Author’s response to reviews

Title: Availability and Use of Essential Medicines in China: Manufacturing, Supply, and Prescribing in Shandong and Gansu Provinces

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Author’s response to reviews: see over
Dear Dr. Signe Flottorp,
Associate Editor
The BioMed Central Editorial Team

We are pleased to submit the revised manuscript entitled "Availability and use of essential medicines in China: Manufacturing, supply, and prescribing in Shandong and Gansu" and the cover letter detailing our responses to each editorial request and all reviewers’ comments.

We thank you and all reviewers for the helpful suggestions to improve our manuscript and for giving us the opportunity to revise it. We look forward to your favorable consideration of the revised manuscript for the publication in BMC Health Services Research.

With kind regards,

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Editorial requests:
- We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service. The manuscript has been edited with a focus on style by the co-authors who are native English speakers.

- Please clarify within the Methods section of your manuscript whether the data used in this study is publically available or whether you obtained permission to use this data. If you obtained permission please be sure to mention who gave approval. We now clarify in the last sentence of the introductory paragraph of the Methods section (p. 3) that WHO funded the study and agreed to use the data for academic research. We have also indicated this in the Competing Interest section (p. 8).

1st reviewer’s comments:
Major compulsory revisions
Background
A bit more information on the place of Chinese medicines in Therapeutics would be helpful for western readers. How frequently are they used compared to western medicines, in particular in hospitals? Are there practitioners/hospitals who use Chinese medicines exclusively? What is their therapeutic value compared to Western medicines? This may explain some of the results obtained and this data are relevant for the discussion as well. The focus of the paper is not primarily on Chinese herbal preparations in comparison to Western medicines; both are included as options in the NEML. However, we have added a sentence in the Methods section on selection of survey medicines explaining that, although the availability of Chinese herbal preparations improves access to essential medicines, especially in rural primary health care institutions, Western medicines are the treatment of choice for the majority of Chinese patients (p. 4).

Please could you give also more information on the roles and differences between primary, secondary and tertiary hospitals, and the functions of retail pharmacies? It is not clear to me if primary hospital are primary health care centers or whether they accept inpatients only. We now briefly describe the services delivered at the three hospital levels in the Methods section covering the Health Facility Pharmacy Survey (p. 3) and the functions of retail pharmacies in the Methods section covering the Retail Pharmacy Survey (p. 3).
How many essential medicines are reimbursable by urban health insurance schemes?

As indicated in Discussion section (p. 8), under the new Chinese health reform, all essential medicines will be reimbursable by both urban and rural health insurance schemes.

Methods

More information is required on the content of the interviews of manufacturers and pharmacy managers.

We have indicated the topics covered in the interviews in the Methods sections on the Manufacturer, Health Facility and Pharmacy Surveys (pp. 3-4).

Prescription review: more detail should be given about the type and accuracy of information kept in medical records.

Data collected in the prescription survey represent prescriptions as written and dispensed in the health facility pharmacies. There is no way to determine their accuracy beyond what is written on the prescriptions.

Random sample of essential medicines: it is clear from the results that this was not the best methodology to choose as many randomly chosen products may be only useful in hospitals and then, the results do not give an accurate description of the availability of essential medicines in retail pharmacies that may provide medicines to primary care patients only (?)

In principle, this is true. On the NEML, it does not specify whether medicines are intended for outpatient or inpatient care. Thus, some medicines in our sample may not be expected to be found in retail pharmacies that focus on outpatient dispensing. We have now pointed this out as a limitation in the Discussion section (p. 6).

Results

What was the response rate of interviews with manufacturers and pharmacy managers?

All manufacturers and pharmacy managers responded to the interviews.

Page 5 4th paragraph: give results in % as well (7 and 19 products)

We have now done so.

Hospital pharmacies: please could you give the overall % of essential medicines from the NEML that have production licenses in the study manufacturers? Please could you give the overall % of essential medicines from the NEML that are produced by at least one of the study manufacturers in each region?

We have now indicated the number of products produced by at least one manufacturer in the Results section on Manufacturing of Essential Medicines (p. 5).

The term median (text and table 4) should not be used for binary variables such as percentages, average and SDs should be used instead. SD are only mentioned in the
text for hospital pharmacies but not for the other results, maybe keep them in tables only.

*Each percentage reported in Table 4 and in the corresponding text is the median percentage of the list of essential medicines that were available across the hospitals at a given level of care in each region.*

**Discussion**

It is stated that manufacturers did not produce 40% of the list of products on the NEML. It’s an ambiguous statement as a higher % could be found if you looked at the overall % (or the opposite: what is the % of essential medicines that is not produced by any manufacturer?)

*In the Discussion section (p. 6), we have modified this statement to make it clear that the percentage applies only to the specific product licenses held by the manufacturers.*

Limitations: it is not clear why you “lacked data on all products manufactured”. The way the article is written gives the impression that you collected all data that you wanted. Please explain a bit further. You could still calculate an overall % of essential medicines produced even if you have not surveyed all manufacturers. What is the proportion of manufacturers surveyed? Can hospitals order their medicines from manufacturers outside the region?

*As stated in the Methods section (p. 3), all manufacturers in the two provinces were surveyed. We did not obtain data on all products manufactured, only on essential medicines. We can thus assess the production of essential medicines according to the product licenses manufacturers held, but cannot assess the proportion of essential medicines produced in relation to all products manufactured. We have clarified this in the Methods section (p. 3) and in the limitations section in the Discussion (p. 6). Hospitals are free to purchase medicines from manufacturers outside their regions.*

**Discussion**

The discussion jumped a bit quickly to an ideological discussion of the current Chinese industry policies (e.g. pricing policy) that do not seem completely relevant to the results of the survey. More attention should be paid to the results themselves. E.g. the most frequent reasons for not purchasing the selected essential medicines was lack of clinical use or availability of clinical alternatives. Is it possible to explore these results further? Did the random list include medicines that were rarely of use? It would be useful to give the list of the medicines you surveyed! Should the NEML be reviewed in light of these comments? What were the preferred alternatives? It is difficult to see the relevance of a discussion about the pricing policies of generic versus originator products if you have no idea of what were the preferred alternatives?

*We have tried to focus in the Discussion on the importance of the study results in the current context of health reform. Medicines availability, pricing, selection, reimbursement, and prescribing are key issues addressed in the reform process. We would be happy to append a list of all medicines surveyed if the editors feel it would be useful. We feel that discussion about the process of constructing the list of*
essential medicines may be beyond the scope of the article. However, we do emphasize that the 2009 NEML is considerably smaller than the 2004 list that was the basis for this survey.

Overprescribing of antibiotics and injections: the conclusions are a bit too quick given that there is no information on the quality of information included in the clinical records. What were the reasons given for prescribing antibiotics? Injections? I think that this part of the study is so few detailed that I wondered whether it should be left out of the article altogether.

We were unable to obtain data on the clinical features of the illnesses treated, only on diagnoses recorded and medicines prescribed. However, this type of prescription survey is recommended by WHO to examine outpatient prescribing patterns in health facilities. (Please see new reference 12.) In this document, WHO estimates that less than 5% of patients in routine outpatient consultations should receive an injection and less than 20% should require an antibiotic. Furthermore, we excluded prescriptions for children and for adult cases treated in hospital infectious disease clinics, so the rate of appropriate antibiotic prescribing in our sample should be even lower. We have clarified these issues in the Methods section covering Prescription review (p. 5), in the Discussion (pp. 8-9), and in Table 5.

Then, when you read the last part of the conclusion, you may think that, yes, the selection of “essential” drugs used in the survey may not be so “essential” as the 2009 revised list only includes now 205 western medicines instead of 773. It would be interesting to know what % of this new list was produced, prescribed and available in pharmacies in the survey.

We agree that this would be interesting. However, our surveys were conducted in 2006 and 2007. Further research would need to be done to examine the production, availability, and prescribing of medicines on the new smaller NEML.

I believe that the discussion should be reviewed to focus on the results of the survey itself, the limitations that may have influenced the results and shorten the section on Chinese industry policies that are no directly relevant to the results.

We have shortened the Discussion section considerably. However, we feel that the focus on pricing policies and incentives that drove manufacturer, supplier, and prescriber behavior prior to health reform and the challenges under the new health reform process are crucial in putting the results of this study in context, so we have kept in briefer discussion of these issues.

Abstract
Second line in results: should be “they were licensed to produce” instead of “they licensed.

Done in Abstract (p. 1).

Most semi-colons should be replaced by full stops.
Conclusions: too strong, I don’t think that you can conclude from your study that prescribing of essential medicines did not coincide with appropriate use if we have no details on which medicines, which indications etc. Especially knowing now that the NEML list has been completely revised thereafter!

As discussed above, by limiting our sample to routine adult outpatient consultations (excluding adult emergency care and adult cases treated in hospital infectious disease clinics), we feel confident that the high rates of prescribing of antibiotics and injections observed in our study indicate inappropriate care. To support this conclusion, we have provided more details about the sample of prescriptions at several points in the article and reference the guidance document from WHO concerning expected rates of injection and antibiotic prescribing in these types of outpatient prescription surveys.

2nd reviewer’s comments:
1. Page 2; Paragraph 3: Is the reimbursement body is governmental? If so why some items on the NEML are not reimbursable?

The insurance systems in China are governmental and all essential medicines are reimbursable. However, according to the National Household Health Services Survey in 2008, approximately 20% of urban residents have no health insurance coverage and thus have to pay for all medicines out of pocket. In addition, most rural residents, even those in the New Cooperative Medicines Schemes, had no coverage for outpatient care at the time of this survey and also had to pay for all medicines out of pocket.

2. Page 4; Paragraph 2: Considering that WHO EML is just a model list for developing NEML by the countries, and if China has an NEML why authors assumed that WHO EML should be fully available in the country. I believe including WHO EML in this study is fruitless and somehow misleading. I propose this part and related discussion and column in table 4 should be removed from the manuscript.

We have removed all comparisons to the WHO EML from the manuscript as recommended.

3. Page 4; Paragraph 3: Why authors excluded antibiotics prescribed for the infectious disease treatment from their survey.

In order to investigate possible overprescribing of antibiotics in routine adult outpatient care, we excluded cases treated in hospital infectious disease clinics, where prescribing of antibiotics might be considered more appropriate. This also minimizes the impact of treatment for severe infectious diseases, which is unbalanced among hospitals and regions.

4. Page 6: Discussion; 2nd paragraph: Authors should explain why they did not use a more logic approach (than simple random sampling) e.g. representatives of clinical
groups present in NELM for their survey.

*Our prescribing survey did not seek to characterize rates of use of individual medicines on the NEML, only the overall rate of prescribing from the list in routine adult outpatient care, as well as the rates of specific potentially inappropriate prescribing practices, including polypharmacy and overprescribing of antibiotics and injections. In this, we were guided by WHO recommendations for this type of prescribing survey (citation noted above). We have clarified these points in the Methods section on Prescription Review (p. 5) and in the Discussion of results of the prescribing survey (pp. 7-8).*

5. Page 7; Discussion line 4-5: I think without presenting data or referring to a reference conclusion about the safety, effectiveness and efficacy of the medicines is very "strong".

*We have edited the Discussion to remove this sentence, according to other reviewer’s comments.*

6. Page 7; Discussion: I assume comparing data presented in this paper especially those regarding prescribing indicators with those reported from other countries will add to the usefulness of the Discussion.

*We have added to the Discussion (p. 8) a comparison to global rates for antibiotic and injection prescribing between 2004 and 2006, reported in a recently published WHO document.*

7. Table 2: What is RMB? Local currency? What is its relation to USD or Euro?

*RMB is the local currency. We have added a footnote in Table 2 on Page 13 indicating the conversion rate for RMB to USD in 2007.*

8. Table 5; Row 3: What is the value for the cost? Local currency or USD?

*We have indicated that the costs in Table 5 on Page 16 are stated in RMB and have added a footnote indicating the conversion rate to USD in 2007.*

3rd reviewer’s comments:

Minor essential revisions

1. I think the column heading in Table 4 should be WHO EML rather than WHO ML.

*The column has been removed according to another reviewer’s comments.*

Discretionary revisions

1. There is comparatively little discussion of the results of the prescription survey in the paper. Table 3 reports the top 10 medicine products manufactured in the two provinces studied. The reader is struck by the differences between these, with the dominance of traditional Chinese medicines in Gansu province. The data in Table 4 show Gansu had higher levels of availability of NELM Chinese medicines, lower availability of NELM Western medicines and lower availability of WHO EML medicines than in Shandong province. Do the authors think there are any implications
for this in trying to implement policies based on EMLs, particularly evidence-based EMLs? The new NEML will have 205 western and 102 traditional Chinese medicines, with facility for local extension and adaptation to meet local needs. However the 2004 NEML had 1260 Chinese and 773 western medicines.

We have extended the presentation on the prescription survey in the Results (p. 7) and Discussion (p. 8), as recommended. Gansu manufactures a high volume of Chinese medicines because of the abundance of raw materials. It is interesting to note that the supply of Chinese medicines in Gansu for each level of hospital is close to that in Shandong, but that Western medicines have lower availability. We might expect that the balance between prescribing of Chinese traditional and Western medicines might change as a result of the substantial increase in Chinese medicines on the new NEML. However, we have not commented on these issues in the manuscript since the focus is on Western medicines.

2. Results from Gansu province also show higher numbers of medicines per prescription, higher proportions of antibiotics per prescription and higher proportions of prescriptions with injections particularly in primary health care settings (Table 5). They authors could comment further on these observations and challenges for changing prescribing practices in different settings within China.

We have highlighted more of the differences in prescribing patterns between Gansu and Shandong in the Results (p. 7) and Discussion (p. 8).

3. The discussion refers to retail pharmacies citing primarily economic reasons for purchasing decisions while hospital purchasing was clinically driven. Pharmacy managers reported market demand as the most common reason for purchasing decisions, however market demand could perhaps be considered clinically driven if it reflected what is being prescribed by local medical practitioners. This is an ambitious program of reform being undertaken in China. If the reforms can achieve the stated objectives, it will provide a model for other health care settings where EMLs exist but procurement and prescribing practices in relation to the EML are suboptimal.

There is a close relationship between economic and clinical determinants, for exactly the reason mentioned. We have now included this point in the Discussion of the results of the pharmacy survey (p. 8). We agree that the reform program in China is ambitious and has far-reaching implications. We highlight this in the last paragraph of the Discussion (p. 9).

4th reviewer’s comments:

Abstract
In the abstract the sentence “the current healthcare reform in China tackles the problem of access to appropriate medicines for its 1.3 billion people by focusing on providing essential medicines”. What was the year of current health reform? Though the reform has been mentioned in the abstract, it has not been explicitly stated in the
introduction. 
*The current health reform was launched in 2009. We mention it as the context for this paper in the last paragraph of the Introduction (p. 3). We have also discussed the importance of medicines as a component of health reform in the last paragraph in Discussion section (p. 8).*

Background
In the background it has been mentioned that China’s pharmaceutical expenditures are over 40%, one of the highest in the world. This could not be true as in developing countries the pharmaceutical expenditure could range up to 70% of non personal cost (Quick et al, 1997). Also as China is not an OECD country and I can’t see the point of comparing it with OECD average.

*We have deleted “one of the highest in the world” in the Background section (p. 2). Although China is not an OECD country, the OECD average is often regarded as a benchmark for comparison.*

In the background several recent references (such as reference 1, 3, 5, 9) have been mentioned, however the study was conducted in 2005 (before these references were published). The author may want to build a problem statement by using the data and references and references which were published before 2005. As this study provide evidence for reform process, in the discussion section, they can use recent references to explore the problem and issues.

*The study was conducted in 2007 and collected the data for production, supply and utilization in 2005-2006. We have now indicated the date of the survey in the Background section of the Abstract (p. 2) and in the Method section (p. 4). Unfortunately there are few references about China’s essential medicines and related policies, so we have included some published after 2007 that we think are relevant to the context of the article.*

Methods
On page 4 under selection of survey medicines, it has been mentioned that 77 western medicines (98 unique dosage forms) were collected. However the strength is not mentioned. How medicines with varying strength but the same dosage form was counted?

*Strength is not defined in the NEML, meaning that all strengths of the listed product licensed by the State Food and Drug Administration can be used. Actually many varying strengths for the same dosage form exist in the market. In our survey, we included any available strength of the sample of survey medicines. We have indicated this in the Methods section on selection of survey medicines (p. 5).*

Discussion
Though it has been discussed that low cost generics were not commonly used in the hospital, however there is a need to add more detail e.g how generics are procured in the hospital? Also, what are patient charges? Do they have to pay for all/some
medicines? Does it differ from one hospital to another? If they have to pay, how much?

*We have expanded the discussion of the results of the hospital availability survey and the reasons underlying the preference for expensive branded medicines (p. 7-8). We have also indicated that patients pay for most medicines out of pocket and thus face additional cost burden due to this preference.*

The same goes for community pharmacies. Is it all out of pocket expenditures? How social health insurance works etc

*Most prescribed medicines in China are dispensed in hospitals. Retail pharmacies can dispense medicines to patients who have a prescription, and patients can then receive reimbursement if they are insured. The copayment requirements are the same for patients if medicines are dispensed in a hospital or a retail pharmacy.*

Overall comments

Overall the study is well written and interesting and can be published after some minor revision. Also, as the study was conducted in 2005, it is important to highlight the pharmaceutical situation and any important changes (since then) in a chronological order.

*The survey was conducted in 2007. We have highlighted the focus on the current China health reform process, which began in 2009.*

5th reviewer’s comments:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes
3. Are the data sound? Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? The discussion is good and authors have discussed according to their findings, BUT the authors did not make conclusion according to the research objectives and research questions.

*We have modified the text in the conclusion in the Abstract and in the Conclusions section to highlight our findings in relation to our two research questions.*

6. Are the limitations of the work clearly stated? Yes. But, need to include in the article the strengths and weaknesses of the study at the end of the Discussion section.

*We have pointed out the limitations of the study beginning in the second paragraph of the Discussion section (p. 6-7).*

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? No

*In the Introduction, we highlight the previous work of the WHO which led up to the commissioning*
of the current study.

8. Do the title and abstract accurately convey what has been found? Yes

9. Is the writing acceptable? Yes, but with considering comments made by the reviewer.

Reviewer's report
Minor Essential Revisions
1. Check grammar in the Data Analysis section
   We have made several changes to improve the grammar of this section.

2. Results section: "Of 107.......in Shandong and Gansu provinces (plural)
   Done on p. 5.

3. Rewrite the conclusion based on the objectives and research questions
   We have rewritten the Conclusion to focus on the findings in relation to our two research questions.