PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of isoniazid preventive therapy on mortality among children less than 5 years old following exposure to tuberculosis at home in Guinea-Bissau
AUTHORS	Gomes, Victor; Andersen, Andreas; Lemvik, Grethe; Wejse, Christian; Oliveira, Ines; Vieira, Fina; Joaquim, Luis; Vieira, Cesaltina; Aaby, Peter; Gustafson, Per

VERSION 1 - REVIEW

REVIEWER	Kabra, Sushil Department of Pediatrics, AIIMS
REVIEW RETURNED	11-Jul-2012

THE STUDY	1. Is the research question clearly defined? Coments: reaserch question is not clear. The manuscript includes "The present study aimed to assess the impact of IPT on mortality in children less than 5 years of age exposed to intrathoracic TB at home in an urban area of Bissau." and in same section it also suggest: "the purpose of the present study was to assess whether this differential excess mortality could be removed" It is suggested that authors may combine both togather (What is impact of IPT on reduction in excess mortality in children exposed to Tb patients) 2. Is the overall study design appropriate and adequate to answer the research question? Comments: The most appropriate design to answer the resaerch question may be randomized controlled trial. Since RCT may not be permitted in present circumstances (as ethically withholding IPT is not possible), authors tried to compare children with TB exposed and received IPT with children Tb exposed wthout IPT and no IPT and No TB exposure. They also tried to comapare results of present study with historical data. It may be better to give more emphasis on two groups (IPTand Tb exposure and No IPT with TB exposure) 3. Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described? Comments: Authors tried to provide as much information as possible. In the process theer are multiple groups (IPT in TB exposed, No IPT in Tb exposed, IPT without TB exposed etc). More confusion when they included pre IPT patients in result section. It is suggested that authors define all the patient groups clearly. No need to include pre IPT data in section of result. 4. Are the methods adequately described? Comments The manuscript suggest "The procedures for identification and diagnosis of the cases within this TB surveillance

	system have previously been described20." It is desirable that authors include summery of screening/ diagnosis and enrolment of patients in the study. Similarly it suggest "Following the census-update, a field assistant and a nurse visited the house to apply TSTs. 48-72 hours later the house was visited by the nurse who read the TST and referred potential TB cases for further clinical examination. Children less than 5 years of age without active TB were eligible for enrolment in the IPT cohort" Authors should clarify whether all children irrespective of TST results were included in the study. 5. Is the main outcome measure clear? Authors documented less mortality in children receiving IPT. However main outcome (Reduction in excess mortality) is not clear.
RESULTS & CONCLUSIONS	1. Do the results answer the research question? Comments: Reaserch question for the study (reduction in excesss mortality with IPT in Tb exposed children) is not clearly answered. Though they could document less mortality in children on IPT as comapred to those without IPT. 2. Are they credible? Comment: a) it is not RCT b) Data compared with historical data (that were collected almost 10 years before the present study was done) c) The moratlity in children on IPT was less in those without exposure and without IPT. 3. Are they well presented? Commnets: Authors have tried to present their data in detail. However there is scope to modify. It is suggested that instead of including Pre IPT data in results they should compare pre IPT data in discussion only.
GENERAL COMMENTS	Authors report result of their study on effect of IPT on reduction in ecxess mortality in children exposed to Tb patients in household. They compared their data with 10 year old historic data. 1. Reaserch question is not clear. The manuscript includes "The present study aimed to assess the impact of IPT on mortality in children less than 5 years of age exposed to intrathoracic TB at home in an urban area of Bissau." and in same section it also suggest: "the purpose of the present study was to assess whether this differential excess mortality could be removed" It is suggested that authors may combine both togather (What is impact of IPT on reduction in excess mortality in children exposed to Tb patients) 2. The most appropriate design to answer the resaerch question may be randomized controlled trial. Since RCT may not be permitted in present circumstances (as ethically withholding IPT is not possible), authors tried to compare children with TB exposed and received IPT with children Tb exposed wthout IPT and no IPT and No TB exposure. They also tried to comapare results of present study with historical data. It may be better to give more emphasis on two groups (IPTand Tb exposure and No IPT with TB exposure) 3. Authors tried to provide as much information as possible. In the process theer are multiple groups (IPT in TB exposed, No IPT in Tb exposed, IPT without TB exposed etc). More confusion when they included pre IPT patients in result

	section. It is suggested that authors define all the patient groups clearly. No need to include pre IPT data in section of result. 4. The manuscript suggest "The procedures for identification and diagnosis of the cases within this TB surveillance system have previously been described20." It is desirable that authors include summery of screening/ diagnosis and enrolment of patients in the study. Similarly it suggest "Following the census-update, a field assistant and a nurse visited the house to apply TSTs. 48-72 hours later the house was visited by the nurse who read the TST and referred potential TB cases for further clinical examination. Children less than 5 years of age without active TB were eligible for enrolment in the IPT cohort" Authors should clarify whether all children irrespective of TST results were included in the study. 5. Authors documented less mortality in children receiving IPT. However main outcome (Reduction in excess mortality) is not clear. 6. Reaserch question for the study (reduction in excesss mortality with IPT in Tb exposed children) is not clearly answered. Though they could document less mortality in children on IPT as comapred to those without IPT. 7. Data compared with historical data (that were collected almost 10 years before the present study was done) b) The moratlity in children on IPT was less in those without exposure and without IPT. 8. Authors have tried to present their data in detail. However there is scope to modify. It is suggested that instead of including Pre IPT data in results they should compare pre IPT data in discussion only.

REVIEWER	H S Schaaf Professor in Paediatrics Stellenbosch University South Africa I have no competing interest
REVIEW RETURNED	11-Sep-2012

THE STUDY	1. Page 8, Recruitment: despite the fact that the identification and diagnosis of adult TB cases was described earlier, it will be very helpful to add at least whether only acid-fast bacilli smear-positive or also AFB smear-negative adult cases were included? 2. An important limitation of the study is also the unknown HIV status of the study group children, and if HIV-infected, who got antiretroviral treatment and who not (especially those not enrolled for IPT – not coming for IPT may bias to not coming for ART?)
RESULTS & CONCLUSIONS	1. The main concern for the reviewer is the comparison with the previous study performed during 1996-1998. The authors compare mortality in children exposed to tuberculosis (TB) who received IPT during 2005-2008 to those exposed more than 10 years ago who have not received IPT and then deduct from this an improvement due to IPT. However, overall mortality in all children <5 years have decreased substantially over time, and surely even if they would

	compare those exposed to TB NOT receiving IPT in the current study to the previous study there must be a statistically significant difference, therefore in my view using the old study for comparison for effect of IPT is incorrect and not valid. Comparison within the current study comparing exposed children receiving and not receiving IPT for mortality is much more justified, and this showed no statistically significant difference, which was also probably not expected and therefore somewhat ignored in the discussion. 2. Page 14 and figure 2: The group of children exposed but not on IPT is to the reviewer not all that clear: Why were 29 children >5 years included in this group while the study was about children <5 years old? For comparisons they need to be excluded? Also the reviewer is not certain (need a statistician!) whether including those children that already died (<5 years? True exposure?) in this group is not a factor biasing the not-IPT group? 3. Discussion, first statement: The reviewer is not convinced that this statement can be based on the provided statistical results. Although there was a strong trend towards less mortality, none of the groups in the recent study had statistically significant results to prove this (exposed with IPT vs exposed without IPT). In the comparison with previous study, even the current study group exposed without IPT would probably have a statistically significant improvement over the 1996-1998 exposed group without IPT due to other factors improving child survival? In the following sentences at the END of the paragraph the authors mention a TREND which the reviewer would be much more agreeable to.
REPORTING & ETHICS	Page 11, Ethical approval: can caregivers give informed consent in Guinea Bissau, or was it the legal guardians giving consent?
GENERAL COMMENTS	Thank you for the opportunity to review this important manuscript. This is a large study looking at the effect of isoniazid preventive therapy (IPT) in tuberculosis exposed children on all-cause mortality. Unfortunately (or fortunately for the children) things have changed for the better regarding mortality rates in children <5 years old in the studied communities, which to some extent has limited the findings of the study. The reviewer thinks that it is an excellent study, but has some concerns regarding the interpretation of the data. Comments are as follows (and the reviewer admits that he is not a statistician and may sometimes be ignorant): Major comments: (included in specific comments above) 1. The main concern for the reviewer is the comparison with the previous study performed during 1996-1998. The authors compare mortality in children exposed to tuberculosis (TB) who received IPT during 2005-2008 to those exposed more than 10 years ago who have not received IPT and then deduct from this an improvement due to IPT. However, overall mortality in all children <5 years have decreased substantially over time, and surely even if they would compare those exposed to TB NOT receiving IPT in the current study to the previous study there must be a statistically significant difference, therefore in my view using the old study for comparison for effect of IPT is incorrect and not valid. Comparison within the current study comparing exposed children receiving and not receiving IPT for mortality is much more justified, and this showed no statistically significant difference, which was also probably not expected and therefore somewhat ignored in the discussion. 2. Page 8, Recruitment: despite the fact that the identification and diagnosis of adult TB cases was described earlier, it will be very helpful to add at least whether only acid-fast bacilli smear-positive or also AFB smear-negative adult cases were included? 3. Page 14 and figure 2: The group of children exposed but not on

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	8. Page 9, last paragraph: Is it a correct interpretation that the children on IPT were treated for 9 months – if not, the duration of IPT needs to be added? 9. Page 11, Ethical approval: can caregivers give informed consent in Guinea Bissau, or was it the legal guardians giving consent?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Sushil Kabra
Department of Pediatrics, AIIMS

1. Is the research question clearly defined?
Coments: reaserch question is not clear. The manuscript includes "The present study aimed to assess the impact of IPT on mortality in children less than 5 years of age exposed to intrathoracic TB at home in an urban area of Bissau." and in same section it also suggest: "the purpose of the present study was to assess whether this differential excess mortality could be removed"
It is suggested that authors may combine both togather (What is impact of IPT on reduction in excess mortality in children exposed to Tb patients)
A1.1: We have rephrased the last paragraph of the introduction. We now write “The aim of the present study was to compare mortality between exposed children on IPT and community control children, and to compare this relative mortality to the previously observed excess mortality.”

2. Is the overall study design appropriate and adequate to answer the research question?
Comments: The most appropriate design to answer the resaerch question may be randomized controlled trial. Since RCT may not be permitted in present circumstances (as ethically withholding IPT is not possible), authors tried to compare children with TB exposed and received IPT with children Tb exposed wthout IPT and no IPT and No TB exposure. They also tried to comapare results of present study with historical data. It may be better to give more emphasis on two groups (IPTand Tb exposure and No IPT with TB exposure)
A1.2: The group of exposed children without IPT is a special group who ideally should have received IPT. Therefore we focused on the comparison between exposed children with IPT and community controls. Also, this facilitated the comparison with the previous study.

3. Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?
Comments: Authors tried to provide as much information as possible. In the process theer are multiple groups (IPT in TB exposed, No IPT in Tb exposed, IPT without TB exposed etc).
More confusion when they included pre IPT patients in result section.
It is suggested that authors define all the patient groups clearly. No need to include pre IPT data in section of result.
A1.3: After the section “Pre-IPT cohort” under “Recruitment of participant and patients” we have added the section “Groups in the study”. This section summarizes the 5 groups in the study. It is a part of our objective to compare with the pre-IPT cohort. Pre-IPT data is therefore included in the results.

4. Are the methods adequately described?
Comments The manuscript suggest "The procedures for identification and diagnosis of the cases within this TB surveillance system have previously been described20."
It is desirable that authors include summery of screening/ diagnosis and enrolment of patients in the study.
Similarly it suggest "Following the census-update, a field assistant and a nurse visited the house to apply TSTs. 48-72 hours later the house was visited by the nurse who read the TST and referred

potential TB cases for further clinical examination. Children less than 5 years of age without active TB were eligible for enrolment in the IPT cohort"
Authors should clarify whether all children irrespective of TST results were included in the study.
A1.4: In the section “Identification of adult TB index cases” under “Recruitment of participant and patients” we have added the phrase “As previously described in more detail20, a TB case was defined as an adult with symptoms of TB disease with sputum smear positive or negative for AFB, presenting abnormalities in CX-ray with no improvement under treatment with broad spectrum antibiotics for two weeks.” In the section “Enrolment in the IPT cohort” we added the phrase “Children without TB disease were eligible for enrolment in the IPT cohort regardless of the TST result and were invited to attend the enrolment visit at the local health centre”

5. Is the main outcome measure clear?
Authors documented less mortality in children receiving IPT. However main outcome (Reduction in excess mortality) is not clear.
A1.5: In the abstract the main outcome is now described as “The all-cause mortality rate ratio (MRR) between exposed children on IPT and unexposed community control children.” In our opinion this outcome measure is clear

6 (1.) Do the results answer the research question?
Comments: Reaserch question for the study (reduction in excesss mortality with IPT in Tb exposed children) is not clearly answered. Though they could document less mortality in children on IPT as comapred to those without IPT.
A1.6: In the last section of the introduction the research question is now stated as “The aim of the present study was to compare mortality between exposed children on IPT and community control children, and to compare this relative mortality to the previously observed excess mortality.” We believe this is clearly answered in the results.

7 (2.) Are they credible?
Comment:
a) it is not RCT
b) Data compared with historical data (that were collected almost 10 years before the present study was done)
c) The moratlity in children on IPT was less in those without exposure and without IPT.
A1.7:
a) We agree, the reasons for not doing an RCT are pointed out in the summary section “Strengths and limitations”.
b) This has been added as a limitation in “Strengths and limitations”.
c) In 1996-1998 the excess mortality only started 6 months after exposure. The same was the case in 2005-2008. Also, exposed children not on IPT may have been a more mobile group with less contact with the TB case.

8 (3). Are they well presented?
Commnets: Authors have tried to present their data in detail. However there is scope to modify. It is suggested that instead of including Pre IPT data in results they should compare pre IPT data in discussion only.
Authors report result of their study on effect of IPT on reduction in ecxess mortality in children exposed to Tb patients in household. They compared their data with 10 year old historic data.
A1.8: Even with 10 year old historic data we maintain that the pre-IPT data are important for our intended comparison and should be presented in the results section.

Reviewer 2: H S Schaaf
Professor in Paediatrics
Stellenbosch University
South Africa

I have no competing interest

Thank you for the opportunity to review this important manuscript. This is a large study looking at the effect of isoniazid preventive therapy (IPT) in tuberculosis exposed children on all-cause mortality. Unfortunately (or fortunately for the children) things have changed for the better regarding mortality rates in children <5 years old in the studied communities, which to some extent has limited the findings of the study. The reviewer thinks that it is an excellent study, but has some concerns regarding the interpretation of the data. Comments are as follows (and the reviewer admits that he is not a statistician and may sometimes be ignorant):

Major comments: (included in specific comments above)
1. The main concern for the reviewer is the comparison with the previous study performed during 1996-1998. The authors compare mortality in children exposed to tuberculosis (TB) who received IPT during 2005-2008 to those exposed more than 10 years ago who have not received IPT and then deduct from this an improvement due to IPT. However, overall mortality in all children <5 years have decreased substantially over time, and surely even if they would compare those exposed to TB NOT receiving IPT in the current study to the previous study there must be a statistically significant difference, therefore in my view using the old study for comparison for effect of IPT is incorrect and not valid. Comparison within the current study comparing exposed children receiving and not receiving IPT for mortality is much more justified, and this showed no statistically significant difference, which was also probably not expected and therefore somewhat ignored in the discussion.
A2. 1: It is important that we compare mortality relative to mortality in the community control children. Even though overall mortality in children < 5 years has decreased substantially, we could still have observed 66% higher mortality in the TB-exposed children on IPT compared to the community control children in 2005-2008. We have emphasized this at several places in the manuscript.

2. Page 8, Recruitment: despite the fact that the identification and diagnosis of adult TB cases was described earlier, it will be very helpful to add at least whether only acid-fast bacilli smear-positive or also AFB smear-negative adult cases were included?
A2.2: See A1. 4.

3. Page 14 and figure 2: The group of children exposed but not on IPT is to the reviewer not all that clear: Why were 29 children >5 years included in this group while the study was about children <5 years old? For comparisons they need to be excluded? Also the reviewer is not certain (need a statistician!) whether including those children that already died (<5 years? True exposure?) in this group is not a factor biasing the not-IPT group?
A2.3: In the results section “Index TB cases and included children” we now explicitly explain the phenomenon with 29 children > 5 years at enrolment “Twenty-nine children were < 5 years old when exposure started, but > 5 years old at the time of enrolment. They did therefore not receive IPT. These children counted as exposed without IPT until end of follow-up at 5 years of age.” All children in the study were at risk of dying before IPT enrolment, both those that was never enrolled and those that was eventually enrolled. It is therefore correct to include the 7 dead children in the exposed without IPT group.

4. Discussion, first statement: The reviewer is not convinced that this statement can be based on the

provided statistical results. Although there was a strong trend towards less mortality, none of the groups in the recent study had statistically significant results to prove this (exposed with IPT vs exposed without IPT). In the comparison with previous study, even the current study group exposed without IPT would probably have a statistically significant improvement over the 1996-1998 exposed group without IPT due to other factors improving child survival? In the following sentences at the END of the paragraph the authors mention a TREND which the reviewer would be much more agreeable to.
A2.4: We have weakened the first statement in the discussion and emphasized that it is not significant.

5. An important limitation of the study is also the unknown HIV status of the study group children, and if HIV-infected, who got antiretroviral treatment and who not (especially those not enrolled for IPT – not coming for IPT may bias to not coming for ART?)
A2.5: No children got ART as this was not available at the time. In “Strengths and limitations” we now state the following regarding HIV “Another limitation was that the children were not HIV tested, it might bias the results if there were more HIV infected children in the IPT group compared to the no IPT group. However, we would then expect higher mortality in the no IPT group compared to the community controls.”

6. Page 19 of discussion: It is not correct that children receiving IPT had a statistically significant lower mortality ratio compared to community controls – a trend maybe, but it crosses 1.0!
A2.6: This statement is reworded.

7. Page 20 – agree with “although not reaching statistical significance” in line 4, but not with: “Our study clearly shows that children less than 5 years of age exposed to TB at home have a high mortality that can be prevented with IPT”. Although the reviewer beliefs this to be true, this study unfortunately only showed a trend, rather than clear improvement.
A2.7: This statement is reworded.

Minor comments:
1. Page 5: WHO – only abbreviation used; TB abbreviated in first line, but not consistently used throughout manuscript; second last line: age of 5 years (add)
2. Page 6, line 3 and further: “active TB”, although often used in articles, is not a good term, as what the authors are referring to is TB disease compared TB infection (not passive TB or inactive TB). The reviewer thinks active TB should be replaced by TB disease.
3. Page 5 & 6: In the last paragraph page 5 and first paragraph page 6, the authors use “chemoprophylaxis, prophylaxis, isoniazid preventive therapy and tuberculosis preventive therapy with isoniazid” – all probably referring to the same thing, which it is not. They should either define what they mean with each of these terms, or if they refer to isoniazid preventive therapy, use this term throughout.
4. Page 6: INH and isoniazid – inconsistent use; tuberculin skin test should be abbreviated in line 8 (and add “tuberculin” to “skin test”) and use abbreviation in line 11.
5. Page 7, Setting: add dates study start/end. Add city and country where BHP is situated (not only in abstract).
Is data on hospitalisation/death only collected for children <3 years of age and not <5 years?
A2.Minor1-5:
1. WHO and TB are first written out and then abbreviated throughout the paper.
2. Active TB is replaced by TB disease.
3. We use the term isoniazid preventive therapy throughout.
4. We no longer use the abbreviation INH. Instead we write isoniazid. The TST abbreviation is used as suggested.
5. Dates for study start/end are added. City and country are added. Information regarding

hospitalisations and deaths is collected every 3 months for children under 3 years of age. Mortality information on children 3-5 years of age was obtained from regular censuses of the general population.
Note: not all these small changes have been tracked en the document with track changes.

6. Page 7-8: Were all houses with >1 family extended families staying in the same house, or were there houses with >1 family who were not extended families and therefore not seen as household member despite staying in the same house?
A2.Minor6: In the "Material and methods" section "Houses and household contacts" we now write "Houses in the study area are one-storey, rectangular constructions, usually with 6-8 rooms and are inhabited by 2 to 4 households (families), which can be extended families or not."

7. Page 8, Enrolment in the IPT cohort: Children <5 years of age were actually screened for possible TB disease using the Keith Edwards score – diagnosis confirmed only if screen was positive?
A2.Minor 7: We combined the score, which is a clinical assessment, with laboratory methods, for those with signs and symptoms suggestive of TB disease. In the section "Enrolment in the IPT cohort" under "Recruitment of participant and patients" we write "Prior to the initiation of IPT, the children were investigated for TB disease in a clinical examination for signs and symptoms using the Keith Edwards score21. If the investigation suggested TB disease the children were submitted to a careful and thorough assessment of all evidence from history, clinical examination and relevant investigations, e.g. laboratory examination, including HIV testing, and chest x-ray".

8. Page 9, last paragraph: Is it a correct interpretation that the children on IPT were treated for 9 months – if not, the duration of IPT needs to be added?
A2.Minor 8: Yes, children on IPT were treated 9 months (described at the end of page 9 and beginning of page 10)

9. Page 11, Ethical approval: can caregivers give informed consent in Guinea Bissau, or was it the legal guardians giving consent?
A2.Minor 9: In reality it has been caregivers in some cases, but there is no a legal aspect in terms of the laws of Guinea Bissau. In our setting a caregiver is someone from the extended family, usually a relative. To clarify we have reworded in the "Ethical approval" section.

VERSION 2 – REVIEW

REVIEWER	Prof H S Schaaf Dept of Paediatrics and Child Health Stellenbosch University Cape Town South Africa
REVIEW RETURNED	21-Nov-2012

GENERAL COMMENTS	Thank you for the revised manuscript and the opportunity to comment. The authors have addressed the main issues previously mentioned by both reviewers. I still have a few more comments on the current version: Major comments 1. Page 3 of 62. Article summary – focus: the reviewer thinks that there should be a third focus and discussion – current cohort of TB exposed children comparing those with and without IPT. 2. The last sentence in Article summary (page 4): Does this expected higher mortality referred to in this sentence due to possible HIV infection refer to the current or previous study's "no IPT group"?

	It will only make sense to me if it is the current study. What is the HIV prevalence in Guinea-Bissau or in Bissau where this study was done? 3. The authors planned this study to compare use of IPT in preventing mortality in child household TB contacts in this study to the previous study of almost 10 years before. They have managed to explain why, but they also have the opportunity to make more of the comparison between TB exposed children receiving and not receiving IPT in this study. There also seems to be a slight trend towards better outcome in the contacts receiving IPT, although definitely not significant – why would this be? The reviewer still does not understand why there is no difference between control group of unexposed children and exposed children without IPT – could this also be to greater awareness of health issues amongst the exposed children because of home visits? 4. Page 7, setting: Death information was collected every 3 months for children <3 years of age, but how was the information about deaths collected for the age group 3-5 years in this study (especially in those not regularly visited)? 5. Page 10, Pre-IPT cohort: I may have missed it somewhere, but how long were the children in the previous cohort followed up compared to the current study cohort? Could there be any methodological explanations for the differences found both then (e.g. duration of follow up of different groups, establishing deaths in two groups 1996-1998 study) and in comparison to current study group (e.g. duration of follow up)?

VERSION 2 – AUTHOR RESPONSE

Reviewer: Prof H S Schaaf
Dept of Paediatrics and Child Health
Stellenbosch University
Cape Town
South Africa

Thank you for the revised manuscript and the opportunity to comment. The authors have addressed the main issues previously mentioned by both reviewers. I still have a few more comments on the current version:

Major comments
1. Page 3 of 62. Article summary – focus: the reviewer thinks that there should be a third focus and discussion – current cohort of TB exposed children comparing those with and without IPT.
Answer: We compared exposed children with IPT to unexposed controls and exposed children without IPT to unexposed controls. We now write that explicitly in the summary: “Impact of IPT on mortality among children exposed to an adult with intrathoracic TB at home: comparing 1) exposed children who received IPT to unexposed children and 2) exposed children who did not receive IPT to unexposed children”. The estimate comparing exposed +IPT/-IPT is 0.31 (0.1-1.4) (Please, see page 3, lines 60-62).

2. The last sentence in Article summary (page 4): Does this expected higher mortality referred to in this sentence due to possible HIV infection refer to the current or previous study’s “no IPT group”? It will only make sense to me if it is the current study. What is the HIV prevalence in Guinea-Bissau or in Bissau where this study was done?

Answer: We have added “in the present IPT cohort” to the sentence (Please, see page 4, line 86). From 1996-2006 in Bissau the prevalence of HIV-1 was 4.6% and the prevalence of HIV-2 was 4.4% among individuals aged at least 15 years (Please, see page 7, and lines 138-139). We have no data on the prevalence among children.

3. The authors planned this study to compare use of IPT in preventing mortality in child household TB contacts in this study to the previous study of almost 10 years before. They have managed to explain why, but a) they also have the opportunity to make more of the comparison between TB exposed children receiving and not receiving IPT in this study. b) There also seems to be a slight trend towards better outcome in the contacts receiving IPT, although definitely not significant – why would this be? c)The reviewer still does not understand why there is no difference between control group of unexposed children and exposed children without IPT – could this also be to greater awareness of health issues amongst the exposed children because of home visits?
Answer:
a) See response to 1
b) In the discussion under “Unexpected observations”, p.20, line 423-37, we have added a discussion regarding possible explanations such as those not receiving IPT were likely travelling and therefore less exposed to the index case and perhaps vulnerable during travel.
c)Table 3 showed no difference in overall mortality between unexposed controls and exposed who did not get IPT, but did indeed show an effect among the oldest children with +12 months since exposure. With the limited number of events available we were not able to show an overall difference in mortality which would be expected. Yet despite the limited number of events, it was possible to show a significant effect of exposure in a subgroup of the un-treated children, namely among those most likely affected, ie the mobile children + 3 years of age with the longest observation time since exposure.
We therefore do not agree with the reviewer that there is no difference, but hold that we just have too few events to show the difference for the entire group of exposed children.

4. Page 7, setting: Death information was collected every 3 months for children <3 years of age, but how was the information about deaths collected for the age group 3-5 years in this study (especially in those not regularly visited)?
Answer: In material and methods under “Settings” section we now write “Information about children older than 3 years of age is obtained from general censuses carried out approximately every 3rd year (Please, see page 7, lines 144-145).

5. Page 10, Pre-IPT cohort: I may have missed it somewhere, but how long were the children in the previous cohort followed up compared to the current study cohort? Could there be any methodological explanations for the differences found both then (e.g. duration of follow up of different groups, establishing deaths in two groups 1996-1998 study) and in comparison to current study group (e.g. duration of follow up)?
Answer: Follow-up and methodology was the same in the previous and the present study cohort.

6. Page 19, last paragraph and page 20, first paragraph: There is still no clear explanation of why exposed children (with or without IPT) did so much better compared to control children. The home visits, making parents/caregivers aware of health issues could partially explain this, but why also better in no IPT group compared to controls?
Answer: See answer to comment 3.

Minor comments
1. The WHO recently published child TB estimates in the 2012 Global Report on TB which could be used in the first paragraph in the introduction instead of the 2000 data.
Answer: Changed accordingly (Please, see page 6, lines 114-115): The use of isoniazid for IPT in low

income countries…? Also, the following sentence is repetition of this sentence and should be deleted – the last phrase of that sentence could easily be included in this sentence. (The manuscript is already very long and I think there are ways to cut on the word number if this is necessary)
Answer: This paragraph has been made shorter.

3. Page 6, line 20-21: add space between “TB disease”
Answer: Changed accordingly

4. Page 6, line 20-21: Authors use both HIV-infected (hyphen usually used) and HIV-positive in this manuscript. It is preferable that same terminology should be used throughout if the same meaning is implied, otherwise need to define what difference is
Answer: Changed accordingly through out the manuscript.

5. Page 8, lines 15-23: Suggest rewrite as follows: “An intrathoracic TB case was defined as an adult with symptoms of TB with sputum smear microscopy positive or negative for acid-fast bacilli, presenting abnormalities in the chest X-ray (CXR) with no improvement on treatment with broad spectrum antibiotics for two weeks.” Change all chest x-ray/chest X-ray
Answer: Changed accordingly (Please, see page 8, and line 166-170).