer: Thanks for the reviewer’s valuable suggestion. The study was based on questionnaire (not face-to-face interview) conducted in three universities. All the three universities recruit students nationwide. For the following reasons, we chose the certain three universities for this survey: 1) The medical university takes a typical medical education form of China, and some of the authors are the staff in the medical university making it convenient for us to locate the respondents; 2) The other two
universities are representative in China, both university have no medical school, and we were able to get permission and assistance from their students’ affairs office to locate the random selected students from pursuing different majors from year 1 to year 4 in their respective lecture halls. We obtained information on the time and venue of large-sized classes. With permission granted, we went to the selected classes in person and briefly introduced our study before distributing the questionnaires and giving them adequate time as we waited for them to respond and return the questionnaires. None of our questionnaires was administered online. In the revised manuscript we correct the description as followed (line 100, page 4):

“Respondents in this study were students from three nation-wide recruit universities in Northeastern China. All the clinical medicine students (1250) of one representative medical university of Chinese medical education participated in the study. Students from pharmacy, nursing and dentistry programs were not included. Paired 1250 non-medical respondents were randomly selected based on ID number registered in Students’ affairs office from the other two universities without clinical medicine course.”

4. Materials and methods, background of respondents: further detail should be included on the selection and randomization process. There are more medical student respondents than non-medical student respondents, yet only one medical university was included in the study, how did this occur? Were 2500 students randomly selected from all students at all the universities? Or was there some form of proportionate sampling used? Also, were all the medical students from the medical university and all the non-medical students from the other two universities, or was there a mixture of both non-medical and medical students selected from each university?

Answer: Thanks for reviewer pointing out what we didn’t describe clearly. In this study, all the medical respondents are clinical medicine students from one university (Harbin Medical University) which is the only tertiary-level medical school in the city. We chose clinical medicine students because of the certainty will possess the right to prescribe medicines (including antibiotics) upon completing of the program and becoming clinicians. All the 1250 students from this department consented and participated in the study. The 1250 non-medical respondents came from the other two universities, which do not offer clinical medicine or medicine-related courses. Therefore, these students’ KAP towards antibiotic use may not be influenced by professional knowledge. Among the returned questionnaires, 852 were valid. The corresponding revision is list in question 3.

5. Materials and methods, design and implementation of questionnaire: why were two marks allocated for correct answers? This should be explained. Also, it would be very useful for the supplementary material questionnaire to indicate in each instance which responses were considered ‘right’ or ‘wrong’. Similarly, for responses to part iii) of the survey it states that five choices were provided with different points for different responses; there should be more transparency as to what was considered a correct response, since the results for these answers are a) higher for NS than MS (which as is
mentioned is unexpected) and b) a chart is presented rather than a table meaning it is not possible to infer what has been considered a ‘correct response’ here.

**Answer:** We thank the reviewer for pointing out that we did not clearly explain the allocation marks. A common grading process was used for each question in all the four categories. We graded the answers as ‘right’ or ‘wrong’ for the single-answer questions generally considering whether it corresponded with the natural situation, and 2 or 0 points assigned, respectively. For the multiple-answer ones, 1 and 0 point was assigned for each ‘right’ and ‘wrong’ ones. A higher score in the first three categories presented better knowledge and more positive attitude and perceptions on antibiotic usage. Also, the five-answer questions in the behavior section were graded with 1-5 point. A higher score here presented a lower dependency on antibiotics corresponds to better antibiotics usage behavior. We accept the reviewer’s suggestion to revise it in the manuscript as followed (line 131, page 6) and add the grading standard in the Supplementary materials.

In line 131, page 6: “We graded the answers as ‘right’ or ‘wrong’ for the single-answer questions generally considering whether it corresponded with the natural situation. 2 or 0 points were assigned to the ‘right’ or ‘wrong’ answers, respectively. For the multiple-answer questions, we assigned one point for each ‘right’ answers and 0 points for the ‘wrong’ ones. A higher score in the first three categories presented better knowledge of antibiotics usage and more positive attitude and perceptions. Also, the five-answer questions in the behavior section were graded with 1 point for ‘always’, 2 for ‘often’, 3 for ‘sometimes’, 4 for ‘seldom’ and 5 for ‘never’. A higher score here presented a lower dependency on antibiotics corresponds to better antibiotics usage behavior.”

6. Materials and methods, statistical analysis: it does not appear that any adjustment has been made here for the large number of statistical tests that has been conducted; as there are at least twenty comparisons throughout the paper, at least one of these results would be expected due to chance if the significance level is set at <0.05.

**Answer:** We appreciate the reviewer’s valuable suggestions. As the reviewer point out, we adopted statistical test on the 30 questions respectively, and did not take into account for multiple test correction, in the manuscript. Here, we use the most stringent Bonferroni method to solve this problem. The results display that 6 significant differences in antibiotic knowledge still has 5 notable, 7 ones in antibiotic attitude are all still significant, and 11 ones in antibiotic practice still has 10 stayed (p<0.0017). The strict multiple test correction produce no significant effect on the overall conclusion. At the prompt of the reviewer, we amend the data of table 2, table 3 and table 4 and add marks to present the still notable questions after multiple test correction. The Bonferroni method is also added to the statistical section of the manuscript:

7. Results, behaviour: It is stated that ‘MS would advocate use of antibiotic almost without exception’ for symptoms of respiratory tract infection, yet this does not
appear to agree with table 4, where for each of the subcategories mentioned only 10.9-37.9% would ‘always’ or ‘often’ use antibiotics in these cases.

**Answer:** Thanks for the important observation. Regarding behavior towards antibiotic use, MS would advocate use of antibiotics more actively than NS since they scored higher than NS in each question (after multiple test correction). The way we had described the data ‘MS would advocate use of antibiotic almost without exception’ was not appropriate, and have revised this in the manuscript as followed(line 197, page 8):

“…When symptoms of respiratory tract infection occur, MS would advocate use of antibiotics more frequently than NS (Table 4)…”

8. Results, different grades: it is stated that attitude of MS is ‘greatly enhanced’ yet in figure 1b their ‘score’ appears to be 8 for first years and final years, briefly going to 9 for 2nd/3rd/4th years. If the chart is correct, this is quite an overstatement.

**Answer:** Thanks for the reviewer pointing out this question. we repeated the analysis of inter-grade data, the result shows Figure 1 is correct. And Chart 1b only shows a slight increase in the MS’ attitude towards antibiotics with the increase in academic years. The phrase ‘greatly enhanced’ used here is inappropriate. And we delete this phrase and correct the context as followed (line 210, page 9):

“…Similarly, their attitude on the use of antibiotics was only slightly improved (year 4) over the same period with a clearer recognition of antibiotic abuses and development of drug resistance in bacteria (Figure 1b).…”

9. Discussion, paragraph 2: this is quite hard to follow at points. The studies cited should be directly compared to the results from the present study; currently there is not a comparison made to the studies in the first sentence (in Sweden and the UK). I feel the comparisons with the study in Holland is inappropriate and must be removed: firstly, MS in China are being compared with public in Holland; secondly, a very selective set of results have been compared as being ‘much higher’ which is an overstatement given that there is only a ~10% difference; thirdly, 60% of the respondents in the survey from Holland advocated using antibiotics in acute bronchitis, substantially more than the 29.5% of MS and 13.5% of NS in the present study. More generally, if comparisons are to be made, there should be an attempt at interpreting why such differences exist between countries. I do not understand the two sentences starting ‘On treatment of common cold, 19.15% of MS resolved to…’; this needs re-writing.

**Answer:** Thank you for the valuable suggestions. We accept the reviewer’s observations and delete the overstated comparisons from the Discussions. And we regulation and rewrite the partition of Discussions under the advice of the reviewers with a result related order, and compare with the proper citations.

In line 228, page 10: “The result of knowledge studies show that medical students can get more information about antibiotics than other students or public, The increase of knowledge can be well presented by the relative specialized question whether
antibiotics can cure viral infection which is described in result partition, whenever it is compared between MS and NS and between grades of MS (69% of year 5 and 49% of year 1). Some similarity can be drawn from the study in Jordan in 2012 by Suaifan et al and in 2011 by Shehadeh et al that highlights existing gaps in the knowledge of MS and NS on antibiotics use[22,23]. The difference, however, lies in the fact that in Jordan self-medication as a result of lack of knowledge on antibiotics plays a leading role in the misuse antibiotics while in China it is the clinicians with the right to prescribe that are at the forefront of antibiotic abuse.”

In line 238, page 10: “Our study result also prompt that the antibiotic knowledge and attitude education should be strengthened in China. More many MS believed that antibiotics can speed up recovery of common cold, cough and a number of other related illnesses arising from viral infections. This is previously an important cause of antibiotic over-use.”

10. Discussion, paragraph 2: it is stated that ‘the most remarkable finding was that many MS attributed antibiotics abuses to prevailing view in the society that antibiotics can speed up recover of various illnesses’; firstly, I do not think this is the most remarkable finding of the study; secondly, there was only a 10% difference between MS and NS for this question; thirdly, the results of this question in the survey (question 28) may be quite hard to interpret as any important real difference, since respondents could include between one and four answers. It may be more sensible to present the responses to this question in a chart format in the results section to allow easier comparison of the results, which are currently only very briefly mentioned in the text of the results section.

Answer: Thanks for the valuable suggestion. As the reviewer pointing out, we did over-stress the significance of the finding. It reflects the assumption about the causes of antibiotics abuses. So in this revision, we have deleted the overstatement contents, and rewrite this paragraph as describing as question 9.

**Minor Essential Revisions**

1. Abstract background section: the use of ‘is always focussed…’ is too strong; there are other instances in the text where absolute terms are used inappropriately. It would be better to use a word such as ‘typically’ or ‘normally’ or ‘usually’.

Answer: Thanks for reviewer pointing out this question. We accept the reviewer’s suggestion and rewrite this sentence as followed (line 28, page 2):

“Recently, many scientists including bacteriologists have begun to focus on social aspects of antibiotic management especially the knowledge, attitude and practice (KAP) among the general population regarding antibiotic use.”

2. Materials and methods, background of respondents: this section also needs to include a statement about whether participation was voluntary (assume so) and whether any incentives were provided.
Answer: Thanks for the careful review. We have indicated in the revised manuscript that the participation of the students in this study was voluntary following a signed consent and no incentives were offered to the respondents in line 105, page 5:

“All the respondents joined in with no incentives and signed the informed consents.”

3. Materials and methods, design and implementation of questionnaire: was the questionnaire in Chinese or English?

Answer: Thanks for the careful review. The questionnaire was conducted in Chinese considering many students might misunderstand the English questions. We then translated their responses into English before embarking on analyses and writing.

4. Materials and methods, design and implementation of questionnaire/results concerning students’ knowledge of antibiotics: table 2 shows six questions, whereas the methods state that eleven questions were used here. Were all eleven questions used to generate the overall comparisons between MS and NS (the first sentence in this results section) or just the six in the table? Just needs a brief clarification, along the lines of ‘when comparing the results of all eleven questions concerning…’.

Answer: Thanks for the careful review. The significant differences in knowledge on antibiotics between MS and NS were found only in the six questions in table 2. No significant differences were found in the rest five questions. All eleven questions used to generate the overall comparisons between MS and NS. And we add the sentence “When compare the overall results of each partitions all questions are concerned.” in line 128, page 6 under the reviewer’s advise.

5. Response rate: this is currently stated as 84.5%, which is the proportion of returned questionnaires that were ‘considered valid for analysis’. The true response rate should be stated as 83.5%, which is the proportion of valid questionnaires divided by the total number of questionnaires sent out (i.e. 2088/2500). The response rate is really quite high for such a survey; it may be worth mentioning this as a particular strength of the study in the discussion.

Answer: Thanks for the reviewer’s valuable suggestion. We accept the reviewer’s suggestion and add it in the Discussions partition as followed (line 277, page 12):

“This is a large sample size(2500) and high response rate(83.5%) research on KAP towards antibiotics usage of MS and NS. And we compare year groups for both MS and NS from representative universities which would reflect the national situation of China, to some extent.”

6. Discussion, paragraph 1: it is stated that ‘NS are better behaved in use of antibiotics’. This phrasing really only applies to some of the questions posed in the survey, i.e. where NS would individually have responsibility for decisions (when to stop antibiotics, what do you follow when you use antibiotics); the questions concerning personal use of antibiotics with bronchitis/cough with fever etc. may not
be directly related to the students’ behaviour, but rather the behaviour of their doctors. It is important to clarify this.

**Answer:** Thank you for this observation. NS responses concerning the use of antibiotics may be directly related to their behavior. As medical management system has not been well-developed, there is no strict regulation on antibiotics use. This has led to the increase in self-medication in China, which is also one of the results in this study: 64.7% respondents would take antibiotics without prescription. It is common among them to use antibiotics to treat common cold. Based on the above factors, it can be inferred that it is their personal behavior instead of following doctors’ prescription when taking antibiotics.

7. Discussion, paragraph 2, concerning the questions posed on education and establishing a course on ‘rational use of antibiotics’: the English translation may need to be amended for these questions in the table and questionnaire, perhaps substituting the word ‘education’ for ‘information’. Similarly, the ‘need to establish a course…’ is presumably specifically within medical schools, so consider prefacing the question with ‘within medical schools there is a need to…’ or similar.

**Answer:** Thanks for the review pointing out these questions. The inappropriate translation has been corrected as suggested in the tables under the advice of the reviewer.

8. Discussion, final paragraph: this should be more specific as to the limitations of the study (geographic region, possibly how the survey was administered [could/would students look up correct answers online]), and its strengths (large size, randomized, comparisons between year groups and MS vs. NS), and subsequently an interpretation as to where the results might be more generalizable to – is it likely that similar results would be found in other regions of China? Do these findings therefore suggest a need for antibiotic stewardship education education programmes throughout Chinese medical school curricula? The final two sentences are also a little confusing at the moment, it is unclear what ‘loophole’ in a medical school curriculum actually means.

**Answer:** Thanks for the review’s valuable suggestions. We accept the reviewer’s advice and rewrite the final paragraph of the Discussions as followed (line 277, page 12):

“This is a large sample size(2500) and high response rate(83.5%) research on KAP towards antibiotics usage of MS and NS. And we compare year groups for both MS and NS from representative universities which would reflect the national situation of China, to some extent. On this basis, we propose that it should extra focus on the antibiotic usage and prescription practice introduction of MS in the medical curriculum, and at the same time strengthen the antibiotic knowledge education for MS and public. However, we suggest that future surveys of this nature may endeavor to cover wider geographical regions of the country.”

9. Conclusions: it is stated that a correlation analysis showed students’ antibiotic
knowledge was related to attitude and awareness; I cannot recall reading this in the results section at all.

**Answer:** Thanks for the reviewer’s valuable suggestion. In the analysis, we use Spearman correlation test to carry on the relations between knowledge, attitude, awareness and practice. And corresponding contents are added into Methods and Discussions partitions:

In line 151, page 7: “We also apply Spearman correlation test to estimate the relations of knowledge, attitude and practice.”

In line 249, page 10: “When we carried about the relationship of knowledge, attitude and behavior, our correlation analysis showed that students’ knowledge on antibiotics had a positive correlation with their attitude and awareness of importance of public education, indicating that there was a direct relationship between their knowledge level and attitude towards promotion of public awareness (Spearman correlation coefficient R=0.3474, p<0.0001).…”

10. Conclusions: ‘this was somewhat puzzling’ needs clarification and interpretation, in the discussion section rather than the conclusions section.

**Answer:** Thanks for reviewer pointing out this question. We accepted the reviewer’s suggestion, and rewrite the conclusion section as followed (line 286, page 12):

“This survey of 2500 MS and NS reveals that the Chinese medical curriculum significantly improves students’ knowledge on antibiotics and antibiotic-related issues. The study also shows an excessive use of antibiotics especially among more senior medical students, reflecting a deficiency of antibiotics usage instruction in their curriculum. This survey also truly reflects some of potential causes of antibiotic abuse in the typical Chinese hospital. To curb the proliferation antibiotic misuse and its consequent effects, we propose the establishment of a special course on rational prescription of antibiotics that emphasizes more on the behavior of medical students towards antibiotics use rather than advance of knowledge alone.”

11. Discussion and conclusions: these should be greatly shortened overall, in particular the conclusions section. The conclusions should summarise the results rather than provide further references for the importance of public education etc. The final sentence goes considerably beyond the results of the present study, and whilst it may be correct, it is perhaps inappropriate to state this as a conclusion to the results found in this study.

**Answer:** Thanks for the reviewer’s suggestion. According to the reviewer’s opinion, we have modified the section Conclusion, in which some unsuitable contents are corrected (see question 10).

12. References: some references are incorrectly formatted, for instance missing a year of publication.

**Answer:** Thanks for the pointing out these questions. We accept the advice of the
reviewer and have corrected the mistakes references with specified form.

13. Table 2: Is the data on the question ‘have you heard of antibiotics resistance’ incorrectly presented for final year students (10.8 [final] vs. 89.7 [first])? I suspect this is probably meant to be 100 - 10.8 = 89.2.

**Answer:** Thanks for pointing out the question. Followed with the suggestion, we have corrected the mistakes in table 2.

14. Table 4: question 30 in the questionnaire is asked as ‘Have doctors prescribed you antibiotics when you catch a cold’, whereas it is included in the table as ‘Asked doctors to prescribe antibiotics when you catch a common cold’; these are completely different questions, the former is not a behaviour/practice of the students but rather of the doctor, whereas the latter is a behaviour/practice of the students. Also it appears that the question ‘are antibiotics obtainable without prescription…’ is considered to be ‘wrong’ in terms of behaviour when answered ‘yes’; however this may have been interpreted as a general rather than individual question (i.e. not whether the individual gets antibiotics, but rather whether they are accessible in general). If the question were instead ‘should antibiotics…’ this would be different.

**Answer:** Thanks for the valuable suggestions. As noticed by the reviewer, in order to simultaneously investigate the initiative and passive of respondents towards antibiotic usage, we set two questions ‘Have doctors prescribed you antibiotics when you catch a cold’ and ‘ Asked doctors to prescribe antibiotics when you catch a common cold’, respectively. All the questions in the questionnaire can be seen in the supplementary material. We also set the question ‘are antibiotics obtainable without prescription…’, which considers the management rules of antibiotics. The translation of the primary manuscript is ambiguous, and we accept the reviewer’s advice to correct it as ‘Should antibiotics be obtained without prescription at drugstores or pharmacies’. For the same reason, we delete the question from the Table 4.

15. Figure 1: The description of the table should include a mention of whether a high score is ‘good’ or ‘bad’. Also if errors marked are true error margins for each year group, then in the results section for ‘comparisons of different grades’ the comparisons should be presented as trends, as it looks highly unlikely that there are any statistical differences.

**Answer:** Thanks for the valuable suggestion. We accept the reviewer’s advice and rewrite the related section in the revised manuscript as followed (line 262, page 11):

“We analyze from the level of different grades to research the KAP towards antibiotics use, which is an important feature of our study. Figure 1a, b, c and d show the comparisons between MS’ and NS’ levels of knowledge, attitude, perception of public education and behavior towards antibiotic use. The MS’ knowledge, attitude and perception on antibiotic use improved as they progressed in course peaking at year 4 with a slight scale-back at the year 5. It is worth noting that the clinical medicine students are introduced antibiotics and antibiotic-related information from
the second year in courses such as microbiology (year 2), pharmacology (year 2), internal medicine (year 3), and epidemiology (year 4). Although they could touch prescription of antibiotics during the years 4 and 5, MS do not prescribe any medicines until after they have completed the course. The most senior (years 4 and 5) MS’ scores on behavior towards antibiotics use were lower than those of their junior colleagues (years 1, 2 and 3) indicating that there could be some negative impact on students’ erstwhile good antibiotic practices by the hospital environment during clinical. This fluctuation of KAP could be due to inherent flaws in the medical curriculum. And it reflect that add some courses on rational antibiotic practice in the medical curriculum in China is urgently needed.

Discretionary revisions
1. Materials and methods, design and implementation of questionnaire: it is stated that the questionnaire is subdivided into four categories; it may be helpful in the supplementary material to indicate these four categories as different sub-sections.

Answer: Thank for reviewer’s suggestion. We have included details of categorizing the questions in the Supplementary material.

2. Results: for non-significant p values, there is no need to include four decimal places, two is sufficient since the significance level is set as <0.05. Similarly, as the number of participants in each group is ~100, two decimal places is overly precise for the percentages. Including one or even no decimal places is sufficient.

Answer: Thank for reviewer’s suggestion.. We used the Bonferroni method to obtained the significant results (P<0.0017).

3. Table 2: it is an interesting result that 69% [final] vs. 49% [first year] MS think that antibiotics can cure viral infections; since this is a leading cause of antibiotic over-use this result is probably worthy of mention in the text of the results/discussion.

Answer: Thank for reviewer pointing out this question. We are sorry for the description questions puzzling reviewer. the original meaning is that MS do a correct answer of the rate 69% and 49% for final and first grade, respectively.

4. Table 4: A number of the questions from the questionnaire are not included in this table, such as antibiotics for pneumonia, allowed to stop antibiotics when complaints lessen; for transparency in terms of interpretation, these results should probably be included.

Answer: Thank for reviewer’s suggestion. At this stage, the main goal for the study was to compare the differences in antibiotics KAP between MS and NS. Therefore, we did not analyze the non-significant difference questions.

5. Ethical considerations: It may be worth including a note on any permissions/other considerations necessary for extracting data using students’ numbers at the university – who was permissions sought from, are these ALL students or just students who have
their numbers publicly available?

**Answer:** Thank for reviewer’s suggestion. The permission to obtain students information (i.e. ID details or course majors) was sought from student affairs office in the two non-medical universities. Such offices in universities in China would also assist in informing the students of any ongoing research projects seeking their participation. Informed consent was signed by the participants before they filled in the questionnaires.