Author's response to reviews

Title: Cause-specific mortality patterns among hospital deaths in Thailand

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Author's response to reviews: see over
Dear Professor Murray,

RE: Submission of revised manuscript No: MS 1834017849315084 – Verifying causes of death in Thailand: rationale and methods for empirical investigation

Thank you for providing an opportunity to submit a revised manuscript for consideration by Population Health Metrics. Our detailed responses to comments from each of the four reviewers are as follows.

**Reviewer 1: Seval Agkun**

**Major Compulsory Revisions:**

1. *The article would need editing to make it more easily readable for an English speaking audience.*

**Response:** We have carefully reviewed the manuscript, and have made essential grammatical revisions as well as simplified the text to improve its readability.

2. *The authors specify 4 study objectives; however, the article includes only data about the distribution of the death causes. The results and the objectives are not concordant, some of the objectives of the article – especially the 4\textsuperscript{th}, mentioned in page 8 might be the long term objectives of the study.*

**Response:** This manuscript is the first in a set of four articles that describe the study in detail. The first three objectives stated on page 8 are the focus of the second, third and fourth manuscripts in this set of articles, and have been cross referenced accordingly. We agree with the reviewer that the 4\textsuperscript{th} objective stated on page 8 is essentially an outcome that would serve Thailand in the longer term, and have therefore modified the text on page 8, to state three objectives, and the beneficial long term outcome.

In this article which is intended to provide an overview of the study, we chose to include a brief summary of the overall findings (i.e the comparisons between the cause of death distributions from the raw data and the final study results for males and females) to give the reader an indication of the broad implications of this research for epidemiology and health policy in Thailand.

3. *The information about the Verbal Autopsy (VA) methodology isn’t clear. There is no information when the data was collected. Usually it is suggested that the VA study take place as soon as possible following the death. The validity would be higher if the data are collected in as short a period as possible.*

**Response:** Details about the VA methods which we used to investigate the cause for deaths in the study sample, including the recall periods, are provided in reference 7

4. *The other important problem besides time for VA studies is developing a standard questionnaire. There is no information regarding questionnaire form in the article. Usually the aim of VA is to diagnose deaths that have not been recorded by the routine reporting vital registration so the underlying and immediate causes*
can be differentiated using the standard questionnaires. The authors should explain the VA tools, data collection methods, standardization etc, clearly in the methodology part.

5. There is also no information about who collected the data. Was there any training, supervision of the interviewers?

**Responses to comments 4 & 5:** These are indeed important observations. We clarify (see amended text on page 4) that these aspects have been addressed in the manuscript describing the methods and results of the VA component of this research study, cited as reference 22 in this manuscript.

6. The authors give detailed information on the sampling methodology but this section is disorganized and difficult to follow. It requires to be rewritten to provide information more clear and brief.

**Response:** While we appreciate the reviewer’s call for concise description, we have not made any changes to our description of the sampling methodology. We have thought through our approach carefully, and decided to organize this section to first explain the principles and statistical methods applied in determining the sample size for the study. Subsequently, we have described the steps taken to select this statistically determined study sample, going into detail with reference to the stratification applied in this selection. We believe that readers would be interested in these details, which demonstrate the meticulous approach taken to enable generalisability of the final study findings, and therefore their utility in estimating national level cause-specific mortality in Thailand. We are unaware of any other nationally representative cause of death verification study of this type and hence thought it important to stress this aspect in our sampling description of the methodology.

**Minor Essential Revisions:**

7. Table 1 and its explanation in the results section should actually be given in the methods section. The shown in Table 1 are not the findings of the study, the table gives detailed-visual-explanation of the deaths included in the study sample.

**Response:** This is a reasonable suggestion. The data presented in Table 1 overlap the methods and the results of the study. The initial columns present the distribution of the study sample, and therefore represent the study methods in terms of intended data collection. The subsequent columns provide information on the actual numbers of deaths recruited into the study, which represent a baseline finding of the study, and form the starting point for all further analyses. Hence, we chose to include Table 1 in the Results section of the manuscript.

8. There are a lot of repetitions all over the article, same issues are repeated in methods, results and conclusion sections. The authors should try and make more precise and “easy to understand” the article.

**Response:** As per the reviewer’s advice, we have carefully edited the manuscript to remove repetitions, in order to improve the clarity of the article from a reader’s perspective.

**Reviewer 2: Elisabeth Franca**

1. The most important issue is that the reader should be clearly informed right up at the Introduction section about the importance of the overall project which was described in this paper and in three other papers already submitted. I suggest to include one phrase in the second paragraph to show why it was important to conduct “A comprehensive field research project….”

**Response:** We agree with the reviewer, and have added the following text in the second paragraph on page 3; after the sentence which ends with “……described in detail elsewhere. [5]”

‘However, the reliability and validity of registered causes of death, including misclassification patterns, should also be periodically assessed to guide the utility of available vital statistics for health policy and planning.’
Minor Essential Revisions:

1. As pointed out above, in the whole paper it is important to differentiate the overall project and the study which is the object of this paper. Sometimes I was a little confused by the use of identical words throughout the text.

Response: As per the reviewer’s suggestion, we have clarified the text on page 4, second paragraph, to clearly state the focus of this paper, as well as the focus of other papers in this series.

2. In the Abstract Results, please consider including the major differences between the percent specific cause of death in vital registration and after adjustments for misclassification and VA (verbal autopsy) validation findings. I think the authors could have done a better job in discussing this kinds of results in a paper such as this, which presents the methods for investigating causes of death.

Response: Owing to word limits, we chose to mention our findings only for the final leading causes, by sex, in the Results section of the Abstract. We feel these results would give readers an appreciation of the current health priorities in Thailand, based on corrected vital registration data. This was the principal purpose of the overall study. In other sections of the Abstract we have highlighted the limitations of the registration data (40% ill defined causes), and believe that the study findings summarised as final leading causes more succinctly draw out the principal outcomes of the study.

3. At the end of the first paragraph of the Introduction on Page 3, please check the presentation of the objectives of the overall project because the correction of the estimates of cause-specific mortality for Thailand was not included.

Response: We did not include any mention of the overall objectives of the study in the first paragraph of the Introduction. As mentioned above (see Response 2 to Reviewer 1), we have clarified the specific objectives of the study on page 8.

4. In the first paragraph of the Introduction on Page 4, the authors should indicate the references of the other three articles of the overall project.

Response: We have added the references, as suggested by the reviewer.

5. On page 9, first paragraph, I would appreciate a more specific and detailed description of the methods used to adjust biases for VA diagnoses of individual causes of death. This had important implications in the results of proportionate mortality for some causes of death as shown for HIV/AIDS for males in Figure 5. So I think it would useful to put this issue into context for readers who would not read the VA specific paper submitted.

Response: A detailed description of the methods applied to adjust biases in VA diagnoses using the VA validation results is available in Reference 22 of this manuscript. More generally, we have applied appropriate cross-referencing of manuscripts in this series throughout all four papers, to avoid unnecessary repetitions. We anticipate that interested readers would access the VA specific article for the relevant aspects of the methodology.

6. Some of the most interesting themes in the manuscript can be found in the items on “Data collection and processing” and “Data analysis” of the Methods section, but in general the presentation needs to be more informative for the average reader. For example, on page 13, first paragraph, it is mentioned that to ascertain the cause of death for deaths in health facilities two independent sources were used: the medical record and the VA cause of death. At the first instance I was curious about the procedure used when there is no agreement between them but this was mentioned only in the second paragraph of page 14. On the other hand, in the first line of page 14 it was mentioned that underlying causes were available from three sources, the two mentioned earlier and also from the vital registration system. I feel that the description of these topics could be improved and please consider being more specific on the description of Figure 2, which is summarized in only a few phrases at the end of the second paragraph on page 13.
Response: We thank the reviewer for these comments which appreciate the detailed information provided in the Methods section. For clarity, we have described the sources of underlying cause of death data for hospital and home deaths only once on page 13.

Regarding Figure 2, we feel that the flow chart is largely self explanatory, and is adequately supported by information provided on page 13. Further details relevant to data processing and quality control for each arm of the study are provided in the individual papers on hospital deaths (21) and home deaths (22).

7. I was a little confused by the choice of comparison of the proportionate distributions of registered causes of death on the sampling frame (n=395374) with the sample drawn for the study (n=11984) and the sample recruited (n=9644) as shown in Table 2 to evaluate if losses to follow up could affect the generalisability of the study results. I assume that the cause of death considered in the recruited sample is the original cause of the vital statistics but it would be good if this was specified.

Response: The reviewer is correct in stating that the cause of death considered for comparison from the recruited sample is the registered cause from vital statistics. For clarity, we have therefore changed the text in the third paragraph on page 15 to state this clearly (changed text as underlined):

“There is clearly a very close approximation of the proportionate distributions of registered causes in the sampling frame, the study sample and in the registered causes for the recruited sample, indicating that any effects………”

We have also amended the title and the heading of the first column in Table 2, to clearly reflect that these comparisons are based on registered underlying causes of death from these three sample aggregations.

7a. Also on this topic, I was curious to know if there were any important differences in the age and sex distributions between the sample recruited (n=9644) and the losses (n=2340) as had occurred with the distribution of the study sample across provinces pointed out by the authors on page 15, last paragraph.

Response: Our analyses indicated that that there were no significant differences in the age and sex distributions between the study sample and the recruited sample. We have indicated these findings in individual tables in the respective articles. (Table 1 in [21] for hospital deaths; and Table 2 in [22] for home deaths).

8. Finally, please consider emphasizing and discussing the steps of the data processing and analytical plan presented in Figures 2 and 3. A small point to mention is that they could become more comprehensible if some intermediary boxes with further information were included, especially at the end of the figures.

Response: Figures 2 and 3 effectively summarise the key quality control and data analytical processes used across the two study arms. Relevant details of each step in these processes for hospital and home deaths are explained in References 21 and 22 in this manuscript, and we have added these cross-references on page 13, just before Figure 2 is shown. In addition, Reference 23 provides details of the final steps in Figure 3. We believe that the addition of intermediary boxes would complicate these flow charts, and instead, have referred readers to the individual manuscripts for the necessary explanations.

Discretionary Revisions:

1. Maybe the sub-title “Study objectives” (p.8) could be removed and the text included in the precedent sub-title ‘Rationale for current research’.

Response: Based on comments from Reviewer 1, the manuscript now states 3 objectives of the study. The ‘Rationale for current research’ section explains why we set out to do this research; and therefore precedes the ‘Study objectives’ section which states what we hoped to achieve from the study. Hence, we have chosen to retain these as distinct sections that follow in sequence, rather than merge them into one.

2. I am not sure if Figure 1 is really essential for the paper. I so, the authors should differentiate the regions and point out in the map which provinces were selected for the study.
Response: If the Editors do not impose space constraints, we would prefer if Figure 1 could be retained, to demonstrate the geographical spread of the study sample. This is important in arguing generalisability.

3. Page 16, last paragraph. The first four lines could be omitted.

Response: We agree with the reviewer, and have deleted the text. We have slightly modified the subsequent sentence, to reflect the fact that Figures 3 and 4 provide a summary of the overall results from the study.

Reviewer 3: Mohsen Naghavi

Major compulsory revisions:

1. The most important problem is that: details of method is not clear and results are not related to the method that you explained; for instance:

   a. Why after correction of causes there are more than 5% ill-defined codes (Figure 4 and 5), what was your method exactly?

Response: In deriving our estimates, we corrected registration data using findings from the field studies on a sample of deaths in hospital and deaths at home. We only present findings from our field research, and have not made any other adjustments to the data. Hence, although field research does identify specific causes for the vast majority of deaths originally registered with ill-defined causes, a small proportion remain so, as would be expected, given that verbal autopsy is not a precise diagnostic tool.

It is important for readers to appreciate that it is not possible for empirical investigations such as this to identify specific causes for each ill-defined death. It is inevitable in some home deaths that relatives of the deceased did not notice any specific signs/symptoms to report in the VA interview; or in a very small proportion of hospital deaths, that death occurred too soon after admission to allow clinical investigation or diagnosis. Our study demonstrates an empirical basis to reduce the proportion of ill-defined causes in the sample of deaths from about 40% to 5%, and greatly improving the utility of the data for epidemiology and public health.

   b. What is the meaning of ill defined codes (just “R” codes) and what about other ill defined code like X59?

Response: In our analyses, we reported findings according to the ICD Mortality Tabulation List 1, which consists of 103 cause categories. This has been specified in the Methods section. According to List 1, the codes included in the ill-defined cause category are R00-R99. Also according to List 1, deaths coded to X59 are included in the category of “All other external causes”.

   c. What was the format your data source: ICD 10 detail or ICD 10 Tabulation 1?

Response: The data were available according to ICD 3 or 4 character codes. We chose to use Tabulation List 1 for convenience in analyses and presentation of results to meet the objectives of our research. Detailed ICD codes are available in the dataset, for regrouping into other lists of causes of interest; or for manipulations/adjustments based on epidemiological considerations.

   d. If you corrected by ICD 10 detail what did you do with other ill defined codes like: X59, Y10-Y34, Heart failure, cardiac arrest, C26, C57, C80, D00-D48 and all ICD codes that cannot be cause of death (they are cause of morbidity) but they coded as cause of death in mortality data?

Response: As mentioned in response to comment ‘1a” above, we did not make any further corrections to the coded data derived from our field studies. This could be done by researchers who were interested in estimating the burden of disease in Thailand using current GBD methods.
e. And if your correction was based on ICD10 Tabulation 1 what did you do with these codes: 1-046, 1-047, 1-057, 1-062, 1-063, 1-068, 1-083, 1-103 many of ill defined codes are hidden in these compact codes?

**Response:** Please see responses to comments 1a-d above.

2. Your 4th objective is “improve the quality of causes of death recorded at registration in Thailand” How this study can improve capacity of physicians and paramedical staff.....For diagnosis, classification and coding of underlying causes of death? May this study could helps but its mechanism is not understandable.

**Response:** In response to a similar comment from another reviewer, we have removed the 4th item as an objective, and have stated this as a study outcome of long term benefit to Thailand. In this study, we have trained personnel in medical certification, coding and medical records review in 9 provinces of Thailand. The feedback from the study and the death certificate audit review will be disseminated to the provincial and district hospitals, and will be used in making recommendations to improve quality of death certification and ICD coding at each level. We believe that these actions are desirable long term outcomes of the study. We hope this adequately addresses the reviewers comment.

3. In page 13 you mentioned about data collection process, but answer to these questions are very important:
   a. Who was the reviewer of medical records? With which level of education? Do they know registered causes or not?
   b. Who was the interviewer for VA? Do they know registered causes?
You mentioned that you described these detail in separate articles, but you should explain some details here. This paper is not a comprehensive paper.

**Response:** This information is provided in the relevant sections of the manuscripts on hospital deaths and home deaths respectively, which have been cross referenced in this manuscript.

4. In page 14 have been mentioned that you can find underlying causes from VR, but your explanations in page 5 is not compatible with this address.

**Response:** We are afraid that we do not understand the reviewer’s comment. An underlying cause of death is available from VR for every death, whether a specific cause or an ill-defined cause. The objective of this study was to either confirm or correct the registered cause, based on field investigations.

5. In page 15: age, sex and cause pattern in hospital mortality data is different with age, sex and cause pattern in home mortality data, how can you show this different pattern is not significant for that adjustment between hospital VA and home VA?

**Response:** We have mentioned that the adjustment of VA results for home deaths is based on an assumption that VA characteristics for hospital deaths are applicable to the home deaths. We agree with the reviewer that this assumption may or may not be valid, and have discussed this issue in the article on home deaths.(see reference 22).

However, there is no possibility to assess validation characteristics of VA for home deaths, since there are no reference diagnoses for validation. Hence, we attempted this adjustment using available VA validation characteristics from hospital deaths, based on the mentioned assumption. While the assumption is inherently questionable, it might well be that community comprehension of, and responses to specific VA questions, could be similar in all Thai populations, due to common language or cultural issues. This could lead to systematic misclassification biases that could be common to the use of VA in Thai language or Thai communities *per se*, rather than being specific to the population sub group in Thailand where VA is being used. Of course, these issues would require further sociological/anthropological exploration, and are beyond the scope of this article.

In Figures 4 and 5 of this manuscript we have compared mortality estimates that were derived from the field study with estimates derived from the VA validation adjustments, to demonstrate the impact of such an adjustment. We have also included a statement on page 17 summarising the impact of the adjustments for specific causes.
believe that readers would be interested in noting these findings, and to be able to decide which of these estimates is more plausible from their perspective.

We hope these comments help clarify this issue for the reviewer.

6. Limitation of this study is important and you have to have this part.

Response: We thank the reviewer for alerting us to this omission. We have modified the text on page 17 to explicitly state the overall limitations, while referring readers to specific limitations of each arm of the study in references 21 & 22. Further, the limitations of the demographic estimations of completeness of Thai registration data are discussed in detail in the final article of this set of manuscripts; see Reference 23.

7. In page 9 you mentioned about “appropriate adjustment for biases in individual causes” this adjustment is not clear in your method.

Response: We thank the reviewer for this comment. In this sentence on page 9, we have replaced the word ‘appropriate’ with ‘subsequent’. As described in the response to Comment 5 above, we have described the method for this adjustment in the article on home deaths.

8. In figure 4 second causes of mortality for female is “Diabetes” and after correction from 2% increased to 8%, this fraction is not an usual fraction for all ages, if I want to check process of this estimation based on this paper and your methodology in this paper, I cannot, because your description about your method is not compatible with results that you present.

Response: As reported in Figure 4, and in Table 3 of the fourth manuscript in this series, we estimate that diabetes causes about 8% of deaths among females across all ages in Thailand in 2005. The methods used to derive this estimate are described in Figure 3 of this paper, and supported by detailed descriptions of each aspect of data collection, processing and analysis in References 21, 22 and 23.

Minor Essential Revisions:

1. In page 16, last paragraph, ‘Figures 3 and 4’ have to changes to ‘figures 4 and 5’

Response: We have corrected the numbering of Figures as pointed out by the reviewer.

Reviewer 4: Peter Byass

Comment from reviewer:

Overall, my impression is of a solid body of work, well executed. It may not be startlingly new or exciting, but it provides an important perspective on mortality in a transitional country. If they are going to be published as a group then it will be very important for the accompanying comment (which you suggested I might write) to perhaps go a little beyond comment, towards synthesis, as it is rather hard at present to work out how the four papers fit together. In fact I am still struggling slightly to see what is the logical order in which the papers should be presented.

As individual papers, they each present important and distinctive findings. I would rate all four papers more or less equivalently in terms of their publishability.

Thus, my overall conclusion is that, subject to the views of reviewers on the individual papers, this is a set of papers that could usefully be published together in PHM, provided they are accompanied by a synthesising comment to help readers find their way around them.
Response: We thank the review for his overall general appreciation of the four manuscripts, his rating regarding their publishability, and his recommendation for an overall synthesising comment to pull the papers together as a set. We strongly support such a recommendation.

The reviewer’s comment on the order of the manuscripts is critical. In response, we outline below our logic for ordering we have proposed. The first paper in the series lays out the rationale, need, methods and broad policy implications of the study, which has been conducted along two axes, deaths in hospital and deaths outside of hospital. The second paper identifies the principal misclassification patterns among hospital deaths, and there are many. This may come as a surprise to a public health audience who might (reasonably) expect that hospital deaths are correctly certified and coded. The third paper describes the application and validation of verbal autopsy methods in Thailand to estimate the probable cause of home deaths. Again, our findings differ substantially from Thai vital registration. Finally, the fourth paper brings together the findings from the two different arms of the project to derive a corrected set of age-sex-cause-specific mortality distributions for Thailand. This final paper goes on to demonstrate the value of these findings for health policy debates and program evaluation in Thailand, and the extent of capacity building that has resulted.

We believe this order and content of the papers appropriately mirrors the objectives and conduct of the study, as also depicted in Figure 2 of this manuscript. We would of course welcome the reviewer’s or editors’ comments and/or suggestions on our justification for the current order of presentation of the manuscripts. It is important that this be clear, logical and understandable.

As instructed by the PHM Editorial Team, we are submitting a revised version of the manuscript via the electronic manuscript processing website. We have formatted the revised manuscript according to PHM guidelines.

I look forward to hearing the outcome of this submission, and in case any further information or clarification regarding the manuscript is required, please let me know.

Yours sincerely,

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