PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to Thorax, a BMJ Group journal, but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open. Below, are the review received originally at Thorax, published with permission of the reviewers.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of screening strategies to improve the diagnosis of latent tuberculosis infection in the HIV positive population; a cohort study
AUTHORS	Katrina M Pollock, Herman Tam, Lisa Grass, Sharleen Bowes, Graham S Cooke, Manish Pareek, Damien Montamat.Sicotte, Moses Kapembwa,Graham P Taylor and Ajit Lalvani

VERSION 1 - REVIEW

REVIEWER	**Jonathan Golub, Assistant Professor, John Hopkins Bloomberg School of Public Health**

GENERAL COMMENTS	Comments to the Author This is straight-forward study retrospectively assessing the increase in detection of LTBI that would be garnered if risk factors were addressed prior to LTBI screening. It clearly shows that asking about risk factors increases yield, while decreasing number screened. I am a bit surprised that this is considered a novel approach, as I had always thought that risk factors for TB often drive the decision to place a TST. Minor issues: 1. This is a retrospective analysis of pre-recorded data. Is it safe to assume that the quality of the data was adequate for determining the risk factor profile of all patients? Were these data collected systematically in the parent study? 2. I think it is important to present the diagnostic criteria for the 16 patients diagnosed with LTBI. How many were TST+/IGRA-, TST-/IGRA+, TST+/IGRA+? As presented, I cannot easily tell how many of each. 3. Though not statistically significant, new entrants tended to be LTBI (only 2 less than alcohol which was statistically significant - small numbers!) Same with prison/IDU - very similar. I think the raw data in a study like this is much more telling than the adjusted

	values, particularly if they are ALL placed in one model as presented.

REVIEWER	Gerritt Woltmann, Consultant Respiratory Physician at University Hospitals Leicester, UK

GENERAL COMMENTS	Comments to the Author The paper presents results of screening for latent Tb Infection (LTBI) in the domains of contact and new immigrant screening by including foreign born HIV positive individuals even if arrival was more than 5 years ago, provided additional recognized risk factors were present. In addition they include test results obtained as part of routine clinical work. This study design deserves a number of comments: 1. The authors refer to current NICE guidance (reference 9) on diagnosing latent Tb infection (LTBI) and aim to compare what they perceive as current guidance on who should be tested with testing in a wider cohort of 115 HIV infected individuals. They are probably correct in stating that current screening for LTBI in the UK is generally performed in contact and new immigrant clinics predominantly. However, the NICE guidance document CG117 does not refer exclusively to these screening scenarios but includes statements on "people who are immunocompromised" (sections 1.1.1.10 - 1.1.1.14), where screening, used here as a very generic term, may be appropriate. Box 1 correctly states this fact. 2. As they are seeking to address and examine current guidance on the management of HIV positive individuals more explicit reference needs to be made to current guidance documents designed for this patient group (BHIVA including draft guidance out for consultation). 3. In their testing methods they do not refer to dual testing as recommended for individuals with HIV and CD4 counts less than 200 cells/mm3 (NICE CG117 1.1.1.11) although 15 individuals (13%) tested fell into this bracket. It is therefore not known if following more recent NICE guidance rather than BHIVA in this respect would have affected the overall case detection rate. Suggesting this approach is cost effective in other screening scenarios does not necessarily mean it will achieve this goal in a HIV positive cohort. A small number of missed cases of LTBI in this

	at risk population may well put the cost effectiveness of the whole screening effort in jeopardy. 4. Table 1 contains no reference to Tb contact. Table 4 does contain a reference to Tb contact but it is not clear if contact was close or recent. The reported case detection rates clearly deserve further examination as disease prevention in this group of individuals may not only reduce HIV disease associated morbidity but also mortality. However, the data are difficult to interpret in the context of existing studies on contacts and/or immigrants as these two risk factors were not examined in any kind of detail (details of contact / region of origin) or with sufficient power.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

This is straight-forward study retrospectively assessing the increase in detection of LTBI that would be garnered if risk factors were addressed prior to LTBI screening. It clearly shows that asking about risk factors increases yield, while decreasing number screened. I am a bit surprised that this is considered a novel approach, as I had always thought that risk factors for TB often drive the decision to place a TST.

We entirely agree with reviewer one that 'risk factors for TB often drive the decision to place a TST'. In our study we have shown that by standardising this approach, recording multiple TB risk factors and by using both IGRAs and TST, we significantly increased the frequency of LTBI cases detected.

Minor issues:

1. This is a retrospective analysis of pre-recorded data. Is it safe to assume that the quality of the data was adequate for determining the risk factor profile of all patients? Were these data collected systematically in the parent study?

The data was collected prospectively and systematically using a standardised, ethically approved clinical research form as part of the parent study.

2. I think it is important to present the diagnostic criteria for the 16 patients diagnosed with LTBI. How many were TST+/IGRA-, TST-/IGRA+, TST+/IGRA+? As presented, I cannot easily tell how many of each.

Additional data on the diagnostic criteria is provided in table form (Table 2).

3. Though not statistically significant, new entrants tended to be LTBI (only 2 less than alcohol which was statistically significant - small numbers!) Same with prison/IDU - very similar. I think the raw data in a study like this is much more telling than the adjusted values, particularly if they are ALL placed in one model as presented.

We agree that reporting the raw data and unadjusted values is more useful in this dataset and have therefore not included adjusted values in the revised manuscript.

Reviewer: 2

Comments to the Author

The paper presents results of screening for latent Tb Infection (LTBI) in the domains of contact and new immigrant screening by including foreign born HIV positive individuals even if arrival was more than 5 years ago, provided additional recognized risk factors were present. In addition they include test results obtained as part of routine clinical work.

This study design deserves a number of comments:

1. The authors refer to current NICE guidance (reference 9) on diagnosing latent Tb infection (LTBI) and aim to compare what they perceive as current guidance on who should be tested with testing in a wider cohort of 115 HIV infected individuals. They are probably correct in stating that current screening for LTBI in the UK is generally performed in contact and new immigrant clinics predominantly. However, the NICE guidance document CG117 does not refer exclusively to these screening scenarios but includes statements on "people who are immunocompromised" (sections 1.1.1.10 - 1.1.1.14), where screening, used here as a very generic term, may be appropriate. Box 1 correctly states this fact.

2. As they are seeking to address and examine current guidance on the management of HIV positive individuals more explicit reference needs to be made to current guidance documents designed for this patient group (BHIVA including draft guidance out for consultation).

Reply to 1 and 2: We agree that 'current screening for LTBI in the UK is generally performed in contact and new immigrant clinics predominantly'. We considered that the NICE statement on people who are immunocompromised ;

'For people with HIV and CD4 counts less than 200 cells/mm3, offer an interferon-gamma test and a concurrent Mantoux test. If either test is positive perform a clinical assessment to exclude active TB and consider treating latent TB infection'

referred to how to test at different thresholds of CD4 count and who to test. We have therefore now compared this recommendation with our data, in addition to the first comparison and found that stratifying screening based on CD4 count would detect less than half the LTBI cases. This has significance for the BHIVA guidance, which also recommends stratifying screening by CD4 count.

3. In their testing methods they do not refer to dual testing as recommended for individuals with HIV and CD4 counts less than 200 cells/mm3 (NICE CG117 1.1.1.11) although 15 individuals (13%) tested fell into this bracket. It is therefore not known if following more recent NICE guidance rather than BHIVA in this respect would have affected the overall case detection rate. Suggesting this approach is cost effective in other screening scenarios does not necessarily mean it will achieve this goal in a HIV positive cohort. A small number of missed cases of LTBI in this at risk population may well put the cost effectiveness of the whole screening effort in jeopardy.

Tuberculin skin testing was only sporadically used in our cohort due to BHIVA guidance available at the time on TST testing. We consider that dual testing could be a cost effective option for HIV patients but that there is insufficient data in our study to test this. We therefore used a positive result in any assay (IGRA or TST) to denote LTBI. We agree that a large study is needed to test which screening approach should be used and that our data will aid the call for such a study.

4. Table 1 contains no reference to Tb contact. Table 4 does contain a reference to Tb contact but it is not clear if contact was close or recent.

Table 1 does not refer to TB contact as this was data that we specifically collected in addition to the clinically available data presented here.

The reported case detection rates clearly deserve further examination as disease prevention in this group of individuals may not only reduce HIV disease associated morbidity but also mortality. However, the data are difficult to interpret in the context of existing studies on contacts and/or immigrants as these two risk factors were not examined in any kind of detail (details of contact / region of origin) or with sufficient power.

Whilst we are aware that the study numbers are small, we agree with the reviewer that our case detection rates required examination. We are also aware that current guidance is informed by insufficient evidence and that even a small data set may be useful in informing the shape of future research and guidance. Given the increasing number of HIV-infected patients accessing all NHS services and the increasing burden of TB in the UK, we felt that these data would provide empirical data to aid the call for a large study in this area. We therefore hope that you will find it suitable for publication in BMJ Open.