Author’s response to reviews

Title: Burden of Paraquat Poisoning in the Department of Antioquia, Colombia

Authors:

Jefferson Antonio Buendia (jefferson.buendia@gmail.com)
Gabriel Restrepo Chavarriaga (gabrielrestrepo0176@gmail.com)
Andrés Zuluaga (andrezuluagasalazar@gmail.com)

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Author’s response to reviews:

Dear.

Natália Brucker
BMC Pharmacology and Toxicology

We send the corrections with a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text

We look forward to your prompt reply

Reviewer 1

1. In the current study, authors estimated the burden of PQ poisoning using different and in some cases irrelevant sources of information. For example it has been noted "The values of duration of the disease and rate of remission for acute poisoning and paraquat-induced pulmonary fibrosis were obtained from the literature (13-15)"these references belong to other countries (Korea and
Japan). It seems that the information from different sources were enrolled. Please explain about these variabilities and unconformities in target group (PQ poisoning in the Department of Antioquia, Colombia) and source of information (literature related to other countries). These cannot be representative of your target population and can cause the bias.

Response: Suggestion is accepted and the text is modified clarifying in the discussion the way in which this possible information bias was handled.

“To minimize the possible information bias due to the use of probability values extracted from the literature, which come from populations other than the Colombian population; sensitivity analysis was performed for each of these parameters taking a range of possible values and assuming a distribution. As it was evidenced the final result of DALYs was not sensitive to the change in the values of said probabilities guaranteeing the robustness of the model”

2. Perhaps the most important limitation is that the authors retrospectively analyzed admissions due to acute paraquat poisonings reported to the national epidemiological surveillance system (SIVIGILA) in the 2010-2016 period

Response: Suggestion is accepted and the text is modified clarifying in the discussion the way in which this possible information bias was handled.

“Regarding the possible information bias due to the use of retrospective information and despite the fact that the case report of poisoning by chemical substances is mandatory for all institutions in the country; some degree of underestimation in cases of poisoning by PQ is possible. However, in the department of Antioquia there has been a tendency since 2008 to increase the reporting of intoxication cases to SIVIGILA, which may reduce the risk of this information bias”

3. The methodology of study is ambiguous and the studied population should be defined more clearly with sufficient details to allow replication

Response: was rewritten the methodology clarifying and detailing all aspects for its reproducibility.
4. In this study I did not see clear details about calculation of two main variable of years of life lost (YLL) and years of life lived with disability (YLD). It need to report a very precise details.

Response: was rewritten the methodology clarifying and detailing all aspects for estimation of YLL and YLD

5. Statistical analysis section should be improved. In other words, this data would prove more useful if you provide distribution of variables used for sensitivity analysis in this data

Response: was rewritten the methodology clarifying and detailing all aspects of statistical analysis.

6. One general concern I have is with the identification of patients who are paraquat poisoned. My concern is how can the reader be sure that we are looking at PQ poisoning in all recorded cases? Please clarify the methodology

Response: was rewritten the methodology clarifying and detailing this aspect taking into account the retrospective nature of the information:

“We calculated the mortality and/or morbidity based on the 10th revision of International Classification of Diseases (ICD-10) classification. First all records of patients intoxicated by PQ during the 2010-2016 in the department of Antioquia to the national epidemiological surveillance system (SIVIGILA) were analyzed. In SIVIGILA all patients intoxicated by chemical substances are reported online or in paper form to the SIVIGILA by each hospitals; being this report obligatory and made by personnel trained. The information recorded is age, sex, ingestion at hospital admission, amount ingested, symptoms, ethnicity, and type of exposure and mortality”

7. In the material and methods section, some essential questions remain unanswered. Please explain your inclusion and exclusion criteria more clearly
Response: was rewritten the methodology clarifying and detailing this aspect. We do not have exclusion criteria, we included all patient intoxicated by PQ.

“First in our study all records of patients intoxicated by PQ during the 2010-2016 in the department of Antioquia to the national epidemiological surveillance system (SIVIGILA) were analyzed”

8. Did you include data related to patients with the history of co-ingestion of poisons or unknown agents? How did you considered the cases with co ingestion of drugs/poisons in your statistical analysis?

Response: Text is modified clarifying in the discussion: “we do not consider the exclusion of patients with other concomitant poisonings since the presence of other toxic substances could not be validated in all cases.” The objective of this study was to determine the disease burden, in terms of DALYs, of paraquat intoxication, regardless of whether there was concomitant intoxication by other substances; and not to make a descriptive study of intoxication cases during the study period

9. Please clarify and elaborate were some variables such as out patient's visits and days of hospital stay, severity of PQ poisoning and etc.included in your statistical analysis?

Response: It was rewritten the text clarifying in the results. In the descriptive analysis of population were included: age, sex, ingestion at hospital admission, amount ingested, symptoms, ethnicity, and type of exposure and mortality

10. It is recommended to report additional information about the demographic characteristic of participants at the beginning of results section
Response: It was rewritten the text clarifying in the results. In the descriptive analysis of population were included: age, sex, ingestion at hospital admission, amount ingested, symptoms, ethnicity, and type of exposure and mortality.

11. The Discussion would be improved by detailing more specific implications for future studies.

Response: was rewritten the discussion clarifying and detailing all aspects of implications for future studies.

“Further studies are needed to evaluate potentially modifiable factors associated with the suicide attempt with paraquat, especially in the young and farmer population, where the highest burden of disease is presented by this condition.”

12. Please explain more about the implication of this study results. How the study results can help clinically?

Response: was rewritten the discussion clarifying and detailing all aspects of implications for medical system and physicians.

“For medical systems our results may lead to the generation of risk management policies prioritizing strategies for the prevention of suicide with paraquat in young people in order to mitigate the impact of such poisoning in our countries.”

13. In your introduction Please indicate the prevalence rate of PQ poisoning and its cause specific mortality in the world and Colombia.

Response: was rewritten the introduction clarifying this aspect:
“Globally, 250,000 to 370,000 people die from pesticide poisoning each year, and more than 90% of the individuals with acute poisoning attempted to commit suicide by intentionally ingesting PQ.”

“According to the National Institute of Health in Colombia, pesticides resulted in 1231 deaths in the period between 2008 and 2015, with a worrying positive trend accentuated in northeast of this country.”

14. The ethical considerations must be addressed more clearly in the material and methods section.

Response: was written the ethical considerations in methodology section.

“No personally identifiable information was recorded all information obtained from health surveillance systems were kept confidential. This study was approved by the Institutional Review Board of University of Antioquia”

15. More references are needed to support author’s statements in the introduction

Response: was included more references to support author’s statements in the introduction.

Reviewer 2

Consider commenting on the regulatory environment of Colombia either here or in the discussion.

Response: was rewritten the discussion, including the regulatory environment of Colombia.
Please check how reference 11 is referred to in the text. Consider including a table similar to Figure 1 in reference 11 that would assist in describing your methods.

Response: was rewritten including the basic formula of DALY mentioned in this reference

“Then we calculated the DALY for acute poisoning using methods described by Murray and Lopez in the GBD study (18); which summed the YLL and YLD components. The basic formula is expressed as follows: \( \text{DALY} = \text{YLL} + \text{YLD} \)”

The reference life tables are almost 25 years old. Do the authors feel that the results will be influenced by differences in life expectancy?

Response: We use these life tables for our calculations, since they are the reference patterns for the calculation of the years of life lost due to premature mortality, more used, with more publications; which guarantees us greater degree of comparability of our results with the previous publications.

Is there a reason that incidence was higher in 2012? Consider commenting here or discussing in the Discussion.

Response: No other environmental, social phenomena related to the increase in the incidence of intoxications were presented; neither did there exist alterations or changes in the epidemiological surveillance system of that year. We consider that this is an epidemiological variation since the increase was homogeneous throughout the department and was not related to any specific area.

What regulations currently exist for paraquat or herbicides in general in Colombia? Consider extending this discussion on what type of policies and regulations may be necessary, including an example or of where regulation, and potentially other changes, have improved social outcomes

Response: was rewritten the discussion, including the regulatory environment of Colombia, and other type of policies and regulations may be necessary to improved social outcomes
Reviewer 3

1- Did you have any inclusion or exclusion criteria?

Response: was rewritten the methodology clarifying and detailing this aspect. We do not have exclusion criteria, we included all patient intoxicated by PQ.

“First in our study all records of patients intoxicated by PQ during the 2010-2016 in the department of Antioquia to the national epidemiological surveillance system (SIVIGILA) were analyzed”

2- As you have also mentioned, 2012 is the year with most of the PQ poisonings. I just wondered if you could provide p values in your Table.

Response: No other environmental, social phenomena related to the increase in the incidence of intoxications were presented; neither did there exist alterations or changes in the epidemiological surveillance system of that year. We consider that this is an epidemiological variation since the increase was homogeneous throughout the department and was not related to any specific area.

3- There are some minor grammatical errors in the text. Please re-check the manuscript grammatically

Response: We correct all grammatical errors.

4. How long did you follow the patients who had referred in 2016?
Response: It was based on transversal information collected from the epidemiological surveillance system; this system does not have information regarding the longitudinal monitoring in the time of the patients; only the case report.

5-How did you determine the severity of PQ poisoning in your patients?

Response: There is no information on severity according to clinical symptoms or laboratory levels within the epidemiological surveillance system for paraquat intoxications.