Author's response to reviews

Title: Pulmonary Tuberculous: Symptoms, diagnosis and treatment. 19-year experience in a third level pediatric hospital

Authors:

Napoleon Gonzalez Saldaña (drnagosal@hotmail.com)
Marte Hernandez Porras (martehdzinp@yahoo.com.mx)
Patricia Saltigeral Simental (psaltigeral@yahoo.com)
Valeria Gomez Toscano (vgomez@hotmail.com)
Hugo Juarez Olguin (juarezol@yahoo.com)

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Author's response to reviews: see over
Dear Editors

We are re-submitting to you as editors of BMC INFECTIOUS DISEASES, the new version of the original article entitled: “Pulmonary Tuberculous: Symptoms, diagnosis and treatment. 19-year experience in a third level pediatric hospital”. The new version includes the answers and comments to all suggestions made by reviewers, for the purpose of its publication in your prestigious Journal. We transfer all copyright ownership of the manuscript to BioMed Central in the event that the work is published. Authors warrant that the article is original that it is not under consideration by another publisher. Authors confirm that final manuscript has been read and each author’s contribution has been approved by the appropriate authors. The authors have not published or submitted none related papers from the same study. The study was approved by Ethics Committee of this Institution. The authors declare that they have no competing interests.

Looking forward to your answer we remain truly yours.

Sincerely

Hugo Juárez Olguín
Correspondent author

Correspondence and reprints:
Hugo Juárez Olguín
Laboratorio de Farmacología, Instituto Nacional de Pediatría.
Avenida Imán N° 1, 3rd piso Colonia Cuicuilco CP 04530, Mexico City, MEXICO
Tel & Fax 5255 1084 3883 E-mail: juarezol@yahoo.com
Author’s answers:
Dear Editor
Next are the answers for queries and comments to the suggestions made by reviewers.

Major Compulsory Revisions
Rev: Before accepting this article some serious issues have to be addressed. The question what the authors is asking in this paper is not clear. They describe it as to know the real situation of PTB in the population of children. This needs to be rewritten and better clarified. They have chosen a population from 0 to 18 years and we know that PTBb presents very different in this large age range and this needs to be addressed. Comparisons is made between definitive and probable TB as well as radiological and culture findings but no stats is done to show if this is significant. This needs to be done to make this article of value. This is a retrospective article and although it may be of value to the Mexico area it adds not a lot of new information. The authors must include the limitations of this research.
Authors: Patients of 0 to 18 years old were included in study for being the age range of the population attended at this hospital. The X-ray differences in accordance with age are described in the results. Moreover, the results are added due to the differences found in the cultures.
A probable limitation of the work is that being a retrospective study, there are some disadvantages when compared with prospective ones for lacking strict control of information or absence of the same which is expected to analyze in a precise form.

Abstract
Rev: 57(65.5%) had bacteriological conformation and the later on 24/79 (30.4%) were culture positive. This is confusing.
Authors: The 57 (65.5%) subjects include patients with Ziehl-Neelsen (ZN) test and/or positive culture. Out of these subjects, 30 had a positive cultura.

Rev: BAAR is used but not written out what it means
Authors: Sorry, the correct term is acid-fast bacilli (AFB) instead of BAAR, which was changed.

Rev: One patient died but in under results section has 3 died.
Authors: During the study, 3 of the patients die done of which had HIV.

Rev: Conclusions based on no data
Authors: The new conclusion: PTB in pediatric population represents a diagnostic challenge for the fact that clinical manifestations are unspecific and the diagnosis are not confirmed in all cases reason why clinical suspicion, X-ray findings and dermatological contact are indispensable for opportune start of treatment.

Background
Rev: The role of HIV should be mention in the high incidence of PTB in the developing world.
Authors: Although, it has been reported that the presence of infection by the human immunodeficiency virus is a contributing factor by increasing the cases of tuberculosis.
However, in spite of Mexico being a moderately TB endemic country, its association with HIV in pediatric population is approximately only 5.8% which is different with 8% reported in adults. Meanwhile, in other developing countries such as Peru and Brazil, an incidence of TB/HIV association of 1.5% and 42% was reported respectively.


Rev: The incidence of HIV in Mexico should be discussed
Answer: See previous answer

Methods
Rev: The authors did not describe what type of study this was and how were the patients identified and what date they have recorded.
Authors: A retrospective and descriptive study was carried out where clinical files of less than 18-year old patients with diagnosis of pulmonary tuberculous (PTB) on discharge that were hospitalized at National Institute of Pediatrics (NIP) of Mexico city from 1994 to 2013 were reviewed. The survey was carried out based on PTB diagnosis on admission and discharge and by revision of all the samples sent to Microbiology Department in this period for ZN and culture of M. tuberculosis.

Rev: Statistical analyzed mention under methods but not use in article
Authors: In the new version, statistical analysis is used

Rev: Mediastinal lymph nodes are recorded but not specified which ones.
Authors: Most of them were parahiliar nodes

Rev: Describe what is baciloscopy and what is mean by bacteriological conformation and culture conformation. It is perhaps better to talk about ZN positivity.
Authors: Ok, this change was made in the new version of manuscript.

Results
Rev: Total of 1601 patients were found with TB. Is unclear if they are all under 18 years. And if so what form of TB do they then have if only 87 has PTB.
Authors: They had extra-pulmonary tuberculosis or disseminated or miliar tuberculosis.

Rev: 98.9% had a epidemiological with identification of 41.9% positive cases . This is confusing and this contact rate is much higher than previous report. The authors must explain what the reasons for this are.
Authors: 98.9% refers to the total number of patients in which epidemiological contact was checked even when it was positive in 41.9%.

Rev: No information about the weight is provided or z scores
Authors: 8 patients (9.7%) had mild acute malnutrition, 15 (18.3%) severe malnutrition, and the rest are eutrophic.

Rev: The radiological findings must be described in more detail. What is mean with consolidation is it lobar segmental or bronchopneumonia and which lymph node groups is involved and is there any airway compression
Authors: In all the cases, consolidation was lobar.
**Rev:** Sputum had a higher yield than gastric lavage. But this must be use accordingly to age because a child of 18 y is not going to have a gastric lavage done and the chance for being ZN positive is much higher in older children with cavities. The investigations for culture must be reported accordingly to age to make it relevant. Most young children are not ZN positive due to pauci bacilli.

**Authors:** We totally agree with your observation. In the new version, this information is added to the results. Sputum Bacilloscope was carried out in patients of 5 years and above with this being highly significant in sputum samples. However, it should be taken into consideration that this was performed in patients older than 5 years whose lesion type as in cavities is more frequent when compared with children of less than 5 years in whose case pauci bacilli are habitually present.

**Rev:** The comparisons between definitive and probable TB must be done statistically to be of value.

**Authors:** Statistically significant differences were observed when p< 0.05, an information which is mentioned in the result.

**Rev:** How many patients was ZN positive And how many children was ZN positive and culture positive according age.

**Authors:** Results were as follows: Zn + 50/87, culture + 37/87
- < 12 months old, Zn + 5/14, culture +4/14;
- from 12 to 59 months old, Zn + 16/31, culture +8/31;
- from 60 to 179 months, Zn + 20/29, culture + 13/29;
- and 180 to 220 months, Zn +4/5, culture + 2/5.

**Discussions**

**Rev:** Explain what the other forms of TB is if only 5% is PTB and why so little PTB versus the other forms of TB

**Authors:** The 5.4% which corresponds to PTB could be explained on the basis that the majority of the patients were managed as outpatients and only patients with complicated pulmonary tuberculosis, extra-pulmonary tuberculosis, disseminated or miliar tuberculosis were hospitalized. This information was included in the new discussion.

**Rev:** Tendency for greater number of cultures in patients with history BCG. This is an statement with significant consequences. But no stats are provided and this must be corrected.

**Authors:** BCG coverage was practically 80 or more in all age groups and the highest number of positive culture are found in older ages, stats were added.

**Rev:** The authors must refer to the article of Marais et al on symptoms, chronic cough and diagnosis

**Authors:** That reference was considered and added as follows: Marais BJ, Gie RP, Hesselinc AC, Schaaf S, Lombard C, Erarson DA, Beyer N. A defined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics 2006; 118: e1350-1359.

**Rev:** Hemoptysis is mostly only seen in children with cavities and thus in older patients. Authors must describe the radiological findings in the children that had hemoptysis.
Authors: The 4 patients had lobar consolidation with one of them having pleural discharge and another with cavern.

Rev: The statement: It has been identified that the presence of fever and cough of 2 or more weeks, plus a positive PPD of 10 or more milimeters, have a positive predictive value of 73% with a sensitivity of 44% for tuberculosis confirmed by culture., must be referenced

Conclusions
Rev: Does not refer to any of the findings of the research and has to be redone.
Authors: Conclusions was modified in the new version

Tables
Rev: Table one and two can be included in table 4
Authors: OK, those tables have been included

Rev: Table 3. Definitive TB vs. Probable TB. No stats done on this
Authors: OK, Stats has been inserted

Rev: Table 4. No stats done on this table
Authors: OK, Stats has been included for that data
Reviewer's report
Major Compulsory Revisions
Rev: The methods used in the study are appropriate since it was a retrospective review of clinical files. However, the authors have not described in full and detail a number of issues that are important for the reader to understand. For example:
1. The setting of the study is not well described, is the National Institute of Pediatrics (NIP) a referral hospital? What types of patients are referred to the hospital and from where? What numbers of patients are seen at this hospital annually?
Authors: NIP is a reference teaching hospital with an average yearly admission of 6,000 patients less than 18 years old From Mexico city and other states of the republic (48%).

Rev: The pediatric age used in the study is below 18 years, however, the WHO figures quoted here and in most studies, the age group used for pediatric TB is below 15 years. Can the authors justify the use of this age group when referring to pediatric TB?
Authors: For the fact that the hospital attends children until they are 18 years old, all the patients with diagnosis of PTB were included.

Rev: The authors have used some abbreviations which they have not explained such as BAAR for diagnosis, can they clarify what this is and how is it used as a diagnostic method? If they mean isolation of acid-alcohol resistant bacillus they should indicate that and mention what methods specifically were employed. How was the quality assurance conducted?
Authors: Sorry, correct term is acid-fast bacilli (AFB) instead of BAAR, which was changed.

Rev: What were the culture methods used for diagnosis and how were samples collected? What were the issues with quality assurance for whatever culture method which was applied?
Authors: Ziehl-Neelsen dyeing, Lowesten Jensen and Mildebrook culture were used.

Rev: PCR is not mentioned as a method for diagnosis but is later mentioned in the results section. Can the authors clarify if this was also used for diagnosis and how were cases classified if diagnosed by PCR?
Authors: In the manuscript, PCR for tuberculosis test was included and the results, if any since it is not a routine test, for the patients they were requested were reported.

Rev: The authors should also describe the treatment regimens that were used during this period in the methods section, including any changes that occurred over the period in treatment regimens.
Authors: From 1994 to 1997, the antituberculous treatment used was isoniazid, rifampin, and pyrazinamide while from 1998 to 2005 and due to questions of resistance to rifampin, a new scheme of four drugs comprising of the addition of streptomycin or etambutol to the former emerged. This information is included in the new manuscript.

Rev: In the results Section the authors indicate that they identified statistically significant differences in relation to expectoration, haemoptysis, consolidation, caverns, calcification, mediastinal lymph nodes, BAAR and with pleural effusions but there is no clear statistical analysis or methods shown to indicate significant
differences in the stated table 4, except proportions.

**Authors:** This information is added in the new manuscript.

**Minor Essential Revisions**

**Rev:** The question posed by the authors is well defined and important as it addresses the issue of pediatric TB which is a major public health problem and has had limited attention until just recently.

However, clarity has to be made on the objective: in the abstract, the authors state that the, “objective of the present study is to know the real situation of PTB in the population of children in terms of its diagnosis and treatment in a third level pediatric hospital”, but then in the introduction they state that, “the objective of the study is to evaluate the clinical, radiological, microbiological and immunological spectra of pulmonary tuberculosis……..”. Can the authors be clear and consistent with the objective of the study?

**Authors:** We agree with this observation. The objective of this study was to evaluate the clinical, radiological, microbiological and immunological spectra of pulmonary tuberculosis seen in children hospitalized in a third level pediatric hospital.

**Rev:** The third sentence in the abstract, third line, which reads, “However, the difficulty in diagnosis of TB in children, scanty…….” Is not clear and should be rephrased.

**Authors:** Sorry that term was changed as “However up dated information of TB in children is scanty”

**Rev:** The title and the abstract do not convey what was found, for instance, the abstract conclusion does not capture what the objective of the study was about.

**Authors:** We agree. A new conclusion which is in accordance with the title and objective is included.

**Rev:** Figure 1 is not labelled on the "Y" and "X" axes

**Authors:** Sorry, that mistake has been arranged.

**Rev:** The discussion and conclusion is not well balanced in relation to the title.

**Authors:** We have considered and improved this suggestion

**Rev:** Some grammatical errors need to be attended to e.g. the first sentence in the results section.

**Authors:** Sorry, this part and all manuscript were checked for grammar

**Level of interest:** An article whose findings are important to those with closely related research interests.

**Authors:** THANKS