Author's response to reviews

**Title:** Acute adverse events from over-the-counter Chinese Herbal Medicines: A population-based survey of Hong Kong Chinese.

**Authors:**

Jean H Kim (jkhkim@cuhk.edu.hk)
Vincent CH Chung (verspertine@gmail.com)
John CO Lee (john_10235@hotmail.com)
Terry Wong (twong@twong.com)
Albert Cheung (albert-cheung@cuhk.edu.hk)
Elizabeth M Kwong (lizkwong@yahoo.com)
Sian M Griffiths (siangriffiths@cuhk.edu.hk)

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**Author's response to reviews:** see over
Dear Associate Editor:

My co-authors and I have worked hard to address the comments and concerns of the reviewers and the editorial board of BMC Public Health. The major changes to the article are as follows:

1) The abstract was rewritten to include the logistic regression results.
2) We have tried to incorporate a more international perspective of Adverse events in TCM by putting TCM under the umbrella of Complementary and Alternative Medicine (CAM). In doing so we now compare our rates of adverse events with those reported in other countries such as Germany as well conventional allopathic drugs.
3) As the Reviewer requested, we cite other studies of adverse events rates in order to allow the reader a better context of our prevalence numbers.
4) The reviewers seem to feel that the Tables were difficult to follow and were unwieldy. We have therefore, reorganized the information in tables so that:
   a. Table 1 shows the data for the entire study population (including non-COTC users). We put in the COTC-related knowledge questions for entire study population since knowledge about COTC related harms and uses are relevant for the general population and useful for comparisons with other future population-based studies.
   b. Table 2 shows COTC-related perceptions and adverse event preventive practices (among COTC users only). A large proportion of the items in Table 2 are only relevant to people who use COTC (I tell my doctor about COTC use, COTC helps to reduce my medical costs).
   c. Table 3 shows a comparison of COTC users who did experience adverse events versus those who did not by conditions for which COTC was used, the usual source of information and by summative scores for knowledge, attitudes, and behaviors.
   d. Table 4 shows the unadjusted, multivariable logistic regression of socio-demographic factors, and full multivariable logistic regression (socio-demographic + perceptions, behavioral factors) for the outcome variable (past year adverse events).
5) The Editor requested that we include use the entire study sample as the denominator for analysis of the prevalence of COTC adverse events (rather than using COTC users as a denominator). In the abstract and results, we provide the actual numbers of all adverse events and the actual denominators so that different readers can easily divide these numbers to obtain the percentage relevant to their research interests. However, for Table 4, we were unsure which denominator the Editor felt would be most relevant. We have included 2 versions of table 4 (Table 4 and Table 4B). The multivariable results remain the same (many of the behavioral items were only asked of COTC users), however the “% reporting adverse events” changes slightly and the unadjusted p-values are slightly different. The results do not substantively change.

Below are the responses to individual comments.

Sincerely,

Professor Jean H. KIM

The Chinese University of Hong Kong.
Associate editor's comments:

1) More detail is needed to flesh out the Materials and Methods. Please provide a CONSORT type diagram outlining the recruitment process for the survey. How many calls were made in total? How many numbers were out of service? Business telephone numbers? Incorrect? Unanswered? Hang-ups? Refused to answer “last birthday question?” Ineligible because of age?

We now include a CONSORT type diagram in the Methods section to detail the recruitment process. In all, calls were attempted at 7404 different phone numbers. From this number, Business numbers, fax lines, and out-of service numbers, phone numbers generated that were invalid numbers all totaled 2509 numbers.

Of the remaining numbers, 2813 went unanswered despite repeated attempts at calling. Of the 1986 calls that successfully made contact, 514 did not have an eligible respondent in the household despite repeat calls (people present were ineligible for being non-Chinese, non-Cantonese speakers, or under 18 years of age), 449 refused to participate and 19 respondents only partially finished the interview.

2) How was the sample size of 1100 derived? Based on Power calculations? Other reasons?

The sample size was derived based upon power calculations. Our sample size was derived to be adequate for multivariable logistic regression analyses. We now state very briefly in the Methods section that the sample size was derived from power calculations.

3) At what point in the interview was informed consent obtained? I assume this was verbal, but needs to be stated in manuscript. How many people refused to consent?

Respondents were asked to give verbal consent at the beginning of the interview after the interviewer briefed them about the purpose of the study. This is now stated in the Methods section.

4) How was list of “symptoms” derived? How was list of “adverse events” derived?

The original study instrument was given to TCM researchers to suggest a list of symptoms and adverse events based upon their clinical and research experience. Research assistants also visited drug stores that sold COTC to see whether all the symptoms for which COTC may be used would fall under the suggested categories (two categories of symptoms were added (vision problems and memory functioning). The instrument was piloted using revised list with extensive probing for other categories of symptoms and adverse events. Responses from the pilot study of 50 respondents yielded no other new symptoms or adverse events, indicating that the major categories of adverse events and symptoms were covered. A recent systematic review that has been published subsequent to our data collection confirm these listed categories: Clin Med. 2013 Feb;13(1):7-12. Nonetheless, in case, we had missed other conditions or adverse events, the questionnaire included an “Other” response option. Only 1% of COTC users used COTC for conditions not in the given checklist of the final instrument. For adverse events, three respondents described adverse events not enumerated as options in the final instrument.
(blistering, exacerbation of illness, and spasmodic coughing) and these adverse events were then input into the database for analysis.

5) Was survey piloted tested or otherwise validated? If so, provide details. If not, this would be a clear limitation of the study and would need to be addressed in the Discussion.

The survey was pilot-tested on 50 respondents and small revisions were made for clarity, improved comprehensibility, and to shorten the questionnaire. The study could not validate the adverse events (since most did not seek medical care, hence there were no clinical records to validate the self-report) but the time frame (past year) should greatly reduce the recall error. We comment on this in the Discussion section as a limitation of the study.

6) Were the summative scores validated and/or the psychometric properties examined. If so, provide details. If not, this would be a limitation of the study and would need to be addressed in the Discussion.

The summative scores were not criterion validated (only checked for face validity by two experts in TCM utilization research). We now include discussion of this as a limitation of the study in the Discussion section of the paper. The reliability of the summative scores ranged between 0.51-0.69, indicating that these scales should be used to explore the data and examine general trends. We discuss this as a limitation in the Discussion.

7) The models for the logistic regressions should be specified – Independent variable, dependent variable, covariates. Were the models assessed as to whether all assumptions underlying the logistic models were achieved (homoscedasticity, linearity, normality, absence of substantial collinearity)? If not, they need to be and the results clearly stated in the manuscript.

In the Methods section, we now clarify the modeling strategy for the adverse events. Given that the modeling strategy used was binary logistic regression, we had examined the existence of substantial collinearity among the variables using Variance Inflation Factor (VIF) statistic of the final model and by comparing the standard errors of the covariates with the standard errors from the unadjusted models. The VIF statistic for the final logistic regression model was only 1.19, (safely under the recommended cut-off of 10). The final model was also examined for goodness-of-fit with Hosmer-Lemeshow statistics. For the final model, Hosmer-Lemeshow statistic=0.595, indicating that the model fit the data well. We include this information in the footnotes of the last table and in the methods section of the manuscript.

8) Negative data are just as important as positive data. As such, please provide the data all variables in the logistic regressions (odds ratio, 95% CI)

In the tables, we now include the data for non-significant covariates in the stepwise regression model. The OR (95% CI) for non-significant variables are shown for the variable before it was dropped from the final multivariable regression model. The footnotes of the table clarify this and we now clarify the modeling strategy in the Methods section.

9) Confidence intervals or standard errors need to be listed anytime a percentage is presented in a table
or text or figure. Data where standard errors exceed 50% of the point estimate should be presented with extreme caution, as the point estimate will be highly unstable.

We now give the confidence intervals for Tables 3 & 4 which present the main findings of the paper—the prevalence of adverse events and the associated factors. In Table 1 (the description of the study sample), we only give the 95% CI for the total study sample to keep the table from becoming too large. Table 2 is also a descriptive table (and not part of the main hypotheses) so we have left the %s as is to reduce the table size and to keep it from becoming multiple pages in length. If the editorial board feels that it would improve the manuscript and would not make the table excessively long, we can add 95% CI to Tables.

10) Please provide actual event rates for each type of adverse event for the entire sample of 1100.

In order to facilitate calculation of the different types of adverse event rates using various denominators (in entire study population (n=1100), among COTC users only (n=789), among all reported adverse events (n=27), the manuscript now presents the actual numbers of each type of adverse event rather than the percentages. It is assumed that different readers will be interested in each of these statistics for comparative purposes with their population of interest. Although the adverse event rates in the general population are of interest to government health regulators and policy makers, direct comparisons between different countries need take into consideration the pervasiveness of CAM/TCM use in their respective populations which can vary considerably across countries. Many studies of alternative medicine, report adverse event rates among users. Hence, for purposes of direct comparison of CAM/TCM users across difference regions of the world, it may be more informative to examine COTC adverse event rates among CAM/TCM users only. For researchers or clinicians interested in the dosage forms that cause adverse events, it is probably most informative to look at the prevalence of each dosage form among respondents reporting adverse events. To reduce confusion, we have simply listed the actual numbers in the abstract.

11) The overall event rate of 3.2% needs to be put into some context. What have other similar studies in the literature found? How does this event rate compare to that for Rx drugs and OTC drugs? Or even placebos in clinical trials?

Given that the prevalence of adverse events depends on the nature of the drug, the condition of patient using the drug, as well as the nature of the reaction, it is difficult (and possibly uninformative), to provide a figure that is applicable to all Rx, OTC and herbal medicines. The international literature of adverse drug events are largely hospital-based and indeed, the most directly comparable studies are conducted in hospital-based setting among patients prescribed either alternative or allopathic medicine. Sussman found that an adverse drug reaction rate of 4.6% among patients prescribed complementary medicine which is largely comparable to our study. We also now cite a prospective JAMA study from the US that looked at adverse drugs reactions in a hospital-based setting for allopathic drugs. This is now put into the beginning of the Discussion to allow readers some context. We thank the Editor for highlighting this issue and helping to improve the paper.

12) In the first line of the Discussion, the authors state that the study exposed previously undetected cases of COTC adverse events. This makes it sound like the participants hadn't realized they had an
adverse event until asked by the authors? Obviously they did have these events whether or not they had reported it to anyone.

**Based on the Editor’s suggestion, we have now rewritten this part to clarify that the study was reporting adverse events that had not been detected by previous studies which were based on emergency room data. The main limitation of previously conducted studies was the data was sourcing of data only from very severe cases of adverse events that were documented by clinical staff. This paper attempts to address the limitation of past studies by doing a population-based survey of Hong Kong adults; the data includes less severe and minor adverse events.**

13) Also, since the list of possible adverse events include many items that might be quite minor, the statement in the Discussion about whether participants did not seek professional medical treatment for these events may be true, but might have no real clinical relevance. The fact that the actual severity of events (such as a Likert scale) was not collected (at least not that I could find in the manuscript) is a limitation of the study and should be mentioned.“

**As the Editor noted, we did not ask the respondent to rate the severity of the adverse event. The majority of the respondents did not seek medical care for their adverse events suggesting that the reactions were either mild or self-limiting. However, 8 respondents (approximately 1% of COTC users) stated that their adverse event required medical treatment. This proportion could be taken as a rough estimate of the more severe adverse event rate among COTC users that has been only partially captured by previous clinic-based studies and case reports. We now highlight this in the Discussion.**
Responses to Reviewer’s 1 (Reviewer: T. Ostermann) comments

In their article „Acute adverse events from over-the-counter Chinese Herbal Medicines: A population based survey of Hong Kong Chinese.” the authors aimed at presenting safety data for Over-the-counter traditional Chinese herbal medicine (COTC) by means of a cross-sectional telephone survey conducted among Hong Kong Chinese adults in 2011 (n=1100). Although this is a highly interesting topic, there are some methodological remarks concerning the manuscript and in particular the methods of logistic regression modeling.

1) Abstract:
- The abstract does not reflect the content of the full text. While the objective and method section is rather short the results only state percentages and no results from the logistic regression.

Originally, we had excluded the results of the logistic regression to comply because had thought that there was 250 word limit and tried to highlight findings that we felt would be of most interest to readers. We have now rewritten the abstract to be more succinct so that we can include the results of the logistic regression. We thank the reviewer for his comments. We feel that the abstract is greatly improved.

2) Introduction:
- The analysis of adverse events is the major topic of the manuscript. And indeed CAM has seen several publications on adverse events (i.e. the publications of Jeschke et al.) which also use logistic regression models to make assumptions for the risk of ADRs. Unfortunately the authors miss the international perspective of ADR research in their introduction, which should be more emphasized.

Based on the Reviewers well-considered comment, we have now rewritten part of the introduction to include a more international perspective. The Introduction now discusses Traditional Chinese Medicine under the broader umbrella of Complementary and Alternative Medicine to allow for a broader discussion of Adverse Events and to allow comparison with regions outside of East Asia.

3) Methods:
- The methods talks about multivariate logistic regression models. Although this approach is well suited, the authors miss to describe how the results are presented. I.e. Standard analyses like the calculation of adjusted odds ratios with 95% CI should be described. Which quality criteria is chosen for model validity.

We include more description in the methods section about how the multivariable logistic regression analysis is conducted and now include the results of model fit statistics (Hosmer & Lemeshow statistics >0.05) to show that the model fits the data. The final models were assessed for collinearity of the covariates by examining the Variance Inflation Factor and by checking the covariates’ standard errors against the covariate’s standard errors in the unadjusted model. The VIF statistic =1.19, indicating that multiple collinearity in the logistic regression models was not a major concern. These are now in the footnotes of Table 4 and briefly mentioned in the statistical analysis section of the manuscript.
4) Results:

- Again the authors miss to present the results of the logistic regression model adequately (see above). OR-Results should be clearly integrated in a table. - I’m a bit confused whether table 4 on “Correlates of adverse events among over-the-counter Chinese medicine users” is the desired table. If so, the table is unstructured and should present the OR in a straightforward manner.

We try to clarify the Table for the reader based on the collective comments of the reviewers. The first column shows the % of respondents in each category that reported adverse events with (95%CI), followed by the unadjusted p-values. In order to determine sociodemographic factors associated with COTC-related adverse events, we ran a multivariable logistic regression model of only demographic variables. These results are meant to assist government agencies target the groups that are at high risk of COTC-related adverse events. It was found that only respondents with lower levels of education were at risk of COTC-adverse events.

The full multivariable logistic regression then included behavioral & attitudinal factors as candidate variables, in order to determine whether these covariates could offer some clues as to what other factors are independently associated with adverse events. Although, respondents with adverse events experience appeared more cautious in their informational seeking behaviors, it was found that the source of COTC-information was independently associated with the likelihood of having an adverse event in the past year.

Discussion:

- The authors discuss the “importance of increasing risk perception” for alternative medicine use. Thus the discussion should compare the data with other survey data like mentioned earlier.

At the suggestion of the reviewer, we have now included data from studies conducted internationally to compare Adverse Drug Events rates with other CAM patients. We highlight that increasing risk perception is an important aspect of drug safety education since our own population showed extremely low rates of perceived susceptibility to adverse events and perceived that the severity of COTC adverse events to be mild. Although the risk perceptions were not independent predictors of adverse events, there was low perceptions of susceptibility to TCM adverse events across all respondents. Our findings mirror what was found in other international studies.

6) I strongly recommend to reorganise and revise the manuscript before publication.

We have reorganized the tables and heavily edited the Introduction and Discussion sections of the paper. We heartily thank the Reviewer for his/her well-considered comments.
Responses to Reviewer #2:

Reviewer’s 2 report. Major compulsory revisions:

1) Abstract section

Method subsection: Please specify if all study participants have provided the informed consent. Otherwise, the same phrase reported in the Method – Study population (“Research ethics approval was obtained from the ethics board of the sponsoring university.”) should be added.

We have now added that informed verbal consent was given by the study participants.

2) Introduction section

Second paragraph: authors should clarify the meaning and the differences between “transitional licensure scheme” and “formal registration”.

We have tried to clarify the difference between the transitional licensure scheme which allows products to have temporary permission to be sold in Hong Kong until the products can undergo the full formal licensure registration.

3) Third paragraph, lines 11-13: Authors should explain why they considered that study carried out “from emergency room admissions” “may present a highly biased picture of the COTC-related harms in the general population.” Data coming from the emergency department are often useful in the evaluation (and indicative) of the severity and seriousness of adverse reactions.

We agree that emergency room admissions represent a source of severe and serious adverse events, less serious adverse events which are likely to represent the vast majority of adverse events will go undetected by relying solely on emergency room reports. We now clarify that the emergency room data is likely to be a “tip of the iceberg” of adverse events in the population.

4) Method section

Measurements - Socio-demographic and background information, lines 4-7: authors should better elucidate the meaning of “decoction from TCM shops” and of “COTC is sold as mass-manufactured, pre-dosed forms”.

We now clarify these sentences for Western readers who are unfamiliar with East Asian TCM practices. In the East Asia region, it is a common practice to take prescription given by TCM practitioners to a TCM herbal store where the herbalists will prepare a custom blend of herbal medicine (usually in soup-type form) in quantities specified by the TCM doctor. (called “decoctions” in TCM literature). These decoctions are prepared individually for the customer and not-manufactured in a factory or distributed.

By contrast, COTC, is sold in the same manner as western OTC medicines (pre-dosed in caplets, or tinctures, or lozenges, packets). These products are produced similar to western drugs in pharmaceutical factories with commercial packaging. COTC are sold in western drug stores side-by-side with OTC western drugs.
Result section

5) The results should be considered as Results, without the addition of any comments (i.e., “incorrectly”, fourth line of the second paragraph) and avoiding the repetition of numbers and data in the text, as well as in the Tables (see lines 3-16, etc.).

This is now re-worded in accordance with the Reviewer’s suggestions.

6) Since various pharmaceutical forms (e.g. pills/capsules, plasters, ointments/creams) are only listed, without any relation with the type of the adverse reactions (ARs), authors should better clarify why was so important to emphasized the pharmaceutical form that has been involved in the adverse reactions (ARs).

The main points of regulatory interest from the standpoint of COTC safety (given the absence of a reliable reporting structure in HKG for drug adverse events) are 1) the pervasiveness of this problem in the population (there are no population-based data on this in Asia) and the forms of medicines that are causing the adverse events to help formulate better regulatory

Due to the enormous number of COTC products on the market in Hong Kong and China, the vast majority of

7) Table 1: please check the queuing of the table, because appears totally incorrect; specify the superscript “a” and “b” meaning and their relation with “2011 Hong Kong Census provisional figures” and “2006 Hong Kong Population By-Census”.

The table has been corrected and the footnotes have been redone. We thank the Reviewer for her thoroughness.

8) Tables are too many and too long, please try to synthesized and to discuss more data (without repetition) in the text.

We have reformatted the tables and reduced the redundancy in the text to streamline the paper. More specifically, Table 2 is now limited to COTC users since the perceptions of COTC, COTC-related behaviors are primarily relevant to COTC users only.

Minor (but important) issues not for publication

9) The language, grammar and punctuation need a thorough revision, all over the paper. Some phrases should be restructured. For examples, in the Abstract section – Conclusion subsection: “… the inaccessibility of reliable information and widespread misperceptions among consumers present major challenges for safe complementary medicine use” should be rewrite in “… the inaccessibility of reliable information and widespread misperceptions among consumers present the major challenges for the safe use of complementary medicine”. Moreover, Introduction section (third line): “There has, however, in recent years been greater availability of the TCM products in non-Asian countries” should be rewrite as “In recent years, there has been a greater availability of the TCM products in non-Asian countries”.
In accordance with the Reviewer’s suggestions, the sentences have been edited or restructured for better flow and greater comprehensibility.

10) Other sentences should be also revised, including:

Introduction section, first paragraph, line 6-8; second paragraph, line 1-3 (please, check also the punctuation); Method section, fourth line of the Study population subsection;

Method section, first line of “Socio-demographic and background information” (“information of respondents were asked of respondents…” could be changed in “information of respondents were recorded…”)

Results section, first line of the fourth paragraph, etc., etc.

These lines have been edited in accordance to the reviewer’s comments. We thank the reviewer for her thoroughness and attention to language.

11) Results section: What authors mean for “Qi imbalances” (lines 4-5)? Please, specify.

“Qi imbalances” is a everyday term in East Asian countries such as China, Korea and Japan and a basic concept of Oriental Alternative Medicine—that does not have an exact translation into English. In Traditional Chinese Medicine precepts, Qi, can be thought of as “energy” or “life force” that must be balanced in order to prevent the onset of disease. We now include a “yin-yang bodily disharmony” in the table as well as include a reference to avoid a long paragraph describing this fundamental TCM concept.

12) Table 2: How can be considered as “inconvenient” (or as a barrier) to get information from TCM doctors? Please, answer to this question.

The main barrier for getting information for COTC from TCM doctors is finding a TCM practitioner, making an appointment and then paying for their consultation in order to ask questions about a COTC product. This is particularly inconvenient (and not cost-effective) if the person does not ordinarily seek professional TCM care. We now clarify this in the tables of the manuscript for readers since it was not clear in the original submission.

Minor points/Discretionary revisions:

Abstract section

a) Second line of the Results subsection the phrase in parenthesis “(3.2% of COTC users)”, in my opinion, it is not clear and can be omitted.Line 6 of the Results subsection the word “plasters” is already exhaustive of the pharmaceutical form, so that “dressings” can be deleted.

We have omitted the phrase in the parenthesis and removed the word “dressings” in accordance with pharmaceutical nomenclature suggested by the reviewer. We thank the reviewer for these suggestions

b) Keywords: “Drug Policy” should be deleted, as it is not relevant. The keywords have been deleted.

Method section:
c) - third line of “Socio-demographic and background information”: “(Yes, No)” can be omitted, fourth line “.(See Table 1 for response categories).” punctuation must be revised and the sentence should be changed in “… (Table 1).” These changes have been made in the resubmission.

d) - - third line of “Knowledge and perceptions of TCM and proprietary Chinese medicine”: “(Yes/Agree, Not Sure, No/Disagree)” can be omitted; and in the lines 5-6 of the same paragraph “of” should be added between “and the perceived severity” and “these effects.” These edits have been done as suggested by the reviewer.

e) Results section: “Of the study sample 2.3% (3.2% of COTC users)” do not add any significant information and it is not so clear, therefore can be deleted.

Based on interviews with the press and requests from TCM professionals, the key point of interest is the pervasiveness of COTC adverse events. We consider this to be main point of the paper and prefer to keep it in the manuscript. We have rephrased the sentence for clarity to simply state that 2.3% of the study sample reported COTC-related adverse events.

f) Table 1: specify “PT” and “NA” in the footnotes; “c” superscript is in red colour, instead of black. “PT” is now written out as “part-time” in the tables and “NA” is now shown in the footnotes. The superscripts have been changed in accordance with the Reviewer’s suggestions.

g) Table 2: specify “N” and “Y” in the footnotes: Instead of footnotes, we have now written out the full words “Yes” and “No” in the tables for clarity. The reviewers requested restructuring the tables and these items are now put into Table 1 since knowledge about COTC harms in the general population should be of interest to readers.

h) Figure 1 is of poor quality, please improve its format/pixel number: We have increased its pixel number.

i) References: Insert a “new line” between “Scheid” and the other reference “Sin”.: A new line was included between the two references. We thank the reviewer for their comments.

We wish to express gratitude to Reviewer #2 for his/her detailed reading of the manuscript.