Reviewer's report

Title: Prevalence and predictors of tuberculin skin testing positivity in Hellenic Army recruits: a cohort study

Version: 1 Date: 29 May 2006

Reviewer: Frank G Cobelens

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General

This is an interesting paper that provides potentially relevant results on the trend of tuberculosis and the effect of repatriation in Greece. However, some issues need to be addressed or clarified to allow meaningful interpretation.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Title: this is not a cohort study (no-one is followed up for outcomes).

2. It would be important to have more information, e.g. in a graph, on the distribution of reaction sizes, preferably stratified by native-repatriate status.

3. There should be a clearly stated research question.

4. The authors draw two types of conclusions from their data: on trend in infection prevalence over time, and on risk factors for latent TB infection. Both are relevant, but it is important to note that both pose different requirements with regard to representativeness of the study population and interpretation of the tuberculin reactions, and this should be discussed in the methods and discussion sections, see below.

5. With regard to representativeness: in order to say something about the trend in TB infection prevalence in the native Greek population, the reader must be assured that the study population reflects the population at large, and if it does not, what the expected direction of possible selection bias would be. It is thus important to know whether the conscripts tested are all men enlisted during the inclusion period, whether all repatriated young men are enlisted and whether there are seasonal variations in enlistment (inclusion was during only one quarter), e.g. by region. For the comparative analysis, representativeness is less of an issue.

6. With regard to the TST cut-off, the authors seem to confuse its use in an epidemiological study with that for individual patient management. For the latter purpose, cut-offs are basically policy decisions, based on positive and negative predictive values and the importance of treating particular individuals, whereas in a study as presented here the choice should be based on sensitivity and specificity, and comparability with other studies, i.e. on study validity. In other words, whether or not the cut-offs used in this study are in accordance with guidelines by ATS or others is basically irrelevant.

7. The cut-off of 15 mm used in this study seems a good choice for the comparative analyses since it provides relatively high specificity for latent TB infection and maximizing the specificity of the outcome parameter reduces misclassification bias in any comparative study. Reducing the cut-off to 10 mm for repatriates (as they suggest in the discussion section) would definitely not be a good idea because it would introduce substantial bias. For an interpretation of the trend in infection prevalence however, the cut-off should be the same as that used in the earlier studies to avoid potentially strong bias. I have not been able to check the references given, but this may well have been 10 mm. In addition, it would be important to know that the earlier studies used the same tuberculin in the same strength. Finally, the tested population should have (roughly) the same mean age; an alternative would be to compare the age-adjusted prevalence expressed as the annual risk of TB infection.

8. The authors insufficiently acknowledge the limitations posed by the lack of data on BCG status. The problems this may cause are 2-fold, and both need to be addressed appropriately to judge whether this invalidates their findings. First, the proportion of individuals with >15 mm due to cross-reaction with BCG may differ between the previous surveys done among Greek conscripts, which would bias the trend in
infection prevalence. For this it is important to know in more detail the BCG vaccination policy in Greece, possible changes in this policy over time, and the BCG coverage that applies to the age cohorts studied. Age at vaccination and revaccination are important to mention as well, since BCG in the first year of life has virtually no effect at cut-offs of 10 mm or higher, whereas BCG given later affects the TST response to an unpredictable extent. Second, this may be different between native Greek and repatriate conscripts. To my information, the Sovjet Union used to have a nationwide policy of BCG (re)vaccination around the age of 6 and revaccination of those who did not respond with a positive TST. Also the BCG vaccine used may have been different from that used in Greece, potentially resulting in differences in cross-reactivity. The authors should thus note that the higher infection prevalence observed among repatriates may in part reflect a higher proportion of BCG cross-reactions. Graphs of reaction size distributions (see above) could shed more light on this. Their statement that “Differences in immunization practice do not seem to fully explain the observed difference” is not supported by data and should be omitted. The ATS guidelines, as said, are not relevant here.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Methods, TST: “Denmark”. Assuming that the RT23 was in Tween-80, this should be added (as it affects test sensitivity). What is meant by “appropriately counseled”?

2. Id, data collection: where the interviews standardized (e.g. by structured questionnaire)? “Former” instead of “previous”.

3. Discussion, 3rd para, 1st sentence (“The identification of”). I am not sure this is a correct statement. It is not the identification of persons with a positive TST that serves as an estimate of disease burden, but the observed infection prevalence. I would also prefer “indirect estimate”, and “accounting for” instead of “after excluding”. The main problem however is that the proportion vaccinated is unknown, making it impossible to infer a disease burden from these data.

4. Id, 4th para, 1st sentence: The Hellenic Army has participated

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Discretionary Revisions (which the author can choose to ignore)

Background, 1st sentence: the death toll by malaria and HIV is higher.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.