Author's response to reviews

Title: Tuberculosis diagnosis delays in Chad: a multicenter, hospital-based, survey in Ndjamena and Moundou.

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Version: 3 Date: 6 February 2012

Author's response to reviews:

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February, 6th 2011

Dear editorial board of BMC Public Health, Dear reviewers,

Thank you for considering the revised manuscript enclosed: “Tuberculosis diagnosis delays in Chad: a multicenter, hospital-based, survey in Ndjamena and Moundou”.

We thank you the reviewers for their comments which enable us to improve this work.

The title, the method, the discussion and the conclusion were improved on advices of the reviewers. The text was revised by an English native writer to
improve the level of English.

A figure of the study profile was included to reduce the size of the results section and median delays were added in the table showing univariate analysis.

We hope that these changes and these clarifications fulfill the requirements to make the manuscript acceptable for a peer review and for a publication in BMC Public Health.

Thank you for your time and consideration.

Please find below the answers to the questions of the reviewers.

Sincerely yours,

Corresponding author: Ndeindo NDEIKOUNDAM NGANGRO

Reviewer # 1: Ibrahim Sendagire

- How were three health facilities selected for your study?

The three hospitals were not randomly selected. We have chosen the facilities on the advice of the national TB control program. The aim of this selection was to reach the needed size of study population.

- When was the study conducted?

The study was conducted from August to October 2009.

- How did you decide on the sample size?

As no information on TB diagnosis delay determinant was available in Chad and since the literature showed that many factors were associated with long TB diagnosis delay, the sample size was estimated assuming a frequency of long total delay of 60% among exposed and 40% among the unexposed.

- What was the sampling procedure?

Newly diagnosed pulmonary TB patients were consecutively and prospectively recruited.

- Did you take into account the differences in the populations for the different hospitals?

We took into account the differences in the populations firstly with a bivariate analysis adjusted on the treatment site and then by adjusting the multivariate
analysis on the hospital where the patients were treated, on the age and on the wealth score.

- The study setting should describe some more details on populations, health facilities, and the referral pattern

The study setting was more described in this revised manuscript. More details on the populations, health facilities and referral pattern were added.

833 531 live in Ndjamena while 142 000 among 650 000 inhabitants of Western Logone reside in Moundou. Hospitals are planned to care a population of 100 to 200 000 persons in Chad but reference hospitals are called upon to handle patients beyond this health care coverage. Patients are supposed to visit health centers first. Afterward, the referral system is supposed to direct the more severe cases from health centers to district hospitals, then to regional hospitals and finally to the HGRN.

Concerning TB, patients are supposed to enter the health system by visiting health centers. If TB is suspected, patients are referred to hospitals where microscopy and radiography are performed. Then TB treatment is initiated in hospitals and patients should be referred back to first level services. Only multidrug TB and chronic cases should be referred to the HGRN according to the recommendations of the national TB program. Nevertheless, in fact this theoretical pattern did not suit to the reality.

- Including a figure to describe the study profile would be helpful in reducing the number words written in the results section

A figure of the study profile was included to reduce the size of the results section.

- Discussion of limitations could be left to the last paragraphs before conclusions

A discussion of limitations was left to the last paragraph before conclusions.

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

Some improvements are required

The discussion, limitations and conclusions were improved considering the advices of the first reviewer.

- Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

We reviewed the literature, we discussed with the managers of the national TB
control program, with Chadian TB specialists, with physicians, with nurses and with TB patients to build this work. There was no data in Chad that could have been used to build this study.

- Do the title and abstract accurately convey what has been found? Yes: but some improvements needed.

The title and abstract were improved in accordance to the suggestions of the first reviewer.

- Is the writing acceptable? The English needs some improvement: see details in Discretionary Revisions

The English was improved by an English speaking writer on the advice of the reviewers.

- The evidence for the association between the “knowledge about the relation between Aids and TB” and extended HSD is neither given in the table showing multivariable analysis nor in the text

The evidence for the association between having “no opinion about the relation between Aids and TB” and long HSD is given in the table 4.

- The data do not support a huge missed opportunity for HIV testing; best to leave it out of the discussion and conclusions

We removed the comment on “the missed opportunity for HIV testing” from the discussion and conclusions. Indeed, the first reviewer is right. Our data do not support this conclusion even if our results showed that majority of TB patients were not tested for HIV.

- Title could be fine-tuned to reflect delays in “pulmonary tuberculosis” Diagnosis

The title was improved to reflect delays in pulmonary TB diagnosis.

- Are there earlier studies that have been carried out in Chad concerning diagnostic delay; and if so what is the gap in knowledge?

Only one study by Martin A et al was conducted in the Hopital General de Reference National (HGRN) in 2003 on 103 patients. This study showed that total TB diagnosis delay was 75 days, patient delay was 45 days and doctor’s delay was 3 days. The definitions of delays used in this study biased the delays according to us. Patient delay was defined as the time interval between the symptoms onset and the first visit to HGRN and the doctor delay was the period between this first visit and the TB diagnosis confirmation. Consequently, the patient delay did not only reflect the patient delay because it also included the
referral delay until the first visit to HGRN and the doctor’s delay was a part of the institutional delay and was in fact the time to suspect a TB case in the HGRN. These definitions made the patients responsible for delaying the TB treatment initiation and this study did not assess the patient delay and the health system delay as defined by Storla et al. Our study tried to take in account the impact of informal care and it also tried to distinguish the patient delay from the health system delay by defining the patient delay as the time interval from the symptoms onset to the first care used whether formal or informal. The second point was their 90 days and 15 days considered as thresholds to judge if total delay and patient or doctor delay were too long. Our study was the first in Chad, which try to take in account the setting and the distribution of the delays by assessing factors associated with delays longer than their median value. Finally the gap in knowledge was the patient delay, the health system delay and the determinants of the diagnostic delays.

- Table 3: one variable in the table is described in another language; please translate it to English.

Sections written in another language were translated in English.

- Are there lower level health facilities in these two cities? If so, are TB diagnostic services decentralized to lower level health facilities?

There are lower level health facilities (health center) in these two cities but the TB diagnostic services (sputum smear test and radiography) are not decentralized to these facilities. TB is suspected in these services considering clinical suggestive symptoms. Then patients are referred to hospitals to be diagnosed.

- It is stated that a few patients are detected in private practices and then referred to the public hospital. If detecting in this context means diagnosing, then not including private practices would limit the conclusions.

Detecting TB in private practices means mainly identifying probable TB cases and referring them to hospitals which perform the TB diagnosis. Even if some private doctors may diagnose TB in Chad, most of them don’t. Indeed, private pharmacists are not allowed to sell TB drugs in Chad and the TB treatment is given for free in public services. Therefore private doctors refer patients with suggestive signs of TB to hospitals to initiate the treatment, but some of them may perform TB diagnosis. Not including private practices could limit the conclusions even if most of patients begun their TB treatment in hospitals. Nevertheless, our limitations section stated that our conclusions were limited to patients who accessed the TB treatment in public hospital.

- Conclusions of the diagnostic delays could possibly be limited to the public tertiary institutions in Ndjamen and Moundou.
Conclusions were limited to the public tertiary hospital in Ndjamen a and Moundou.

Discretionary Revisions

-To make the article easier to read and comprehend consider the following:

Improvement in the use of some English words

The text has been reviewed by an “English native writer” to improve the use of some words in order to make the article more suitable to a publication.

- Be consistent with the decimal points you give to the p-values in the text

The p-values were reported in the text according to the tables.

-Page 28; use capital letters for “AIDS” also in other areas in the text

AIDS was written in capital letters in the whole text.

-In order get a better feel of the data it would be nice to also show numbers in the various categories in table 2; percentages alone only give half the picture

Table 2 shows numbers and percentages.

-You may discuss only those factors that were significantly associated with the patient delay in the multivariable analysis to make the manuscript a shorter and more interesting read

We discussed factors that were significantly associated with the patient delay in the multivariable analysis to make the manuscript shorter and easier to read.

REVIEWER #2: Rachel Royce

-Abstract Objectives para: Delays were estimated for more than “case-management”. This term needs to be changed to be more accurate.

The term “case management” was withdrawn from the objectives section of the abstract. Indeed, this study assessed more than only the case management.

-Abstract Objectives para: Should include that the estimate is for TB cases that were seen in hospital.

We also clarified in this section that the study was limited to TB cases that were seen in hospital.
Abstract Results and Discussion para: Should include interquartile ranges for each median delay time reported.

The interquartile ranges were included for each median delay time reported.

Abstract Results and Discussion para: AOR should be defined.

AOR was defined as adjusted odd-ratio in the abstract.

Background Para 3. What would be the rationale for using cough as the starting point? Of cough onset as the starting time point does not take into consideration other significant TB symptoms that may precede cough such that the time calculated may underestimate the delay.

Thank you for underlining this point. In fact, we applied the criteria of TB case suspicion of the Chadian TB control program which use cough of more than 15 days as the main sign for TB screening, but other TB symptoms were also used to detect cases. We should have reported “the onset of symptoms” instead of “cough onset” as the starting time point because it is what we did. We regret this lack of accuracy in our reporting. We took in account your comments in this revised version of the text to make our definition more explicit.

Methods Para 2. What about cases who die before reaching the hospital? How frequent is that in Chad? How would the exclusion of these cases affect the study results and the generalization to all TB cases? What about the cases who were too ill to be interviewed. How might their exclusion affect the results of the study?

Data on TB cases that died before being diagnosed are not available in Chad. However, according to the literature, longer delays of TB diagnostic are associated with more morbidity and mortality. Therefore, excluding cases that died before reaching hospitals and the exclusion of cases that were too ill to be interviewed might underestimate the TB diagnostic delay in this study. We discussed explicitly this point in the limitations paragraph of the revised version of the manuscript.

Methods Para 3. Not all patients with TB have a cough. Were there any patients in this study that did not report a cough? If so, how was delay defined?

We regret a lack of accuracy in the reporting of the patient delay definition in the method section. Some patient reported symptoms other than cough and the patient delay was defined as the time interval from the onset of TB symptoms to the first care received.

Methods Para 3. Total delay is a composite of two pieces, patient delay and
health care delay. The constellation of factors influencing each delay is distinct (as demonstrated in the tables) though there are some overlapping factors. There is something conceptually incorrect to analyze factors associated with total delays when the factors leading to patient delay might operate differently for health system delay. If the association for a factor is associated positively with one piece of delay and negatively with the other piece of delay then what is the meaning of its contribution for total delay? It is, however, useful to present the actual medians for the total delays because that represents the amount of time that cases were left untreated in the community, increasing their chance for more severe morbidity and for transmission to others. For example, 61.5% of those that went to hospital for first care for cough exceeded the median time for the patient delay (positive association with delay) however 32% of them exceeded the median time for the health system delay (negative association with delay). Or, another example, in Table 4 the HU being a woman is associated with shorter patient delays and longer health system delays. Thus, the total delay is a mishmash of these associations. One could imagine that a public health intervention on delays might need to target the pieces of the delay differently in this case.

Our goal was to find the way to shorten the delay of TB diagnosis. The literature shows that the same factors can influence patient delay and the health system delay in opposite manner. Analysing factors associated with patient delay, with health system delay and with total delay enabled us to try to understand the way the risk factors may influence the different periods of the diagnosis delay, and also how these factors were associated with the overall delay of diagnostic.

We believe that a public health intervention might need to target the pieces of the delay differently in some cases. The patient delay was shorter than the health system delay in this study. As a result, reducing the health system delay would probably have more impact on the total delay than an intervention targeting the patient delay. The way each risk factor influence the different period of the delay of diagnosis should also be considered. For example, if women sought care earlier (shorter patient delay) and then hardly progress through the health system (longer health system delay), we can assume that there is no particular obstacle to women’s access to first level care or that they can make easily the decision to visit a health professional, but that some gender specific obstacle may occur when women try to reach higher level of care. Consequently, the total delay is a mishmash of these associations and the decision to implement an intervention should take in account the potential impact of this action on the different times of the TB diagnostic delay.

-Methods Para 4. Income variable really should be named wealth as it is a composite of various aspects of wealth.

Income variable was named wealth on the advice of the reviewer.
-Methods Para 4. No info was included on definition of rural.

Rural residency was defined as living outside the town.

-Methods Para 4. Some variables have response categories that could be overlapping. For example, people could believe that medicine and traditional treatment could cure TB. How might that be accounted for in the responses? Did the authors simply count the one the that patient did first? Another such variable is the one about how patients pay for additional expenditures. Patients could pay with working and using savings, for example. Please explain.

When several answers could overlap in questions such as the one about the treatment or the other concerning how patients would pay for additional expenditures, we counted the first choice according to the patient’s ranking.

-Methods Para 8. Some of the variables that are ordinal should have their association with the outcomes of interest assessed for trend. For example age and score for wealth (income).

We assessed the associations of ordinal variables such as age and score for wealth with the patient delay (age (p=0.05) and score for wealth (p=0.02)), with the health system delay (age (p=0.80) and score for wealth (p=0.03)) and with the total delay (Age (p=0.53) and score for wealth (p= 0.04)).

-Methods Para 8. One wonders whether there might be some important interactions in these data. There is no mention of looking for these in the methods section. For example, where someone first went for care and the hospital that they were registered as a case are both significant factors for health system delays. Please report whether interactions were examined or not.

Interactions were examined but no important interaction was found.

-Results Para 2. The authors need to explain why there is such a dramatic difference in the reported proportion of cases with HIV seropositivity according to hospital. What was the denominator for this proportion? Was it all cases or only among those with test results?

The denominator for the proportion for HIV seropositivity was all cases. The main reason why there was such a difference in the proportion of cases with HIV was probably the small number of HIV test done. The second reason might be the manner how AIDS is stigmatized in Ndjamena and in Moundou. The higher rate of HIV and the numerous interventions done by many associations of HIV positive people in Moundou, could be associated with a better acceptability of the HIV test in this town. Another hypothesis is the fact that ESTHER, an NGO specialized in the fight against AIDS support the hospitals (HGRN and HM) and
their HIV patients. This situation might urge the physicians to systematically test the patients and it may stimulate the patients to accept the test. Whatever there is a real need to analyse deeply this situation in another study.

- Discussion Para 2. The reader wonders about the different hospitals and what the catchment area is like for each.

Hospitals are planned in Chad to care a population of 100 to 200,000 persons but reference hospitals are called upon to handle patients beyond this health care coverage. 833,531 people live in N'djamena, whereas 142,000 among 650,000 inhabitants of Western Logone live in Moundou.

- More importantly, it is common that an important proportion of TB cases are diagnosed at death. The authors talk about patients who do not use health facilities but they do not mention how TB mortality might affect their study results.

Patients who do not use health services and the mortality due to TB might affect the study results by underestimating the delay of TB diagnostic.

- Discussion Para 5. The first sentence belongs in the results section of the report.

The first sentence was withdrawn from the discussion paragraph. It belongs obviously to the results section.

- Discussion Para 5. The discussion of delays in other countries is very tedious. Perhaps these studies should be dropped into a table or summarized more cogently or restricted to the ones with most relevance for Chad. Perhaps this discussion should be driven by the Storla review that is cited rather than listing results.

We used a table to summarize the discussion of delays in other countries.

- Discussion Para 6. The point about including getting care from non-medical sources is a very good one but then it makes the reader wish that the authors had included an analysis of the actual trajectories of care in order to make sense of the results. What was the timing like between informal care and medical care?

The trajectories of care are analysed in another submitted manuscript. The median total delay was 48 days (interquartile range= [30-83]) for formal trajectories of care and it was 68 days (interquartile range= [47-105]) for informal trajectories of care. Nevertheless, the point discussed in the manuscript is the fact that the way the starting point of health system delay is defined can make the patient responsible of the delay of TB diagnosis even if he sought care early.

- Also, defining the starting point as onset of cough might have had an impact on
the findings.

The starting point was not only the onset of cough but the onset of pulmonary TB symptoms. The definition of starting point is more accurately reported in this revised version of the manuscript.

- Discussion Para 7. Just because TB treatment is free does not mean that all have access. Presumably there are many potential barriers to care such as lack of time off work to go to doctor, etc.

We agree with the reviewer that the free treatment does not mean that all have access and that there are many potential barriers to care. This work aims notably to identify some of these remaining barriers.

-Discussion or conclusion should tie back to the themes of the beginning of the report. Are the delays reported here important to the spread of TB in Chad?

Lin X et al. demonstrated that TB spread in the index case’s household after 30 days of infection. Thus, median total delay (57.5 days) and median health system delay (36 days) are important to the spread of TB in Ndjamea and in Moundou and probably in Chad.

-Conclusion Para 1. The first few sentences include very interesting results that should have appeared in the results section. The results section needs more information on the distribution of the delays measured in days. Then, the authors could tie the results back to the population transmission dynamics.

The distribution of the delays was included in the table 1 to shorten the text. The results discussed in the first sentences of the conclusion paragraph were added in the results section.

- Tables 2, 3, and 4. Inconsistent terms are used across tables so the reader gets confused whether the factors are the same or not. For example in Tables 2 and 3 there is a factor called “First care received” but in Table 4 it does not appear; but there is a factor called “Treatment considered first”. The levels for this second factor, however, are not the same as those for the first factor. What is going on here?

-Some mistakes occurred in the translation of the study report. The "first care received" was not selected in the regression model and does not appear in the table 4. The “treatment first considered” was an inconsistent way to shorten the label of the variable “which treatment can cure TB”. Terms used in the table were improved thanks to the comments of the reviewers.

- Table 2 Instead of dichotomizing the outcome into above and below the median delay this table would be more informative if it simply displayed the median delay (and interquartile range) for each level of the factors. This is especially the case
because the cut point used for the dichotomous analysis is the median of all patients without regard to hospital. Hospital is an important predictor for delay so both the percent of each category above or equal to the median and the percent below the median.

We included the median delay and its interquartile range for each level of factors in the table 2 to make the table more informative.

-Tables 2 and 3. There are too many variables included in Tables 2 and 3. The factors that are not associated with delays could be omitted. Also, the table would be more readable with subheadings of categories of factors such as sociodemographic; clinical; knowledge, attitudes and beliefs; and health services access and utilization.

Subheadings were included in the tables 2 and 3 to make it more readable. We omitted some factors that were not associated with delays but we kept adjustment variables such as age and gender. We will omit all the factors that are not associated if the reviewers consider it as necessary.

- Table 3. One of the factors is in French – Nombre d’année d’instruction.

The factor’s name written in french was translated in english.

-Table 3, the last few lines of the table. There are new abbreviations introduced here that are not explained – CHAG and MDOU. These lines do not appear to be in the right place as there are no factors defined in the first column for these lines.

CHAG and MDOU correspond respectively to HU and HM. These abbreviations were corrected. The factor in the first column was defined for these lines but the line was omitted on the reviewer advice since de factor was not significant.

- Table 4, the results for hemoptysis are missing for extended patient delay and extended health system delay.

The results for haemoptysis are missing for extended patient delay and extended health system delay because this variable was not selected in these two models.

-Table 4. The blanks in the table should be explained in footnote (i.e. reason that there are no modeling results for the last two factors in some of the columns of the table).

The blanks in table 4 correspond to non selected variables. An explanation was given in footnote below the table.
Discretionary Revisions

-Background Para 3. Use of the term “patient delay” is somewhat unfair, same with “health system delay”. The former seems to blame the case when there might have been barriers out of the case’s control such as clinic hours that prevented getting care. Similarly, the health system delay might be heavily influenced by patient’s behavior, especially if it was necessary to go from one source of care to another to finally get on treatment. Consider using a more objective label for these two components of delay.

We regret the lack of accuracy of these labels but “patient delay” and “health system delay” are the labels commonly used in the literature (Storla et al 2008; Sreeramareddy et 2009 al; Finnie et al 2011) although systemic and individual factors can influence these type of delays. Some authors used the terms: “time interval” for delay, “application interval” for “patient delay” and “referral interval” or “diagnosis interval” or “treatment interval” or “doctor’s delay” instead of health system delay (Okur et al 2005) to stigmatize less the patient and the health system but these terms also remain inaccurate. We have chosen to use the most common labels in the literature without prejudices on the mechanism of diagnosis delay.

-Methods Para 6. What was measured was distance to closest health facility and not distance to first place of the case sought care. That seems like it would be most relevant to patient delay and might have influenced what the first place of care was. The distance to closest health facility might be more relevant to health system delay.

The distance to closest health facility might be more relevant to health system delay. However, we tested the assumption that closer health facilities might shorten the patient delay by enabling an earlier visit.

Minor issues not for publication

- Abstract Background para: English in last sentence is not grammatically correct.

The sentence was corrected.

- Results Para 4 (and other places) AIDS is not properly capitalized. It is written as “Aids”.

AIDS was properly written in the whole manuscript.

- Tables. The labelling of the tables should be revised to be simply “Table x.” where x is the number of the table.
The labelling of the tables was revised to be simply “Table X”.

- Table 1. Define IQ.

IQ was defined as the interquartile range.

- Refs. Many of the references are missing the page numbers of the article cited.

The references with missing page numbers were completed.

- There are many instances of grammatical errors, awkward or incorrect use of words or phrasing, inconsistent use of terminology.

  • Interrogation, in English this is used almost exclusively in a situation of conflict/custody and is never used to refer to questionnaire administration.

  The term “interrogation” and this section were withdrawn and replaced by Figure 1.

  • Delays should not be called “superior”.

  Delays were not called “superior” in this version of the text but longer.

  • Discussion para 8. “women’s non emancipation” This is not a common term and this reader has no idea what is meant by this.

  The term was withdrawn. In fact, we wanted to discuss the impact of financial dependence and women’s social status in sub-Saharan areas on the delays of diagnosis.