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Geographic and ethnic variations of long-term efficacy and immunogenicity of hepatitis B vaccination in Hualien, a HBV hyperendemic area

Li-Yu Wang [a], Chi-Tan Hu [b], Tzu-Ying Ho [c], Hans Hsienhong Lin [b,*]

[a] *Graduate Institute of Aboriginal Health, Tzu Chi University, Hualien, Taiwan*
[b] *Tzu Chi Center of Gastroenterology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[c] *Graduate Institute of Public Health, Tzu Chi University, Hualien, Taiwan*

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Abstract

It is uncertain whether immunologic memory persists for 15 years or more after immunization and whether the efficacy of universal hepatitis B vaccination program (UHBVP) in socio-economically disadvantaged area with hyperendemicity of hepatitis B virus (HBV) infection is similar. We assayed hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) on 2839 students aged 15 years or more born before ($N = 248$) and after ($N = 2591$) UHBVP. We found that students born after UHBVP had significantly lower positive rate of anti-HBs than those born before UHBVP (44.6% versus 75.0%, $p < 0.0001$). Seropositive rate of HBsAg for students born after UHBVP was also declined significantly (1.9% versus 9.3%, $p < 0.0001$). Preventive fraction of UHBVP on HBsAg-seropositivity was 78% (95% confidence interval, 0.64–0.87), which was at least 10% lower than previous studies. Preventive fraction in Han Chinese (74%) and Atayal (78%) students were lower than Amis students (94%). In 2264 Han Chinese students, preventive fraction was 16% lower in those resided in rural than urban areas. These observations indicated that UHBVP was less effective in socio-economically disadvantaged area where HBV infection was hyperendemic and the long-term efficacy and immunogenicity of vaccination were modified by host factors and factors associated with urbanization.

Keywords: Hepatitis B vaccination; Long-term efficacy; Geographic variation

1. Introduction

Liver cirrhosis and hepatocellular carcinoma (HCC) was one of the leading causes of death in Taiwan [1]. The age-standardized mortality for liver cirrhosis and liver cancer were 23.0 and 31.1 deaths per 100,000 populations, respectively. Hepatitis B virus infection (HBV) was the major risk determinant. Greater than 80% of liver cirrhosis and HCC was attributable to HBV chronic infection [2,3]. The seropositive rate of hepatitis B surface antigen (HBsAg) in the general population was as high as 15–25% [4]. In high-risk area of HBV infection, greater than 80% of children were infected before 10 years old and the HBsAg seropositive rate was greater than 30% [5]. It was estimated that 40–60% of chronic HBV infection was attributable to perinatal transmission in Taiwan [6,7].

To control HBV infection, the Government of Taiwan initiated an universal hepatitis B vaccination program (UHBVP) in July 1984 [8]. In children born after the start of the UHBVP, the coverage rate, which was defined as receiving at least three doses of HB vaccine, of children aged 2–6 years was 94% in Taipei City [9] and 96% in central Taiwan [10]. Significant reduction in the HBsAg carrier rate in children was

Abbreviations: Anti-HBs, antibody against hepatitis B surface antigen; HB, hepatitis B; HBsAg, hepatitis B surface antigen

* Corresponding author at: Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien 970, Taiwan Tel.: +886 3 8561825x3426; fax: +886 3 8463989.
E-mail address: hoholin@ms10.hinet.net (H.H. Lin).

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observed in a series of cross-sectional studies conducted in Taipei city, the most populated area in Taiwan [9,11,12]. The overall prevalence rate of HBsAg of children aged less than 12 years old decreased from 9.8% in 1984 to 1.3% in 1994 [9]. The overall prevalence rate of anti-HBc also decreased significantly from 26% in 1984 to 4.0% in 1994 [9]. Similar declines in HBsAg seropositive rates were observed in other countries [13–17]. Ten years after the implementation of this program, the incidence of HCC in children 6–14 years of age also declined significantly [18–20].

Hualien County is located in the east of Taiwan island and it is one of the poorest areas in Taiwan. Seropositive rate of HBsAg in children aged 7–12 years in mountainous townships was as high as 31.9% [5], a figure significantly higher than that of the general population in Taiwan. Recent studies showed that only a small proportion of vaccinees were infected by HBV and the prevention fractions on HBV chronic infection were 90% or more after 9–15 years of HB vaccination [11,12,14,16,21–24], which indicated that immunologic memory in healthy vaccinees can last over different durations ranging from 9 to 15 years. It is uncertain whether immunologic memory can maintain longer than 15 years after immunization and whether the HB vaccination program has similar efficacy in socio-economically disadvantaged area with hyperendemicity of HBV infection. Consequently, we conducted this seroepidemiological study to assess the long-term efficacy and immunogenicity of HB vaccination on 2839 senior high school students born before (Period I, $N = 248$) and after (Period II, $N = 2591$) the start of UHBVP.

2. Materials and methods

2.1. The universal HB vaccination program (UHBVP)

In July 1984, the Government of Taiwan initiated a HB mass vaccination program aiming primarily at interrupting mother-to-infant vertical transmission. Infants whose mothers had hepatitis B e antigen (HBeAg) or reciprocal serum titers of HBsAg higher than 2560 were given 5 μg of a plasma-derived HBV vaccine (Hevac B, Institut Pasteur, Marnes-la-Coquette, France) and a single dose of 0.5 ml (145 IU) of hepatitis B immune globulin (Abbott Laboratories, Cutter, or Green Cross, Taiwan) at birth. Three additional doses of HB vaccine were given at 1, 2, and 12 months of age [8]. The efficacy of the immunoprophylaxis against perinatal transmission of HBV was excellent [25]. In July 1986, this program was extended to all neonates, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990. Since 1991, the vaccination records of first grade children were checked and unvaccinated or incompletely vaccinated children were given catch-up vaccinations. Although the efficacies of plasma-derived vaccine and yeast-derived recombinant vaccine were similar, the former was replaced by the latter in 1 November 1992 to avoid plasma-derived infection [26].

2.2. Study area

Hualien County is located in the east Taiwan. It has an area of 4629 km^2 and a population of 348,539 citizens in 2004 [27]. These figures are 12.9 and 1.6% of the whole Taiwan area, respectively. The population density for Hualien County and the whole Taiwan area were 75.9 and 625.9 persons per km^2, respectively. In Hualien County approximately 90% of the land area is constituted by mountains in which the Central Mountain Chain lays at the west and the East Coast Mountains lay at the east. Hualien has one city, nine rural and three mountainous townships. Fifty-four percentages of the total population of Hualien County resided in Hualien City and Jian Township in which both are located on the northern Hualien. Approximately 88,000 of the residents in Hualien are Taiwanese aborigines, accounting for 25% of residents in Hualien County and 20% of the total population of Taiwanese aborigines. In 2002, the average disposable income per household in Hualien was $21,884 US dollars that was 27% lower than the average in the whole Taiwan area [28]. Among residents aged 15 years or more, 23% of them had a schooling year greater than 12 years; the corresponding figure for the whole Taiwan area was 30% [29]. These statistics shows that population density and socioeconomical status of Hualien was significantly lower than the whole Taiwan area, and the population composition of Hualien was significantly different from the whole island of Taiwan.

2.3. Participants

There were 13 senior high schools in Hualien County and the total number of freshmen was approximately 40 hundreds yearly. From September 2002 to July 2004, 1749 male and 1965 female freshmen of six public senior high schools, including Hualien Senior High School, Hualien Girls' Senior High School, Hualien Vocational High School in Agriculture, Hualien Commercial High School, Guanghu Commercial and Industrial Vocational High School, Hualien Physical Experimental Education Senior High School, were invited to participate this study. A total of 1284 male and 1555 female freshmen had blood drawn and completed a self-help questionnaire voluntarily. About 248 (8.3%) and 2591 (91.7%) students were born before (Period I) and after (Period II) the start of UHBVP, respectively. All students born in Period II were aged 15–18 years at enrollment (mean age, 15.8 years; standard deviation [S.D.], 0.5 years). Seventy-one percent of those students born in Period I were aged 15–18 years at enrollment (mean age, 18.6 years; S.D., 5.6 years). Serum samples were kept at −30 °C until laboratory examination. The study protocol was approved by the Institutional Review Board of Tzu Chi Medical Center and signed consents were obtained from each participant.