Author's response to reviews

Title: Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study

Authors:

Anamarija Jurcev-Savicevic (anamarijajs@gmail.com)
Prof Rosanda Mulic (rmulic@hotmail.com)
Bozica Ban (bbozica@yahoo.com)
Prof Karlo Kozul (kozul.karlo@yahoo.com)
Ljiljana Bacun-Ivcek (bacunivceklj@hotmail.com)
Jasna Valic (valicjasna@hotmail.com)
Gordana Popijac-Cesar (gordanapopijaccesar@yahoo.com)
Snjezana Marinovic-Dunatov (MarinovicDunatov.S@gmail.com)
Majda Gotovac (gotovac.majda@hotmail.com)
Aleksandar Simunovic (aleksandars07@hotmail.com)

Version: 3 Date: 4 September 2013

Author's response to reviews:

Dear Editor,

We answered to all comments and we accepted all suggestions of reviewers. It is clearly pointed in the manuscript as well as in the answers to the reviewer’s comments. Their comments and suggestions were very useful and significantly improved this manuscript. We hope that the revised version will better fit with their expectations and suggestions. We hope that the presentation of data has been improved and that it will be suitable for the publication in your esteemed Journal. We are willing to make any additional changes if necessary.

Reviewer:
Marieke J. van der Werf
Reviewer’s report:
This is a case control study in which the authors set out to assess the risk factors for tuberculosis in Croatia. Their argumentation to do this is that even though many studies have looked at risk factors for TB none has done so in a middle incidence country.

Methods
Major compulsory revision
The main challenge in a case control study is the selection of the control group which has to come from the same source population as the case population. The description of how the cases were selected is not completely clear but it seems
that cases were not selected from general practitioners offices. Since it is clear from the methods section that the controls were selected from general practitioners offices there is an inherent risk of bias as the cases and the controls are not from the same source population.

Two health insurance types operate in Croatia: mandatory health insurance (provided only by Croatian health insurance fund- CHIF) and supplementary, non-mandatory insurance (provided by CHIF and/or private insurance companies). Contributions for mandatory insurance are also mandatory for all employed citizens, i.e. their employers or self-employed workers. The dependents obtain their health care coverage through contributions paid by working members of their families. Retired people and persons with low income are insured by Croatian Health Insurance Fund and have free access to health care covered by mandatory insurance.

Primary health care, including general medicine, is covered by mandatory insurance provided by CHIF and general practitioners are his contracted partners. Therefore, general practice is provided free of charge for all insured Croatian citizens (98.3% of the total Croatian population at the time of this study) and 95% of the total population was registered in general practitioners’ registers. The diagnostic procedures and drugs recommended by general practitioners are also mainly free of charge. Some participation may be asked (usually covered by supplementary, non-mandatory insurance) but tuberculosis prevention, diagnosis and treatment are completely free of charge.

That is why we believed that the control group represent the total Croatian population and that virtually every Croatian had an equal chance to be selected as a control.

The cases were included in the study at the time they were reported to the epidemiologists as TB cases which is mandatory in Croatia. We do not extract them from GPs registries for study purpose. But 95% of the Croatian population, where all cases and controls came from, are registered in GPs’ registers. In our opinion that is why cases and controls came from the same source population.

The best way to select the control group would be Census. Unfortunately, it was not possible to have such data for this purpose and we used the next best possible way.

We included this statement in the Methods hoping that we explain your concern successfully.

Minor essential revisions

Please specify from how many counties the 7 were selected randomly.

The idea was to include more than 50% of the Croatian population and more than 50% of TB patients registered in the preceding year. This study was started in eight randomly selected counties out of the 21, covering 60.8% of the Croatian population and 53.6% of all registered TB patients in the preceding year. In the course of the study, one county was later excluded along with all interviewees
because the investigator was moved to another non-participating county.
Therefore, seven counties with 48% of TB patients and 53.9% Croatian population were finally covered.

Page 6: The sentence ‘Dual TB notification ....had been made’ is not clear. Please rephrase

The dual TB notification system (physician and laboratory notification) had been successfully implemented since 1998. This mean that epidemiologists (authors of this study) will receive two notifications for single laboratory confirmed TB patient, one from the physician and another from laboratory- microscopy results immediately (24 hours) and culture results upon cultivation. This notification system reassures that all confirmed cases were included in this study. This explanation is included in the paper.

Page 7: In the sentence ‘Many demographic variables ....Tables 1, 2, 3’ the word ‘demographic should be deleted.

It is deleted.
Page 7: The description of how household equipment is graded is not clear. It is suggested that the number of items is counted however, this is not clearly written down.

It is added.
Page 7: The authors should check the numbers. I believe that the mean underweight (<18.5), however, they use a comma and a space which makes it difficult to understand.

It is corrected.

Please also specify how the cases were contacted.

In Croatia, infectious TB patients have to be interviewed by epidemiologists, independently of this study, for contact tracing purposes. For this purpose, the interviews were different and longer than routine one. They were conducted usually in hospital (Croatian patients usually have to be hospitalized during initial phase or at least 2-3 weeks after treatment initiation) or in their homes (if they start TB treatment at home).

All authors of this study are epidemiologists and they have been involved in TB control at county level (including interviewing of TB patients) and one author has been working at national TB registry.

The authors mention that they used the Pearson Chi-squared test for categorical variables. Since the result section does not provide any Pearson Chi-squared test result this sentence can be deleted.
It is deleted.

Results

Major compulsory revisions

The data were collected in 2006-2008. This makes the study a historical description of a situation of 5 to 7 years ago especially since the TB situation has changed considerably with only 14 TB cases notified per 100,000 population in 2011, which makes Croatia no longer a middle incidence country. It is unclear how the presented data are useful today or why the study is only submitted for publication now.

Yes, we probably should have written and published the paper earlier, the reasons are personal. However, this is well-designed and performed study and we find it one small, but interesting piece of the puzzle of the huge TB picture. We would like our results to be visible to readers.

To make the results section accessible to the reader I suggest to only report on very interesting findings and not to repeat everything that is also illustrated in the Tables, especially for the bivariate comparisons.

We correct the section results and delete bivariate analysis results.

Minor essential revisions

Page 8: Please explain why the other 6 cases were excluded.

It was explain in results: unavailability (3), death (3), serious illness (3) and refusal (2). We rewrote this sentence to be more clear.

Page 8: Please delete the sentence ‘The study population was gathered on the basis of 300 cases and 300 controls’. This sentence should be in the methods section.

It is moved in method section.

Page 8: The sentence ‘Frequencies of demographic .... Table 1, 2, 3’ should be in the present tense.

It is corrected.

Discussion

Minor essential revisions


We rewrote this sentence and added that it refers to the study population.

Page 11: The sentence ‘but it can have much greater impact can have’ seems to
be incorrect.
It is deleted.

Page 12: The sentence ‘This study showed that the likelihood of developing diabetes’ seems incorrect since the study is about developing tuberculosis.
Yes, thank you for noticing, we corrected this statement.

Page 13: Please clarify the sentence ‘Study design and complex statistical analysis may control the effect of potential confounding variables’. Does this sentence refer to the current study?
It is deleted.

Figure 1
Minor essential revision
The title of figure 1 does not describe the content of the figure.
We changed the title. (Reasons for exclusion of individuals from the control group)

Reviewer:
Guy Harling
Reviewer’s report:
This paper provides descriptive data on correlates of TB disease in Croatia using a population-based sampling frame for generating controls to match to controls. The study seems straightforward, the analysis well executed and the authors make some efforts to link their findings back to existing literature.

Minor Essential Revisions:
1. The authors should have this manuscript reviewed by a native English speaker. The standard of English used is generally good, but grammatical errors are noticeable and sometimes make comprehension difficult. In similar vein, the use of European-style commas and English-style decimal points is inconsistent. English editing has been done by a native speaker. His cover letter is attached.
2. As the authors note, this study appears to be the first to look prospectively at risk factors associated with Croatia. This is interesting, but have there been any other studies in Eastern Europe and/or the Former Soviet Union? The authors mention variation in risk factors across Europe in the Introduction, but it would be of interest to this reader to see the findings of the study compared to risk factors
seen elsewhere.

Two studies were cited both in the Literature section and Discussion (Russia-Coker et al, Estonia-Tekkel et al). To the knowledge of these authors and the review of published literature in English, studies related to this particular issue (risk factors for TB) in Eastern Europe and/or the Former Soviet Union are not numerous. There are more studies which describe and comment on routinely collected data, especially the issue of resistant TB.

3. More generally, the Introduction and Discussion does not help place the findings in the broader context of TB research in middle-income countries worldwide. Given the framing of the article as an insight into a middle-income, middling-prevalence setting, it would be of great interest to the reader to understand how Croatia is similar or different to similar settings, and to richer/poorer or higher/lower incidence settings.

Croatia has been high income country since last few years. At the time of this study, Croatia was on the border between middle and low TB incidence. We discussed data about similar European countries (high-income, low prevalence) in the introduction and discussion and added a few additional references.

4. Introduction. The introduction seems very brief. What information exists on risk factors in middle-income countries with reasonably high TB burdens (e.g. Brazil, Peru, China, Russia, other Eastern European countries)? How does it differ from developed or developing countries? My goal here is to understand what we might expect to see in the Croatian analyses, so as to better interpret the study’s findings.

We presented data about similar European countries (high-income, low prevalence) and added a few additional references.

5. Results. The inclusion of many odds ratios and CIs appears to be largely repetition of information provided in the Tables, and additionally makes reading the Results difficult. I would recommend removing the statistics which are already provided elsewhere.

We deleted redundant results.

6. p11, first paragraph. The authors seem surprised that having a parent born in Bosnia Herzegovina is a risk factor. However, this variable is likely to be strongly associated with being born there oneself (a bivariate risk factor in their analysis), and thus to having been exposed to infected persons. I would also suggest that the authors refrain from suggesting nationality-based genetic susceptibility
without evidence, given the large number of other risk factors (as noted in their analysis) that might explain the differential risk in Bosnia Herzegovina.

We agree with your suggestion.

7. p11, second paragraph. The authors note the association between low socioeconomic status to TB, and then note that crowding may be a mediator for this effect. However in this study crowding is negatively associated with TB. Can the authors explain this finding?

It was associated with TB in bivariate analysis, but probably due to confounding. In the multivariate model, when confounding was neutralized, this variable was not significant.

8. p12, third paragraph. Could the authors provide some idea of the prevalence of LTBI in the population – is the prevalence high enough that even low levels of immunosuppressed patients may make this an important population to focus on for TB prevention?

Unfortunately, there is no such data. The ERS European Forum for TB Innovation, discussing the new World Health Organization post-2015 Strategy and on how to direct TB control, highlighted that TB elimination requires focus on sterilizing the pool of latently infected individuals from which future TB cases would be generated.

9. Conclusion. The framing of the conclusion – that TB is more than a social disease – is an interesting approach, but does not seem well-connected to the rest of the paper. Are the authors trying to separate TB in Croatia from that in the rest of the EU and/or high-burden, poorer countries? If so, this might be worth saying explicitly here.

We stated that dimension of TB in Croatia is complex and the correction in discussion is made.

10. Figure 1. The title to this figure does not appear to clearly define the content, but rather to be describing the main finding. A more neutral title, e.g. “Reasons for exclusion of individuals from the control group”, might be more appropriate.

Thank you for this advice, it is corrected.

Reviewer's report

Title:
Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study
I think that this manuscript would benefit from some minor revisions.

1. The standard of English used is generally good, but there are some grammatical errors (I am not expert, of course!).

English editing has been done by a native speaker. His cover letter is attached.

2. Abstract: The authors might want to make clear what (individual or groups of) variables are not associated with TB in this dataset.

Some variables from each groups were found to be significant. Unfortunately, there is no space in the abstract section to underline non-significant variables, but this is visible in the tables.

3. Introduction. This study seems to be the first to look prospectively at risk factors associated with TB in Croatia. Have there been any other studies in Eastern Europe and Former Soviet Union?

Two studies were cited both in the Literature section and Discussion (Russia-Coker et al, Estonia-Tekkel et al). To the knowledge of these authors and the review of published literature in English, studies related to this particular issue (risk factors for TB) in Eastern Europe and/or the Former Soviet Union are not numerous. There are a few studies which describe and comment routinely on collected data, especially the issue of resistant TB.

4. Methods. It would be of interest to this reader to see how the follow-up of the controls during two months period was organized?

It was designed that tuberculosis development in a control group should lead to the exclusion of such a participant. After interviewing the control group, none of them had developed tuberculosis in a two-month period.

All authors are epidemiologists and they have been involved in TB control at regional level (notification, surveillance and contact tracing) or working at the national TB registry. That is why all new TB patients have to be reported to these epidemiologists and they checked their names in the database of controls. They would also recognize them during interviewing, this time as TB patients.
5. Discussion. Is there any data of prevalence of LTBI in the general population in Croatia?

There is no such a data.

6. Table 1. What do missing values mean in Table 1?

Missing values mean that there is a lack of data on some patients - there are no 600 data, but 599 or similar.