Author's response to reviews

Title: Chinese patent medicines for the treatment of common cold: a systematic review of randomized clinical trials

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Author's response to reviews:

Reviewer's report

Title: Chinese patent medicines for the treatment of common cold: a systematic review of randomized clinical trials

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Reviewer: Karen KP Pilkington

The authors have addressed a number of the comments. However, problems with the interpretation remain.

In the previous reviews of this paper, the authors were asked to explain the effectiveness or otherwise of the control treatments and whether the control treatments were actually appropriate. The authors have responded by omitting one trial because the control was an antibiotic which would not cure a viral infection (although it might be necessary for a bacterial infection as a
We thank Dr. Pilkington’s valuable comment. However, we actually did not omit the trial of Wu 2012 from this review, just deleted its result from the abstract because we think that the control of Wu 2012 was inappropriate and that the abstract should only report the important and main result. We had commented on the use of inappropriate controls in the discussion part.

However, the authors have not addressed the questions about the possibility of complications and whether the condition being treated was actually a simple common cold, which as they point out is usually a mild and self-limiting condition. As mentioned previously, the use of antiviral therapy suggests that a more serious respiratory tract infection was being treated. In the UK and USA, ribavirin is only used for severe respiratory infections such as respiratory syncytial virus bronchiolitis in infants and children or severe acute respiratory syndrome (SARS) (or for chronic hepatitis). Oseltamivir is used for influenza in specific circumstances. It is not clear why, if these were cases of common cold, these treatments were used as controls.

We do agree with Dr. Pilkington on the use of antibiotics and antiviral therapy, and this is also what we want to reveal and warn the TCM investigator for future studies. In China, antibiotics and antiviral drugs are quite commonly used for common cold in clinical practice even if in most cases there is no sign of complications of bacterial infection or severe respiratory infections, which is regrettable to be admitted. Some of the reasons that antibiotics are so commonly prescribed include people’s expectations for them, physicians’ desire to help, and the difficulty in excluding complications that may be amenable to antibiotics. The supervision mechanism for the antibiotic and antiviral drugs use is imperfect. Therefore in the clinical trials, control of antibiotics and antiviral drugs for common cold is not uncommon. In this case, the purpose of this article is rather to reveal the problems on the control setting and give suggestions on how the problem could be addressed in future trials, than to explore the curative effect of CPMs on common cold compared with antibiotics or antiviral drugs. In this review, all the included 5 RCTs stated that they included patients with simple ‘common cold’ and provided the diagnostic criteria. We have tried to contact the author of the RCTs but did not get response. The treatment period of the included RCTs is 3-5 days. Considering the short treatment period, we could infer that it is not likely for severe respiratory infections. We have emphasized the issue of inappropriate control setting in the Discussion part.

Major compulsory revisions
1. In the Introduction, the authors state that there is no proven treatment for the common cold but need to discuss how it is usually managed in order to clearly show what would be considered appropriate control treatments and outcomes. If there are differences between practice in China and other countries, this needs to be explained.

We thank Dr. Pilkington’s comment, and have added the part of proven treatment for the common cold in the Introduction. As for the differences between practice in China and other countries, we have explained in the Discussion part.
2. The diagnosis and rationale for treatment in each trial need to be confirmed and described in more detail. Is the condition being treated the common cold or a related condition? How was it diagnosed? Is there any mention of which virus? Were patients in particularly high risk categories? If the patients did indeed only have a common cold, then the risk-benefit of using drugs such as ribavirin needs further discussion. Is this usual practice in China because, as mentioned above, this would not be standard treatment in countries such as those in Europe or USA. If it was not the common cold being treated, then the whole systematic review would need to be revised substantially with additional searches conducted to reflect the change in focus.

We thank Dr. Pilkington’s valuable comment. The diagnosis criteria have been added in the Table 2 and in the Result part. Two RCTs used the diagnosis criteria from textbook, two RCTs used diagnostic criteria issued by the State Administration of Traditional Chinese Medicine of the People’s Republic of China, and one RCT included patients based on clinical symptoms and laboratory test results. All the diagnosis criteria were for simple common cold. No symptom of complication was reported in the articles, and the treatment period of the included RCTs is 3-5 days, which is too short for a severe condition. Therefore, we believe the treatment they used is for common cold, but we do admit that inappropriate control setting is an issue need to be concerned, and have discussed it in the Discussion part. All the RCTs did not conduct virological examination because in clinical practice most of the common cold is diagnosed based on clinical symptoms and laboratory test results, virological examination is not a routine examination. As for whether the patients were in particularly high risk categories, we could not find any related description from the text, and considering the average short treatment period, it was less likely that the enrolled patients were in particularly high risk categories. The risk-benefit of using drugs such as ribavirin and the difference between China and foreign countries have been discussed further in the Discussion part.

3. The location of treatment should be reported. A mild, self-limiting condition would not usually be treated in hospitals but the use of injectable treatments suggests treatment did take place in hospitals in some of the trials. This affects generalizability of the results.

In this review, all the RCTs included the outpatients. Injectable treatments could also be given in outpatient clinic.

4. What criteria were used to assess cure and who assessed this?

We do agree with Dr. Pilkington on the importance outcome assessment and it also what we want to address to the TCM investigator for future studies.

All RCTs used ‘cure rate’ as the outcome measurement. It is a composite outcome including the clinical symptom disappearance and abatement of fever. It is not internationally recognized outcome measurement but is commonly used in Chinese TCM trials. However, subtle differences existed in the criteria or cut point in different trials, which made it difficult to interpret the effects of CPMs. We have discussed this issue in the Discussion part.

As for the outcome assessor, the included RCTs did not state that they have
independent outcome assessors. We believed that the outcome assessors were
the investigator themselves. This approach is very easy to introduce bias,
especially for subjective outcome such as cure rate. We have also discussed this
in the Discussion part.

5. The discussion section needs to reflect the above aspects.
We have discussed all the above aspects in the Discussion section.

6. The trials reported in the text, tables and Forest plot do not correspond. The
text states 6 CPMs in several places but only 5 are reported in the tables. One of
the 4 trials presented in the Forest plot is not included in the text or Tables (Zhao
2010).

We apologize for our mistake. The trial of Zhao 2010 had been deleted in
previous revision because it is not a real RCT after contacting the author of the
trial, and that is why it was not included in the text or Tables. Therefore all
together there were 5 RCTs in the review.

Minor essential revisions
1. In Results, Adverse Effects, the second sentence needs to be rewritten as The
remaining five RCTs did not mention whether adverse effects were monitored.
We apologize for our mistake. But there were 5 RCTs in the review; one RCT
stated that no adverse event was identified and the rest four RCTs did not
mentioned whether they monitored the adverse events.

2. In the discussion, the same point about lack of evidence for clinical use and
decision-making appears in the first and second paragraphs.
We thank Dr. Pilkington for the suggestions and have made the corresponding
revision.

3. withdraws should be changed to withdrawals
We apologize for our mistake and have made the corrections.

4. children patients should be changed to children aged between …. or to
patients aged between….
We thank Dr. Pilkington for the suggestions and have made the corresponding
revision.

Level of interest: An article whose findings are important to those with closely
related research interests
Quality of written English: Needs some language corrections before being
published
Statistical review: Yes, and I have assessed the statistics in my report.

Associate Editor’s Comments:
Thank you for responding to the comments on your paper. Two main points still
need to be addressed:
Addressing how the common cold is usually treated so that the use of antivirals,
which are used as control treatments, is clear (in my more detailed comments I explain why this is relevant) Ensuring that it is clear in the text, tables and figures how many trials and how many comparisons were carried out and which trials were included (see my more detailed comments on this query)

We have addressed the usual treatment for the common cold.

The number of trials and comparisons has been checked to be clear and coincident in the text, tables and figures.

We thank the associate editor’s comments and concern about our manuscript again!