PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice
AUTHORS	Merve Nazli Eralp, Stefan Scholtes, Geraldine Martell , Robert Winter and Andrew Robert Exley

VERSION 1 - REVIEW

REVIEWER	Marie A. de Perio, MD Medical Officer Centers for Disease Control and Prevention National Institute for Occupational Safety and Health United States I have no competing interests.
REVIEW RETURNED	29/11/2011

THE STUDY	Methods 1. It should be made more clear in the methods that the T-Spot TB test is the IGRA used here. The T-Spot TB test is known to have a higher market cost than the competing test (QFT-GIT) though it has been demonstrated to be more sensitive. Using the QFT-GIT in this model would likely have the same overall results, but the ICER of the IGRA strategy might be different. It would be interesting for the authors to have included the QFT-GIT as an additional decision arm. 2. The methods section is missing the perspective of the analysis- is it the societal perspective? It is also missing what year the pounds they are reporting monetary amounts are in and whether or not they were all converted to the same year. This is pretty standard in cost-effectiveness analyses. 3. The authors use a BCG vaccination rate of 52.8% for their base case in Table 1. However, it is unclear from their model in Figure 1 how they accounted for the differences in TST specificity among BCG-vaccinated and non-BCG-vaccinated groups; this is a significant flaw of the paper. The authors use a specificity of 0.59 for the TST, which is derived from studies of BCG-vaccinated populations in the Pai et. al meta-analysis from 2008. However, Pai et al. also estimated the pooled specificity for the TST for non-BCG-vaccinated populations to be 0.97. The much improved specificity of the TST for non-BCG-vaccinated populations should be used in the model for the 47.2% of healthcare workers who are not BCG-vaccinated. It is also noted that, in the sensitivity analysis of TST specificity, the authors use a range of 0.46-0.73. The maximum of 0.73 is far below the pooled sensitivity of 0.97 calculated by Pai et al. for non-BCG-

	vaccinated populations.
	4. Table 1. It is is unclear what "repeat due to operational inefficiency" refers to. The authors should describe what the operational inefficiencies of the TST are, especially since their reference is not readily accessible to readers. The base case value of 0.324 seems quite high. It is unclear how this input influences the model in Figure 1. One of the assumptions (v) on p. 10 is that "no diagnostic tests are repeated due to operational inefficiencies; this variable is addressed in the sensitivity analysis." This needs to be cleared up in the paper. 5. Table 2. It would be helpful for the reader if the authors had broken down the components of the costs of the interventions (ie. test materials/kit, supplies, indirect costs, etc). Also, the NICE guidelines referenced as #16 do not contain any cost information that I can see. Should there be a different reference for these costs? 6. The methods section should also clarify that one-way deterministic sensitivity analyses were conducted. The authors varied only one variable at a time. It might be also be useful to conduct probabilistic sensitivity analyses using Monte-Carlo simulations to vary all the variables across ranges. This should be considered to be added to the paper. Discussion 1. The discussion section is missing a limitations section.
RESULTS & CONCLUSIONS	The authors do not give a discussion of their findings within the context of previous cost-effectiveness analyses looking at issue. It would augment the paper if such a discussion was included.
GENERAL COMMENTS	This is a very nice analytic decision model with comprehensive Markov states.

REVIEWER	Prof. Dr. Albert Nienhaus Head of the Competence centre for epidemiology and health service research in nursing (CVcare) University clinics Hamburg Eppendorf (UKE) Germany I declare, that i do not have any competing interests concerning the paper reviewed.
REVIEW RETURNED	06/12/2011

GENERAL COMMENTS	The authors compare the cost-effectiveness of pre-employment screening of HCWs in the UK using different strategies: A) TST, B) IGRA, C) IGRA if TST positive. Data on LTBI prevalence and progression rates as well as data on test performance were taken from literature. Cost for test and disease as well as for preventive treatment were taken from NHS National Tariff. Sensitivity analysis revealed that a screening using IGRA alone is more cost-effective than strategies based on TST on a wide range of asumptions. The study is well done and the paper is well written. The methods applied are well chosen and no mistake is apparent.

There are only some minor aspects I want to mention.

1) For those not familiar with preventive treatment (PT) of LTBI, it probably should be stated more clearly that hepatitis is a potential side effect of PT.

2) Page 6 out of 36: Line 3-7: I am not sure what this sentence is telling us. Are you talking about the application of both tests simultaneously? Please reconsider this sentence.

3) Footnote table 1: Why is Martell 2010 mentioned in the footnote of the table and not as a reference?

4) Footnote table 1: Last sentence: "Sensitivity analysis test the impact ……?" I do not understand why this sentence is put there.

5) Table 2: Costs: What is "Midpoint band 6 with on costs 2010" telling us?

6) Page 10 of 36: Markov model assumption vi: Do I understand the following correctly? As there is no gold standard for LTBI, probability of a positive test result of LTBI is assumed to be the same as for active TB on the condition that either LTBI or active TB is given. If I am right, it took me awhile to figure it out. Therefore reconsider to render your statement "vi" more explicit.

7) Page 14 of 36: line 34: "There is a premium on the skills". I am not sure whether I understand this correctly: Are workers with these skills paid extra fee? Is there potential of savings or of shortage of the particular skill?

8) References: A recent review on cost-effectiveness of IGRA was published recently: Nienhaus et al BMC public health. You might want to consider to include this in your references

REVIEWER	Roland Diel, M.D., M.P.H., Department of Pneumology, Medical School Hannover, Germany. Conflict of Interest: R.D. has received travel reimbursement and/or fees for speaking at symposia sponsored by Cellestis Ltd., Oxford Immunotec Ltd. and Pharmore Ltd. (exclusive supplier of Tuberculin RT23 for Germany).
REVIEW RETURNED	07/12/2011

THE STUDY	The manuscript of Eralp and co-workers is an interesting contribution to cost-effectiveness of screening and subsequent treating of LTBI and TB among health care workers (HCW). The economic model itself and the calculations performed appear to be proper in principle. However, the results are biased by several assumptions, especially unproven cost estimates for treating TB and LTBI, a 100% compliance to preventative chemotherapy given test-positivity of any test and assumptions on test accuracy in disfavor of the TST (low basic specificity, unclear repetition of the TST, lacking sensitivity analysis of sensitivity estimates, no estimate of the percentage of people who do not come back for reading and thus will not start preventive treatment). In my view the authors should be given the opportunity to recalculate their results with respect to the addressed concerns in order to prove

	whether their conclusions remain robust.
GENERAL COMMENTS	My comments are listed in detail below: Introduction, page 5, line 13: Hepatitis is not a "complementary disease" of TB. Do the authors mean hepatitis as possible adverse side effect of TB treatment or preventative chemotherapy? Introduction, page 5, line 36: Are there any guidelines available justifying that procedure? Introduction, page 6, line 13: "Health life years gained refers to the number of TB or complementary hepatitis cases avoided…" Do the authors mean hepatitis due to treatment of TB disease? Introduction, page 6, line 31: "ii. The higher relapse rate of active TB…" "Higher" compared to what? Methods, page 9. Line 13 and table 1: TST specificity of 59% in Pai´s analysis refers only to a thoroughly BCG vaccinated population. The basic assumption for the study population of HCW in the submitted manuscript, however, is a coverage of BCG vaccination of 52.8% Thus, I recommend using the specificity pooled estimate (all populations) of 63% in Menzies´ and Pai´s meta-analysis published in the Annals in 2007. Table 1: "Probability a second TST is placed" There is no reasonable explanation why in about 17% of the HCW a second TST should be placed . The authors provide the paper of Dosanjh et al. as reference no. 13, but there no such estimate is shown. Instead the authors should provide an estimate how often people do not come back for treading the TST. However, such a probability is not provided in Table 1. Table 2: Costs How was the estimate for treating TB been derived? There is no cost data of GBP 1,637 provided in the NICE guidelines that was cited as reference! Indeed, the amount of GBP 1,637 seems to be quite low! What about the estimates for the other TB related costs? Please, clarify! The authors state that "TB treatment costs derived from discussions with NICE 2010 and Cambridge TB service". Apart from the logical error (how can one have discussions with NICE 2010?), such informal means are not sufficient for arriving at a valid and transparent assessment of costs! "Total model costs for TB treatment are TB treatment, plus contact tracing x5 contacts per case" Is there any collection of studies available in which a mean number of 5 contact persons per case was assessed? Model constructions, page 9, line 53: "All patients with positive results for LTBI accept treatment, consistent with conditions of employment in the NHS". This assumption does not appear to be realistic! Please provide an appropriate estimate of compliance based on published (or otherwise referenced) evidence! Page 10, line 52: "The initial analysis was then subjected to sensitivity analysis applied to key variables including IGRA sensitivity and specificity". What were the lower and upper bounds of

	the values of the parameters subjected to sensitivity analysis? Please include these bounds in the respective tables containing the basic values. Why was there only a sensitivity analysis on IGRA sensitivity (up to 99%) performed but no respective analysis on TST sensitivity?
	Discussion, line 23, page 14, "The health economic model does not include an allowance for health care workers time to attend for testing, but staff costs are greater when two – three visits are required for TST then IGRA." This statement is not explained and seems to be unreasonable.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers Comments
We are most grateful for the reviewers helpful comments which prompt the following responses and revisions.

Reviewer I
Methods
1. i. We revise write page 7 line 19 from
"We apply an IGRA specificity of 98% for the base case analysis guided by our clinical and market experience with T-Spot TB, and then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model." To
The analysis is guided by our clinical and market experience with the T-Spot TB test, applying an an IGRA specificity of 98% 15 for the base case. We then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model.
ii. A comparison between different IGRA is dependent on the market costs and operational characteristics of the assays including clinical case mix and blood sampling. This comparison is commercially sensitive and controversial and is not the purpose of this study.
iii. We have investigated the impact of IGRA operational characteristics including costs.
iii. We include in the discussion page 14 line 40 "Critical aspects of blood sampling are defined including the impact of the test population and sampling conditions on the performance characteristics of IGRA 13, 25, 26, 27. "
iv. We also include in the discussion, page 14 line 48 "The relative merits of different IGRA tests are controversial 21, 15, 4 but where there is a consensus on the assay characteristics this model should allow further investigation."

2. i. The perspective of the analysis was removed during editing!
We now include in the first paragraph page 5 line 31 "The analysis is from the NHS and societal perspective."
ii. We add to page 7 line 27 "Direct and indirect costs are shown (table 2) drawing on data supplied by NICE (see appendix 6) 16, the Cambridge TB service, and the NHS National tariff 2010, with costs adjusted to the 2010-2011 financial year." Revised costs are cited and used in the model, and references added.

3. TST specificity
i. This issue was also raised by reviewer III who recommended using an overall specificity of 0.63 derived from the meta-analysis of Menzies et al 2007. We are grateful for this suggestion and now adopt the value of 0.66 from figure 2, Menzies et al 2007.
ii. A similar value of 0.67 was applied to the German population, our reference 9.
iii. Conservative / liberal estimates of the impact NTM infection has on false positive TST are provided by Weir 2003, and Winje 2008 which we now cite, new references 32, 33. Weir 2003 investigated SE

England school children prior to BCG, and reported a false positive rate of 14%. These data generate an overall TST specificity of 0.72.This appears a conservative estimate based on the older age of health care workers and the increasing evidence of NTM infection in adults Fowler 2006, new reference 31.

iv. TST specificity over a range of 0.43 – 0.73 was tested in the original sensitivity analyses. Reviewer 1's proposal would generate a value of 0.77. We revise our sensitivity analysis to include a TST specificity range of 0.46 – 0.86, Menzies 2007 new reference 15

v. We extend this analysis by including TST specificity in the Monte Carlo analysis

#vi. We revise and extend the discussion page 13 line 58 "Our model accommodates substantial enhancement of TST specificity greater than expected in BCG-vaccinated populations, but the outcome may be different in non-BCG vaccinated populations with low NTM infection rates 4." to "Our model accommodates substantial enhancement of TST specificity greater than expected in BCG-vaccinated populations or mixed populations including non-BCG vaccinated health care workers 15. The outcome may be different in non-BCG vaccinated populations with low NTM infection rates 5 but NTM infection is an increasing problem in adults 31. Studies testing children prior to BCG immunisation have revealed false positive TST rates of 14% in SE England 32 and 79% in Norway 33. It seems likely therefore that previous infection with NTM has a significant role in reducing the specific of TST."

4. There are few data on the proportion of TSTs that need to be repeated in order to achieve a result.

i. Table 1 Base case data
We agree including a repeat rate of 0.324 from our own experience in medical students is incorrect and misleading here

ii. We revise page 12 line 3 to now include "TST repeat rates were estimated using the 17.4% rate of failure to achieve a TST result in a UK study of routine practice 14. This compares with 53%, 35/66, of medical students who failed to attend their first Mantoux appointment 25 and a 12% failure rate to read the 1st TST 11.

iii. page 10 line 5 is incorrect and is revised as "The repeat rate for diagnostic tests is further addressed in the sensitivity analyses"

5. Costs
i. We now include in a new supplementary table 1 a breakdown of estimated treatment and TST costs derived from the Cambridge TB service, the NHS national tariff, and NHS national pay scales adjusted for 2010/2011.

ii. Our reference 16 includes cost data within appendix 6, which we now refer to in the main text

iii. page 9 line 16 citing reference 16 is incorrect and is deleted

6. page 7 line 34. We now revise and extend to "The impact of regional or national differences in disease parameters and costs are examined in one-way sensitivity analyses. The impact of uncertainty within multiple parameters is then examined using Monte Carlo probabilistic sensitivity analysis."

The section on Monte Carlo simulation is added to the results and included in the discussion

Discussion
i. The key limitations of the study are highlighted in the article summary, page 4 line 47
"• Neither TST not IGRA differentiate LTBI from TB, and the specificity of IGRA is inferred from studies in populations at low risk of TB".

ii. The study findings are placed firmly in the context of previous cost-effective analyses throughout the discussion which we suggest is more appropriate here than a separate section on limitations. For example
page 13 line 11 "Healthy life years, despite being a conservative benefit metric, may be particularly useful in evaluating novel screening and monitoring tests by avoiding the assumptions inherent in generating quality adjusted life years 20, 1, 7, 10, 21."

page 13 line 52 "The health economic model is sensitive to IGRA specificity, which is derived from estimates of false positives in populations at low risk of TB 24 21, 15. An IGRA specificity of 98% is conservative by current literature 24 21, 15 but higher than analyses potentially confounded by data from studies in populations at intermediate rather than low risk of TB 4, 14, 16."

Reviewer II.
1. page 2 line 23 "TB and its complementary diseases such as hepatitis" is revised as "TB and complications of treatment such as hepatitis" and apply this throughout at page 2 line 25, page 6 line 15.

2. page 6 line 3 – 7 We agree this is confusing and adds little so is deleted

3. Martell 2010 is now included in the references

4. Footnote Table 1 We agree this is unnecessary and confusing, so is deleted

5. Table 2. costs Sorry, this is NHS speak! We now cite Pay Circular (AforC) 2/2010, new reference 23, point 26 £30,460, plus 22% overheads £37,161

6. page 10 line 9 point vi is revised as "The probability that LTBI generates a positive result is assumed to be the same as the probability that active TB generates a positive result, as there is no gold standard for LTBI"

7. page 14 line 34 Is revised, with new reference 4, as "In contrast, carrying out a TST requires registered nurses with proven competence and recent training or administration of TSTs, which is more expensive than phlebotomy and may be limiting during peaks in demand such as in contact tracing"

8. We had missed this recent reference which now adds to the discussion.
"Studies including the relative risk of progression to active TB suggest additional limits to TST specificity, reviewed recently 34. IGRA positive cases with LTBI are more likely to progress to active TB than TST positive cases. In particular, IGRA positive cases showed a 19% greater chance of progression to active TB than expected solely from the increased specificity of IGRA over TST 10. This advantage would lead to further domination of TST only approaches, by sequential TST then IGRA and IGRA alone strategies."

Reviewer III
Introduction
1. Revised as for reviewer II point 1

2. page 5 line 36 revised to include new citation, as for reviewer II point 7

3. Revised as for reviewer II point 1

4. page 6, line 31 "ii. The higher relapse rate of active TB within three years of treatment 12" is revised to "ii. The higher relapse rate of active TB within the first three years of treatment in comparison to the years thereafter 12

Methods
1. page 9, line 13 and table 1 Thank you. We have revised our analysis by applying the data from this paper. Please also see reviewer I point 3

2. Table 1 Revised as for reviewer I point 4

3. Table 2 Costs. Revised as for reviewer I points 2 and 5. We originally considered using the same costs as NICE were proposing to apply for the revision of their guidelines. We supplied our cost estimate to NICE in May 2010 and identified significant differences between us. Base case test costs were obtained from discussions with NICE. The treatment costs are derived from the Cambridge TB service, NHS staff costs and the NHS tariff, and then subjected to sensitivity analyses.

4. Contact tracing
The number of contacts traced per TB case identified, 5, is derived from a rate of 4 – 5 contacts shown in figure 7 in Tuberculosis: Clinical diagnosis and management of tuberculosis and measures for its prevention and control; Royal College of Physicians of London 2006; old reference 19, now added to the key to table 1.

5. page 9, line 53 Compliance with treatment for LTBI is a condition of employment in the NHS, and will be supported by the three month course. The efficacy of LTBI treatment at 0.65, incorporated into the model, will include the consequences of limited compliance with treatment
We revise this point to now include "The impact of limited compliance is allowed for within the efficacy of LTBI treatment
"
6. i. The range of sensitivity analyses are included in the main text and figures, and detailed in the supplementary tables to avoid any confusion. We revise this to include range tested in tables 1, 2
ii. We revise page 12 line 42 to include "The calculation and apportionment of treatment costs is likely to vary between centres, but a four fold variation, 0.5 times – 2 times baseline, in treatment costs for LTBI, TB, or hepatitis is also accommodated by the market standard model."

7. It seems legitimate to not include costs for HCW time to attend for testing since they may be screened for several conditions at 1 visit.
We revise page 14 line 23 to "The health economic model does not include an allowance for health care workers time to attend for testing, but these staff costs would be greater when two – three visits are required for TST then IGRA further limiting cost-effectiveness of strategies incorporating TST."

VERSION 2 – REVIEW

REVIEWER	Dr. Roland Diel, M.D., M.P.H, Department of Pulmonary Medicine, Medical School Hannover, Germany
	The manuscript has been largely improved. The authors have considered the reviewers´comments sufficiently. I suggest acceptance as is.
	Conflict of interest: RD has received travel reimbursement and/or fees for speaking at symposia sponsored by Cellestis Ltd., Oxford Immunotec Ltd. and Pharmore Ltd. (exclusive supplier of Tuberculin RT23 for Germany).
REVIEW RETURNED	07/01/2012

GENERAL COMMENTS	The manuscript has been largely improved. The authors have considered the reviewers´comments sufficiently. I suggest acceptance as is.

REVIEWER	Marie A. de Perio, MD

	Medical Officer Centers for Disease Control and Prevention National Institute for Occupational Safety and Health United States
REVIEW RETURNED	11/01/2012

GENERAL COMMENTS	This paper would still benefit from more of a discussion of their findings within the context of the findings of previous cost-effectiveness analyses looking at IGRAs vs TSTs in healthcare workers. While the authors do include differences in their methodology compared to previous CEAs, there is no discussion of how the actual results compare to those from the previous CEAs. Although the main outcome measure is different, it is still important to include that other studies have found IGRAs to be either cost-effective or cost-saving. While this point is not significant enough to warrant mandatory revision, it should be considered by the authors.