Author’s response to reviews

Title: "Cough officer screening" improves detection of nosocomial pulmonary tuberculosis

Authors:

Ching-Hsiung Lin (mrmr914@gmail.com)
Cheng-Hung Tsai (97167@cch.org.tw)
Chun-Eng Liu (63557@cch.org.tw)
Mei-Li Huang (3766@cch.org.tw)
Shu-Chen Chang (53098@cch.org.tw)
Jen-Ho Wen (6060@cch.org.tw)
Woei-Horng Chai (80690@cch.org.tw)

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Iratxe Puebla, Senior Editor
BMC-series journals

Dear Dr. Puebla,

Thank you for your continued interest in our manuscript and for your further review. We have reviewed you comments and have revised the manuscript accordingly. For your convenience, we have included your comments and our point-by-point responses below.

We look forward to your continued support of our work and correspondence.

Sincerely,

Ching-Hsiung Lin, MD
Division of Chest Medicine, Department of Internal Medicine
Changhua Christian Hospital,
Tel: 886-910-440307; Fax: 886-4-722-8289
E-mail: 47822@cch.org.tw
Comments from Iratxe Puebla, Senior Editor, BMC-series journals

Competing interests? Please remove this information from the title page and include it as a separate section between the Conclusions and Author's contributions. If there are none to declare, please write “The authors declare that they have no competing interests”.

Response: Done!

Funding information - Please remove this information from the title page and include it under the Acknowledgements.

Response: Done!

Referee 1

General comments

The paper addresses important aspect of tuberculosis case finding in health institutions. This could help to reduce delay due to the health service including the health workers to improve early case finding. It also reduces nosocomial transmission. The authors describe important topic in tuberculosis control but requires more work on the methods and discussion to improve the manuscript. The title should also be in line with the methods and discussion.

Response: Done! We changed the title to: “Cough officer screening” improves detection of nosocomial pulmonary tuberculosis

Major compulsory revisions

1. Under the methods section add a subtopic that describes the setting of the study.

Response: Done! See paragraph #2 in the “Methods”.

The section on “cough officer screening protocols” (paragraphs #3 and #4 in “Methods”) was also modified to provide more detail.

2. Under statistical analysis, the Wilcoxon rank-sum test was used to measure the delays in health care system while the objective of the study was to measure the effect of cough officers on detection of pulmonary tuberculosis. What the statistical test is intended for differs from the objective. The objective of the study should be eared with the statistical test used and discussed accordingly.

Response: Our objective is addressed in the last paragraph of the “Introduction”. The outcome of analyzing health care system delays is in Table 3. Part of the outcome relating to evaluating the effect of a COS program is in Figures 1 and 2.
To more specifically address the effect of COS program, we have added a new table (Table 1) showing the sensitivity, specificity, PPV and NPV of the COS system based on the data in Figure 1. We also discuss these findings in the Discussion.

Minor essential revisions
1. Page 4 paragraph 1, line 4, the sentence ‘When local healthcare facilities are functioning efficiently and when TB prevalence is low, additional strategies may not be required’ may be omitted or add some notes on the importance adequate health service coverage.
   Response: Done!

2. Page 4 paragraph 1, line 7, the phrase ‘for its cost effectiveness may be omitted or add a sentence that describes DOTS as a cost effective strategy.
   Response: Done!

   The cost effective strategy and DOT are beyond the scope of this study. We will analyze the cost effectiveness of COS in our next project.

3. Page 4 paragraph 2, may be shortened and describe about case finding in DOTS strategy and the role of active and enhanced case finding.
   Response: Done!

   Since we did not take effect of DOT into consideration, the paragraph has been re-edited.

4. Page 6, paragraph 2, describe more on the stages of screening and reasons for excluding patients.
   Response: Done!

   In our Medical center, several special units, such as ICU, have patients under mechanical ventilation. During Stage I, we found it difficult to actually measure cough for ICU patients. We therefore strongly suggest screening for TB in patients with lesions or infiltration in lung whether or not the infection was suspected. The TB screening should test three sets of sputum smear. The patients in ICU were excluded from our subjects in Stage II, and we will report these findings concerning ICU in another manuscript. In addition, we found that most pediatric patients who had a cough for more than 5 days did not have M. tuberculosis infection. There is a low incidence (12 per
million in 2002) of pulmonary TB in children (0~14 years old) from Taiwan. Besides, it is difficult to collect sputum from pediatric patients. We therefore excluded patients from the Pediatric Department in Stage II.

5. Page 6 paragraph 3, line 1, add selection criteria of cough officers and if they had received special training to conduct the screening.
Response: Done!
This information was added to the “Methods”

6. Page 6, add a subtopic before statistical analysis to describe tuberculosis diagnostic procedures. How does it compare with the National Tuberculosis Programme recommendation? Also add some notes on data collection.
Response: Done!

7. Was not ethical clearance required for the patients?
Response: (a) Our COS system is recommended by Center of Disease Control (Taiwan) to minimize the chance of nosocomial transmission, and monitoring of coughing is one of the items under inspection by CDC.
(b) Before the sputum was collected, the physician would have to explain the situation and the purpose of the examination to the patient.
(c) The present study is a retrospective study, so all data were retrieved from database anonymously. There is no effect on patient privacy.

8. Page 8, paragraph 1, among patients for which the COS alarm was given only 40% (7998/19836) and 55% (6221/11323) were examined by the physicians in stage I and II respectively. Explain why the rest were not examined.
Response: The inclusion criteria for our COS system are rather simple. Any patient who had a cough for more than 5 days would be alarmed. There are several reasons why a physician may not take action:
• The patient was excluded from possibility of TB before the COS alarm (i.e. the cough was caused by another respiratory disease);
• The patient has been confirmed as having M. tuberculosis infection, and there was no need for further check;
• The patient refused to receive a TB examination;
• Based on clinical experience, the physician did not think the patient had TB.
9. Page 8, paragraph 1, in addition, 77.2% and 90% of the cases were examined before the alarming system. Explain more about this and comment on this in the discussion section.

Response: As mentioned earlier, the COS inclusion criteria are rather simple. That is any patient who had a cough for more than 5 days would be alarmed. However, the incidence of TB ranks number one among the notified infectious diseases in Taiwan. Therefore, it is not surprise that a total of 77.2% TB patients were confirmed by physicians as having M. tuberculosis infection before COS alarm in Stage I. Interestingly, the number of pre-diagnosed TB patients was 90% in stage II, suggesting that implementation of the COS system may have forced physicians to pay more attention to the symptoms of tuberculosis.

10. Page 9, paragraph 2, in the sentence ‘The average time from admission to diagnosis was 24 days for stage I and 19 days for II (Table 1); however, these numbers were strongly influenced by the presence of a small number of patients (outliers) who were diagnosed with TB long after admission to the hospital (up to 163 days)’ the role of outliers is not a problem if when Wilcoxon rank-sum test is used for median is the test statistic.

Response: We agree and deleted this sentence, and revised Table 1 accordingly.

11. The next sentence ‘Our COS recorded all patients’ coughs for as long as they were in the hospital’ should be included in the methods. The next sentences’ in fact…till the end of the paragraph should be part of the discussion.

Response: Done!

12. Page 10, paragraph 1, the second and third sentence could be described as ‘the COS system has led to high rates of examination but lower rates of tuberculosis diagnosis’. The sentences could be explained with the limitation of the study.

Response: Done!

13. Page 10, paragraph 3, could be shortened and add on the reasons why the COS system used 5 days and compare it with the national Tuberculosis
Programme recommendation. Explain how it leads to high false positives.

Response: The reason for using 5 days as the cut-off point are:

- The average length of stay for inpatients is 7 days. A time greater than five days will not allow us time to collect sputum and see the results of the sputum-smear examination. If the cut-off point is 2 weeks of coughing, many suspected TB patients will return to the community, possibly resulting in community transmission.

- If the cut-off point is reduced (e.g. 3 days), the number of false positive patients will be significantly increase. In the present 5-day cutoff COS system, we already have approximately 99% of patients who are COS(+) but have no infection by M. tuberculosis.

- The reason for our large number of false positives is that acute cough is a complication of many diseases. We have discussed that in Discussion section. In addition, not every patient alarmed by COS would receive a TB examination. As shown in Figure 1, approximately 60% (Stage I) and 45% (Stage II) of COS(+) patients did not receive TB examinations after a COS alarm. The reason for not being examined by a physician has been discussion previously (Comment #8, above).

14. Page 11, paragraph 3, line 4, 90.4% in stage II were examined before COS alarming while it was stated to be 90% in page 8 paragraph 1. Which one is correct?

Response: Done!

It was changed to 90%.

15. Page 12, paragraph 1, and paragraph 3, the comment on the possibility of the patients to be ignored and risk of nosocomial transmission should be cautiously explained in relation to the objective of the study.

Response: Done!

16. What is the limitation of the study?

Response: We added a paragraph on study limitations near the end of the “Discussion”.

17. Comment on the application of the study results in other settings.

Response: Done!
18. Write the conclusion of the study in line with the objective of the study.
Response: Done!

19. Reference 4 & 19 and 12 & 16 are the same and require revision.
Response: We fixed this.

20. Add one Table showing the baseline characteristics of the patients like by age,
sex, duration of cough and tuberculosis classification etc. In addition, show the
duration of cough vs. tuberculosis diagnosis to see the yield of the alarm system.
Response: We added a table showing demographic data of confirmed TB patients.

Discretionary revisions
1. Page 5 paragraph 1, line 7, add more on the reported nosocomial infections.
Response: Done! We added a brief discussion of two closely related publications:
Hsieh MJ, Liang HW, Chiang PC, Hsiung TC, Huang CC, Chen NH, Hu HC, Tsai
YH. Delayed suspicion, treatment and isolation of tuberculosis patients in
pulmonology/infectious diseases and non-pulmonology/infectious diseases
Wu YC, Hsu GJ, Chuang KY, Lin RS. Intervals before tuberculosis diagnosis and
isolation at a regional hospital in Taiwan. J Formos Med Assoc. 2007
Dec;106(12):1007-12.

2. Page 5 paragraph 1, line 7, the phrase ‘for its cost effectiveness may be
omitted or ad a sentence that describes DOTS as a cost effective strategy.
Response: Done!

3. Page 5, paragraph 2, line 9, the sentence ‘WHO’s Practical Approach to Lung
Health (PAL) is similar to our COS program’ may be omitted. And the next
sentence could be explained under case finding strategies as mentioned above.
Response: Done!

4. Page 6, paragraph 1, the second sentence should be put under methods.
Response: Done!
5. Page 7, paragraph 1, line 1, what is the importance of mean and standard deviation? Reporting the findings related to median is enough.
Response: The mean and standard deviation were deleted from text and related table.

6. Page 7 paragraph 2, the first sentence should describe the statistical software followed by the ‘Wilcoxon rank-sum and the description about median, minimum and maximum…
Response: It was revised in section on statistical analysis.

7. Page 8, paragraph 1, line 6 and the last sentence of the paragraph, qualify the sentence if the patients would be ignored or delayed.
Response: Done!

8. Page 8, paragraph 2, show the diagnostic procedures by the type of examination done to the patients in figure 2 and then rewrite the percent of physicians who took action following the COS system. Then the number of actions in both stages could be commented on.
Response: This paragraph has been rewritten.

9. Page 10, paragraph 2, high prevalence of HIV and tuberculosis and low health service including diagnostic facilities and physicians could be the reasons for the difference.
Response: Done!

10. Page 11, paragraph 2 delete the list of diseases. What is the duration of cough in Morocco suspects?
Response: We modified this paragraph accordingly. The cough duration of Morocco patients is unknown.

11. Page 11, paragraph 3, could you classify the patients in to smear-positive and smear-negative to comment on disease transmission.
Response: This paragraph has been rewritten.
12. Add one variable showing duration from alarm to diagnosis in table.
Response: It has been shown in Tables 2 and 3.

13. Figure: tuberculosis diagnosis in COS (-) and COS (+) in action and no action arms was reported.

<table>
<thead>
<tr>
<th>Stage</th>
<th>COS (-)</th>
<th>COS (+) action</th>
<th>COS (+) no action</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>16/82905=0.002%</td>
<td>184/7998=2.3%</td>
<td>10/11838=0.08%</td>
</tr>
<tr>
<td>II</td>
<td>21/67549=0.03%</td>
<td>125/6221=2%</td>
<td>0/5102=0%</td>
</tr>
</tbody>
</table>

From the report, there were TB patients missed by the COS system as shown by COS (-) right? Please comment on this. What was the gold standard test used to classify the patient into TN and TP? Comment on the sensitivity, specificity, PPV and NPV of the COS system if possible.

Response:
(1) The gold standard test used to classify the patient into TN and TP was the outcome of Mycobacteria culture.

(2) Table 1 shows sensitivity, specificity, PPV (Positive predictive value), and NPV (Negative predictive value) of the COS system, based on this gold standard.

(3) The reason for “missing” TB patients (n=16 in Stage I; n=21 in Stage II) was because hospitalized patients showed TB symptoms after 5 days of monitoring were ignored by nurses or physicians. The mean intervals between the first admission from outpatient clinics, emergency department and hospitalization and suspected TB were < 1 day, 6.07 days and 25.53 days, respectively [Wu et al., 2007], suggesting that TB symptoms are somehow ignored at the early days of hospitalization. Another reason for not being alarmed by COS system was that the patient already undergoing pulmonary TB treatment, and the cough symptom was reduced by the medication.

Referee 2

Reviewer’s report:

Major Compulsory Revisions

1. What was the rationale for subdividing cough duration as the authors have done, and using the threshold of cough > 5 days to trigger investigation with chest radiograph and sputum smear / culture?

Response: This is explained in the response to comment #13 of Referee-1 (see
above).

Were all three investigations performed for all patients picked up by the COS alarm?

Response: The physician could choose between Chest X-Ray and sputum smear/culture.

The yield of the COS was 0.5% (42/7998) in stage I and 12/6221 (0.2%) in stage II. Cost-effectiveness analysis should ideally be carried out.

Response:

(1) In this 5-day cutoff COS system, approximately 99% of patients who were COS(+) were eventually confirmed to be uninfected. However, the average length of stay is 7 days in our hospital. Thus, it would be impractical to extend cutoff of our COS system to increase cost-effectiveness. “What threshold of cough duration would be appropriate and more cost-effective for us to raise the suspicion of PTB and arrange examinations?” is an aim of our ongoing research.

(2) Any single missing case of TB may cause events of nosocomial transmission or community transmission, which will inevitably increase the medical cost of the country. Therefore, we thought there was benefit even if a massive screen can detect just one TB patient.

2. 60% and 45% of patients identified by the COS system were not examined by physicians in stage I and II respectively - what were the reasons for this? Yet, figure 1 shows that there were 10 TB cases in stage I - how were these cases diagnosed? Could the authors be sure that there were no other TB cases from among those who were not examined by the physicians?

Response: The inclusion criteria of our COS system are rather simple. Any patient who had a cough for more than 5 days would be alarmed. There are several reasons that the physician may not take action.

• The patient was excluded from possibility of TB before the COS alarm (i.e. the cough was caused by another respiratory disease);

• The patient has been confirmed as having M. tuberculosis infection, and there was no need for further check;

• The patient refused to receive a TB examination;

• Based on clinical experience, the physician did not think the patient had TB.

3. Was the diagnosis of TB based on positive sputum TB cultures in all patients? If not, what was the proportion of bacteriologically negative patients, ie those in whom the diagnosis was made based on chest radiograph features? (These patients are likely to be less infectious, and of less public health impact.)
Response:

A section on “Tuberculosis diagnostic procedures” was added to the “Methods” section. The physician could make choice between Chest X-Ray and sputum smear/culture, but a true positive in our study required a positive Mycobacterial culture.

4. The authors could, from their data, make suggestions for refining their COS alarm system for better targeting of patients with cough for TB evaluation. Were there risk factors identified (eg. age, BMI, co-morbidities such as diabetes or malignancy) which may be helpful in more efficient targeting of patients?

Response: Our suggestion is that, under cost-effective consideration, other hospitals or health care centers should consider implementation of a COS system in the Internal Medicine Department first, since a majority of COS (+) patients were in this department. We included this information in the “Discussion” section.

5. That the time from COS alarm to clinical action was significantly longer in stage II may suggest some complacency. The authors attributed it to the exclusion of ICU cases in stage II. Was subanalysis of stage I data on non-ICU patients performed to substantiate this?

Response: We did not analyze data for on non-ICU patients (exclusion of ICU population) in stage I because both ICU and non-ICU patients used the same COS system to early screening for TB patients in Stage I. However, in Stage II, we use different strategy of TB screening for ICU patients. Therefore, we have to exclude ICU patients from our study group in Stage II.

6. The conclusion that the COS system "appears to reduce nosocomial transmission of TB" cannot be made from the study findings. Risk of nosocomial transmission was not specifically measured as a study outcome. There are also other factors besides diagnostic delay which influence the risk of nosocomial transmission.

Response: Done! We rewrote the Conclusion accordingly.