

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Healthcare professionals knowledge, attitude and practice of adverse drug reactions reporting in Ethiopia: a cross-sectional study
<b>AUTHORS</b>	Gidey, Kidu; Seifu, Mohammedamin; Hailu, Berhane; Asgedom, Solomon Weldegebreal; Niriayo, yirga

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Maxine Gossell-Williams University of the West Indies, Jamaica
<b>REVIEW RETURNED</b>	22-Oct-2019

<b>GENERAL COMMENTS</b>	- The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.
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<b>REVIEWER</b>	Narumol Jaremsiripornkul Department of Clinical Pharmacy Faculty of Pharmaceutical Sciences Khon kaen University Thailand
<b>REVIEW RETURNED</b>	24-Oct-2019

<b>GENERAL COMMENTS</b>	<p>Specific comments</p> <p>Thank you for the opportunity to review this manuscript. There are some comments that the authors need to address.</p> <ol style="list-style-type: none"><li>1. Title<ul style="list-style-type: none"><li>• Please confirm about the term of “adverse drug reaction reporting “ or “reporting adverse drug reactions”</li></ul></li><li>2. Introduction<ul style="list-style-type: none"><li>• What is the need to conduct this study since there have been a number of similar studies? Is there any different context in Ethiopia regarding the reporting of ADRs?</li></ul></li><li>3. Methods and materials<ul style="list-style-type: none"><li>• Please provide more detail about stratified random sampling among different healthcare professionals (HCPs). How to select HCPs from units/ departments?</li><li>• Is there any validation of questionnaire by experts? If yes, please clarify.</li><li>• How to distribute the questionnaires to different HCPs? Any reminders to increase the response rate?</li></ul></li><li>4. Results<ul style="list-style-type: none"><li>• Mean (SD) of respondents’ age is needed.</li><li>• Table 2: I was wondering whether the question “Are you aware of any drug that banned due to ADR?” can be assessed as knowledge.</li><li>• Is stepwise or backward logistic regression used in the analysis?</li></ul></li></ol>
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	<p>5. Discussion</p> <ul style="list-style-type: none"> <li>• It would be of benefit to provide more discussion about some strategies to improve attitude and knowledge apart from educational training.</li> </ul>
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer 1

#### abstract

Page 1: The application used for statistical analysis is not information. Remove. The text should refer to type of descriptive and inferential statistic applied.

**Authors' Response:** We thank the reviewer for this suggestion. We corrected it.

Page 1: Requires direction of measure.. positive or negative

**Authors' Response:** Thank you the reviewer for this suggestion. We modified it accordingly as follow:

“...**Poor** knowledge (Adjusted odds ratio (AOR)= 2.63, 95% confidence interval (CI): 1.26- 5.45), and lack of training on ADRs reporting (AOR= 7.31, 95% CI: 3.42- 15.62) *were both negatively associated* with ADRs reporting practice, *whereas* higher work experience ( $\geq 10$  years) (AOR= 0.36, 95% CI: 0.13- 0.97) were positively associated with ADRs reporting practice.”

#### Introduction

Page 2 : Information from a systematic review article is more appropriate rather than from France

**Authors' Response:** We appreciate this comment, as it helps us to include more complete data instead of using data from a single study. We have modified this information based on evidence from the review and the meta-analysis.

“.....ADRs have become a major public health problem in developing countries [2]. The median prevalence (with interquartile range [IQR]) of ADR-related hospitalization in developing countries was 5.5% (1.1-16.9) [3].”

Page 2: Revisits this sentence. ADRs as define by WHO do not include pre-clinical studies.

**Authors' Response:** We have corrected and clarified this sentence from the study of the World Health Organization. “.... The information collected during the pre-marketing phase of drug development is inevitably incomplete with respect to possible ADRs. This is due to the participation of a limited and selected number of patients who are studied before marketing, the conditions of drug use in clinical trails are different from those of clinical practice, the duration of the clinical trails is short, and high-risk patients (such as elderly patients) are often excluded.”

Page 2: Unrealistic statement and not useful. Consider removing.

**Authors' Response:** We have removed and replaced with the following sentence. "Therefore, post-marketing surveillance is important to allow detection of less common, but sometimes very serious ADRs."

Page 3 line 20: Bold statement made from a one study done in Australia

**Authors' Response: This was replaced by** a systematic review of studies

"...A spontaneous reporting system of ADRs is fundamental to effectively discovered new adverse reactions but under-reporting is its major limitations [7, 8]. A systematic review of studies conducted in the European Union showed a significant and widespread healthcare professionals under-reporting of ADRs with a median rate of under-reporting of 94% [7]. The low rates of ADRs reporting may delay regulatory actions to remove drugs with an unacceptable safety profile from the marketplace. A worldwide systematic review of 462 medicines removed from the market for safety reasons showed that the median interval between the first reported adverse reaction and the year of first withdrawal was 6 years (IQR, 1-15) and the interval did not consistently shorten over time [9]."

Page 4 : Limited may not be the best choice of word, if authors are referring to paucity of reports

**Authors' Response:** We thank the reviewer for this suggestion. We corrected it.

"Since the introduction of the pharmacovigilance system, only a small number of adverse drug reactions have been reported to the center"

#### **Materials and Methods**

Page 6: As count data..ie.. number of right answers for each HCPs, use of median is more appropriate.

**Authors' Response:** Thank you for your suggestion. We calculated the median of the knowledge score and we reported the median as your suggestion. The mean (SD) score is  $4.17 \pm 2.07$  and the median (IQR) score is 4 [3, 6]. Since the mean and the median score are similar, we get similar number of participants in the good/ poor knowledge category even after we replace it with median.

Page 6: Revisit this scoring system. the neutral opinion weights more than disagree.

Thus is an assumption that neutral weighs close to positive attitude. A subject may be neutral because they know nothing of the topic and/or never trained and therefore cannot have opinion. Considering making it '0'.

**Authors' Response:** The reviewer makes an interesting point on the attitude scoring system. We very much appreciate for this logical comment. However, subjects who chooses neural are either they know the topic but not want to agree/disagree or as you explained they don't know the topic. We believe majority of the respondents are very familiar with the attitude questions and we focused whether they agree on these issues or not. In this case neutral may weighs from the disagree. Actually, the neutral score is not close to agree (positive attitude) **rather it is in the middle between agree and disagree. We also tried to see some references on this issue, but we did not get a study that reported neutral score below the disagree score. Most of the studies make the score of neutral '2' on three-point Likert scale and '3' on five Likert scale. In both case neutral score**

**is on the middle of agreeing and disagreeing. Some studies similar with our study that proved a score of '2' for neutral are cited here [1, 2].**

**With regard to the attitude score**, the median with inter-quartile range (IQR) of the attitude score of ADRs reporting among HCPs was 20 (17–22) and the mean (SD) score was 20.0098 (3.267) out of 30. As your recommendation for the knowledge score, we also used a median score for the attitude part as it may have some skewed data. therefore participants having more than 20 score (more than two third) are perceived to have positive attitude.

## **Results**

Page 8: Unnecessary table. Information can be placed in text. data appears again in later tables ....

**Authors' Response:** Although the demographic variables are repeated in the later table (in the logistic regression analysis table), the frequency of participants is different in both tables. While the first table summarizes variables of all the participants (n=307), the later table contains reduced sample (n=230). In the later table those participants who didn't never get ADR were not included. ADRs reporting practice was determined from those participants who did get ADRs in their practice.

Page 10: Grammar

**Authors' Response:** We thank the reviewer for this suggestion. We corrected it.

Page 13: Change to unadjusted

**Authors' Response:** Thank you for your suggestion. We have done so with our resubmission

Page 13: Adjusted for what is not stated anywhere

**Authors' Response:** We corrected it.

Page 14: Justification of age grouping required. Justification for experience grouping is required

**Authors' Response:** We thank the reviewer for these questions. Although there is no universal clear limit for the grouping of age and year of experience, we consider that participants with less than 5 years of experience have less experience, participants from 5 to 10 years have average experience and those over 10 years have a good experience. we also used other similar studies in this area as a reference for grouping the age and year of experience [1, 3].

## **Page 15: Discussion**

The discussion needs work, as it represents a report of percentages of frequencies from different settings and years apart. A discussion should not be used to report a plethora of number with not effort to provide systematic assessment. Suggested that rather than giving raw data different settings, note this study is consistent was at least two studies from other Ethiopian settings. For example, With more HCP having poor knowledge, give reasons why this is so and provide literature to support the speculations.

**Authors' Response:** **We very much appreciate the reviewer for this important comment. we tried to include all possible explanations for our findings rather than comparing with many other similar studies. We believe we improved the discussion section significantly. We added explanation to our results, and detail explanation was provided on the possible strategies to improve attitude and knowledge and reporting practice. (please see the discussion part)**

Page 15: Not sure these add value, as they are from other countries and from 2007 and 2015.

**Authors' Response: We removed these data.**

## **Reviewer 2**

### 1. Title

Please confirm about the term of “adverse drug reaction reporting “ or “reporting adverse drug reactions”

**Authors' Response:** Thank you for your suggestion. We tried to search similar studies on the terms. Although both terms are used in a number of studies, the majority of studies used the term " adverse drug reactions reporting ". Moreover, it would be better if we first use the subject (adverse drug reaction (Subject) + report(verb)). Hence, we consider changing the title with your suggestion as follow “Healthcare professionals knowledge, attitude and practice of adverse drug reactions reporting in Ethiopia: a cross-sectional study” **We have also tried to use this term consistently throughout the manuscript.**

### 2. Introduction

What is the need to conduct this study since there have been a number of similar studies? Is there any different context in Ethiopia regarding the reporting of ADRs?

**Authors' Response:** You are right, there are a number of similar studies in other settings. However local data is very important to inform policymakers and other responsible stakeholders in this area about the status of ADR reporting, the gaps, and factors for underreporting. The level of reporting, the reasons for underreporting, the level of training of HCPs and other factors may be different in different contexts and we feel it is very important to study this in our context. Moreover, policy makers value local data and usually depend on it when asked to provide short trainings, continuing education, and other capacity building strategies in these areas. Hence we stressed this idea in the introduction section.

### 3. Methods and materials

Please provide more detail about stratified random sampling among different healthcare professionals (HCPs). How to select HCPs from units/ departments?

**Authors' Response:** We appreciate the opportunity to include details in the sampling methods as this will help our readers to understand easily. We have included the details of the sampling method as follow:

“Subjects were recruited using stratified random sampling technique. A list of HCPs (pharmacists, physicians, and nurses) working at the hospital was obtained from the hospital's human resources department. All HCPs were first stratified according to the type of profession and this list was used as a sampling frame. Depending on the size of the profession in each category of HCPs, participants were randomly selected. We used a lottery method to randomly select a set of healthcare professionals as respondents from each category. We used this lottery method from the complete list of each category assuming that all the HCPs working in a similar profession (for example, all physicians) in different departments and/or units were homogeneous with respect to knowledge, attitude, and practice of ADRs reporting. “

Is there any validation of questionnaire by experts? If yes, please clarify.

**Authors' Response:** We very much appreciate the reviewer for this important comment. We did the questionnaire validation during the proposal development and defense but we missed to report in the final manuscript. However, the questionnaire was only subjected to face and content validity, and we didn't determine the construct validity and criterion validity of the questionnaire. Only the pretest (pilot study) was mentioned and now we included the following statement in the manuscript:

"....The questionnaire was reviewed for its content validity by consensus of a panel of three expert's in the field derived from *academia* (one expert from *pharmacoepidemiology* and two experts from clinical pharmacy departments). The Index of consistency of the questionnaires was 0.86, suggesting that the questions strictly adhered to the objectives of the study. **A pre-test was performed on 5% of the sample (19 HCPS) in a different hospital and a face validity of the questionnaire was tested.** Minor modifications have been made accordingly to avoid ambiguities and **improve clarity.** These participants were not included in the final study."

How to distribute the questionnaires to different HCPs? Any reminders to increase the response rate?

**Authors' Response:** We thank the reviewer for this comment to add an explanation about the distribution of the questionnaires, which is not specifically shown in the manuscript. Here is the detailed explanation ".....The questionnaires were distributed by two pharmacists in person. The completed questionnaires were then collected by the pharmacists in person at the end of the first, second, third, and fourth weeks. A reminder was provided to non-respondents twice (i.e. at the end of second week and at the end of third week). If the questionnaires did not return by the end of the fourth week, the participant was considered non-respondent."

#### 4. Results

Mean (SD) of respondents' age is needed.

**Authors' Response:** We thank the reviewer for this comment. We have included the mean (SD) of respondents'.

Table 2: I was wondering whether the question "Are you aware of any drug that banned due to ADR?" can be assessed as knowledge.

**Authors' Response:** While we agree that this question sounds like information rather than knowledge, it indirectly measures participants' knowledge. If a participant never knows any drug that has been banned due to ADR, it indirectly implies that the participant does not know those very severe and known reactions that have occurred so far. Knowing drugs previously banned because of an adverse reaction may also suggest that their occurrence may result in withdrawal, which helps HCPs to pay enough attention. Many other studies have also used this question to assess knowledge, including studies by Nisa et al 2018 and Desai et al 2011[4-6].

Is stepwise or backward logistic regression used in the analysis?

**Authors' Response:** We used backward logistic regression in this study.

#### 5. Discussion

It would be of benefit to provide more discussion about some strategies to improve attitude and knowledge apart from educational training.

**Authors' Response:** We thank the reviewer for this important comment, as it has been proven that multiple interventions appear to have had more impact than single interventions. According to your suggestion we included the following sentences: “ ...The low level of knowledge of the ADR and its reporting among HCPs should be enhanced by designing different strategies. A systematic review of strategies to improve ADRs reporting has shown that multiple interventions appear to have had more impact than single interventions [13]. Several studies have shown improved knowledge and attitude scores after educational interventions, including oral workshops, oral presentations, group discussion, designing ADR newsletters in hospitals, **and** ongoing training in pharmacovigilance and ADR reporting's, [36-40]. Other studies have shown that ADRs reporting has been improved by offering incentives to health professionals [41, 42]. A study conducted in Spanish that involves both economic incentives and educational activities, resulted in up to six-fold increase in the average ADR reporting [43]. Increasing the availability of yellow cards on wards as well as encouragement to use web-based reporting had improve reporting rates [43].”

#### References for clarification of certain information provided in the response

1. Seid MA, Kasahun AE, Mante BM, Gebremariam SN. Healthcare professionals' knowledge, attitude and practice towards adverse drug reaction (ADR) reporting at the health center level in Ethiopia. *International journal of clinical pharmacy*. 2018;40(4):895-902. Epub 2018/08/11. doi: 10.1007/s11096-018-0682-0. PubMed PMID: 30094559.
2. Sabblah GT, Darko DM, Mogtari H, Harmark L, van Puijenbroek E. Patients' Perspectives on Adverse Drug Reaction Reporting in a Developing Country: A Case Study from Ghana. *Drug safety*. 2017;40(10):911-21. Epub 2017/06/28. doi: 10.1007/s40264-017-0563-9. PubMed PMID: 28653291.
3. Necho W, Worku A. Assessment of knowledge, attitude and practice of health professionals towards adverse drug reaction reporting and factors associated with reporting. *J Pharmacovigilance*. 2014;2(4):135.
4. Nisa ZU, Zafar A, Sher F. Assessment of knowledge, attitude and practice of adverse drug reaction reporting among healthcare professionals in secondary and tertiary hospitals in the capital of Pakistan. *Saudi Pharm J*. 2018;26(4):453-61. Epub 02/06. doi: 10.1016/j.jsps.2018.02.014. PubMed PMID: 29844715.

5. Desai CK, Iyer G, Panchal J, Shah S, Dikshit RK. An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. *Perspectives in clinical research*. 2011;2(4):129-36. doi: 10.4103/2229-3485.86883. PubMed PMID: 22145123.
6. Gonzalez-Gonzalez C, Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Strategies to improve adverse drug reaction reporting: a critical and systematic review. *Drug safety*. 2013;36(5):317-28. Epub 2013/05/04. doi: 10.1007/s40264-013-0058-2. PubMed PMID: 23640659.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Maxine Gossell-Williams Univ W Indies, Pharmacology & Pharmacy
<b>REVIEW RETURNED</b>	29-Nov-2019

<b>GENERAL COMMENTS</b>	<p>The discussion needs lots of work. It is unnecessarily too long and extensively filled with speculation. Bridging studies across countries, which show similarities or differences, but adding no evidence to support speculations does not inform the readers. For example, If Pakistan has been knowledge of PV then provide the evidence of why this is so rather than speculate. I have place further comment boxes in the document.</p> <p>All other concerns from previous report were addressed satisfactorily.</p> <p>- The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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<b>REVIEWER</b>	Narumol Jarernsiriornkul Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand
<b>REVIEW RETURNED</b>	11-Dec-2019

<b>GENERAL COMMENTS</b>	No further corrections is needed.
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#### VERSION 2 – AUTHOR RESPONSE

##### Response to reviewer

We wish to express our appreciation to the Reviewer for the insightful comments, which have helped us significantly to improve our manuscript. According to the suggestions, we have thoroughly revised our manuscript. Point-by-point responses to the comments are listed below.

##### General comment

The discussion needs lots of work. It is unnecessarily too long and extensively filled with speculation. Bridging studies across countries, which show similarities or differences, but adding no evidence to support speculations does not inform the readers. For example, If Pakistan has been knowledge of PV then provide the evidence of why this is so rather than speculate. I have place further comment boxes in the document.



Authors' Response: We very much appreciate the reviewer for the important comments. We tried to compare and interpret our results in the discussion section based on the available studies in our country (local data) and with studies with similar objectives. Some of the sentences which are not supported with the primary literatures were removed from the discussion section.

#### Abstract

Reviewer comment: AOR- adjusted for what

Authors' Response: We performed multivariable regression by including several independent variables and produces adjusted odds ratios (AORs). An adjusted odds ratio (AOR) is an odds ratio that controls for other predictor variables in the model. In our study when we want to determine the association of one variable (e.g. knowledge) with reporting practice, we should control other confounding variables to control their influence on the dependent variable (reporting practice). So we adjusted the effect of confounders by controlling all additional variables (i.e all the variables which are listed in table 5) in the in logistic regression model.

Reviewers comment: (table 4) This table could be formatted better, as no an like 48 is reporting the same in line 50

Authors' Response: we tried to improve the formatting of the table. The lines are now clearly separated and are not confusing.

Replace with the term unadjusted

Authors' Response: Thank you for your comment, we corrected it.

May be more informative to use the terms good and poor practice, since these are the terms used for the discourse.

Authors' Response: We appreciate your comments. We replaced the terms based on your suggestions.

#### Discussions

These studies did not research reasons for insufficient knowledge. The did however report similar findings for not reporting ADR. The authors need to keep discussion in context.

Authors' Response: we removed one of the references and we only included a reference that explains with context of "knowledge". A research conducted in amhara region identified the factors that affect the knowledge of ADR reporting among healthcare professionals in amhara region and we tried to discuss our research relative to this paper.

The evidence from the literature that low level of knowledge is associated with insufficient training in undergraduate in PV has not been provided by authors.

Authors' Response: From our observation in our country and considering other countries reports, we included this statement. However, we do not have published data on this area to use as a reference and we omitted this reason.

I am not seeing the benefit of discourse from other country findings which offer higher figures on knowledge with no evidence that the study showed that government involvement is the reason for better figures. The Kuwait study for example just pointed to the fact that most of the health care is by Government run hospitals. Furthermore, the authors of this current paper use the words 'may be due to' Using speculative data from another study to justify another speculation does not add to the body

of the literature. Of note, the authors of the Kuwait study stated in speculating the reasons for their findings

" Some of these barriers included lack of training and education, lack of communication between private and government sectors, lack of governing legislation and reporting system"

Authors' Response: as we have some studies to compare our results across the regions in Ethiopia, we removed the discourse from other country findings. As your concern, comparing these papers from different countries with different population background is affected by a lot of factors and we tried to use similar studies in Ethiopia.

Same issue her. Throughout the whole discussion, there is discussions of other country findings where the data is similar of different, where the objectives of the study are the same. If the authors should focus on studies which support there speculation. For example, studies which show training interventions can increase ADR reporting

Authors' Response: Thank you for your comments. We replaced almost all the studies from other countries since they have very different settings. We included studies from Ethiopia in other regions and also with similar objectives.

Rationalizing why this difference across regions would be good. Perhaps the reason relates to the fact that Seid did not use the median as a cut-off to decide on attitude group, but rather seemed to have chosen an arbitrary value of above 75%, of which the calculation was not explained.

Authors' Response: we thank for the reviewer's comment. We tried to put the possible rationale for the attitude difference across the regions.

Speculations, not proven by Seid[21]

Authors' Response: we gave detailed explanations using other relevant studies from Ethiopia.