Author's response to reviews

Title: Epidemiology aspects in 11,507 Mexican children with cancer under a national public health insurance program (Descriptive Epidemiology in Mexican children with cancer under an open national public health insurance program.)
Running title: Childhood cancer among Mexican children

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Author’s response to reviews: see over
Ms. Patricia Marie Ratin  
Journal Editorial Office  
BioMed Central

Dear Patricia:

We are sorry it took us so long to re-submit this manuscript, however it needed major modifications that were requested by the revisers.

In this new manuscript the title has been changed to: “Descriptive Epidemiology in Mexican children with cancer under an open national public health insurance program”. We have added another year (2012) of analysis so the results could have a stronger and solid results. The manuscript was re-done, and corrected by an official translation agency. I will like to remind the revisers that all this material was extracted from an official information that belongs to a national health program from the Federal Government of Mexico. That this program is not a private instance and therefore some of the questions that have been raised by the revisers are answer under our best ethical and scientific knowledge.

Some of the questions are mentioned in the text of the previous manuscript have been omitted because the context of the manuscript has changed. With all due respect It appears that the first reviser does not read it carefully.

Sincerely,

Prof. Roberto Rivera-Luna, MD

Reviser: Scott Howard

Title
Please include more description of the components of the study, such as “epidemiology and outcomes of …”, remove the number of patients, and add the time interval reviewed.
- Title was corrected according to the suggestion, it was changed to: “Descriptive Epidemiology in Mexican children with cancer under a national public health insurance program”.

Abstract
Please redo after revising the manuscript according to the recommendations below.
- It was corrected
Provide a reference for the 148,000 number in LMIC and the “5 times higher than expected in developing countries”. This number is fairly close to what would be expected in LMIC, especially if about 35% of children do not get diagnosed.
- We revised and modified the data according with published information, reference was included

Methods
1. Ethics – identifiable data on living human subjects in most countries would require review by ethics committee or IRB. What was the basis for a waiver of approval in this case
   - The explanation was included in the text

2. Define abandonment
   - The term abandonment was defined, and we included a new reference

3. Scope – epidemiology, but outcomes were included
   - The terms that we included were mortality and abandonment

4. 51 institutions mentioned in Abstract and Methods, but 59 in Background
   - The data was corrected to 55 in the year 2012

5. 6 areas mentioned, but no analysis by region
   - We included the analysis of the 6 regions

6. Incidence – measured as a whole? What about by region?
   - The article is about the national incidence, we did not consider to include the incidence by region

7. Minimum follow-up of 48 months is mentioned, but patients diagnosed in 2011 could have a maximum of 3 years of follow-up
   - We agree with the comments, the maximum follow up period was 36 months, it was corrected
   . When was the data frozen for analysis?
     - The frozen data was on December 2012

9. Please include 2005 and 2006 data for leukemia patients
   - We only included the data from 2007 to 2012 because until this date were included all the malignant neoplasm.

10. The number of cases of cancer among children covered by PMI grew much more rapidly than the number of covered children in the plan. However, this could be the result of children with cancer being preferentially registered into the program, more so than children living in rural areas who do not develop a severe disease and therefore do not come to treatment centers where registration would occur.
   a. Please describe the process of registering in the system and how healthy Children from rural areas are registered
   b. Please analyze incidence by region by year, which could help identify where the increases have come from (for example, the pattern of change in Chiapas may differ from that in Mexico City, where most children may have already been registered.
c. How many children were eligible for PMI in 2007-2012 of the 31,972,300 children in Mexico?
   a. The register system is homogenous, and all the children are registered by the same form in rural and urban areas whose parents live and work in their community.
   b. The objective of this paper was not analyzed the incidence by region, this information will be analyzed in a different paper.
   c. We present that data in the table 1, and this is referred in the manuscript (page 3). The patients included in the PMI are all the patients that do not have a social security health system (socialized medicine)

11. When was each national protocol developed, approved, and activated? Were all protocols activated for all cancers before 2007?
   - All protocols were activated by 2007, for a presidential decree and disposition after three years of working on them. All this questions are perfectly answered in the text.

12. Please include the protocols as appendices
   - National technical protocols consist of a book of 374 pages edited as a book format, so it is impossible to include as appendices. If the revisor wishes the Protocols we will gladly send him this document as a gift thru Fed Express

13. What monitoring was done to assure that all patients were treated according to the national protocol for each cancer?
   - The financial committee of PMI and CENSIA (the normative part of the PMI) has a specific random method to monitor and assure that each protocol nationwide is not violated (this statement is described in the manuscript)

14. Increased treatment compliance is mentioned on page 8 – how was this measured? What source documentation was provided? Who did the audits?
   - It was answer in the comment number 13

15. The abstract mentions 2-year overall survival, but this is not mentioned in Results. Please provide Kaplan-Meier curves for EFS for the following groups of patients (ok to include in a supplementary appendix):
   a. All patients
   b. By the 6 regions
   c. By state
   d. By centers (without mentioning names of centers, just by a number is fine)
   e. By diagnosis (ALL, AML, etc.)
   f. By sex
   g. By diagnosis year
   h. By average socioeconomic status
   i. By the 6 regions
   ii. By state
   - The aim of this study was not to perform a survival analysis; this will be a different paper, we excluded all the survival data from this manuscript

16. Please provide the cumulative incidence of abandonment of treatment (by groups in #15)
   - We did not include this analysis in the paper
17. Please provide the cumulative incidence of relapse (by groups in #15)
   - We did not include this analysis in the paper, and the follow up period was too short to performed the relapsed analysis, and it is not the aim of this article

Results
1. Numbers in the text of the results should be identical to those in the Tables – please double check all of them (e.g. 49.8% leukemia, 9.2% CNS tumors)
   - Done

2. Please carefully edit the manuscript, including all details (e.g. Table I, for example, should be Table 1).
   - Done

3. Please review the English throughout.
   - The language in the document was revised by an American Editorial agency, we attach certified translation

4. Classification of LCH should be in Methods
   - Classification of LCH was changed to the methods section

5. Prevalence is used several times when incidence should be used.
   - The term was revised and corrected

6. 75.6 cases of leukemia per 1,000,000 children per year is almost double that observed in any population of the world.
   a. How do the authors explain this?
   b. What is the incidence among children in Mexico without PMI?
   c. This is accompanied by a 49.9% proportion of children with leukemia – how is this explained?
   a-c. This needs a different analysis, and we did not included this data. We have previously published a paper in regards to incidence in Mexican children with cancer (reference No.4). The incidence in this paper is slightly under 75.6. With the assistance of an Epidemiology Expert by the Mexican Federal Government this data was published.
   b. we do not have this data. Mexico has 3 Medical Systems as a whole. One is the Socialized Medicine Program, One of the PMI program and a very small section is private Practice. All this systems work completely independent-please see the explanations in the manuscript.

7. The number of Hodgkin and non-Hodgkin lymphomas is compared but was “not statistically significant” – what statistics were done? What is being compared?
   - It was analyzed by a chi 2

Conclusions
Needs to be a short summary of the major finding (which will be determined by the analyses in the Methods comment #15). No references or explanations in the Conclusion please (move to Discussion)
- Done
Figures
1. Please label Figures
2. Figure 2 – M:F should be 1.2:1, should include “All patients” on the far right in Figure 2
3. Please add survival curves and cumulative incidence (see Results Suggestions)
   - We corrected the table according to the changes, we removed all the survival analysis which we consider to be not pertinent in this manuscript.

Reviewer’s report: Eva Steliarova-Foucher

This paper relates to the potentially important message about childhood cancer burden in Mexico. However, the way the reported figures were derived is not clearly described. Although the aim of this paper is to describe the epidemiological characteristics of cancer in Mexican children, a large proportion of the text describes the management of these children. Under the assumption that all the listed authors had worked hard on this paper, it might be beneficial to include another author experienced in reporting cancer registry data and interpretation of the ensuing results.

- We add Alejandro Gonzalez-Garay, MD,PhD who is the expert in statistical analysis in our group and at the National Institute of Pediatrics

MAJOR COMPULSORY REVISIONS:
1. The population at risk, used as a basis for calculation of the incidence rate, is not clearly described. If we assume that the population at risk is all the insured persons (representing about a half of Mexican population), then a precise description of this population should be provided; including how it differs from the general population of Mexican children. The insured population is clearly a selected section of population and the selection criteria should be described succinctly in Methods section. In particular, the reason for admission to the system as well as release from the system should be described.
   - the text was corrected and these data were included

2. It should be explicitly described which tumors are covered by the insurance system and if there were any exclusions of malignant tumors or inclusions of non-malignant tumors.
   - At the end of patients and methods we detailed the tumors covered by the program “The program started on January 5th 2005 [9], the number of original participating institutions was 16. At the beginning only acute leukemia was introduced into this program. However progressively all childhood cancer were included, until January 2007 in which all types of childhood cancers were registered and treated under the national protocols.”

3. The calculated incidence rates seem to be providing the crude incidence, which makes a comparison with incidence rates in other populations difficult. Age-standardized incidence rates should be provided.
   - In table 4 we represented the age-standardized incidence rates

4. Standard age-groups for which population data are available in most countries are 5-year age groups. In this paper incidence rates are calculated for age-group 15-18, which is 4-year age group. Again, these rates cannot be compared to those reported in other countries.
We defined the age in a 5 years intervals, until 15 year, the interval 15-18 year included only this ages, because after 18 year the patients do not enter to the PMI program and under Health system in Mexico patients beyond 18 years are consider and treated as adults.

5. The definition of the prevalence on page 6 is incorrect and unclear. Looking at the tables, the numbers of cases are referred to as prevalence, which is incorrect.
- At the end of page 6 we add the definition: “Prevalence was defined as the percentage of the disease in Mexican children registered between 0 to 18 years in the period of time of the study.” A reference is added to this definition

6. Survival seems to be estimates as a simple proportion of those alive 48 months after the diagnosis of all patients, but this is again not comparable with the results of survival from elsewhere. Reporting the survival data may be a subject of a separate communication with properly described methods of follow-up and the methods of survival analyses.
- We agree with the comment and we decide only to analyze mortality and eliminated all the survival analysis, considering that it is not the scope of this manuscript.

7. The definition of mortality also requires a revision. The method of calculation of mortality rates is not clearly described.
- We added in page 7 the correct definition.

MINOR ESSENTIAL REVISIONS

8. English: both style and terminology needs revision. More information should be added in Methods section (see above) and some repetitions of the text currently present in the paper removed.
- The language in the document was revised by an editorial agency, we attach certified translation

9. Page 3, reference to Globocan: Globocan data do NOT result from a survey. The cited figures and the reference should be updated according to the Globocan 2012 release.
- We corrected the data

10. Some of the cited references do not convey the message they are deemed to support in the text. E.g. references 10, 11 and 14 do not deal with increasing incidence rates in age 0-18 in developing countries.
- The references were checked however some of them were misplace REFERENCES 10 AND 11 DO NOT SUPPORT INCREASE IN CANCER INCIDENCE.
- REFERENCE 14 DESCRIBES HOW SEGURO POPULAR HAS INCREASE THE COVERAGE SINCE THE START.

11. The 3rd dimension used in Figure 3 does not add anything to a 2-dimensional figure: no depth is needed for the columns.
- THE CORRECTION WAS MADE.

12. A clearer presentation should be sought for data in Figure 3. For example, there is no need to connect the incidence rates across different provinces in Mexico.
- DATA WAS EXPOSED BY REGIONS IN MEXICO TO GIVE A PANORAMA NOT DETAILED BY PROVINCES.

Revisor: RAJARAMAN SWAMINATHAN

1. The database does not include variable on incidence date. This is an essential component for computing incidence rate. In this study, the numerator has been the same for calculating both prevalence and incidence proportions. By definition, prevalence includes old+new cases. Hence, the incidence statistics are wrongly computed. It will not be prudent to include incidence statistics in this study.

   - We correct the data, and we have the right information for the incidence, prevalence (the reference is in the text)

2. Population estimation for the age group 0-18 years is not clearly stated. This is very essential in the computation of incidence rates. Are the annual population statistics based on inter-censal estimates or post-census? How are they derived? Does the census population give statistics for individual ages (say, 0,1,2,3,4, ...,16,17,18) or 5-year intervals (0-4, 5-9, ...)?

   - We defined the age in a 5 years intervals, until 15 year, the interval 15-18 year included only this ages, because after 18 year the patients do not enter to the PMI program and under the Health System in Mexico patients beyond 18 years are consider and treated as adults.

3. How complete is the mortality statistics of childhood cancers? Are all deaths occurring among children with cancer whose deaths are not certified as cancer included? Is the quoted figures relate to official vital statistics or result of compilation of events from the hospitals' databases? All of these have implications in the final interpretation.

   - We have the completed data for mortality, because all cases have to be register in the ensure program base. All death were by cancer or secondary of the cancer treatment

4. Follow up mentioned here appears to be entirely done by passive linkage of hospital databases. The closing date of follow up is not mentioned. Also, what about the proportion of cases who might be lost to follow up? In other words, what is the proportion of cases whose vital status (alive/dead/etc.) was not known at time of closing of follow up? In developing environment, active methods of follow up have to be employed to optimize complete follow up. This will have implications in the computed survival statistics.

   - The evaluation of this parameters were done by each institution, and we removed all the survival analysis because this is not the aim

5. Overall survival estimation is not done by conventional life-table methods. This is essential because censoring has to be anticipated in follow up studies.

   - We removed all the survival analysis