Author's response to reviews

Title: Effectiveness of DNA-recombinant anti-hepatitis B vaccines in blood donors: a cohort study.

Authors:

Emil J Kupek (kupek@ccs.ufsc.br)
Denise ER Souza (danierig@terra.com.br)
Andrea Petry (deapetry@yahoo.com.br)

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Author's response to reviews: see over
**Response to reviewer Leslie H. H. Tobler** (authors’ response in italics)

**General**

I have a problem with premise that the authors put forward, effectiveness of DNA-recombinant vaccine among blood donors. In my opinion there is no reason to believe that the effectiveness of DNA vaccination should be any different among blood donors compared to other groups that have been monitored. What the authors are really concerned with is transfusion-transmission of HBV in Brazil and the beneficial impact of wide spread, government sponsored, HBV vaccination of blood donors in HBV endemic areas of Brazil. Unfortunately, the authors never use the terms of “transfusion recipients” or “transfusion recipient safety”. It is my opinion that this issue should be addressed in both background and discussion sections of the manuscript.

*We share the view that there are no reasons to believe that the efficacy of DNA-recombinant anti-HBV vaccines among blood donors should be much different from the efficacy in other healthy adults. However, vaccine effectiveness does not necessarily follow this logic because it is dependent on a particular setting due to selection bias. In the blood donor context, this bias may arise because protection factor (getting vaccinated) is likely to be influenced by a more general attitude towards health which also reduces risk behavior for HBV infection. Differently from a RCT of vaccine efficacy, it is ethically unacceptable to randomly allocate anti-HBV vaccine to blood donor candidates because its protective effect has already been proven beyond any doubt. It is therefore necessary to try to adjust post hoc for risk factor imbalances between vaccinated and non-vaccinated blood donors, i.e. after data collection. As for the transfusion-transmitted HBV in Brazil, it is indeed our primary concern. However, the benefits of a widespread anti-HBV vaccination in Brazil cannot be evaluated with much precision yet because vast majority of the vaccinees have not yet reached the minimum age for blood donation (18 years). As government-sponsored mass vaccination against HBV has started approximately a decade ago and has so far been reasonably implemented only in the first year of life, vast majority of blood donor population in Brazil remain unvaccinated against HBV. This underlies the need for targeted vaccination of blood donors in addition to the children vaccination.*

The above issues have now been addressed both in background and discussion sections.

**Minor essential revisions**

**Abstract:**

1. Background: “a group of great importance for reducing the transmission of hepatitis B” should be changed to “a group of significant importance in the reduction of the transfusion-transmitted hepatitis B”

2. Methods: “double cohort study of repeated blood donors” should be changed to “double cohort study of repeat blood donors”
1. Background: “a group of special importance to prevent HBV transmission” should read “a group of special importance in preventing HBV transmission”.

2. Background: “state capital Florianopolis has reduced considerably” should read “state capital Florianopolis has been reduced considerably”.

Discussion:

1. “Brazilian blood donors should be systematically encouraged to take up anti-HBV vaccine” should be changed to “Brazilian blood donors should be systematically encouraged to get vaccinated with the DNA-recombinant anti-hepatitis B vaccine”.

2. “thus leaving a period of several moths before anti_HBC” spelling error should be corrected.

3. “The incidence of this order has left more space for its reduction due” should be changed to “An incidence of this order could be significantly reduced by vaccination compared to the impact of vaccination in low endemic areas”.

4. “to minimize the impact of confounding” should be changed to “to minimize the impact of confounding factors”.

5. “providing important information for reduction of HBV infection in adult population” should be changed to “providing important information about the reduction of HBV infection in the adult population”.

Conclusion:

1. Something about recipient safety should be added to the first sentence of this section. An example would be “The results showed a very high effectiveness of DNA-recombinant anti-hepatitis B vaccination among blood donors resulting in the enhancement of blood recipient safety in the State of Santa Catarina.”

All minor essential revisions have been made as indicated by the referee.
Response to reviewer Fransisco Souto (authors´ response in italics)

Major compulsory revisions

1. I suggest that the authors consider to show important numbers such as the N of groups and the average of follow-up time in “Results” and “Abstract”. The readers only can know the total N of groups if they calculate the sum of the categories of one of the variables in Table 1.

*We added the above information as required.*

2. I am in doubt about the incidence ratio that the authors presented (2.33 per thousand person-years). In the Table 2, we can see that the numerator and the denominator of the non-vaccinated group are 4 and 2747, respectively. The result is 1.45 instead of 2.33. I think this result appears because “half-time between the dates of the last seronegative donation and the positive serologic test” was considered in case of HBV infection. If it is the explanation for this IR (2.33/1,000) then it would be reasonable to insert another column (between “person-years” and “incidence”) showing the denominator in fact considered when the IR was calculated.

*Total follow-up time has been inserted in the Table 2 as suggested.*

3. I would like to know why the authors chose not to show a KM survival curve and Cox regression results of this interesting cohort study.

The main reason for omitting Kaplan-Meier and hazards ratio distribution for the groups under comparison was an extremely low number of events of interest (only 4 cases of HBV infection, all among non-vaccinated), thus severely limiting the applicability of time-to-event regression methods.

This has now been mentioned among other limitations in the discussion.

Minor essential revisions

1. “Cirrhoses” appears wrongly written
2. In the last sentence of the third paragraph of “Background”, I suggest change “…recent indication…” for “…recent evidences…”
3. The last paragraph of Background seems unnecessary since it is just an introduction to the following sections…It seems to me that the authors should change this paragraph for other one summarizing the goals of the study or giving a justification for carrying it out.

*Above corrections have been made.*

Discretionary revisions

1. In the third paragraph of “Methods”, first sentence, I think the authors changed the position of the two groups “vaccinated” for “non-vaccinated”.
Indeed; this has been corrected.

2. I would suggest that the authors consider to introduce a line about “the time average of follow-up” in the Table 1.

The information on average follow-up has now been added in the beginning of the “Results” (Table 1 uses percentage headings, so it was easier to report means in the text rather than mixing them with percentages in the table).