PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of women-led community interventions in improving tuberculosis preventive treatment in children: results from a comparative, before-after study in Ethiopia
AUTHORS	Jerene, Degu; Assefa, Dawit; Tesfaye, Kalkidan; Bayu, Samuel; Seid, Samuel; Aberra, Fikirte; Bedru, Ahmed; Khan, Amera; Creswell, Jacob

VERSION 1 – REVIEW

REVIEWER	Yuen, Courtney Brigham and Women's Hospital
REVIEW RETURNED	08-Mar-2022

GENERAL COMMENTS	This paper reports a multifaceted intervention to increase child contact screening, TPT initiation, and TPT completion in Ethiopia. The intervention relied on leveraging an existing type of social group called Iddirs, which normally provide economic support, but were in this intervention used to improve contact management. The intervention model should be of interest to readers in many places in the world, where there may also be untapped partnerships between TB programs and economically focused community support groups. However, before considering publication, there are several issues with the clarity of the methods and the reporting of the results that need to be addressed. Major comments: (1) Abstract: The second sentence of the “participants” section does not make sense to me (“We included all child contacts in whom active TB and contraindications to TPT regimens as being eligible for TPT.”). Presumably those with contraindications to TPT would not have been eligible. (2) Abstract: In the first sentence of the “results” section, I assume that the second set of figures corresponds to the control zones? If so, then it should read “while it increased from 34.6% to 43.2% in the control zones.” (3) The abstract defines the primary outcomes, but this does not correspond to the way that the outcomes are presented in the methods and results (see comment 5). In addition, I do not understand why the percentage of eligible children who initiate TPT would be considered a primary outcome for an intervention that does not seem to impact TPT prescription or acceptance but rather impacts getting children into care in the first place and promoting adherence (see comment 4).

	(4) It is unclear to me what part of the intervention package was directed at increasing TPT prescription/uptake. That is, what part of the intervention would be expected to lead to an increase in the proportion (not the absolute number) of eligible children who initiated TPT, which is one of the study outcomes. The Iddirs' activity seem to be directed at getting children into care (affecting the total number of eligible children) and TPT adherence. Is there an element of the supportive supervision/mentoring alluded to in the figure but not described in the methods that was supposed to increase TPT usage? Or is the increase seen in this outcome (in table 2) mainly the effect of broadening TPT eligibility to include all contacts under 15? (5) Because of inconsistencies throughout the methods and results section, I am confused about what the study's outcomes are. The "Study design" section says that the study was meant to measure "TPT uptake" (lines 134-135), which to me refers to the proportion of children who initiate TPT out of those who were prescribed TPT (although I realize others use this term to mean the proportion who initiate TPT out of those who were eligible). Lines 217-218 then refer to assessing "trends in TPT improvement," which is not defined. The "Data sources and analysis" section says, "we calculated total numbers and proportion of eligible children treated with TPT; and number and proportion of treated children who successfully completed treatment." (lines 224-227), but then the results describe the number of child contacts screened and the "number of eligible enrolled." (The number screened was never mentioned in the methods, and it is not clear what "enrolled" means). All these inconsistencies in terminology. Please standardize the language across the methods section and clearly define the analytic outcomes in a way that they correspond with the results presented. (6) I am confused by the definition of "eligible" since TPT eligibility seems to have changed during the study period from children <5 during the pre-intervention period to children <15 during the intervention period. At line 221-227 and, it says that "eligible children are screened children in whom active TB was excluded and contraindications for TPT ruled out….Eligibility for TPT was based on the national guidelines described under the standard of care above." But according to the standard of care description at line 149, in the pre-intervention period, only children <5 were actually eligible for TPT, and this changed just as the study started to children <15. Does that mean that in Tables 1 and 2, eligible children in the pre-intervention period are only <5's and eligible children in the intervention period are <15's? If not, and the denominator is in fact all contacts <15 for both periods, then the eligibility definition needs to be clarified. If the eligibility definition is in fact changing in the analysis, then this really needs to be clarified and discussed, because greater numbers of eligible children in that care could reflect changing guidelines as opposed to the intervention's success at getting children into care. (7) In the "data sources and analysis" section, it is not clear which data sources are used for which outcomes. Two data sources are described – the DHIS and Excel-based data collection. However, it is not clear which outcome data were in the DHIS versus collected via Excel, or how the outcome data were derived from these sources. For instance, how was eligibility assessed (is information on the TB rule-out or contraindications available in DHIS)? Was

	eligibility determined by the study team during the data collection (e.g. via chart review at the facilities) or is there actually a variable in the register corresponding to eligibility? Please be explicit about what outcomes were assessed, in which age groups, which data came from each source, and how these data were captured in each source. (8) The statement “Since the DID analysis for the U15C data was based on aggregate data, no statistical significance was tested” (lines 230-231) is not a valid justification for a lack of statistical testing. Statistical testing of a difference of differences can be done on aggregate data (e.g. a Poisson regression with count data aggregated at the level of health facilities with dummy variables representing pre/post period and +/- intervention, which can often be done using surveillance data). Ideally the authors would do this, but I am not trying to require that the authors add a statistical assessment to their report if it is not feasible or appropriate. However, if the authors wish to justify the lack of statistical testing, the reason should be scientifically valid. (9) In the tables that show the difference of differences, please include the % change, which is currently just alluded to in the text. For instance, the sentence at lines 262-265 “the improvement in the intervention sub-city in Addis Ababa was lower than that of the comparator sub-city” is only understandable if the reader manually calculates the % change for the two (78/156 = 50% increase in the intervention sub-city, while 55/43 = 128% increase in the comparator sub-city). (10) A confounding reason for seeing an increase in the numbers of contacts screened or put on TPT would be an increase in the number of TB index patients, which could happen for various reasons (e.g. migration in/out of particular areas, improved case-finding, introduction of better diagnostic technologies). Presenting the total numbers of TB cases in the intervention and control areas during the intervention and pre-intervention periods would be a simple way to show that whether this was the case. I noticed that one of the reviewers of the original version of the manuscript also raised this issue, but the authors replied that this information was not available. How is it possible that they have surveillance data on numbers of contacts from the DHIS but not total numbers of TB patients? (11) In the paragraph discussing why the intervention failed to increase the number of child contacts enrolled in the urban versus the rural site, I do not understand the logic leading to the concluding sentence, (“however, once eligible children are enrolled, their chances of initiation were higher in Addis Ababa, which clearly shows the impact of the Iddirs intervention”), and I think it may be a misleading interpretation of the results. First, from the description of the intervention, the Iddir members’ main roles were to refer the child for evaluation (which should increase enrollment in care) and promote adherence to treatment once; it is not clear how the Iddirs were supposed to improve initiation of treatment, so it is not clear to me how this shows the impact of the Iddirs. Second, while it is true that a greater percentage of eligible children initiated TPT in the intervention sub-city of Addis, the intervention sub-city started out with nearly twice the TPT initiation rate than the control sub-city, and comparing fold-increase over baseline, the increase was in fact higher in the control sub-city (the

	control area increased from 13.9% to 59.2%, or a 4.3-fold increase, while the intervention area increased from 21.1% to 77.3%, or a 3.7-fold increase). (12) The authors should discuss the impact of the guideline change, which coincided with their study start date. The fact that TPT eligibility was expanded presumably led to numerous changes in recommendations or practices, from prioritizing which contacts are evaluated to changing the way that registers are filled out or indicators are reported. I am not disputing the conclusion that the intervention had an impact, but it is important to discuss the effect of this major driver of secular change (which was presumably responsible for the substantial increase in TPT initiations in the control area) and/or its potential interaction with the intervention. (13) In the limitations, the authors should discuss whether the support provided to the intervention health facilities for filling out the registers and data reported is likely to have biased results toward showing improved TPT initiations simply because the data were being recorded and reported properly. The limitations right now acknowledge the general limitation that because the intervention was multifaceted, the impact cannot be solely attributed to the involvement of the Iddirs. However, I think that the specific example of recording/reporting strengthening should be discussed because it is possible that better recording/reporting could lead to an apparent increase in children being screened or in children initiating TPT where no real increase existed (that is, if the programs were doing these activities all along, but they just were not recording/reporting it). This is particularly important in the context of changing national indicators, which the authors allude to at lines 336-337. Control areas might have under-reported TPT in older child contacts since they would not be used to this reporting and did not have the benefit of support from the intervention. If the authors have any additional insight into the potential magnitude of the effect of information bias (including reasons why they think it might not have made a difference to their conclusions), this should be discussed. (14) Normally having authors who are employees of the funding agency is declared as a competing interest since the funder generally has an interest in presenting results a certain way. (I make this as a general comment – I think TB REACH is great, and there is absolutely no problem with Stop TB Partnership staff being co-authors). I defer to the journal whether it wishes this to be declared. Minor comments: The manuscript is highly readable but should undergo copy editing for grammar and missing words. Below are some corrections that I noticed, but I have not read through carefully to check the grammar. Throughout, I think the phrase “women-only Iddirs” should contain a hyphen if it refers to Iddirs whose membership is limited to women. The authors might consider making this usage consistent in the title and abstract as well.

	Line 121: The word “a” is missing before “map” in “Figure 1 shows map…” Line 144: The word “is” is missing before “rarely practiced” in “Active search or contact investigation for eligible child contacts rarely practiced”

REVIEWER	Casenghi, Martina Elizabeth Glaser Pediatric AIDS Foundation
REVIEW RETURNED	11-Mar-2022

GENERAL COMMENTS	The authors should be commended for the work done on improving the manuscript and clarifying several important aspects. There are still some minor issues that need to be addressed Please see my comments below Major Comments 1) Line 214-219:The explanation of the different data sources has greatly improved but it still requires some improvement. Authors should explain in more details which key patient level indicators where collected in the Microsoft excel-based database (i.e nr of child contacts identified, nr of child contacts screened, nr of child contacts identified as eligible for TPT etc). The authors only mention that this database collected data on children below 5 years. In addition, the authors should specify if what was extracted from registers were aggregated data, or single patient -level data, allowing to follow longitudinally through the cascade of care every single patient. Finally the authors should explain which analysis in the manuscript are based on the use of the data collected through the Microsoft excel based database. 2)Tables and figures- there is no statistical analysis performed for the differences observed. I do not have expertise in Statistics therefore I do not have the competencies to comment on this. However I wonder if a reviewer with those set of expertise should be involved and advise whether or not statistical analysis is needed . Minor comments: 1) Line 87_ “…led to improvements in TB childhood TB case-finding” TB mentioned twice. Remove the repetition 2) Line 88-89 “…through community health workers childhood TB case detection” -it looks like a word is missing. The meaning of this sentence is not clear 3) Line 109:---" Similarly, engaging saving groups has been groups has been beneficial” repetition of the word “groups” 4) Line 144: “….investigation for eligible child contacts rarely practiced at community level despite its being recommended to be part of the package for HEWs”. English check needed (“is rarely practiced” : add “is”despite ist being…; change into “despite this being”) 5) Line 230: please check consistency in writing the abbreviation of difference-in-difference (sometimes DiD is used, other times DID)

	6) Line 2020-2023: are those the only indicators that were collected ? or do they represent the indicators that were selected for the analysis? 7) Line 255: at the beginning of the paragraph, please state again the data source for this analysis. Is this analysis based on the use of the DHS2 data. Based on the response provided to comments, I understand this is the case and should be stated in the paragraph as well. 8) Table 1 and Table 2 : since the analysis performed have used different definition of pre-intervention period depending on database used, please specify the period considered as "before" and as "after" in the table to ease understanding and interpretation of results (i.e before=July 2019-June 2020?) 9) Line 371 and 374: "number of eligible children enrolled"- did you mean "identified" or enrolled in the study? The word "enrolled" generate confusion as it is often used to indicate enrollment into treatment. Please clarify

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Courtney Yuen, Brigham and Women's Hospital, Harvard Medical School

Comments to the Author:
This paper reports a multifaceted intervention to increase child contact screening, TPT initiation, and TPT completion in Ethiopia. The intervention relied on leveraging an existing type of social group called Iddirs, which normally provide economic support, but were in this intervention used to improve contact management. The intervention model should be of interest to readers in many places in the world, where there may also be untapped partnerships between TB programs and economically focused community support groups. However, before considering publication, there are several issues with the clarity of the methods and the reporting of the results that need to be addressed.

Major comments:

(1) Abstract: The second sentence of the "participants" section does not make sense to me ("We included all child contacts in whom active TB and contraindications to TPT regimens as being eligible for TPT."). Presumably those with contraindications to TPT would not have been eligible.

- ✓ Thank you for this observation. Yes, excluding active TB and contraindications was a pre-requisite for considering a child eligible for TPT. We added excluded", and here is how the sentence reads now: *Child contacts in whom active TB and contraindications to TPT regimens excluded were considered eligible for TPT.*

(2) Abstract: In the first sentence of the "results" section, I assume that the second set of figures corresponds to the control zones? If so, then it should read "while it increased from 34.6% to 43.2% in the control zones."

✓ Thank you for this comment. Correction made as suggested.

(3) The abstract defines the primary outcomes, but this does not correspond to the way that the outcomes are presented in the methods and results (see comment 5). In addition, I do not understand why the percentage of eligible children who initiate TPT would be considered a primary outcome for an intervention that does not seem to impact TPT prescription or acceptance but rather impacts getting children into care in the first place and promoting adherence (see comment 4).

✓ The primary outcome, TPT initiation rate, was set a priori based on the low TPT initiation rate among those eligible. The interventions are interrelated and were designed to have impact along the full cascade of care. Making specific causal attribution in such complex set of interventions is not possible (as described in the limitations section). There was strong bidirectional communication between the Iddir women and health facility staff, the former ensuring the identified child contacts received the right service in the health facility. The purpose of the supportive supervision and mentoring described in lines 203-206 was to ensure eligible children received treatment.

(4) It is unclear to me what part of the intervention package was directed at increasing TPT prescription/uptake. That is, what part of the intervention would be expected to lead to an increase in the proportion (not the absolute number) of eligible children who initiated TPT, which is one of the study outcomes. The Iddirs' activity seem to be directed at getting children into care (affecting the total number of eligible children) and TPT adherence. Is there an element of the supportive supervision/mentoring alluded to in the figure but not described in the methods that was supposed to increase TPT usage? Or is the increase seen in this outcome (in table 2) mainly the effect of broadening TPT eligibility to include all contacts under 15?

✓ As explained in our response to #3 above, there was a supportive supervision and mentoring component as described in lines 203-206. In Table 2, we presented the proportion of children who initiated TPT out of those eligible. The improvement in the TPT initiation rate is unlikely to be due to expansion in the inclusion criteria for two reasons; 1) broadening in the eligibility criteria was implemented both in intervention and control zones, and 2) change in the proportion initiated is independent of the absolute number initiated. See further explanation about this point under comment #6.

(5) Because of inconsistencies throughout the methods and results section, I am confused about what the study's outcomes are. The "Study design" section says that the study was meant to measure "TPT uptake" (lines 134-135), which to me refers to the proportion of children who initiate TPT out of those who were prescribed TPT (although I realize others use this term to mean the proportion who initiate TPT out of those who were eligible). Lines 217-218 then refer to assessing "trends in TPT improvement," which is not defined. The "Data sources and analysis" section says, "we calculated total numbers and proportion of eligible children treated with TPT; and number and proportion of treated children who successfully completed treatment." (lines 224-227), but then the results describe the number of child contacts screened and the "number of eligible enrolled." (The number screened was never mentioned in the methods, and it is not clear what "enrolled" means). All these inconsistencies in terminology. Please standardize the language across the methods section and clearly define the analytic outcomes in a way that they correspond with the results presented.

✓ This feedback is well noted, and corrections made.

(6) I am confused by the definition of "eligible" since TPT eligibility seems to have changed during the study period from children <5 during the pre-intervention period to children <15 during the intervention period. At line 221-227 and, it says that "eligible

children are screened children in whom active TB was excluded and contraindications for TPT ruled out….Eligibility for TPT was based on the national guidelines described under the standard of care above." But according to the standard of care description at line 149, in the pre-intervention period, only children <5 were actually eligible for TPT, and this changed just as the study started to children <15. Does that mean that in Tables 1 and 2, eligible children in the pre-intervention period are only <5's and eligible children in the intervention period are <15's? If not, and the denominator is in fact all contacts <15 for both periods, then the eligibility definition needs to be clarified. If the eligibility definition is in fact changing in the analysis, then this really needs to be clarified and discussed, because greater numbers of eligible children in that care could reflect changing guidelines as opposed to the intervention's success at getting children into care.

- ✓ We agree with the reviewer on the importance of discussing the change in the age limit for eligibility. However, the pre-intervention period for U15C falls within the time frame when the eligibility criteria was expanded to include all children under 15 years of age. Moreover, we checked the proportion of under-five children out of the total both for the pre-intervention and post-intervention period. Accordingly, 65% (1010/1550) of eligible children were under-five years of age during the post-intervention period compared with 39% (126/320) during the pre-intervention time. If there was some increase in the number of children 5-14 due to the change in the eligibility criteria, there should have been decline in the proportion of children <5. Instead, there was a relative increase in the proportion of under-five children, further confirming the impact of the in the intervention. We added this information in the results (lines 288-289) and discussion sections (lines 390-392).

(7) In the "data sources and analysis" section, it is not clear which data sources are used for which outcomes. Two data sources are described – the DHIS and Excel-based data collection. However, it is not clear which outcome data were in the DHIS versus collected via Excel, or how the outcome data were derived from these sources. For instance, how was eligibility assessed (is information on the TB rule-out or contraindications available in DHIS)? Was eligibility determined by the study team during the data collection (e.g. via chart review at the facilities) or is there actually a variable in the register corresponding to eligibility? Please be explicit about what outcomes were assessed, in which age groups, which data came from each source, and how these data were captured in each source.

- ✓ The DHIS-2 data was used for comparing impact between intervention and control zones before and after the intervention for children under 15 years of aged (U15C).
- ✓ Number eligible and initiated TPT are variables included in the DHIS-2
- ✓ The excel based data was collected by the project for children under five years of age. Since this age disaggregation was not available in the control zones (where only the DHIS-2 was available), we used this data to compare treatment initiation and outcome rates before and after the intervention for children <5 years of age in the intervention zones only. Eligibility is determined by the health worker at the health facility and recorded on the health facility TPT register. Women iddir members extracted the information from the register using a paper based data abstraction tool and submitted the data to community mobilizers on a weekly basis. The community mobilizers, after quality check, entered the data in an excel form and submitted to the central coordinator on a monthly basis.
- ✓ We updated the description of the data sources/procedures in the revised manuscript (204-227).

(8) The statement "Since the DID analysis for the U15C data was based on aggregate data, no statistical significance was tested" (lines 230-231) is not a valid justification for a lack of statistical testing. Statistical testing of a difference of differences can be done on aggregate data (e.g. a Poisson regression with count data aggregated at the level of health facilities with dummy variables representing pre/post period and +/- intervention, which can often be done using surveillance data). Ideally the authors would do this, but I am not trying to require that the authors

add a statistical assessment to their report if it is not feasible or appropriate. However, if the authors wish to justify the lack of statistical testing, the reason should be scientifically valid.

✓ We agree with the reviewer that statistical tests can be performed on aggregate data. However, we wanted to keep our focus on percentage changes and visual displays as our main measure of improvement since controlling for some important constants was not feasible in our data.

(9) In the tables that show the difference of differences, please include the % change, which is currently just alluded to in the text. For instance, the sentence at lines 262-265 "the improvement in the intervention sub-city in Addis Ababa was lower than that of the comparator sub-city" is only understandable if the reader manually calculates the % change for the two (78/156 = 50% increase in the intervention sub-city, while 55/43 = 128% increase in the comparator sub-city).

✓ This is well noted and added. Since some of the calculations in Table 2 (eg, proportion eligible) are linked to numbers in Table 1, we merged the two tables into one to make comparisons easier.

(10) A confounding reason for seeing an increase in the numbers of contacts screened or put on TPT would be an increase in the number of TB index patients, which could happen for various reasons (e.g. migration in/out of particular areas, improved case-finding, introduction of better diagnostic technologies). Presenting the total numbers of TB cases in the intervention and control areas during the intervention and pre-intervention periods would be a simple way to show that whether this was the case. I noticed that one of the reviewers of the original version of the manuscript also raised this issue, but the authors replied that this information was not available. How is it possible that they have surveillance data on numbers of contacts from the DHIS but not total numbers of TB patients?

✓ We thank the reviewer for this feedback. We may have misunderstood the comment given during the first round of review. Indeed, surveillance data was available but there was an overall decline in the number of reported TB cases in both in the intervention and control zones. This finding though is contrary to our expectation because we were hoping that the intervention would have an added value in improving overall case detection.

(11) In the paragraph discussing why the intervention failed to increase the number of child contacts enrolled in the urban versus the rural site, I do not understand the logic leading to the concluding sentence, ("however, once eligible children are enrolled, their chances of initiation were higher in Addis Ababa, which clearly shows the impact of the Iddirs intervention"), and I think it may be a misleading interpretation of the results. First, from the description of the intervention, the Iddir members' main roles were to refer the child for evaluation (which should increase enrollment in care) and promote adherence to treatment once; it is not clear how the Iddirs were supposed to improve initiation of treatment, so it is not clear to me how this shows the impact of the Iddirs. Second, while it is true that a greater percentage of eligible children initiated TPT in the intervention sub-city of Addis, the intervention sub-city started out with nearly twice the TPT initiation rate than the control sub-city, and comparing fold-increase over baseline, the increase was in fact higher in the control sub-city (the control area increased from 13.9% to 59.2%, or a 4.3-fold increase, while the intervention area increased from 21.1% to 77.3%, or a 3.7-fold increase).

✓ We thank the reviewer for this important point. As responded to comment #2, the iddir intervention was not an isolated intervention limited to increasing enrolment of eligible children. However, as noted by the reviewer, the relative increase in the number and proportion initiated on TPT is higher in the control zone in Addis Ababa. Although the smaller number of children in the control zone can be a factor in the higher percentage changes post-intervention, we agree with the reviewer that our comment was not in line with the data. Therefore, we deleted the sentence (lines 386-387).

(12) The authors should discuss the impact of the guideline change, which coincided with their study start date. The fact that TPT eligibility was expanded presumably led to numerous changes in recommendations or practices, from prioritizing which contacts are evaluated to changing the way that registers are filled out or indicators are reported. I am not disputing the conclusion that the intervention had an impact, but it is important to discuss the effect of this major driver of secular change (which was presumably responsible for the substantial increase in TPT initiations in the control area) and/or its potential interaction with the intervention.

✓ We thank the reviewer for this good observation. We added this to the limitation section in conjunction with our response to comments #6 and #13 (lines 382-393).

(13) In the limitations, the authors should discuss whether the support provided to the intervention health facilities for filling out the registers and data reported is likely to have biased results toward showing improved TPT initiations simply because the data were being recorded and reported properly. The limitations right now acknowledge the general limitation that because the intervention was multifaceted, the impact cannot be solely attributed to the involvement of the Iddirs. However, I think that the specific example of recording/reporting strengthening should be discussed because it is possible that better recording/reporting could lead to an apparent increase in children being screened or in children initiating TPT where no real increase existed (that is, if the programs were doing these activities all along, but they just were not recording/reporting it). This is particularly important in the context of changing national indicators, which the authors allude to at lines 336-337. Control areas might have under-reported TPT in older child contacts since they would not be used to this reporting and did not have the benefit of support from the intervention. If the authors have any additional insight into the potential magnitude of the effect of information bias (including reasons why they think it might not have made a difference to their conclusions), this should be discussed.

✓ We thank the reviewer for this helpful suggestion. Better recording and reporting is part of the intervention and it can lead both to real and apparent increase- as recorded clients are regularly monitored. Moreover, since Iddir women recorded and reported only the U5C, its impact on U15C enrolment is unlikely to be significant. We also think that potential improvement in the recording and reporting of U15C in all zones due to change in guidelines may have had a counterbalancing effect. Since this is an important point, we expanded the limitation section to accommodate these arguments (lines 382-393).

(14) Normally having authors who are employees of the funding agency is declared as a competing interest since the funder generally has an interest in presenting results a certain way. (I make this as a general comment – I think TB REACH is great, and there is absolutely no problem with Stop TB Partnership staff being co-authors). I defer to the journal whether it wishes this to be declared.

✓ We added a disclaimer that "*The contents of the article are the responsibility of the authors alone and do not necessarily reflect the views of donors or employers of the authors*"in the acknowledgement section.

Minor comments:

The manuscript is highly readable but should undergo copy editing for grammar and missing words. Below are some corrections that I noticed, but I have not read through carefully to check the grammar.

Throughout, I think the phrase "women-only Iddirs" should contain a hyphen if it refers to Iddirs whose membership is limited to women. The authors might consider making this usage consistent in the title and abstract as well.

✓ We made the corrections as suggested by the reviewer.

Line 121: The word “a” is missing before “map” in “Figure 1 shows map…”

✓ Noted and corrected

Line 144: The word “is” is missing before “rarely practiced” in “Active search or contact investigation for eligible child contacts rarely practiced”

✓ Noted and corrected

Reviewer: 2
Martina Casenghi

Comments to the Author:
The authors should be commended for the work done on improving the manuscript and clarifying several important aspects.

✓ We thank the reviewer for the compliment.

There are still some minor issues that need to be addressed
Please see my comments below

Major Comments

1) Line 214-219:The explanation of the different data sources has greatly improved but it still requires some improvement. Authors should explain in more details which key patient level indicators where collected in the Microsoft excel-based database (i.e nr of child contacts identified, nr of child contacts screened, nr of child contacts identified as eligible for TPT etc). The authors only mention that this database collected data on children below 5 years. In addition, the authors should specify if what was extracted from registers were aggregated data, or single patient -level data, allowing to follow longitudinally through the cascade of care every single patient. Finally the authors should explain which analysis in the manuscript are based on the use of the data collected through the Microsoft excel based database.

✓ We thank the reviewer for this comment. We expanded the description of the data sources and variables as advised (lines 204-227).

2)Tables and figures- there is no statistical analysis performed for the differences observed. I do not have expertise in Statistics therefore I do not have the competencies to comment on this. However I wonder if a reviewer with those set of expertise should be involved and advise whether or not statistical analysis is needed.

✓ We have analytic capacity within our team, but we deferred statistical tests because it was not feasible control for some important variables.

Minor comments:

1) Line 87_ “…led to improvements in TB childhood TB case-finding” TB mentioned twice. Remove the repetition

✓ Corrected.

2) Line 88-89 “…through community health workers childhood TB case detection” -it looks like a word is missing. The meaning of this sentence is not clear

✓ Error corrected

3) Line 109:---" Similarly, engaging saving groups has been groups has been beneficial" repetition of the word "groups"

✓ corrected

4) Line 144: "….investigation for eligible child contacts rarely practiced at community level despite its being recommended to be part of the package for HEWs". English check needed ("is rarely practiced" : add "is"despite ist being…; change into "despite this being")

✓ Corrected

5) Line 230: please check consistency in writing the abbreviation of difference-in-difference (sometimes DiD is used, other times DID)

✓ We checked this, and used DiD consistently.

6) Line 2020-2023: are those the only indicators that were collected ? or do they represent the indicators that were selected for the analysis?

✓ These are the indicators we selected for this particular analysis.

7) Line 255: at the beginning of the paragraph, please state again the data source for this analysis. Is this analysis based on the use of the DHS2 data. Based on the response provided to comments, I understand this is the case and should be stated in the paragraph as well.

✓ We updated the description of the data sources based on this and other comments given provided earlier.

8) Table 1 and Table 2 : since the analysis performed have used different definition of pre-intervention period depending on database used, please specify the period considered as "before" and as "after" in the table to ease understanding and interpretation of results (i.e before=July 2019-June 2020?)

✓ Tables 1 & 2 in fact used the same data source. Since the analyses in the two tables are interrelated, we merged the two tables into one. As suggested by the reviewer, we indicated the before/after period in a legend (as the period is repeated in several places).

9) Line 371 and 374: "number of eligible children enrolled"- did you mean "identified" or enrolled in the study? The word "enrolled" generate confusion as it is often used to indicate enrollment into treatment. Please clarify

✓ We meant number enrolled as being eligible for treatment, but not necessarily initiated on treatment.

VERSION 2 – REVIEW

REVIEWER	Yuen, Courtney Brigham and Women's Hospital
REVIEW RETURNED	04-Apr-2022

GENERAL COMMENTS	Thank you to the authors for their work revising this manuscript. The data sources section in particular is much clearer. Many of my comments have been addressed, but not all. The ones that I feel have been inadequately addressed are described below. Major (1) Both the other reviewer and I have raised the issue of the absence of statistical testing for the difference in differences. The authors initially justified the lack of statistical testing in a way that was not scientifically valid; in the revision, they have removed that sentence and give no justification for the lack of statistical analysis. Based on the authors' responses to myself and the other reviewer, it seems that this was the authors' choice as opposed to a limitation in their data or the expertise of their team. I find this explanation unsatisfying, and I want to state that it is a scientific weakness of the manuscript. However, I recognize that not all published papers of this type of have included statistical testing for pre/post differences, and I do not want to prevent the publication of a programmatically useful report by holding it up to a higher standard than similar publications in the past. I leave it up to the editor whether they feel that the issue has been adequately addressed. (2) I am still not understanding what component of the intervention is supposed to have affected the proportion of identified children who initiated TPT. The response to reviewers refers to a description of "supportive supervision" in lines 203-206, but this is a description of data sources. To me, the "active outreach" intervention described in lines 174-184 is aimed at getting children into care – that is, the first step of the cascade. I can easily see how active outreach and giving referral slips would increase the number of children who enter care, which is seen overall in Table 1. The next paragraph then starts (line 185), "Once a child started TPT…" and then describes the adherence support. This clearly would impact completion. But what is missing is a description of the component of the intervention aimed at the prescribing/uptake step of the cascade, which would affect initiation. The paragraph on strengthening data collection, monitoring and evaluation (lines 195-202) describes support to improve filling out of the registers, but while this might improve documentation of initiation, it would not improve initiation itself. (3) Regarding the reporting of outcomes, where "Eligible" and "Initiated" are defined at lines 229-231, "Completion" should also be defined since this is the final step of the cascade and one of the outcomes. How many doses comprised completion, and how was this ascertained? (4) I raised a concern that the TPT eligibility criteria changed between the pre-intervention and intervention periods, but the authors responded that "the pre-intervention period for U15C falls within the time frame when the eligibility criteria was expanded to include all children under 15 years of age." This is not consistent with what is reported in the manuscript. At lines 147-148, it says "Only U5C contacts and people living with HIV were eligible for TPT until the guideline changed in July 2020 to include children below 15 years of age." At lines 208-209 and the table, it says "two time periods: July 2019-June 2020 as pre-intervention and July 2020-June 2021 as post intervention." The discussion (lines 336-338) then says "The expanded age group was nationally approved

	only after the project was launched." It thus appears clear that the guideline changed *between* the two periods. I appreciate that the authors have added the % of children under 5 among contacts among "eligible" children in the two periods, and they have successfully argued in the discussion that the overall increase in "eligible" children not simply due to many older children were coming into care following the guideline change. However, my concern is that those older children in the pre-intervention period were not actually eligible for TPT per national guidelines (hence my confusion about the term eligible). Therefore, one would expect the difference in initiation to be affected by the guideline change. In the text, can the authors age-stratify the initiation result as they have the eligibility result? This could help quantify the potential effect (or lack thereof) of the guideline change. (5) The authors' response to the question about whether the number of index patients changed between the two periods is well noted, and I think that the argument made in the response document would greatly strengthen the paper. The authors could consider adding a sentence to the results or discussion saying that the number of index patients decreased in both intervention and control periods, so the increase in the number of eligible contacts is not simply due to a greater number of patients. Minor: The corrected sentence about inclusion in the abstract still seems to be missing a word. I think the sentence "Child contacts in whom active TB and contraindications to TPT regimens excluded were considered eligible for TPT" is missing the word "were" before the word "excluded."

REVIEWER	Casenghi, Martina Elizabeth Glaser Pediatric AIDS Foundation
REVIEW RETURNED	14-Apr-2022

GENERAL COMMENTS	Comments to the authors: While I continue commending the authors for the work done on the manuscript, there are still aspects that need to be addressed 1. Add a statement in the paragraph that clearly explains why statistical analysis could not be performed 2. Check consistency of language throughout the methods and results section. Eligible enrolled is often used in the manuscript but no definition has been included in the Methods. The methods only provide a definition for eligible children as one of the indicator collected. Authors should include the definition of "eligible enrolled" or just use eligible consistently with the definition provided in the Methods. Similarly, children treated or initiated on TB preventive treatment is used interchangeably but those 2 terms have different meanings and this generates confusion. Based on explanations provided in the Methods, treatment outcomes were only recorded and analysied for the Under 5. Therefore, for clarity, the reporting of results for the Under 15 should consistently refer to TPT treatment initiation 3. Line 357 of the pdf with track-changes: "Despite clear and much greater improvements in TPT initiation rates between intervention and control zones, the 71.3% TPT initiation rate among children below 15 years of age ….". I can't find in the table 1 the data

	relative to the 71.3%. The table has been extensively revised. Maybe the text needs to be revised accordingly? 4. Line 411-415 in the Discussion section. The new paragraph added is not very clear to me. The major confounding that should be discussed here is that the introduction of the new recommendations expanding the target population eligible for TPT to all children < 15 years might have influenced the impact seen. Therefore it is difficult to say if the increase is due to the Iddir women intervention or to the new recommendations. Based on information provided, the new recommendations were enforced in July 2020, therefore at the beginning of the intervention phase. Therefore the data on U 15 reported in Table 1 might have been influenced by this as the total number of U 15 identified as eligible and initiated on TPT might have increased because of the expansion of the TPT target population. In this paragraph, authors emphasized that the main confounding maybe due to the improved recording and reporting process that was brought in as a consequence of the new recommendations but the reasons for this are not well explained. In additions, the control zone data here have a critical role to mitigate this confounding related to change in recommendations and can help identifying the true effect linked to the intervention . However only the data for SNNPR region are supportive. In Addis Abeba the percentage increase across all the indicators analysed was greater in the control zone rather than in the intervention zone, suggesting that the increase seen in this region is probably not due to the intervention but rather the consequence of a number of contributing factors, including the new guidelines ? The authors need to revise this paragraph a more accurately discuss the results

VERSION 2 – AUTHOR RESPONSE

✓ *Reviewer Reports:*

Reviewer: 1
Dr. Courtney Yuen, Brigham and Women's Hospital, Harvard Medical School

Comments to the Author:
Thank you to the authors for their work revising this manuscript. The data sources section in particular is much clearer. Many of my comments have been addressed, but not all. The ones that I feel have been inadequately addressed are described below.

Major
(1) Both the other reviewer and I have raised the issue of the absence of statistical testing for the difference in differences. The authors initially justified the lack of statistical testing in a way that was not scientifically valid; in the revision, they have removed that sentence and give no justification for the lack of statistical analysis. Based on the authors' responses to myself and the other reviewer, it seems that this was the authors' choice as opposed to a limitation in their data or the expertise of their team. I find this explanation unsatisfying, and I want to state that it is a scientific weakness of the manuscript. However, I recognize that not all published papers of this type of have included statistical testing for pre/post differences, and I do not want to prevent the publication of a programmatically useful report by holding it up to a higher standard than similar publications in the past. I leave it up to the editor whether they feel that the issue has been adequately addressed.

✓ **We thank the reviewers for encouraging us to perform statistical tests.**
We performed Poisson regression analysis in SPSS using count data for eligible and initiated children as dependent variables, and Iddir interventions and period as independent factors. The output shows the positive impact of the interventions, and the difference was statistically

significant at p<0.001. We included description of the statistical analysis and its results in the methods and results sections respectively. A new table is added to present this important addition.

(2) I am still not understanding what component of the intervention is supposed to have affected the proportion of identified children who initiated TPT. The response to reviewers refers to a description of "supportive supervision" in lines 203-206, but this is a description of data sources. To me, the "active outreach" intervention described in lines 174-184 is aimed at getting children into care – that is, the first step of the cascade. I can easily see how active outreach and giving referral slips would increase the number of children who enter care, which is seen overall in Table 1. The next paragraph then starts (line 185), "Once a child started TPT…" and then describes the adherence support. This clearly would impact completion. But what is missing is a description of the component of the intervention aimed at the prescribing/uptake step of the cascade, which would affect initiation. The paragraph on strengthening data collection, monitoring and evaluation (lines 195-202) describes support to improve filling out of the registers, but while this might improve documentation of initiation, it would not improve initiation itself.

- ✓ **We thank the reviewer for this important comment.**

We added the following description to the paragraph under the active outreach support (lines 186-189):

The volunteers then cross-checked clinic registers for linkage and initiation of all referred eligible children. The volunteers and clinic TB focal persons made frequent face to face and phone contacts to ensure no eligible child is left unattended. The district and zonal TB officers emphasized linkage and TPT initiation during their quarterly mentoring and supervision meetings.

We also noted under the discussion section (lines 394-397) the difficulty of making specific causal attribution to any particular sub-component of the interventions due to the interrelated nature of the interventions.

(3) Regarding the reporting of outcomes, where "Eligible" and "Initiated" are defined at lines 229-231, "Completion" should also be defined since this is the final step of the cascade and one of the outcomes. How many doses comprised completion, and how was this ascertained?

- ✓ **We thank the reviewer for this feedback. Completion was defined and ascertained according to the national guidelines, as follows (lines 244-249):**
- ***<u>Completed</u>: successful completion was defined as 80% of the recommended doses taken within 120% of planned TPT duration, or 90% of recommended doses used within 133% of planned TPT duration according to the national guideline. The number of recommended doses were 12 for 3HP; 84 for 3HR; and 168 for 6H. Completion status was ascertained by the community volunteers based on their weekly treatment follow-up records cross-checked with the clinic TPT register.***

(4) *I raised a concern that the TPT eligibility criteria changed between the pre-intervention and intervention periods, but the authors responded that "the pre-intervention period for U15C falls within the time frame when the eligibility criteria was expanded to include all children under 15 years of age." This is not consistent with what is reported in the manuscript. At lines 147-148, it says "Only U5C contacts and people living with HIV were eligible for TPT until the guideline changed in July 2020 to include children below 15 years of age."*

*At lines 208-209 and the table, it says "two time periods: July 2019-June 2020 as pre-intervention and July 2020-June 2021 as post intervention." The discussion (lines 336-338) then says "The expanded age group was nationally approved only after the project was launched." It thus appears clear that the guideline changed *between* the two periods.*

I appreciate that the authors have added the % of children under 5 among contacts among "eligible" children in the two periods, and they have successfully argued in the discussion that the overall increase in "eligible" children not simply due to many older children were coming into care following the guideline change. However, my concern is that those older children in the pre-intervention period were not actually eligible for TPT per national guidelines (hence my confusion about the term eligible). Therefore, one would expect the difference in initiation to be affected by the guideline change. In the text, can the authors age-stratify the initiation result as they have the eligibility result? This could help quantify the potential effect (or lack thereof) of the guideline change.

- ✓ **We thank the reviewer for this important comment.**
- ✓ **Here is our response to the concerns raised in this comment:**

(1) There was typo in the sentence at lines 147-148, the guidelines changed in July 2019 not in 2020. We corrected the typo. The draft guidelines were already circulated as an addendum to the main national TB/HIV guidelines. We uploaded the draft addendum as a supplementary material.

(2) We have age-stratified the initiation data, and added the following:

***Despite increments in the number of eligible children aged 5-14 years from 194 to 540 in the intervention zones, the TPT initiation rate for this age group declined from 31.9% (62/194) at baseline to 7.4% (40/540*) post-intervention. (lines 291-293)**

***Similarly, taking July 2019-June 2020 as a common baseline for intervention zones, U5C constituted only 33% of those initiated TPT at baseline (30 out of 92), but increased to 96% (937 out of 977) post-intervention*. (lines 304-307)**

(3) We also merged the subheadings for the U15C and U5C to ensure seamless description of the results for the two age groups.

(4) In sum, there is no evidence in favour of guideline changes affecting TPT initiation rates.

(5) *The authors' response to the question about whether the number of index patients changed between the two periods is well noted, and I think that the argument made in the response document would greatly strengthen the paper. The authors could consider adding a sentence to the results or discussion saying that the number of index patients decreased in both intervention and control periods, so the increase in the number of eligible contacts is not simply due to a greater number of patients.*

- ✓ **We thank the reviewer for this helpful suggestion. We added a short paragraph about the trends in index case notification as follows (lines 283-287):**

<u>Trends in the number of index TB patients notified</u>

The number of all forms of TB cases notified declined both in the intervention and control zones. There was an 11.8% decline in the intervention zones, from 2021at baseline to 1783 post-intervention. The decline in the control zones was less dramatic (2.3%)—from 2589 at baseline to 2529 post-intervention.

✓

Minor:
The corrected sentence about inclusion in the abstract still seems to be missing a word. I think the sentence "Child contacts in whom active TB and contraindications to TPT regimens excluded were considered eligible for TPT" is missing the word "were" before the word "excluded."

This is noted and the missing word is added.

Reviewer: 2
Martina Casenghi

Comments to the Author:
While I continue commending the authors for the work done on the manuscript, there are still aspects that need to be addressed

1. Add a statement in the paragraph that clearly explains why statistical analysis could not be performed

✓ **Statistical analysis is performed as per the suggestion by the editor and both reviewers.**

2. *Check consistency of language throughout the methods and results section. Eligible enrolled is often used in the manuscript but no definition has been included in the Methods. The methods only provide a definition for eligible children as one of the indicator collected. Authors should include the definition of "eligible enrolled" or just use eligible consistently with the definition provided in the Methods. Similarly, children treated or initiated on TB preventive treatment is used interchangeably but those 2 terms have different meanings and this generates confusion. Based on explanations provided in the Methods, treatment outcomes were only recorded and analysied for the Under 5. Therefore, for clarity, the reporting of results for the Under 15 should consistently refer to TPT treatment initiation*

✓ **We thank the reviewer for the important feedback. In our description, "eligible children enrolled" is equivalent to eligible'. 'We corrected confusing wordings. We also used initiated and treated interchangeably with the understanding that all initiated children are treated irrespective of the final status. As advised, we will limit the use of "treated" for the U5C**.

3. *Line 357 of the pdf with track-changes: "Despite clear and much greater improvements in TPT initiation rates between intervention and control zones, the 71.3% TPT initiation rate among children below 15 years of age ….". I can't find in the table 1 the data relative to the 71.3%. The table has been extensively revised. Maybe the text needs to be revised accordingly?*

✓ **We thank the reviewer for this comment. There was typo in this sentence. We replaced 71.3% with 63.05% as shown in Table 1.**

4. *Line 411-415 in the Discussion section. The new paragraph added is not very clear to me. The major confounding that should be discussed here is that the introduction of the new recommendations expanding the target population eligible for TPT to all children < 15 years might have influenced the impact seen. Therefore it is difficult to say if the increase is due to the Iddir women intervention or to the new recommendations. Based on information provided, the new recommendations were enforced in July 2020, therefore at the beginning of the intervention phase. Therefore the data on U 15 reported in Table 1 might have been influenced by this as the total number of U 15 identified as eligible and initiated on TPT might have increased because of the expansion of the TPT target population. In this paragraph, authors emphasized that the main confounding maybe due to the improved recording and reporting process that was brought in as a consequence of the new recommendations but the reasons for this are not well explained. In additions, the control zone data here have a critical role to mitigate this confounding related to change in recommendations and can help identifying the true effect linked to the intervention . However only the data for SNNPR region are supportive. In Addis Abeba the percentage increase across all the indicators analysed was greater in the control zone rather than in the intervention zone, suggesting that the increase seen in this region is probably not due to the intervention but rather the consequence of a number of contributing factors, including the new guidelines ? The authors need to revise this paragraph a more accurately discuss the results*

✓ **We thank the reviewer for this valid observation. We addressed this comment when responding to comment #4 of reviewer 1.**

Reviewer: 1
Competing interests of Reviewer: I have no competing interests

Reviewer: 2
Competing interests of Reviewer: I am currently serving as the Technical Director of a multicountry project focused on pediatric TB which also includes contact investigation interventions and operational studies

VERSION 3 – REVIEW

REVIEWER	Yuen, Courtney Brigham and Women's Hospital
REVIEW RETURNED	20-Jun-2022

GENERAL COMMENTS	Thank you to the authors for their work in this revision. All of my comments have been addressed, and I just have a few suggestions for minor edits. - In the statistical methods, please make clear whether each predictor (time period, region, intervention) was assessed in a separate regression model, or whether the regression model included all the predictors at once. This is necessary to understand whether the effect estimates in Table 2 represent bivariate or adjusted associations Also include region in the list of predictors since it is reported in Table 2. - Thank you for the clarification that the guidelines changed in 2019, prior to the analysis period, as opposed to in 2020. However, the discussion still says: “The expanded age group was nationally approved only after the project was launched and hence it took some time until all sites came on board” (lines 402-403). This statement is presumably now inaccurate and should be removed. - Now that the statistical analysis has been added, the limitation of not having one should be removed. (“As the temporal relationship between the intervention and the outcomes show visible impact of the combination of interventions, it is highly probable that the Iddir intervention made a clear difference as visual evidence is a valid way of making inferences in DiD analysis” (Lines 457-460)).

REVIEWER	Casenghi, Martina Elizabeth Glaser Pediatric AIDS Foundation
REVIEW RETURNED	30-Jun-2022

GENERAL COMMENTS	The authors have adequately addressed and clarified the comments raised during my last review Note for the Editor: this reviewer does not have the required statistical expertise to assess the new Table 2 added to this version

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Dr. Courtney Yuen, Brigham and Women's Hospital, Harvard Medical School

Comments to the Author:
Thank you to the authors for their work in this revision. All of my comments have been addressed, and I just have a few suggestions for minor edits.

We thank the reviewer for the thorough reviews and comments which helped us to enhance the quality of the paper. Below is our point by point response to the minor comments raised:

- In the statistical methods, please make clear whether each predictor (time period, region, intervention) was assessed in a separate regression model, or whether the regression model included all the predictors at once. This is necessary to understand whether the effect estimates in Table 2 represent bivariate or adjusted associations Also include region in the list of predictors since it is reported in Table 2.

Response: It was and adjusted analysis. We added the word “adjusted” in the title of Table 2. We also added region among predictor variables (line 265).

- Thank you for the clarification that the guidelines changed in 2019, prior to the analysis period, as opposed to in 2020. However, the discussion still says: “The expanded age group was nationally approved only after the project was launched and hence it took some time until all sites came on board” (lines 402-403). This statement is presumably now inaccurate and should be removed.

Response: We thank the reviewer for this comment. The sentence is now removed.

- Now that the statistical analysis has been added, the limitation of not having one should be removed. (“As the temporal relationship between the intervention and the outcomes show visible impact of the combination of interventions, it is highly probable that the Iddir intervention made a clear difference as visual evidence is a valid way of making inferences in DiD analysis” (Lines 457-460)).

Response: Thank this valid comment. We agree with the reviewer that much of the sentence does not make sense. Since part of the sentence is still correct (that the visual evidence supports impact), however, we amended the sentence as follows:

It is also highly probable that the Iddir intervention made a clear difference as visual evidence shown in the graphs is a valid way of making inferences in DiD analysis, [35] which is further confirmed by the statistical tests.