Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Antibody response to hepatitis B vaccine is independently associated with hepatitis B breakthrough infection among adults: Results from a three-year follow-up study in China

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ARTICLE INFO

Article history:
Received 11 December 2017
Received in revised form 4 February 2018
Accepted 6 February 2018
Available online xxxx

Keywords:
Hepatitis B vaccine
Hepatitis B breakthrough infection
Antibody response
Adult

ABSTRACT

Hepatitis B breakthrough infection (HBBI) and its risk factors are rarely reported among adults in China. In 2009–2010 in three townships of China, hepatitis B vaccine (HepB) administration and anti-HBs detection after HepB were conducted among the residents aged 18–59 years. HBsAg, anti-HBs and anti-HBc were detected for these vaccinees in 2013. A total of 252 out of 4701 vaccinees turned to be positive for anti-HBc in 2013, but nobody was positive for HBsAg. The HBBI rate was 5.36% (95% *CI* 4.73, 6.04). The highest rate was found in age-group of 18–29 years (7.33%, 95% *CI*: 5.31, 9.82). The rate was significantly different by the residential townships ($P < 0.001$) and by the antibody response to HepB ($P = 0.003$). Multivariate analysis showed that anti-HBs response to HepB was the independent risk factor of HBBI. The study documents the association between hyporesponse to HepB and HBBI among adults. It also suggests more attention should be given to new HBV infection among young adults.

1. Introduction

Hepatitis B virus (HBV) infection remains an important global public health issue, which is the leading cause of hepatocellular carcinoma and leads to 650,000 deaths annually [1]. Hepatitis B vaccine (HepB) is used since 1980 in the world [2]. The long-term duration of antibody against hepatitis B surface antigen (anti-HBs) and immune memory after HepB are documented [3,4]. HepB immunization has achieved great succeeds in hepatitis B control in many countries [5–7]. However, HBV breakthrough infection including chronic infection has been reported to occur after HepB administration [8].

HBV breakthrough infection is defined as "having HBV infection despite receiving three or more doses of HepB" [9], which is usually indicated by positive results of hepatitis B core antibody (anti-HBc), hepatitis B surface antigen (HBsAg), or both among HepB vaccinees. Among those who have completed HepB vaccination as children or infants, the frequency of HBV breakthrough infection was reported to be 12% in Thailand (20 years after HepB) [10], 6% in Greenland (3–12 years after HepB) [11], 3.15% in mainland China (1–14 years after HepB) [12], 1% in Gambia (3 years after HepB) [13] and 0.94% in Taiwan (18 years after HepB) [14]. HBV breakthrough infection is also reported among adults. Acute hepatitis B virus infection with delayed appearance of anti-HBc was reported among an immunocompromised woman who received HepB [15]. In an US study, 2.9% and 0.42% of homosexual men were reported to seroconversion of anti-HBs and HBsAg respectively within five years after HepB vaccination [8].

Anti-HBs ≥10 mIU/ml is usually regarded as protective level after HepB [16]. In recent years, antibody response to HepB has been further divided into four levels, including non-response (anti-HBs < 10mIU/ml), low response (10–99 mIU/ml), normal response (100–999 mIU/ml) and high response (≥1000 mIU/ml) [16,17]. Those who could not achieve normal and high response are sometimes suggested to administrate another three doses of HepB [17,18] because non-responders and low-responders have been reported to be more likely to be infected by HBV [8,9,19]. Although immune response after HepB vaccination and risk factors for HBV infection are different between children and adults, HBV breakthrough infection among adult HepB vaccinees are not well understood.

HBV is endemic in China and the prevalence of HBsAg was 7.18% among the general population according to the third national serosurvey in 2006 [20]. HepB began to use in China in 1985 and was recommended to newborns in 1992 [21]. Although

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https://doi.org/10.1016/j.vaccine.2018.02.039
0264-410X/

great success has been achieved in HBV control among children in the country [5,20], the prevalence of HBsAg is still high among adults (8.57%) [20]. According to 2006 national serosurvey, the coverage of HepB was 13.8% among population aged 15–59 years in China [20]. To improve HepB coverage among adults, HepB was recommended to all adults who had not completed the full series by Chinese Center for Disease Control and Prevention (CDC) and Chinese Preventive Medicine Association (CPMA) in 2012 [22].

We conducted this study to evaluate the frequency of HBV breakthrough infection and its risk factors, especially antibody response to HepB, among adult vaccinees in Chinese rural areas.

2. Methods

2.1. Study population

Shandong province is located in the east of China with the average prevalence of HBsAg of 2.49% according to the latest serosurvey in 2014 [23]. Zhangqiu is a city of Shandong, which has a population of about 1.1 million. HBsAg, anti-HBs and anti-HBc were detected among the residents who were aged 18–59 years and had no history of hepatitis B vaccination and HBV infection in three townships (Baiyunhu, Ningbu, Shuizai) of Zhangqiu city during August and September of 2009. Three doses of HepB were administrated to those who were negative for HBsAg, anti-HBs and anti-HBc on 0–1–6 month schedule from September 2009 to April 2010. Anti-HBs was detected one month after the third dose and those who could not achieve anti-HBs titer above 10mIU/ml were given another series of HepB on 0–1–6 month schedule during June and December of 2010. Anti-HBs were also detected one month after the second series. Those who completed one or two series of HepB vaccination and anti-HBs detection after HepB were involved in the study. The flow chart is shown in Fig. 1.

2.2. Questionnaire investigation

Questionnaire investigation was conducted by the staff at local CDC when the first dose of HepB was administrated in 2009 and when the follow-up was conducted in 2013 respectively. The standardized questionnaire was used and all investigators were trained before interview. The basic information of the participants was collected in 2009, including gender, birth date, occupation, ethnicity, living place, history of HepB immunization and HBV infection, history of smoking and alcohol consumption. The information regarding possible HBV exposure after HepB vaccination was investigated in 2013, including having HBV infected family member, having history of possible sexual contact with HBV patients, dental treatment, surgery treatment, transfusion, endoscope and acupuncture therapy.

2.3. Specimen collection and laboratory testing

The volume of 5 ml blood sample was drawn from each participant before HepB vaccination (in 2009), one month after vaccination (in 2010) and three years after vaccination (in 2013). All serum specimens were stored at −20 °C at Shandong CDC before detection. For pre-vaccination samples, HBsAg and anti-HBs were detected by enzyme-linked immunosorbent assay (ELISA, Xiamen Xin Chuang Biotechnology Co., Ltd) and anti-HBc was detected by Chemiluminescence Microparticle Imunoassay (CMIA, Abbott, USA). For post-vaccination samples, all three indexes were detected by CMIA (Abbott, USA). To decrease the rate of false positivity of anti-HBc, the blood positive for anti-HBc in the first test was retested and a positive result was defined as being positive in both tests. All detection was conducted according to the manufacture's instruction.

2.4. Statistical analyses

HBV breakthrough infection rate across different group of age, gender, and anti-HBs level were assessed with Pearson Chi-square test. Pairwise Comparison of HBV breakthrough infection rate among the groups with different anti-HBs responders was conducted by Bonferroni correction method. Multivariable logistic regression model was built to assess the independent contribution of different risk factors to HBV breakthrough infection. HBV breakthrough infection was defined as positive result for anti-HBc with or without positive result for HBsAg after HepB vaccination [11]. The body mass index (BMI) was categorized into three levels (normal: BMI < 24 kg/m^2; overweighed: 24 kg/m^2 ≤ BMI < 28 kg/m^2; and obese: BMI ≥ 28 kg/m^2) based on the national data collected in China [24]. Anti-HBs response to HepB was categorized to non-response (anti-HBs < 10 mIU/ml), low-response (10 mIU/ml ≤ anti-HBs < 100 mIU/ml), normal response (100 mIU/ml ≤ anti-HBs < 1000 mIU/ml) and high response (anti-HBs ≥ 1000 mIU/ml) [25]. All analyses were conducted with SPSS 18.0. The P value < 0.05 was considered to be statistically significant, except that P value < 0.008 was considered to be significantly different when pairwise comparison was performed according to the rule of Bonferroni correction method.

2.5. Ethical concern

The protocol was approved by Shandong CDC Ethics Committee and a written informed consent form was obtained from each participant before investigation.

3. Results

3.1. General information of participants

A total of 6250 adults completed one or two series of HepB vaccination and anti-HBs detection in 2009–2010. Of them, 4701 subjects (75.22%) participated in the follow-up visit in 2013 and were involved in the final analysis. Their mean age was 39.72 ± 7.46 years at the first dose of HepB. The ratio of male to female was 0.83:1 (2129: 2572). Among them, 3932 participants (83.64%) completed one series vaccination and 769 participants (16.36%) completed two series. A total of 52.12% participants were resided in Baiyun township, 40.80% in Ningbu township and 7.08% in Shuizai township. The non-, low-, normal- and high-responders accounted for 3.19% (150/4701), 6.83% (321/4701), 40.25% (1892/4701) and 49.73% (2338/4701) of the total participants respectively. Nobody reported to have HBV infected family member, nor did they report to have possible sexual exposure with HBV patients, or have received dental treatment, surgery treatment, transfusion, endoscope or acupuncture therapy.

3.2. HBV Breakthrough Infection Rate by Age, Sex, Living Place and Anti-HBs Response to HepB

A total of 252 participants were tested positive for anti-HBc and nobody was tested positive for HBsAg. The rate of breakthrough infections was 5.36% (252/4701, 95% CI 4.73, 6.04). The highest infection rate was found in age-group of 18–29 years (7.33%, 95% CI: 5.31, 9.82), but the difference was not statistically significant by age (χ^2 = 5.45, P = 0.167). The similar rate was observed between males and females (χ^2 = 0.14, P = 0.709). The infection rates were 6.41% (95% CI: 5.47, 7.45), 4.74% (95% *CI*: 3.84, 5.79)

Please cite this article in press as: Zhang L et al. Antibody response to hepatitis B vaccine is independently associated with hepatitis B breakthrough infection among adults: Results from a three-year follow-up study in China. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.039