Author's response to reviews

Title: Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China

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Author's response to reviews: see over
Dear Christopher Morrey,

I was very glad to receive your letter. Thank you very much for the report of the reviewers and your patience. I would like to provide this cover letter giving a point-by-point response to the concerns raised.

**Reviewer:** Jimmy Dr Jose

1. **Title:** Is not clear. The term pharmacoeconomics could be omitted and replaced as ‘Evaluation of cost implicated to adverse drug reactions among…….

   The new title of the manuscript is ‘Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China’.

2. In abstract, it is not clear what is mentioned as 'degree of ADR'

   The term ‘degree of ADR’ has now been replaced with ‘two groups […], namely serious ADRs and general ADRs’.

3. **Introduction:** Some review of literature on cost implicated to ADRs could be added

   This literature [see 9] has been added to the manuscript.

4. **Methodology and results:** It would be ideal to convert and represent the cost in USD as well so as the international readers could comprehend the details more effectively.

   In other similar studies, the home country’s currency was usually used. Therefore, we do not think that this conversion into US dollars is necessary.

5. **Scored below 1’**. Does it refer to Naranjos scale.
Yes. All ADRs were re-evaluated according to the *Provisions for Adverse Drug Reaction Monitoring and Reporting* report issued in 2011 as well as the Naranjo scoring algorithm.

6. Results and discussion: Even though the study is concentrating on cost implicated, there seems to have too much focus on type of ADRs, drugs involved, etc. It would be more appropriate to evaluate the cost implicated based on nature of ADR, drugs involved, body system affected.

In the revised version of the manuscript, the objectives of this study are to (1) calculate the costs associated with different degrees of ADRs and determine total Medicare payments on ADRs as well as their proportion of total healthcare spending and (2) evaluate the incidence of ADRs, characteristics of hospitalized ADR patients, and outcomes of ADRs.

7. Discussion; Kindly clarify 'cost of 3 groups'
The term ‘cost of 3 groups’ has been replaced with ‘cost of 2 groups’.

8. Discussion: Comparison with previous literature is lacking. Limitations for the study needs to be clearly stated.

Some references have been added in the discussion. This retrospective study is based on a spontaneous reporting and monitoring system, where underreporting by healthcare workers is a possibility because of the time constraints under which clinical medical staff work. This retrospective method and possible underreporting in the study are its limitations.

9. Conclusions: Needs to more clearly derived from the study results and should have major recommendations.

The following sentences have been added into the conclusions: ‘Although severe ADR incidence was lower, the cost of treatment for severe ADRs was relatively high. Therefore, we should focus on the prevention of severe ADRs through ADR monitoring programmes. Further, for ADRs that automatically improve after drug withdrawal, the cost is relatively low, suggesting that stopping the medicine altogether is the best treatment for these kinds of ADRs.’
Reviewer: Jian-Xiang Xie

Major Compulsory Revisions

1. All ADR cases were enrolled from inpatients of hospital. However, outpatient was appeared in the context of measurement of indirect costs. Please explain it.

In China, ADRs are monitored by the medical staff in the outpatient care department. However, outpatients are often unable to identify ADRs in the absence of medical staff, meaning that the monitoring of these kinds of ADRs is missing.

2. The data of table2 is not complete.

The data presented in Table 2 have now been completed.

3. All the ADR cases were divided into two groups. But three groups were appeared in results and discussion. Please explain it.

Please accept our apologies for this oversight, which has now been corrected.

Minor Essential Revisions

1. This manuscript mentioned all the ADR cases were divided into two groups. Please explain the relationship between two groups and mild, moderate and severe ADR reactions.

All ADR cases were divided into two groups according to the Provisions for Adverse Drug Reaction Monitoring and Reporting report, namely serious ADRs and general ADRs [13]. Group A comprised (1) cases with general ADRs that could be rehabilitated without any treatment, other than stopping the administration of drugs and (2) cases that did not require hospitalization, or did not prolong hospitalization, but could be rehabilitated with other drugs or therapeutics. Cases with serious adverse reactions according to the Provisions for Adverse Drug Reaction Monitoring and Reporting report belonged to group B. An ADR condition belonged to group B if it (1) caused death; (2) posed a threat to life; (3) led to significant or permanent human disability or organ damage; (4) led to brief or prolonged hospitalization; or (5) led to other important medical events. Mild reactions can self-heal after discontinuation, moderate reactions do not result in prolonged hospitalization but can be cured by other drugs/treatment, and severe reactions prolong hospitalization or other important medical events. Thus, mild and moderate ADRs belong to general ADRs (group A)
and severe ADR reactions are in group B.

**Reviewer:** Ji-Fu Wei

Major Compulsory Revisions

1. The abstract is too long. Please re-write it.
   The content has been reduced.
2. The table 2 is incomplete according to the results.
   The data presented in Table 2 have been completed.

Minor Essential Revisions

1. ADR or ADRs should be the same throughout the manuscript.
   This has now been changed (but sometimes ADR is used as an adjective).
2. The numbers of groups should be the same throughout the manuscript.
   We have checked the numbers of groups throughout the manuscript.
3. pharmacoeconomic can be added to Keywords.
   This has been added.
4. Please mention P < 0.0001 in statistics in method section.

MS Excel was used to create the ADR database, and Stata v. 11.0 software was adopted to analyse the data.

**Reviewer:** Hanna Gyllensten

1. The study estimates costs for ADRs identified by spontaneous voluntary reports from healthcare professionals, part of the hospitals pharmacovigilance system. I would have liked this to be clarified earlier in the paper, and preferably also in the abstract.
   This has now been added into the abstract.
2. How was the distribution of cases according to the Naranjo scores? I would have liked a more thorough description, discussion and some references to previous studies on the scoring according to the Naranjo algorithm. To retrieve a score of 1 (possible ADR) it would be enough that the drug was found in a blood sample from the patient, if none of the other items were known or tested for. That appears to be a quite low
level of proof for identifying an ADR. Only ‘possible’, ‘probable’, and ‘definite’ ADRs that scored more than 1 were taken into consideration; the causality of these ADRs was also classified according to the methodology of Naranjo et al.

3. What was meant by sunk costs in this study, and how were these included? Do these only indicate that the cost calculation is retrospective, or do you include the cost of the drug that caused the ADR? Would it be possible to clarify and report the proportion of the total costs these sunk costs represented?

(1) If an expense incurred cannot be recovered, a rational person would ignore it. This type of expenditure is called a sunk cost. From a rational perspective, a sunk cost that cannot be recovered should not affect the consumer’s purchase decision or attitude.

(2) Yes, the cost calculation is retrospective. We included the cost of the drug that caused the ADR. We have clarified and reported the proportion of the total costs these sunk costs represent in Table 2.

4. In the methods you indicate that some HIS records were incomplete. How many were missing?

Of these, cases that scored below 1 and those whose electronic information in the HIS record had been lost or was incomplete (234 cases) were excluded.

5. I have not seen this method for estimating indirect costs, based on GDP, previously. What is the consequence of using GDP instead of e.g. foregone earnings/income in measuring indirect costs? Moreover, what is the effect in an expanding economy such as China? Effect by the method used to calculate GDP? Effects on the productivity loss resulting from ADRs on the GDP?

Only loss of working time was estimated considering the practicability of the study. Therefore, using GDP per capita income in order to calculate the cause of ADRs in lost work time does not produce other effects.

6. Could you please clarify during which time the indirect costs were included: is it only while the patient is hospitalized, during hospitalizations and outpatient visits, throughout the duration of the ADR regardless of healthcare encounters?

I have some questions regarding the comparisons to previous research:
Yes, indirect costs were included: this is when the patient is hospitalized, during hospitalizations and outpatient visits, and throughout the duration of the ADR regardless of healthcare encounters.

7. The ADR incidence in this retrospective study is compared to three previous studies, of which one is a prospective study and two are pediatric ADRs (references 20-22). According to Leendertse et al (2010) prospective studies and medical record review identify more ADRs and ADEs than spontaneous reporting and retrospective studies.

How does your estimate relate to previous studies on voluntary reports of ADRs? The correct references have been added into the discussion and the inappropriate references removed.

8. The ADR definition presented in the discussion appears to be very different to the definition used by e.g. The World Health Organization, and it was a bit unclear what ADRs were actually included in this study. What is the result of your exclusion of “harmful reactions from normal doses of eligible drugs”, which indicates that you do not include any reactions that are considered ADRs according to the definition by WHO?

The World Health Organization defines an ADR as ‘a reaction which is noxious and unintended and which occurs at doses normally used in humans for prevention, diagnosis or therapy of disease, or for the modification of physiological functions’. The Chinese definition does not include harmful reactions from normal doses of eligible drugs administered for medication. Thus, this definition excludes adverse events due to drug quality, administration with no indications, and off-label use. Thus, ADRs caused by off-label use do not include any reactions that are considered to be ADRs according to the WHO definition.

9. There is quite a large body of evidence supporting the result that women experience more ADRs than men, yet the only reference here is to one prospective study with other results. Is there a specific reason for comparing to this reference (similar detection, population, etc)? Moreover, how does your results for age groups and identified drugs compare to published reviews on ADRs in hospitals?
References have now been added to explain the gender differences in ADRs. This result may be because TCM injections, which are used in many hospitals in China, are more commonly administered to women than to men. The other reason may be related to the different sensitivity levels and metabolic processes in men and women.

10. Do you have references for interested readers on the current price reforms in China, or to the “domestic” studies indicated at the end of the discussion? There are some possible limitations to the data and analysis that needs to be more thoroughly described.

This study found that the total socioeconomic loss from the 2739 cases of ADR was ¥817401.69 and that the cost per ADR patient was approximately ¥298.43. This cost is far below the level of developed countries, which may reflect the lower medical care and drugs charges in China. The indirect costs were far less than the direct costs because chaperone charges and intangible losses were not included in the data. Therefore, the true value might be far greater than the value calculated in the present study.

11. What limitations resulted from your selected method for detecting and defining ADRs: what is missed by voluntary reports, are there reactions that may not have been reported or were deleted when using the Naranjo scoring, and are there reactions that were included but may have other causes?

This retrospective study is based on a spontaneous reporting and monitoring system, where underreporting by healthcare workers is a possibility because of the time constraints under which clinical medical staff work. This retrospective method and possible underreporting in the study are its limitations.

12. What limitations occurred due to your selected method for estimating costs: how was extended days in hospital calculated, what would have happened had you used other cost sources, how many records were incomplete?

Direct costs refer to direct medical costs, which include treatment fees, inspection fees, laboratory fees, materials fees, bed charges, drug charges, nursing care, meals, and other expenses from the beginning of the ADR to the termination of treatment. The calculation of direct costs was based on the electronic medical data accumulated in
the hospital information system (HIS). The costs of group A were calculated as the sum of the sunk cost losses and direct costs. Of these, cases that scored below 1 and those whose electronic information in the HIS record had been lost or was incomplete, (234 cases) were excluded. Therefore, the cases enrolled in the study provided full data availability.

13. Which potential costs resulting from ADRs are not included in this analysis? In this study, only direct and indirect costs were calculated; invisible costs were ignored.

14. Was the minimum length of hospitalization 1 or 2 days? And what happened to the outpatient visits mentioned in the methods? The longest period of hospitalization for the most serious ADR case was 32 days, the shortest period was 2 days, and the average was 10.8 days. The indirect costs of groups A and B were calculated according to the formula for the cost of inpatient care. Only when some ADR cases in group A self-heal after stopping drug treatment can the indirect costs of group A (about one outpatient per case) be calculated from lost outpatient income based on actual outpatient visits.

15. What is the consequence of only including indirect costs that occur during the healthcare encounter? As stated above, only when some ADR cases in group A self-heal after stopping drug treatment can the indirect costs be calculated. This does not influence healthcare provision; rather, it only affects the drugs that cannot be used and the loss of settlement costs.

16. On which result do you base the assumption that "When the ADR-related costs are relatively greater, prevention costs against possible occurrence if ADRs would be excessive..."? This sentence has been deleted and replaced by the following: ‘There is also a great cost difference between the two groups, suggesting that the occurrence of ADRs should promptly occur after withdrawal and treatment. Moreover, the reduction and control of the high ADR rate can greatly reduce costs, both for the patient and for the health department, thus mitigating the economic burden of medical institutions.’
17. Why was ”actual proportion are not consistent with this study”?
Because drug choice policies and number of patients covered by Medicare differ across hospitals, the actual proportion of Medicare payments in other hospitals may be inconsistent with those in this hospital.

18. The conclusions could be both elaborated and clarified: If severe ADRs do only representent approximately 50% of the total cost, would it not be important to address the less severe ADRs? From where did the number 0.13% come?
The figure 0.13% refers to the occurrence of severe adverse reactions. Although the severe ADR rate is low, the total costs of severe ADRs are assumed to be much higher.

Discretionary Revisions
19. The aim of the study was well defined (although aim in the abstract and objective in the main text?). I was a bit uncertain of, from the objective, which proportion was to be presented, but that was clear later on in the text.
The aim of the study has been edited.

20. The authors appear to acknowledge the work upon which they are building. It appears that the data is sound, and the manuscript adheres to relevant standards for reporting and data deposition. However, would it be possible to indicate in the paper the viewpoint/perspective of the economic analysis, if there were any adjustments made for timing of costs (were any long-term costs included), and present quantities of resources that are included in the cost analyses?
Such topics could be explored in future research.

21. I would have preferred the title and abstract to indicate the ADR detection method. Moreover, what is meant by sunk-cost losses and the definition of ADRs could be added in the abstract.
The writing is acceptable, although I have some comments/suggestions for changes: We have made these changes, as suggested.

22. The background lack references to the more wellknown review-studies available, both for hospitalizations due to ADRs and costs resulting from drug-related hospitalizations.
These references have been added into the background.

23. It is unclear what is meant by the sentence: "All the uncertainty associated with their estimations was evaluated by many scholars"?

Because studies use a variety specific methods, these different methods have resulted in considerable uncertainty about the resulting estimations.

24. The sentence about ADRs as a key research topic in Europe and the United States should not be referenced by one study from India and one from the US.

Reference [7] has been replaced.

25. The wording "retrospective, descriptive, and investigative research" is not very specific.

This wording has been replaced with the following sentence: ‘In this retrospective, descriptive research based on data derived from a spontaneous reporting system, …’

26. The last sentence under the heading Measurement of indirect costs is not very clear (where do you get the "one outpatient per case" and what happened to the GDP-based estimate).

The sentence has been modified.

27. What is group C?

The word has been deleted.

28. Parts of paragraph 2 in the Results section could be moved to the Methods section.

We have moved these, as suggested.

29. Could you explain in the Methods section the WHO Adverse Reaction Terminology, and indicate a reference for interested readers?

This has been changed.

30. Would it be possible to indicate a relevant exchange rate to e.g. USD or EUR somewhere in the paper?

The RMB exchange rate against the US dollar is approximately 6.061, while the euro exchange rate is approximately 8.197.
The above documents have been submitted in electronic version to *BMC Health Service Research*. If you have any questions or queries, please write to me by the email given below. I look forward to acknowledged receipt of this article by email.

Thank you very much.

Yours sincerely,

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Yours sincerely,

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