PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Cost-effectiveness of GeneXpert Omni compared with GeneXpert MTB/RIF for point-of-care diagnosis of tuberculosis in a low-resource, high-burden setting in Eastern Uganda: a cost-effectiveness analysis based on decision analytical modelling |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Ejalu, David; Irioko, Aaron; Kirabo, Rhoda; Mukose, Aggrey; Ekirapa, Elizabeth; Kagaayi, Joseph; Namutundu, Juliana |

VERSION 1 – REVIEW

| REVIEWER             | Teixeira de Siqueira-Filha, Noemia                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------|
| REVIEW RETURNED      | 15-Mar-2022                                                                                        |
| GENERAL COMMENTS     | This study aims to determine the cost-effectiveness of Xpert Omni compared to Xpert MTB/RIF for point-of-care diagnosis of TB among presumptive cases in Uganda. The study is timely, particularly in a high TB burden scenario, given the End TB strategy goal to reduce catastrophic costs and reduce TB incidence. My main comments to the authors are around areas where I think the manuscript could be improved: |

Abstract

• Participants: I believe the study participants are TB patients (drug-sensitive or resistant TB?) rather than experts in the field of tuberculosis diagnosis.
• Primary and secondary outcomes: the study is a cost-effectiveness analysis so should the primary outcome for the CEA be ICER per additional case detected rather than the cost of the interventions?
• Conclusions: Why the transportation costs would be reduced by using Xpert Omni? Is there any difference in the way the samples are transported using one strategy or another? Please, clarify.

Strengths and limitations

• The first item is not a strength or limitation of the study. It is the main result of the CEA.
• The fourth item may be a limitation, particularly because the results do not contribute to the WHO End TB strategy goal to reduce catastrophic costs for TB patients. However, choose not to include the broader societal perspective does not affect the estimates.

Introduction

• The authors give a good background about the Gene Xpert tests but I missed information on the epidemiological scenario of TB in Uganda (incidence, missed cases). This information also justifies the development of cost-effectiveness analysis in the country.
• Is there any other cost-effectiveness analysis comparing these two technologies in similar settings? If so, it would be important to include it in this section.

Methods
• Study design: I could not understand why health workers and support staff officials are considered "providers" in the study perspective. Do they pay for the implementation of TB diagnosis technologies in Uganda? I agree that they should be included in the cost analysis, but the provider perspective means those who are paying for implementing the technology, that is Ministry of Health or NGOs or hospitals or laboratories.
• Why did the authors use as a reference case adult male HIV-positive? Please justify this choice.

Costing inputs
• Is there any sample transportation costs for GeneXpert Omni? I understand the device is portable and can reach the patients’ location, but this strategy exempts the patient to incur this type of cost, not the health system that still needs to find a way to take the device until the patients’ location, which I understand are mostly in remote areas.

Costing approach
Please, add a reference for the statement “The useful life span of both the Xpert MTB/Rif and Xpert Omni was taken to be five years”, I have seen other studies considering 10 years rather than five.

Valuation of inputs
• The study adopted a 1-month time horizon but states that future costs were discounted at 3% per year. Are the author referring to the costs collected at different time points? If so, why those costs were not adjusted according to inflation rates reported annually by the International Monetary Fund?
• Please, clarify the calculation of cost per test for the GeneXpert machine. Have you included depreciation of the equipment by using an annualization factor to calculate these costs?

Results
• The section "effectiveness outcomes measure" should be in the methods section as the authors applied these parameters to build the model. These are not the results of the study.
• What is the cost-effectiveness outcome? ICER per number of correctly diagnosed TB patients or additional TB cases diagnosed? Please, include this information in the methods section.

Effectiveness and Cost-effectiveness of interventions
• What do you mean by “average cost-effectiveness ratio”? I understand that this is the mean cost of each intervention.

Discussion
• I suggest starting the discussion by giving the headline findings, which is not the costing result. This is a CEA so the discussion should be based on this outcome. Another recommendation is to concentrate the narrative on the implications of findings for policy and research—as well as how this relates to previous findings.
• Is there any reference for this statement “TB diagnosis in patients who harbour lesser quantities of the bacilli such as children, HIV positive cases, and among sputum smear-negative presumptive cases. This would, in turn, reduce early morbidity”?
• The authors did not include time to treatment initiation and loss of follow-up in the model nor include any information on the results section about these two variables. So I don’t think this statement should be part of the discussion section: “The median time to
treatment initiation was 1 day for Xpert at POC and 14 days for Xpert by referral. The likelihood of loss to follow-up was four-fold among the patients whose samples were referred to the GeneXpert laboratory compared to when the Xpert was at the point of care.”

- I do not agree that the use of GeneXpert Omni would eliminate the use of ZN microscopy, particularly in resource constraint settings where this test is still important. Could you please elaborate more on this?

Minors:
Introduction, line 51: standard of care or point of care? Same statement throughout the text.
Methods, lines 33 and 37, pg 5: please include references on cost data provided by the literature.
Methods, line 47, pg 5: sample transport costs mentioned twice.
Methods, lines 27-28, pg 8: please include references in the statement "Analysis was performed from the model by adjusting the model parameters of Xpert MTB/Rif and Xpert Omni tests based on the minimum and maximum values from Published literature".
Methods, lines 29-30, pg 8: please include references in this statement "TB prevalence corresponding to the national estimates as at the time of the study obtained from reports and systematic reviews were used in the analysis."
Results, lines 37-41, pg 9: please include references in the statement "Estimates for sensitivities and specificities of the tests were obtained from pooled values from the systematic reviews and clinical trials that took mycobacterial culture as a reference standard."

REVIEWER
Chang, Lingqian
Beihang University
REVIEW RETURNED
30-Mar-2022

GENERAL COMMENTS
This work compared the cost-effectiveness of GeneXpert Omni and GeneXpert MTB/RIF in various aspects, including transportation cost, reagents, and cost of a single test, with the aim of providing recommendations for TB detection in a low-resource high burden facility. The manuscript is well written with appropriate in-depth discussion. It is recommended for publication with minor revision with some specific points detailed below.
1. How does Xpert MTB/Rif reduce TB morbidity and mortality as a detection device rather than a treatment?
2. Portable and rapid nucleic acid detection chips or devices have also been reported (Biosensors & Bioelectronics. 2022, 195; Research. 2021, 2813643). These technologies are also cheap, portable and fast, and what makes Xpert unique compared to these technologies? Please add a discussion of this section.
3. You mentioned here that “Xpert MTB/Rif has inadequate capacity in lower facilities due to the complexity of its technology and high costs”. Apart from being user-friendly, what special advantages does GeneXpert Omni have that make it acceptable in remote areas, since its price has not been reduced much? How user-friendly it is?
4. In “Description of study alternatives”, there is no specific description of the reagents or instrument units required to run Xpert MTB/Rif and Xpert Omni.
5. How do the performance of the two instruments affect the cost? Including its integration, detection time, throughput, detection limit, sample pretreatment technique, and sample type.

6. Cepheid has some subsidy policies for remote areas. For the two instruments, has the subsidy intensity been calculated in this paper?

**VERSION 1 – AUTHOR RESPONSE**

| Reviewer: 1 |  |
| --- | --- |
| **Abstract**  |
| • Participants: | • I believe the study participants are TB patients (drug-sensitive or resistant TB?) rather than experts in the field of tuberculosis diagnosis. |
| | An explanation has been provide: *Since the TB testing services are offered for free in Uganda. The study considered the providers perspective, and therefore the costs incurred when offering the services were collected from the TB experts rather than patients.* |
| **Abstract**  |
| • Primary and secondary outcomes: | • the study is a cost-effectiveness analysis so should the primary outcome for the CEA be ICER per additional case detected rather than the cost of the interventions? |
| | This is true, the statement has been corrected. |
| **Abstract**  |
| • Conclusion | Why the transportation costs would be reduced by using Xpert Omni? Is there any difference in the way the samples are transported using one strategy or another? Please, clarify. |
| | The use of Xpert Omni has the potential to remove transportation costs to the centralized hub since it shall be provided at point of care as opposed to ferrying samples to the centralised testing center in the case of Xpert MTB/Rif. |
| **Strengths and limitations**  |
| | • The first item is not a strength or limitation of the study. It is the main result of the CEA. |
| | This item has been removed. |
| | • The fourth item may be a limitation, particularly because the results do not contribute to the WHO End TB strategy goal to reduce catastrophic costs for TB patients. |
| | Suggestion accepted |
| **Introduction**  |
| | I missed information on the epidemiological scenario of TB in Uganda (incidence, missed cases). |
| | An introductory paragraph addressing this has been provided. |
| Methods | • Study design |
|---------|----------------|
|         | • I could not understand why health workers and support staff officials are considered “providers” in the study perspective. Do they pay for the implementation of TB diagnosis technologies in Uganda? I agree that they should be included in the cost analysis, but the provider perspective means those who are paying for implementing the technology, that is Ministry of Health or NGOs or hospitals or laboratories. |
|         | • Why did the authors use as a reference case adult male HIV-positive? Please justify this choice. |

| • Costing inputs | • Is there any sample transportation costs for GeneXpert Omni? I understand the device is portable and can reach the patients’ location, but this strategy exempts the patient to incur this type of cost, not the health system that still needs to find a way to take the device until the patients’ location, which I understand are mostly in remote areas. |
|                  | Thank you for this comment. However, the GeneXpert Omni testing shall be done at point of care at the health facilities. This strategy exempts the providers from transporting sputum samples from peripheral health facilities to the hub where the GeneXpert MTB/Rif is located. |

| • Costing approach | Please, add a reference for the statement “The useful life span of both the Xpert MTB/Rif and Xpert Omni was taken to be five years”, I have seen other studies considering 10 years rather than five. |
|                   | Reference provided |

| Valuation of inputs | • The study adopted a 1-month time horizon but states that future costs were discounted at 3% per year. Are the author referring to the costs collected at different time points? If so, why those costs were not adjusted according to inflation rates reported annually by the International Monetary Fund? Please, clarify the calculation of cost per test for the GeneXpert machine. Have you included depreciation of the |
|                    | This a normally has been clarified |
equipment by using an annualization factor to calculate these costs?

**Results**

- The section “effectiveness outcomes measure” should be in the methods section as the authors applied these parameters to build the model. These are not the results of the study.

  This section has been shifted to the methods.

- What is the cost-effectiveness outcome? ICER per number of correctly diagnosed TB patients or additional TB cases diagnosed? Please, include this information in the methods section.

  This section has been included in the methods section.

- What do you mean by “average cost-effectiveness ratio”? I understand that this is the mean cost of each intervention.

  average cost-effectiveness ratio is the ratio of costs to effectiveness per test assay.

**Discussion**

- I suggest starting the discussion by giving the headline findings, which is not the costing result. This is a CEA so the discussion should be based on this outcome. Another recommendation is to concentrate the narrative on the implications of findings for policy and research—as well as how this relates to previous findings.

  This adjustment has been made.

- Is there any reference for this statement “TB diagnosis in patients who harbour lesser quantities of the bacilli such as children, HIV positive cases, and among sputum smear-negative presumptive cases. This would, in turn, reduce early morbidity”?

  A reference has been included.

- The authors did not include time to treatment initiation and loss of follow-up in the model nor include any information on the results section about these two variables. So I don’t think this statement should be part of the discussion section:

  This statement has been deleted “The median time to treatment initiation was 1 day for Xpert at POC and 14 days for Xpert by referral. The likelihood of loss to follow-up was four-fold among the patients whose samples were referred to the GeneXpert laboratory compared to when the Xpert was at the point of care”.

- I do not agree that the use of GeneXpert Omni would eliminate the use of ZN microscopy, particularly in resource constraint settings where this test is still important. Could you please elaborate more on this?

  This comment is true, the Xpert would only supplement but not eliminate the use of ZN.
| Introduction | line 51: standard of care or point of care? Same statement throughout the text. | These are two different statements, standard of care is what the ministry of health recommends as first line test assay, whereas a point care in the test placed at a primary facility for diagnosis at first contact with the patient |
|---|---|---|
| Methods | lines 33 and 37, pg 5: please include references on cost data provided by the literature. | References included |
| Methods | line 47, pg 5: sample transport costs mentioned twice. | One has been deleted |
| Methods | lines 27-28, pg 8: please include references in the statement "Analysis was performed from the model by adjusting the model parameters of Xpert MTB/Rif and Xpert Omni tests based on the minimum and maximum values from Published literature". | References included |
| Methods | lines 29-30, pg 8: please include references in this statement "TB prevalence corresponding to the national estimates as at the time of the study obtained from reports and systematic reviews were used in the analysis." | References included. |
| Results | lines 37-41, pg 9: please include references in the statement "Estimates for sensitivities and specificities of the tests were obtained from pooled values from the systematic reviews and clinical trials that took mycobacterial culture as a reference standard." | |
| Reviewer 2 | Introduction 1.How does Xpert MTB/Rif reduce TB morbidity and mortality as a detection device rather than a treatment? Increase on case detection will reduce community spread of TB as patients get access to timely treatment which ultimately will reduce mortality |
| Reviewer 2 | Description of intervention 2.Portable and rapid nucleic acid detection chips or devices have also been reported (Biosensors & Bioelectronics. 2022, 195; Research. 2021, 2813643). These technologies are also cheap, portable and fast, and what makes Xpert unique compared to these technologies? Please add a discussion of this section. More elaborate discussion added. |
**Description of intervention**

You mentioned here that “Xpert MTB/Rif has inadequate capacity in lower facilities due to the complexity of its technology and high costs”. Apart from being user-friendly, what special advantages does GeneXpert Omni have that make it acceptable in remote areas, since its price has not been reduced much? How user-friendly it is?

More elaborate explanation has been added.

**Description of intervention**

In “Description of study alternatives”, there is no specific description of the reagents or instrument units required to run Xpert MTB/Rif and Xpert Omni.

This has been added to both alternatives.

**Description of intervention**

5. How do the performance of the two instruments affect the cost? Including its integration, detection time, throughput, detection limit, sample pretreatment technique, and sample type.

An explanation has been added.

6. Cepheid has some subsidy policies for remote areas. For the two instruments, has the subsidy intensity been calculated in this paper?

Concessional prices provided by Cepheid for low and middle income countries were used in the calculation of the costs for both machines.

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**VERSION 2 – REVIEW**

**REVIEWER**

Teixeira de Siqueira-Filha, Noemia
Liverpool School of Tropical Medicine

**REVIEW RETURNED**

27-May-2022

**GENERAL COMMENTS**

The manuscript has improved after the review. However, major issues remain. Additional comments are below.

Abstract

I don’t think the conclusions reflect the results: transportation costs cannot be reduced if the objective is to use the equipment in remote areas and at the patient’s house. We cannot say that the intervention is moderately cost-effective without presenting a cost-effectiveness threshold. In addition, the study doesn’t show any data indicating that the test would reduce time to diagnosis and treatment.

Introduction

Please update the figures for the TB epidemic at global and local levels given in the first paragraph. The global TB report 2021 has already been published and can provide current numbers for incidence and mortality. Also, the WHO has published an updated list of 30 high TB burden countries (WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025). Please, update and include it in your reference list.

Methods
Please, include in the provider perspective only those who pay for the implementation of the Xpert test. Health workers and support staff cannot be included in this list as they do not pay for the intervention. They are cost elements rather than providers. The cost-effectiveness analysis is quite limited as it includes only male TB/HIV co-infected. Difficult to generalize this study to the whole country.

The authors mentioned that Xpert Omni does not incur transportation costs because it has been used as a point of care test. However, this statement on page 6 says the opposite: Due to the portable nature of the device, testing can be conducted on-demand at the patient's location, as opposed to a centralized healthcare facility. Please, clarify as the objective is to cover remote areas of the country.

Clarify the statement on page 6: Expert opinion was sought from suppliers, implementing partners, district health officials, laboratory personnel, and sample transporters. Expert opinion on what? Please, standardize the primary outcome as the number of correctly diagnosed TB patients OR additional PTB test diagnosed.

This phrase was repeated twice in the text: The cost per diagnostic outcome was used as a more proximal measure for exploring the key drivers of cost-effectiveness.

Results
I recommend presenting the main result of the analysis according to a willingness to pay threshold rather than a simple cost-effective graph. The decision-makers would have a clear figure about the chance of the Xpert Omini being a cost-effective intervention.

**REVIEWER**

| Chang, Lingqian |
|----------------|
| Beihang University |

**REVIEW RETURNED**

05-Jun-2022

**GENERAL COMMENTS**

This work compared the cost-effectiveness of GeneXpert Omni and GeneXpert MTB/RIF in various aspects, including transportation cost, reagents, and cost of a single test, with the aim of providing recommendations for TB detection in a low-resource high burden facility. The manuscript is well written with appropriate in-depth discussion. I suggest that the manuscript can be published.

**VERSION 2 – AUTHOR RESPONSE**

| Section / Page | Reviewer Comment | Author Response |
|---------------|------------------|-----------------|
| Abstract      | I don't think the conclusions reflect the results: transportation costs cannot be reduced if the objective is to use the equipment in remote areas and at the patient's house. | Clarification to this comment has been provided in the last paragraph of the introduction. Point of care (POC) testing refers to diagnosis done at the peripheral |
| **We cannot say that the intervention is moderately cost-effective without presenting a cost-effectiveness threshold.** | **• This comments on the conclusion has been corrected to align with the results.**

Xpert Omni at the point of care health facility is more effective but with an increased cost compared to Xpert MTB/Rif at the centralized referral testing facility. |
|---|---|
| **In addition, the study doesn’t show any data indicating that the test would reduce time to diagnosis and treatment.** | **• This statement has been removed because its justification is not reflected in this current paper but in another sister paper from the same study yet to be submitted for publication.** |
| **Introduction** | **Please update the figures for the TB epidemic at global and local levels given in the first paragraph. The global TB report 2021 has already been published and can provide current numbers for incidence and mortality. Also, the WHO has published an updated list of 30 high TB burden countries (WHO global lists of high burden countries for tuberculosis (TB), TB/HIV, and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025). Please, update and include it in your reference list.**

This figures have been updated in accordance with the WHO, 2021 TB Report. |
| **Methods** | **Please, include in the provider perspective only those who pay for the implementation of the Xpert test. Health workers and support staff cannot be included in this list as they do not pay for the intervention. They are cost elements rather than providers.**

A correction has been made in the first paragraph of the methods section. |
| The cost-effectiveness analysis is quite limited as it includes only male TBHIV co-infected. Difficult to generalize this study to the whole country. | This comment has been acknowledged in the limitation of the study on page 15 |
|---|---|
| The authors mentioned that Xpert Omni does not incur transportation costs because it has been used as a point of care test. However, this statement on page 6 says the opposite: Due to the portable nature of the device, testing can be conducted on-demand at the patient's location, as opposed to a centralized healthcare facility. Please, clarify as the objective is to cover remote areas of the country. | A clarification has been given |
| Due to the portable nature of the device and it being battery powered, the testing can be done at lower health facilities without electricity supply as opposed to transporting TB samples to a centralized testing laboratory hub. |
| Clarify the statement on page 6: Expert opinion was sought from suppliers, implementing partners, district health officials, laboratory personnel, and sample transporters. Expert opinion on what? | Comment addressed |
| Expert opinion about the cost of inputs was sought from suppliers, implementing partners, district health officials, laboratory personnel, and sample transporters. |
| Please, standardize the primary outcome as the number of correctly diagnosed TB patients OR additional PTB test diagnosed. | The outcome has been standardized |
| outcome measure was incremental cost per additional PTB test diagnosed |
| This phrase was repeated twice in the text: The cost per diagnostic outcome was used as a more proximal measure for exploring the key drivers of cost-effectiveness. | The repeated phrase has been removed. |
| Results | I recommend presenting the main result of the analysis according to a willingness to pay threshold rather than a simple cost-effective graph. The decision-makers would have a clear figure about the chance of the Xpert Omni being a cost-effective intervention. | Thanks for this good recommendation. |
| However, the parent thesis report had not conducted this analysis. |
| Reviewer 2: Prof. Lingqian Chang, Beihang University |
| This work compared the cost-effectiveness of GeneXpert Omni and GeneXpert MTB/RIF in various aspects, including transportation cost, reagents, and cost of a single test, with the aim of providing recommendations for TB detection in a low-resource high burden facility. The manuscript is well written with appropriate in-depth discussion. I suggest that the manuscript can be published. |
| Thank you, Prof, Lingqian Chang for giving ‘green light’ to the article. Very much appreciate your previous comments that helped to improve the paper |