Author's response to reviews

Title: Leading causes of death in Zambians, 2010: Results from Zambia's World Health Organization-standard methodology for Sample Vital Registration with Verbal Autopsy

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Author's response to reviews: see over
RE: MS: 1306610645517621

Dear Ms. Muller,

Thank you for your consideration of our article and the provision of reviews. Attached is a new manuscript with track changes illustrating the extent of revisions to the paper in response to the reviewer’s suggestions and comments.

This letter includes a point-by-point response from the authors to the comments received from Referees 1 & 2 and the PHM paper editor. We hope they address the concerns of the reviewers and editors.

Response to Reviewers

MS: 1306610645517621

Title: Leading causes of death in Zambians, 2010: Results from Zambia’s World Health Organization-standard methodology for Sample Vital Registration with Verbal Autopsy

Referee 1:

1. Is the question posed by the authors new and well defined?

However to enable readers to meaningfully assess the validity of SAVVY in routine settings in Zambia and other countries, some more convincing information needs to be presented in the paper. It would not be a useful paper if feasibility is addressed in the absence of validity in the setting.

Response: See below

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

Evidence needs to be provided to show that the results of SAVVY approximate well estimates from demographic and health surveys and populations censuses (or best available data in Zambia). In the discussion section, the authors provide this comparison only at the level of all-cause mortality. This is not convincing enough and more comparison needs to be presented, particularly on key indicators as

- Infant mortality (rate) and the major causes
• Under-five mortality (rate) and the major causes
• Maternal mortality (rate) and the major causes

How does the pattern of overall causes of death compare with best available data in those provinces in Zambia, and in the country as a whole? The comparison with studies in Ethiopia (references 15), Kenya (22) and at Global (21) level are rather remote and provides little assurance of the validity of SAVVY. If the argument the authors present were to be accepted as it is, then country-level SAVVY may not be necessary after all. We could just take figures from other countries!! In any case why these countries; Ethiopia & Kenya? What about Angola, Botswana, Zimbabwe and Malawi which are closer?

Response: Thanks for the suggestion to look inside the country in addition to the region for mortality estimates. We did find some estimates of maternal, under 5 and infant mortality in the DHS and projections from the 2000 Census. As far as we can tell, however, there are no other published estimates of the major causes of disease (whether overall or by age group). We have added the following section to the discussion section.

“Although this was a pilot and included just four of the nine provinces in Zambia, our crude all-cause mortality rate, 17.2 per 1000 person years, was somewhat similar to the 13.3 per 1000 person years estimated for 2009 and 2010 by the Central Statistics Office’s (CSO), “Population Projections Report” based on projections from 2000 Census data. [33] Our estimate, which included a substantial proportion of residents of Lusaka province, was essentially equal to CSO’s projections for Lusaka Province (17.1 per 1000) and somewhat similar to a recently conducted analysis reporting 14.1-14.5 deaths per 1000 in Lusaka province. [34] Although samples were not drawn to be representative of the country, our crude maternal mortality rate (1.6 per 100,000 women aged 15-49) (DHS 2007) was somewhat similar to the 1.2 per 100,000 rate reported by the Demographic Health Survey (DHS) for 2002-2003 (DHS). However, our under five mortality was substantially less (80 per 1000) than the DHS reported with regard to 2003-4 data (119 per 1000). This difference could suggest an ascertainment issue in our data that should be investigated. Under 5 mortality could also be underreported because of stigma associated with discussing early childhood deaths. Otherwise, few sources of mortality data exist in Zambia. To our knowledge, there is no other source of representative data on the distribution and causes of death in Zambia.”

3. Are the discussion and conclusions well balanced and adequately supported by the data?

Aspects of the discussion (paragraphs 7 & 8 under discussion) depart rather too far from the core intent of the paper: RE: Issue of scale-up of provision of HAART & treatment of HIV/AIDS??

Response: Thanks for this suggestion. We agree that we have focused a bit too much on HIV in this paper. We have deleted some sentences in this paragraph to balance treatment of HIV. We do think that being the leading cause (and more than a quarter of deaths) warrants substantial discussion, even a bit more discussion than the other causes. Please see our revised paragraph below and on page 13/14:
“Despite rapid scale-up of national programs to provide free highly active antiretroviral
treatment (HAART), and prevent of mother to child transmission, HIV is still the leading cause of
death throughout the country. This finding is similar to other countries in sub Saharan Africa
[23, 27] and the entire African region. [22] Research suggests that HIV-related death is most
common in the three months following treatment initiation and is associated with advanced HIV
disease at presentation [34], thought to indicate delays in seeking care. Long distances from
homes to health care centers providing HAART have been linked to delayed treatment,
particularly in rural areas. [35] Zambia is currently incorporating new, more aggressive
treatment guidelines that may improve survival. [36] It is hoped that implementation of these
guidelines will lead to reductions in HIV-related mortality, although they do not address the
distance barrier. Zambia should be able to evaluate trends in HIV-related mortality before and
after implementation of the new guidelines with the continued and ongoing collection of vital
events data using SAVVY.”

How much did implementing SAVVY in four of the nine provinces cost? And how does it
compare with the cost of restoring vital registration system in Zambia as a whole.

Response: Thank you for your comment. The implementation of SAVVY in the four pilot
provinces cost approximately $1m. But with improved efficiencies, the cost could be much lower
than this in the future. Vital registration technically already exists, although it is not a
requirement to have a death certificate for a living beneficiary to claim benefits. Thus, there is no
incentive on the part of the deceased’s family to obtain a death certificate. When they are
created, records of death are not detailed regarding characteristics of the deceased or the causes
of death. There are few personnel trained to determine causes of death. Because we are very far
from having a functioning vital registration system and we are not experts in costing, we’re
unable to report its cost here.

7. Is the writing acceptable?

The authors should take a second look at the use of “decedent”. It is unusual in the literature on
this topic.

Examples (RESULTS)

“People who were married/living with a partner were represented equally in decedents and the
baseline census”

“But decedents were three-to-six times as likely to have been never married…”

Response: Thank you for pointing this out. The word decedent has been removed from the
manuscript. These sentences, found on the 3rd paragraph, starting the 7th sentence on page 9
have been changed to:

“People who were married/living with a partner were represented equally in SAVVY and the
baseline census (approximately 50%). But those who had died were more likely to be married
(322, 50%) than the baseline population (6853, 39%) and three- to six-times as likely to be
widowed (115, 18%) or divorced (67, 10%) compared to the baseline population (5% and 3% respectively; Table 1).”

Some of the phrases and sentences are very difficult to follow meaningfully and need to be revised.

Examples

[RESULTS] “People who were married/living with a partner were represented equally in decedents and the baseline census”

Response: See above, this sentence was changed in response to the previous comment.

[RESULTS] “Adult men died of injury significantly more than adult women…”

Response: The sentence, found on page 10, second to last paragraph, last sentence, now reads:

“Men died of injuries more often than women (10% vs. 4%, \( p<0.01 \); Figure 3).

[DISCUSSION] “However, these efficiencies may not be worth possible reductions in data quality….”

Response: This has been modified (4th paragraph of Discussion) to clarify:

“However, these efficiencies must be weighed against the adverse impact longer recall periods may have on data quality. [6, 24]”

Referee 2: Reviewer’s report:

Minor Essential Revision:

1. I would recommend to report characteristics of the respondents to the VA, as well as the refusal rate (if any).

Response: We addressed this comment by adding the following sentences on page 8:

“A close adult relative (mother, father, sibling or spouse) participated in the VA interview for 687 (65%) reported deaths, a child of the deceased participated for 96 (9%) deaths, other relatives participated for 259 (25%) deaths, and non-relatives participated for 14 (1%) deaths. Of the total 1056 deaths, 1,006 (95%) respondents reported that they had lived with the deceased in the period leading to death. An eligible respondent agreed to participate in the study for each death. There were no refusals.”

Editor Review:
1. Could you discuss the issues related to physicians working as readers/coders of verbal autopsies? We don’t see references supporting or critiquing these methods.

**Response:** We have treated physician coding and compared it to algorithm coding in this passage on page 11 and 12:

“Zambia employed physicians to code interviews into ICD-10 causes of death (PCVA). Two physicians coded each interview, and if their codes differed, they discussed the case to agree on a final code. Physicians were unable to consider medical records in coding deaths as recommended by WHO because most families of those who had died did not keep these medical records. Despite this limitation, we viewed PCVA and duplicate coding as strengths. However, recent publications have suggested a low (30%) concordance between PCVA and a gold-standard, in this case known cause of death. [25] Recent reports have also cast doubt that duplicate-coding improved data quality. [26, 27]

Computer-based algorithms such as interVA and the Symptom-Pattern or the newly-developed Tarriff and Random Forest methods are promising alternatives to PCVA.[28-30] Algorithmic methods have been shown to perform as well as or better than PCVA in cause of death assignment without the personnel cost. [28, 29, 31] For particular individual causes of death, some algorithms have been shown to perform better than PCVA. But algorithms lack the ability to identify and prioritize causes of death that are of public health importance in specific settings, to adapt to changing disease patterns, and to accurately identify less common causes of death. [27, 29] Overall, in recent comparisons, despite statistical differences in results generated by PCVA and algorithm-coded methods, leading causes of disease and groups most burdened have been similar and have had the same policy implications. [17, 27]

During data collection for this pilot phase, we did not use algorithms to code causes of death because they have only recently been developed and validated. Once they are refined and made available for tailoring and testing in Zambia, they could be used here.”

2. We would expect to see deaths from cancer. Why are these not represented in Table 1?

**Response:** The original Table 1 was deleted. We have revised the category “neoplasms” in Figure 3 to read “cancers”. This group consists of malignant neoplasms affecting different organs as defined by the ICD-10.

3. We would like to see the same age/sex group analyses as seen in Table 2, by cause of death (as seen in Table 1).

**Response:** Such a table was created but then removed from the paper before submission. It is revised and shown below. We would prefer not to publish this table in this report because our cell sizes make the estimates statistically unstable. Text highlighting some key differences in causes of death by age group and sex are included in the manuscript on pages 10 & 11 and excerpted below the table and in the results section.

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Number and proportion (%) of deaths listed for the top 14 diseases/illnesses by sex and age group from SAVVY interviews (n=910).
The deaths represented in this table (910) include only the top 14 causes of death, not the total number of deaths (1056).

"Cause-specific mortality fractions varied by disease and gender. Males died most often of HIV/AIDS, and most (125, 82%) of HIV deaths among males occurred in those over 15 years of age. Malaria, injuries (transport related, drowning, falls, exposure to smoke, fire and flames, accidental poisoning and assault) and diseases of the circulatory system were the other leading causes of death for males. Men also died of injuries more often than women (10% vs. 4%, p<0.01) (Figure 3).

The leading causes of death for females were HIV/AIDS, malaria, diseases of the circulatory system and malnutrition (Figure 3). Most (105, 78%) of females dying of HIV/AIDS deaths were over 15 years of age. Approximately 93% of the deaths in females due to malnutrition occurred in children and young teens between 4 weeks and 14 years of age. Meningitis caused a statistically significantly greater number of deaths in girls aged 4 weeks to 14 years vs. boys in the same age group (7% vs. 2%, p<0.05). Maternal conditions also contributed to 13 (3%) of deaths among females. Although not statistically significant, more male infants died of stillbirth than females (1.5% vs. 0.6%, p-value< 0.25)."

4. The manuscript does not discuss the possible misclassification of malaria deaths hiding in causes of other infections, like diarrheal diseases, pneumonia, or measles.

Response: Thank you for your comments. At a recent workshop we discussed the possible misclassification of deaths attributed to malaria in Zambia. From our experience, malaria deaths are not as common as our results suggest. The physicians that coded the questionnaires indicated that they have seen much fewer malaria cases in the clinical work and suspect that there could have been some misclassification. In response to your comment, we have added the following sentence to address this on page 14.

"Sixth, most of the households interviewed could not provide hospital records such as laboratory results. Our reliance on a lay description of the family member’s symptoms likely resulted in misclassification of cause of death."

5. We would like to see external validation of the results using other studies in Zambia or estimates for Zambia.
Response: Please see our response to items 1 and 2 of Reviewer's initial comments on pages 1 and 2 of this document.

6. Finally, we encourage expansion of the results and discussion sections.

Response: Please see new results and discussion sections. We have added some points to each section and have reworked them as noted in these 7 pages, based on feedback received.