Reviewer's report

Title: Pharmacoeconomic Consequences, Measurement, and Evaluation of Adverse Drug Reactions among Hospitalized Patients in China

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Reviewer: Hanna Gyllensten

Reviewer's report:

Major Compulsory Revisions

In this paper, the important issues of adverse reactions to drugs, their characteristics and consequences, are being addressed. Moreover, the study adds knowledge of the situation in Chinese hospitals. Although an important addition to the literature, there are some choices and limitations that need to be elaborated.

There are some methodological issues that need to be clarified:

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.

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.

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?

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

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?

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:
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?

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?

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?

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 throughly described:

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?

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?

13. Which potential costs resulting from ADRs are not included in this analysis?

Minor Essential Revisions
The discussion was supported by the data, but there were some points still to be addressed:

14. Was the minimum length of hospitalization 1 or 2 days? And what happened to the outpatient visits mentioned in the methods?

15. What is the consequence of only including indirect costs that occur during the healthcare encounter?

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..."?

17. Why was "actual proportion are not consistent with this study"?
18. The conclusions could be both elaborated and clarified: If severe ADRs do only represent 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?

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.

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?

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:

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.

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

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.

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

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).

27. What is group C?

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

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

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

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.