Persistence of antibody to hepatitis B surface antigen among vaccinated children in a low hepatitis B virus endemic area

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Background: A potential problem of hepatitis B immunization is that vaccine-induced antibody to hepatitis B surface antigen (anti-HBs) declines to low levels with age. This study investigated the persistence of anti-HBs in vaccinated children in a low hepatitis B virus (HBV) endemic area.

Methods: Plasma samples of 938 children between ages of 8 months and 15 years were tested for the presence of anti-HBs.

Results: The seroprotection rate was 60%. Protective antibody level was detected in 65% of children one year after vaccination, and in 30%, 29% and 24% 5, 10 and 15 years after vaccination, respectively. The mean anti-HBs titer declined with post-vaccination time (to 66 mIU/mL in 1 year, 60 mIU/mL in 5 years, 40 mIU/mL in 10 years to 37 mIU/mL in 15 years after vaccination).

Conclusions: Children vaccinated against HBV during infancy may show low levels of antibody during adolescence. Our data suggest that a booster dose of vaccine may be required in low HBV endemic areas.


Key words: children; hepatitis B surface antibody; hepatitis B virus; Iran

Introduction
The prevalence of hepatitis B virus (HBV) infection varies widely, with rates ranging from 0.1% to 20% in different parts of the world. In high HBV endemic areas, the seropositivity of hepatitis B surface antigen (HBsAg) surpasses 8% of the total population. In regions of medium HBV infection the HBsAg seropositivity is between 2% and 7%, and the areas with a HBsAg seropositivity of less than 2% are considered as low HBV endemic regions. Iran may be classified as a low HBV endemic area.

Universal immunization against HBV is considered to be the most effective means of preventing HBV infection. Vaccination against HBV has been routinely performed for newborns and high-risk groups since 1992 in Iran. After 13 years of implementation, the coverage reached an appropriate level from 62% in 1993 to 94% in 2005 and the epidemiologic pattern of HBV infection was changed as a result, especially in children and adolescents. Antibody to hepatitis B surface antigen (anti-HBs) in vaccinated children declines with time, especially during the first few years of vaccination. Immunity to hepatitis B in children vaccinated during infancy in countries where the endemic rate is high shows that good levels of antibody are maintained. There are controversies over the long-term persistence of post-vaccination immunity to hepatitis B and the need for booster doses of the vaccine. According to the current Iran National Immunization program, the recommended schedule involves administration of the first dose within 24 hours after birth and administration of subsequent...
doses at ages 2 and 6 months. However, the duration of protection provided by the HBV vaccination and the proper timing of a booster dose remain unclear. The present study was designed to investigate the persistence of anti-HBs levels in children who had been immunized with HBV vaccine as part of the Expanded Program on Immunization in a low HBV endemic area and the need for booster doses of the vaccine.

Methods

In this cross-sectional study, all children between ages of 8 months and 15.9 years residing in Tehran, Iran seen in pediatric hospital outpatient clinics were consecutively sampled and tested for anti-HBs from January to May 2009. Children who either suffered from chronic diseases or had received intravenous immunoglobulin (IVIG) were excluded from the study. Informed consent was obtained from all children and/or their parents. The study was approved by the ethics committee at the Pasteur Institute of Iran.

The vaccination schedule consisted of three pediatric doses of 10 μg of recombinant HB vaccine (Heberbiovac Cuba: Heber Biotec S.A., Havana, Cuba) given at the specified intervals (at birth, 2 months and 6 months old) intramuscularly in the deltoid or thigh areas of infants. All the patients had vaccination cards showing they had received all doses of this type of HBV vaccine according to the above-mentioned schedule.

Blood samples were collected and sent to the Clinical Research Department of the Pasteur Institute of Iran. Plasma was obtained and stored at -80°C prior to testing. Plasma samples were tested for anti-HBs using enzyme-linked immunosorbent assay (ELISA) (Delaware Biotech Inc. Dover, DE, USA) following the manufacturer's protocol. The levels of anti-HBs <10 mIU/mL were considered to be negative; samples showing an anti-HBs titer 10-99.9 mIU/mL and ≥100 mIU/mL were considered protective and highly protective, respectively.

The Chi-square test and Fisher's exact test were used with the SPSS 16 Package program (Chicago, IL, USA). ANOVA and post hoc multiple comparisons were made to compare the levels of anti-HBs among groups. Data were presented as mean ± SD or, when indicated, as an absolute number and percentage.

Results

Totally 938 children (548 male and 390 female) aged 15.9 years and 8 months were enrolled in the study. The number of children in each age group was as follows: 6 months to 5 years, 279 children; 6-10 years, 374; and 10-15 years, 285. The overall seroprotection rate (anti-HBs titre ≥10 mIU/mL) was 59.6% (559/938). Anti-HBs titer values across the three standard levels were <10 mIU/mL, 379 (40.4%) children; 10-99.9 mIU/mL, 349 (37.2%); and ≥100 mIU/mL, 210 (22.4%).

Protective antibody levels were detected in 65% of the children one year after vaccination, decreased to 30% by 5 years after vaccination, and further decreased to 29% and 24% in 10 and 15 years after vaccination, respectively. The mean level of anti-HBs in relation to the length of time after vaccination declined from 66±38 mIU/mL in one year to 60±44 mIU/mL in 5 years, 40±41 mIU/mL in 10 years and 37±43 mIU/mL in 15 years after vaccination. Seroprotection rates decreased significantly with increasing age due to waning anti-HBs titer over time (P<0.001).

Anti-HBs titer values were <10 mIU/mL in 40.9% of males and 39.8% of females, 10-99.9 mIU/mL in 36.7% of males and 37.9% of females, and ≥100 mIU/mL in 22.4% of males and 22.3% of females. There was no statistically significant difference in anti-HBs positivity and titer between genders.

Discussion

The present study showed the persistence of anti-HBs levels in children who had been immunized with three doses of HBV vaccine in their first year of life in a low HBV endemic area. In our children, protective antibody levels were detected in 65% of children one year after vaccination, which declined significantly over time to 24% in 15 years after vaccination. Our findings echo the potential problem of hepatitis B immunization that vaccine-induced anti-HBs titers decline to low or undetectable levels with age. Several long-term follow-up studies showed that soon after vaccination, protective levels of antibody (anti-HBs >10 mIU/mL) can be detected in most vaccinated children (83%-99%). The proportion of vaccinated children with protective anti-HBs levels decreases 5 years after vaccination (75%-87%) and further to 50%-70% 10 to 12 years after vaccination.

In a study in American Samoa, only 39% of vaccinated children had protective levels of anti-HBs when tested at a mean of 8.75 years of age. In a study in China, 50% of vaccinated children had protective levels of anti-HBs at 15 years of age. Gold et al reported that 77.1% of children at 8 years after vaccination had detectable antibody levels (≥10 mIU/mL) and 48.4% of them had high antibody levels (>100 mIU/mL). Few studies have been carried out on anti-HBs seroprevalence in Iran. Hassan et al reported that the persistence of responsive anti-HBs levels 6 years after vaccination was 81%, and 29.2% of these children...
had high antibody levels. Jafarzadeh et al[15] found that 47.9% of children had protective levels of antibody 10 years after primary vaccination.

Our results resembled those reported that anti-HBs levels decline with time in low endemic areas of hepatitis B[10,12,16] but run against the findings that vaccine-induced immunological memory persists for at least 12-15 years in children vaccinated in infancy.[7,17]

Because of the progressive decline of anti-HBs and increased likelihood of development of new HBV infections, some investigators suggested the use of a booster vaccination.[8,18] However, a preponderance of data indicate that the protective efficacy of HBV vaccines can last for at least 5 years, and a booster before 5 years is not necessary.[10,12] Our results also support the use of a booster vaccination although the proper timing of HBV booster administration is uncertain. However the limited number of our cases is not sufficient to generalize the results for recommendation of booster vaccination.

In conclusion, children vaccinated against hepatitis B during infancy may show low levels of antibody during adolescence. A booster dose of vaccine may be required in low HBV endemic areas such as Iran. Further studies, especially cohort studies, are needed to determine the duration of HBV vaccine protection and the necessity for or timing of booster doses.

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Competing interest: None declared.

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