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

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Abstract

Background
Although various studies have demonstrated efficacy of DNA-recombinant anti-hepatitis B vaccines, their effectiveness in health care settings has not been researched adequately. This gap is particularly visible for blood donors, a group of great importance for reducing the transmission of hepatitis B.

Methods
This is a double cohort study of repeated blood donors during the period 1998-2002, involving a vaccinated and an unvaccinated cohort, with matching of the two in terms of sex, age and residence. The outcome measure was infection with hepatitis B virus (HBV), defined by testing positive on serologic markers HbsAg or anti-HBC. All blood donors were from the blood bank in Joaçaba, federal state of Santa Catarina, Brazil.

Results
The cohorts did not differ significantly regarding sex, age and marital status but the vaccinated cohort had higher mean number of blood donations and higher proportion of those residing in the county capital Joaçaba. Hepatitis B incidences per 1000 person-years were zero among vaccinated and 2,33 among non-vaccinated, resulting in 100% vaccine effectiveness with 95% confidence interval from 30.1% to 100%. The number of vaccinated persons necessary to avoid one HBV infection in blood donors was estimated at 429 with 95% confidence interval from 217 to 21422.
Conclusions

The results showed very high effectiveness of DNA-recombinant anti-HBV vaccines in blood donors. Its considerable variation in this study is likely due to the limited follow-up and the influence of confounding factors normally balanced out in efficacy clinical trials.

Background

There is a wide consensus that vaccination against hepatitis B virus (HBV) is the best cost-effective measure to combat the disease [1]. In Brazil, its burden is grossly underestimated due to the epidemiologic surveillance which captures primarily severe cases in need of hospital treatment while missing the long term consequences of HBV infection such as cirrhoses and hepatocellular carcinoma. It has been estimated that vaccinating children against HBV in developing countries would prevent loss of three million lives each year, as well as 60-80% of cases of hepatocellular carcinoma [1-3]. More than 150 countries have already given high priority to the vaccination programs against HBV [3], but some of them, including Brazil, have not fully implemented such programs.

Brazil has recently started producing a DNA-recombinant anti-HBV vaccine whose immunogenecity has been confirmed in several studies [4-7]. However, its effectiveness in reducing HBV incidence in health care settings has not been adequately researched. This gap is particularly visible regarding blood donors – a group of special importance to prevent HBV transmission and therefore explicitly targeted for immunization at any age according to the guidelines of the Brazilian Ministry of Health [8].
Although the residual risk of not detecting HBV by routine sorologic screening in the largest blood bank in the state capital Florianopolis has reduced considerably in the decade of 1990, it remains at a level approximately hundred times higher than in the developed countries [9,10]. Another reason to incentivate vaccination among blood donors and verify its effectiveness is recent indication of a high risk group using blood bank sorologic screening to check their HIV status due to the guarantee of obtaining an anonymous, free of charge and rapidly delivered test result in this health setting [10,11].

The manuscript proceeds by describing the material and methods applied in this study, with a particular emphasis on balancing the baseline differences between the vaccinated and the non-vaccinated cohort, followed by the results and discussion of the findings.

**Methods**

A retrospective double-cohort study [12] was used to estimate the protective effect of anti-HBV vaccination by comparing the incidence of HBV infection in the vaccinated and the non-vaccinated cohort of repeat blood donors. For the purpose of this study, case definition of HBV infection was the presence of either of the two sorologic markers used for blood donor screening, namely HBsAg (produced by “Hepanostika–Biomerieux”) or anti-HBe IgM+IgG (produced by “Ortho Diagnostics”), confirmed by at least one positive test result on subsequent sorologic testing with the same markers. The cohorts were matched by sex, age and municipality of residence. The vaccinated cohort was recruited from an earlier study on soroconversion [7]. The inclusion criteria for both cohorts were having done at least two blood donations
during the period of the study (1998-2002) and being between 18 and 65 years of age. For the vaccinated cohort, an additional requirement was that the blood donors soroconverted after three doses of anti-HBV DNA-recombinant vaccine ("Engerix-B®" - SmithKline Beecham Biologicals; "Euvax-B®" - LG Chemical, Korea; "ButaNG®" - Instituto Butantã, São Paulo, Brazil), with the second and third dose following one and six months after the first dose, respectively. The soroconversion criterion was obtaining the titre of at least 10 UI/l of antibody to HBsAg (test anti-Hbs produced by “Biomerieux”) three months after receiving the last dose of the vaccine.

For each eligible vaccinated donor, a non-vaccinated donor was looked after within the same age band (18-29, 30-44, 45-65 years), of the same sex, and in the same municipality. If no sex by age pair could be found in the same municipality, an adjacent municipality of residence was searched to obtain this matching. All blood donations were realized in the blood bank in Joaçaba, a county capital situated in an area endemic with hepatitis B.

For the vaccinated donors, the individual contribution to person-time incidence denominator was calculated as the difference between the date of last blood donation and the date last dose of anti-HBV vaccine was applied. For the non-vaccinated donors, the individual person-time contribution was the difference between the dates of the last and the first donation during the study period. If HBV infection occurred, person-time denominators were reduced by half-time between the positive sorologic test result and the last soronegative donation [13].

The sample size calculation was based on the incidence ratio of 19 for the vaccinated against the non-vaccinated cohort, derived from the reported anti-HBV vaccine efficacy of approximately 95% (against remaining 5% in the same group), the HBV incidence in the non-vaccinated blood donors of 0.67% in the Joaçaba blood bank
[14], and errors type I and II of 5% and 20%, respectively. Assuming these parameters and equal person-time denominator for both cohorts, Breslow-Day method resulted in 2148 person-years and at least 4 HBV cases between the cohorts [15]. Statistical analysis used Stata [16] and WINPEPI [15], with mid-P method to calculate the 95% confidence intervals (CI) and Pearson´s chi-square test for significance of the differences between the blood donors´ baseline characteristics.

**Results**

**Baseline differences between cohorts**

The distribution of risk factors for HBV was similar among vaccinated donors included and excluded from the analysis of vaccine effectiveness, except for larger percentages of donors with frequent donations prior to the study (chi-square of 535 with 3 degrees of freedom and p<0.01) and those residing in the county capital (chi-square of 91 with 2 degrees of freedom and p<0.01) (Table 1).

Among repeat donors included in the analysis of vaccine effectiveness, it is worth noticing a higher percentage of vaccinated (56.2%) than non-vaccinated (37.7%) residing in the county capital, as well as a higher number of frequent donors among the former compared to the latter (Table 1). Consequently, average interval between donations was significantly longer among the non-vaccinated (0.62 years, 95% CI from 0.58 to 0.65 years) compared to the vaccinated donors (0.46 years, 95% CI from 0.43 to 0.50 years).
Anti-HBV vaccine effectiveness

Anti-HBV vaccine effectiveness was calculated as one minus the incidence ratio of vaccinated to non-vaccinated donors. The vaccine was 100% effective, with 95% CI from 30.1% to 100% (Table 2).

The difference in HBV incidence between the cohorts compared was 2.33 (95% CI from 0.05 to 4.62) per thousand person-years. From the perspective of the number necessary to treat (NNT), it would be necessary to vaccinate 429 (95% CI from 217 to 21422) blood donors to avoid one HBV infection in this population.

In order to verify possible confounding due to the two HBV risk factors found to be significantly different between the cohorts compared, a stratified analysis crossing all levels of these two factors was performed. This resulted in 12 strata (4 levels of the number of prior blood donations crossed with 3 levels of the residence area). No statistically significant difference (p<0.05) of the difference in HBV incidence between the vaccinated and the non-vaccinated cohort was found either within any of the 12 strata analysed separately or for the Maentel-Hanzel pooled estimate (mean difference -9.82 with 95% CI from 021.19 to 1.54).

Discussion

The results of this study showed excellent effectiveness of DNA-recombinant anti-HBV vaccines in blood donors, similarly to the results in the general population [17-20]. Wide confidence intervals for the vaccine effectiveness are probably due to the very small numbers in the incidence numerators natural for rare events and presence of other factors influencing the vaccine effectiveness in a health care setting which are better controlled for or balanced out in a clinical trial setting.
The countries that implemented a large scale vaccination against HBV and maintained it for at least a decade managed to reduce the HBV incidence more than ten times during this period [17-20]. Brazilian Ministry of Health has recently introduced a similar anti-HBV vaccination program with mandatory vaccination for children and adolescents up to 15 years of age [8]. However, only children in the first year of life have had reasonable vaccine coverage, thus leaving a vast majority of the population, including blood donors, unprotected against HBV. A catch-up vaccination campaign would be appropriate to accelerate the reduction of HBV in the general population. In addition, Brazilian blood donors should be sistematically incentivated to take up anti-HBV vaccine. Although this group has been clearly emphasized in the recent vaccination guidelines [8], the logistics necessary to meet this target have not been reinforced nationwide, so it is basically up to a blood donor to seek a primary care unit and solicitate anti-HBV vaccination on individual basis.

Several limitations of this study should be born in mind. First, although matching by sex and age has likely removed major confounding factors and the stratified analysis confirmed the main results of the study, it is still possible that residual confounding factors such as motivation to donate blood have not been fully accounted for in the analysis. The motivation is known to influence risk behaviour which in turn influences the chances of being infected with HBV. A prospective cohort study would have better means of controlling for this factor. Second, the absence of HbsAg positive result in the early phase of HBV infection may be as high as 25% [13], thus leaving a period of several months before anti-HBC becomes detectable by routine sorologic testing in blood banks for a considerable proportion of donors. During this period, neither of these two HBV markers can detect the virus, leading to underestimation of the true HBV incidence. Third, very few cases of HBV
seroconversion, as well as the fact that all of them occurred in the non-vaccinated cohort, reduced the statistical power to estimate vaccine effectiveness with precision, thus leading to wide confidence intervals. Fourth, the blood donors resided in an endemic area for HBV where the infection rate in adult population is likely to be high, as indicated by the HBV incidence of 2.33 per thousand person-years observed in the non-vaccinated cohort. The incidence of this order has left more space for its reduction due to vaccination than it would be possible in the areas of low endemicity, therefore limiting the generalizability of anti-HBV vaccine effectiveness from this study to such areas.

Despite the limitations, this is the first study of anti-HBV vaccine effectiveness in blood donors using a cohort study with matched control group to minimize the impact of confounding. The same methodology can be applied to other blood banks without interfering with their daily routine. A multi-centre evaluation of anti-HBV vaccine effectiveness can be set up on a regular basis with this study design, providing an important information for reduction of HBV infection in adult population.

**Conclusions**

The results showed a very high effectiveness of DNA-recombinant anti-hepatitis B vaccines in blood donors. Considerable variation of this estimate is likely due to the limited follow-up and the influence of confounding factors normally balanced out in efficacy clinical trials.
Competing interests

None declared.

Authors' contributions

Emil Kupek and Denise Erig Rocha de Souza designed the study. Denise Erig Rocha de Souza and Andrea Petry collected the data. Emil Kupek did the statistical analysis and wrote the draft of the paper. All authors contributed to the writing of the final version of the paper.

References


### Tables

#### Table 1 - Blood donor characteristics regarding main confounding factors, vaccination and inclusion criteria

<table>
<thead>
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<th>Risk factors</th>
<th>Included in the analysis</th>
<th>Excluded from the analysis</th>
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<tr>
<td></td>
<td>Non-vaccinated repeat donors</td>
<td>Vaccinated repeat donors</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age bands (years)</td>
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<td>18-29</td>
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<tr>
<td>30-44</td>
<td>351</td>
<td>49.2</td>
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<tr>
<td>45+</td>
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<tr>
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<tr>
<td>Feminine</td>
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<td>Number of donations prior to</td>
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<td>6-10</td>
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Table 2 - Effectiveness of anti-HBV vaccine, incidence ratio (IR) and 95% confidence interval (CI)

<table>
<thead>
<tr>
<th>Cohort</th>
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<th>Person-years</th>
<th>Incidence *</th>
<th>IR (95% CI)</th>
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<tbody>
<tr>
<td>Vaccinated</td>
<td>0</td>
<td>2715</td>
<td>0.00</td>
<td>0 (0.000, 0.696)</td>
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<tr>
<td>Non-vaccinated</td>
<td>4</td>
<td>2747</td>
<td>2.33</td>
<td>1.000 **</td>
</tr>
</tbody>
</table>

* per thousand person-years

** reference category

* with at least 20,000 inhabitants

** less than 20,000 inhabitants