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## Critically Appraised Articles

# HLA genotype does not appear to influence long-term antibody response to hepatitis B vaccine

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**English key words:** HLA typing, hepatitis B vaccine, inmunogenicity, vaccine.
**Palabras clave en español:** genes clase II del complejo de histocompatibilidad, vacuna hepatitis B, inmunogenicidad vacunal.

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# HLA genotype does not appear to influence long-term antibody response to hepatitis B vaccine

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**Original article:** Xu B, Zhu D, Bi Y, Wang Y, Hu Y, Zhou YH. Minimal association of alleles of human leukocyte antigen class II gene and long-term antibody response to hepatitis B vaccine vaccinated during infancy. Vaccine. 2017;35:2457-62.

**Abstract**

**Authors' conclusions:** none of the ten HLA class II gene alleles previously reported to be related with short-term antibody response to hepatitis B vaccine is associated with the long-term antibody response after vaccination during infancy.

**Reviewers' commentary:** despite some differences in the study population from the population of our environment, we can conclude that it would not be necessary to determine the HLA class II alleles to detect children at risk of vaccine failure against hepatitis B.

**Key words:** HLA typing, hepatitis B vaccine, inmunogenicity, vaccine.

**El HLA no parece influir en la inmunogenicidad a largo plazo frente a la vacuna de la hepatitis B**

**Resumen**

**Conclusiones de los autores del estudio:** ninguno de los diez alelos de antígenos leucocitarios humanos (HLA) II previamente relacionados con inmunidad a corto plazo frente a la vacuna de la hepatitis B ha demostrado asociación con menor inmunogenicidad a largo plazo tras la primovacunación en la infancia.

**Comentario de los revisores:** pese a diferencias en cuanto a población de estudio con respecto a nuestro medio, no parece necesario determinar los antígenos HLA para detectar los niños en riesgo de fracaso vacunal frente a la hepatitis B.

**Palabras clave:** genes clase II del complejo de histocompatibilidad, vacuna hepatitis B, inmunogenicidad vacunal.

## STRUCTURED ABSTRACT

**Objective:** to assess the association between different HLA class II polymorphisms and the development of long-term antibody response following primary vaccination against hepatitis B in the first 6 months of life.

**Design:** case-control study.

**Setting:** multicentre hospital-based study in rural and urban areas of the Jiangsu province (China).

**Study population:** the study included 374 children born between 2003-2004 in hospitals in the province of Jiangsu, China (including rural and urban regions) that underwent routine primary vaccination against hepatitis B (three doses at 0-1-6 months). Children that had received a booster at a later time were excluded, as were those with antibodies indicating a self-resolved natural infection.

**Risk factor assessment:** determination of ten HLA class II alleles previously reported to be associated with a reduced antibody response against hepatitis B following primary vaccination.

**Outcome measurement:** quantification of the levels of hepatitis B surface antigen antibodies (by immunoassay) 5-7 years following primary vaccination to classify the cases included in the study into two groups: "non-responders", with levels < 10 mIU/ml, and "responders", with levels ≥ 10 mIU/ml.

All children were tested for 10 different alleles in the HLA DR (DRB1*01, DRB1*03, DRB1*04, DRB1*07, DRB1*08, DRB1*11 and DRB1*1301/1302) and DQ (DQB1*0201, DQB1*0401 and DQB1*0501) regions by polymerase chain reaction with sequence-specific primers, and allele frequencies compared in the two groups. The authors calculated the adjusted odds ratios (aORs) for age and sex as potential confounders.

**Main results:** of the total 297 children finally included in the study, 211 (71%) were classified as responders and 86 (29%) as non-responders. The mean age was 6 years, and 168 were boys (56.5%) and 129 girls (43.5%). There were no differences in vaccine antigen-specific antibody production between boys and girls.

The comparison of the allele frequencies in the two groups did not reveal significant differences between them, with the sole exception of the DQB1*0401 allele ($P$ = .047), although this difference was no longer statistically significant once the Bonferroni correction for multiple comparisons was applied. The authors also calculated the frequencies and aORs adjusted for age and sex, which were similar to the unadjusted values.

**Conclusion:** none of the alleles under study was associated with a risk of decreased long-term vaccine immunogenicity against hepatitis B, even after adjusting results for age and sex.

**Conflicts of interest:** none declared.

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## COMMENTARY

**Justification:** since the introduction of routine vaccination against hepatitis B, the incidence of chronic infection in children has decreased considerably. Nevertheless, the levels of protective antibodies generated by 5% to 10% of vaccinated individuals are suboptimal. This phenomenon has been associated with various clinical situations, including HLA genetic factors.[1] However, previous studies have focused on the short-term development of immunity following vaccination. The purpose of this study was to assess the potential association between long-term antibody response and HLA.

**Validity or scientific rigour:** the study design was appropriate. The population under study, exposure (vaccination against hepatitis B) and the effect (levels of protective antibodies) were well defined. The cases in the study were randomly selected from all the births by a group of pregnant women assumed to be representative of the population (discussed in detail in a previously published article). The control group was representative of the level of exposure to the hepatitis B virus in the population. A high number of children in the initial population randomly selected for the study were lost in the application of the inclusion criteria, especially in the control group. This may compromise the internal validity of the study. The exposure was generalised and was similar in the entire population, including cases and controls. There was a temporal association between the exposure and the effect. The results were expressed correctly. The authors took into account potential confounders such as age and sex, adjusting the odds ratio for these factors, and the maternal hepatitis B serologic status. Since the probability of a type I error increases when multiple hypothesis tests are performed simultaneously, the authors used the Bonferroni correction for multiple comparisons to control this effect.

**Clinical relevance:** the study did not find an association between any of the alleles under study and a decrease in the long-term immunogenicity of the hepatitis B vaccine, in contrast to the findings of previous studies that did find an inverse correlation with the short-term antibody response, which has been described for DRB1*0301, DRB1*04, DRB1*07, DRB1*1302 and DQB1*02[2] in a study previously reviewed in this journal,[3] and for DRB1*0301, DRB1*0302 and DRB1*0701.[4]

**Applicability to clinical practice:** the results of this study should be applied with caution to Spain on account of the differences between the two populations. In any case, based on the findings of this study, performance of HLA typing to identify children at risk of hepatitis B vaccine failure seems unnecessary.

**Conflicts of interest:** the authors of the commentary have no conflicts of interest to declare.

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