PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 June 14; 13(22): 3084-3089
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Comparison of three different recombinant hepatitis B vaccines: GeneVac-B, Engerix B and Shanvac B in high risk infants born to HBsAg positive mothers in India

Vijayakumar Velu, Subhadra Nandakumar, Saravanan Shanmugam, Suresh Sakharam Jadhav, Prasad Suryakant Kulkarni, Sadras Panchatcharam Thyagarajan

Vijayakumar Velu, Subhadra Nandakumar, Saravanan Shanmugam, Sadras Panchatcharam Thyagarajan, Department of Medical Microbiology, Dr ALM PGIBMS, University of Madras, Chennai 600113 and National referral Centre for viral hepatitis, India
Vijayakumar Velu, Vaccine Research Centre, Department of Microbiology and Immunology, Emory University, Atlanta, Georgia 30329, United States
Saravanan Shanmugam, Sadras Panchatcharam Thyagarajan, YRG Centre for AIDS Research and Education, VHS campus, Taramani, Chennai 600113, India
Suresh Sakharam Jadhav, Prasad Suryakant Kulkarni, Serum Institute of India Ltd, Pune, India
Correspondence to: Dr. Sadras Panchatcharam Thyagarajan, YRG Center for AIDS Research and Education, Taramani, Voluntary Health Services, Chennai 600113, India. vvjai2000@yahoo.com
Telephone: +91-44-22542929 Fax: +91-44-22542939
Received: 2007-02-15 Accepted: 2007-03-26

Abstract

AIM: To evaluate a low cost Indian recombinant hepatitis B vaccine GeneVac-B® for its immunogenicity and safety in comparison to Engerix B® and Shanvac B® vaccine in high risk newborn infants born to hepatitis B surface antigen (HBsAg) positive mothers.

METHODS: A total of 158 infants were enrolled in the study. Fifty eight infants were enrolled in the GeneVac-B® group while 50 each were included for Engerix B® and Shanvac B® groups. A three-dose regimen of vaccination; at birth (within 24 h of birth), 1st mo and 6 mo. were adopted with 10 μg dosage administered uniformly in all the three groups. Clinical and immunological parameters were assessed for safety and immunogenicity of the vaccines, in all the enrolled infants.

RESULTS: Successful follow up until seven months of age was achieved in 83% (48/58) for GeneVac-B®, 76% (38/50) and 64% (32/50) for Engerix B® and Shanvac B® groups respectively. 100% seroconversion and seroprotection was achieved in all the three groups of infants. The geometric mean titers of anti-HBs one month after the completion of three dose of vaccination were 90.5, 80.9 and 72.5 mIU/mL in GeneVac-B®, Engerix B® and Shanvac B® vaccine group respectively. Furthermore the level of anti-HBs increases with age of babies who were born to HBsAg positive mothers. The GMT values of anti-HBs were 226.7, 193.9 and 173.6 mIU/mL respectively in GeneVac-B®, Engerix B® and Shanvac B® groups one year after the completion of the three doses of vaccine. No systemic reactions were reported in infants during the entire vaccination process of GeneVac-B® and the other two vaccines. Clinical safety parameters remained within the normal limits throughout the study period.

CONCLUSION: The study concludes that there is no significant difference between the three recombinant hepatitis B vaccines. Administration of these vaccines within 24 h of birth to babies, born to HBsAg positive mothers will reduce the incidence of HBV infection.

Key words: GeneVac-B; Maternal screening; High risk infants; Infant vaccination

Velu V, Nandakumar S, Shanmugam S, Jadhav SS, Kulkarni PS, Thyagarajan SP. Comparison of three different recombinant hepatitis B vaccines: GeneVac-B, Engerix B and Shanvac B in high risk infants born to HBsAg positive mothers in India. *World J Gastroenterol* 2007; 13(22): 3084-3089

http://www.wjgnet.com/1007-9327/13/3084.asp

INTRODUCTION

Hepatitis B is a global communicable disease with an estimated 400 million chronically infected patients[1,2]. Mother to child transmission occurs often, either in-utero or through exposure to blood or blood contaminated fluids at or around the time of birth. Such perinatal transmission is believed to account for 35% to 50% of hepatitis B carriers[3]. The risk of perinatal transmission is associated with the hepatitis B envelope antigen (HBeAg) status of the mother. The chance of a child becoming chronically infected with hepatitis B virus, when a mother is positive for both hepatitis B surface antigen (HBsAg) and envelope antigen is around 70%-90%[4,5]. However, if a mother is positive for the surface antigen but negative for

the envelop antigen, the risk of transmission is significantly lower[6-9].

Screening for HBV among pregnant women is not routine in India, as hepatitis B immunoglobulin (HBIG) is not affordable and hence prevention of hepatitis B carriage from perinatal transmission must rely on vaccine alone. Universal neonatal vaccination is effective and has been shown to favorably alter the clinical course of hepatitis B in regions where disease is endemic[10]. Repeated injections over months are required to mount an effective antibody response with vaccination. Hepatitis B immunoglobulin has high levels of antibody to hepatitis B surface antigen. The immunoglobulin is immediately effective and seems protective for several months, after which it wanes[11,12]. Prevention of HBV transmission from HBsAg positive mothers to the children born to them is effectively achieved by administrating hepatitis B vaccine to their babies starting with the first dose at birth.

A recombinant hepatitis B vaccine, GeneVac-B®, a low cost hepatitis B vaccine[13] is manufactured by the Serum Institute of India Ltd., Pune, India. This vaccine is registered in India, and several hundred thousand doses are in use in India and abroad. The immunogenicity and safety of GeneVac-B® was proved in healthy adults [14], adolescents[15-17] and infants[18,19]. The aim of the present study was to asses and compare the immuogenicity, safety and efficacy of GeneVac-B® (Group-1), with two different commercially available vaccines, Engerix B® (Group-Ⅱ) Smithkline Beecham biologicals, Belgium and an Indian vaccine, Shanvac B® (Group-Ⅲ) Shantha Biotechniques Ltd, Hyderabad, India, in infants who were born to hepatitis B surface antigen (HBsAg) positive mothers, with 3 doses of vaccines at birth (within 24 h of birth), 1 mo and 6 mo of age, without passive prophylaxis at birth.

MATERIALS AND METHODS

Ethical review

The protocol of this study was approved by the Institutional review committee of Dr. ALM Post graduate Institute for basic Medical Sciences, University of Madras and the study design was prepared and monitored by National institute of Epidemiology, Indian Council of Medical Research, Chennai. Mothers were informed about the study and prognosis of the hepatitis B viral infection and benefits of vaccination to their babies. The written informed consent was obtained from all mothers prior to their registration in the study.

Vaccines

GeneVac-B vaccine consists of the purified surface antigen (Ag) of HBV obtained from the genetically engineered *Hansenula polymorpha* yeast cells expressing the surface antigen gene of the virus. It does not contain any material of human or animal origin. Each pediatric dose of 0.5 mL contains 10 μg of surface Antigen adsorbed on ≤ 0.40 mg of aluminum hydroxide, with ≤ 0.025 mg thimerosal added as a preservative. While Engerix-B used *Saccharomyces cerevisiae* as a host system, Shanvac B utilized *Pichia pestoris* as the expression system, the absorbent and the preservative being the same for all the three vaccines. The vaccines were stored at 4℃. Use and storage of the vaccine were under the supervision of responsible medical and research staff participating in the study.

Design of the study among infants born to HBsAg positive mothers

A total of 3000 healthy asymptomatic pregnant women attending the following hospitals in and around Chennai were studied: Institute of Obstetrics and Gynecology, Egmore, Chennai-600008; Kasthuribai Gandhi Hosptial, Triplicane, Chennai-600005; Department of Obstetrics and Gynecology, Rajamuthial Medical College and Hospital, Chidambaram. Among the 3000 pregnant women 5.9% (178/3000) was positive for HBsAg. All the enrolled mothers and their infants were subjected for the screening of HBsAg, anti-HBs, anti-HB core antigen. Mothers positive for HBsAg were also tested for the HBeAg. Babies born to these HBsAg positive women with acute febrile illness; any other infection; conditions associated with immunosuppression due to disease or therapy; seropositive for HBsAg; HBeAg and/or anti-HBs antibody; and participation in another clinical trial were excluded from the study. Thus, out of the 178 mothers and baby pairs, only 158 were included in the study.

One hundred and fifty eight infants were randomly recruited into 3 groups, 58 infants were administered with the recombinant hepatitis B vaccine, GeneVac-B® (group Ⅰ) and 50 infants each with the commercially available recombinant vaccines Engerix B® (group Ⅱ) and Shanvac B vaccine (group Ⅲ). All the infants were administered with 10 μg of hepatitis B surface antigen per 0.5 mL of dose. The vaccines were administered intramuscularly on the lateral aspect of the thigh within 24 h of birth, at birth as first dose, second dose at one month after birth and the third dose at 6 mo after birth. The follow-up visits were scheduled according to the vaccine administration and also at 3 mo intervals until the infants were 12 mo old. Strict adherence to the follow-up schedule was maintained; detailed information was collected using the structured proforma at every follow up. All the mother- baby pairs were asked to return within 3 d of the target date and those who did not were visited at their homes by the field visit official consisting of medical and research staff. The infants were bled using a scalp vein bleeding needle from the cubital vein at 0 mo (if they were more than 2 kg), 1, 2, 7, 9 and 12 mo. 3 mL of blood samples were collected from all infants prior to vaccination. The serum was separated and stored at -70℃ until tested.

Methodology

Detailed information was collected using the structured proforma at the period of antenatal check-up, at the time of delivery and on follow-up of mother and child. At each well-child visit, blood samples were collected from infants and information was obtained on illnesses, and physical examination findings. All the mother and child pairs were tested for HBsAg, anti-HBs, anti-HBC by using commercially available (BIORAD) elisa kits respectively. They were assayed for quantitative levels of anti-HBs

using Monolisa anti-HBs (BIORAD) 3.0 commercial kits. The anti-HBs standards were supplied by M/s. Sanofi Pasteur were used to develop the calibrated linear graph by the software installed in the ELISA Reader-Biotech Model ELx 800. The titer of anti-HBs was expressed as milli international units per milliliter (mIU/mL). Seroconversion and seroprotection rates were defined as anti HBs titer of < 10 mIU/mL and ≥ 10 mIU/mL respectively. Seroconversion and seroprotection rates after administration of the three vaccine doses were calculated. The anti-HBs concentrations were log transformed, and the antilog of the mean log values was calculated for the geometric mean titers (GMTs). Potential differences between the vaccines were statistically analyzed by Tukey's multiple comparison tests.

For reactogenicity assessment, subjects were physically examined during all their visits for vaccination. Parents were asked to report any adverse event assumed to be causally associated with vaccination until the total follow-up period of 7 mo ended. In these special circumstances, the child was examined thoroughly and the details were recorded. Infant's body temperature was recorded by measuring the oral temperature using a standard mercury thermometer. Fever was considered as mild when the temperature ranges 37.0℃ to 38.0℃ and moderate when it exceeds 39.0℃.

RESULTS

A total of 3000 pregnant women visiting the above hospitals were screened for HBsAg. Among the 3000 pregnant women only 178 (5.9%) were positive for HBsAg. Out of 178 HBsAg positive pregnant women, 158 mothers and infants pairs were enrolled in the study after fulfilling the study criteria, while the remaining HBsAg positive mothers were excluded from the study due to the various personal reasons. In addition among the 158 HBsAg positive mothers 28 (17.7%) were positive for HBeAg. No infants were positive for HBsAg, anti-HBs or anti HBC IgM during prevaccination visit and all the babies received the respective vaccines. After the three doses of vaccination, we could follow-up only 118 infants, while the remaining 40 (25.3%) infants were lost in follow up due to various reasons. Of the 118 successfully followed up infants, 48 babies were administered with GeneVac-B®, 38 with Engerix B® and 32 with Shanvac B® vaccines. It could be seen that the seroconversion and seroprotection on completion of the vaccination schedule of 0, 1 and 6 mo were 100% in all the three groups of infants. After seven months, the GMT values of anti-HBs titers were 90.3 mIU/mL with GeneVac-B®, 77.5 mIU/mL with Engerix-B® and 61.9 mIU/mL with Shanvac-B®. Notably the difference in anti-HBs level of GeneVac-B® was not statistically significant ($P > 0.05$) when compared with either Engerix B or Shanvac B groups. Thus the study validates that all the three studied recombinant hepatitis B vaccines had elicited protective levels of specific immunogenicity in the vaccinated infants.

The adverse effects of the three vaccine groups in our study population are given in Table 1. The most common systemic reaction effects in the infants were mild to moderate fever; excessive crying, rash, and irritability. However all the effects reported were transient and resolved without any further sequelae. None of the infants were hospitalized due to vaccine-associated adverse effects. Post vaccination safety profile was similar for the three test groups under study.

Table 1 Adverse effects reported by infant vaccinees in GeneVac-B, Engerix B and Shanvac B groups *n* (%)

Symptoms	GeneVac-B (48)	Engerix B (38)	Shanvac B (32)
Mild fever	4 (8.3)	3 (7.8)	3 (9.3)
Moderate fever	3 (6.2)	2 (5.2)	2 (6.2)
Excessive crying	1 (2)	1 (2.6)	1 (3.1)
Irritability	2 (4.1)	1 (2.6)	1 (3.1)
Local swelling	2 (4.1)	3 (6.8)	2 (6.2)
Local erythema	2 (4.1)	2 (5.2)	2 (6.2)
Induration	1 (2)	1 (2.6)	1 (3.1)
Rash	1 (2)	nil	1 (3.1)

Table 2 Immunogenicity data of GeneVac-B, Engerix B and Shanvac B in babies born to HBsAg positive mothers

Parameters	1st dose	2nd dose	3rd dose	After one year
	Group- Ⅰ - GeneVac-B			
No. of infants	58	48	48	35
Seroconversion	57.10%	94.20%	100%	100%
Seroprotection	22.80%	82.80%	100%	100%
GMT (mIu/mL)	11.6	35.4	93.5	226.7
	Group-Ⅱ - Engerix B			
No. of infants	50	43	38	21
Seroconversion	57.10%	90.00%	100%	100%
Seroprotection	19.00%	71.40%	100%	100%
GMT (mIu/mL)	8.4	24.4	80.9	197.9
	Group-Ⅲ Shanvac B			
No. of infants	50	45	32	12
Seroconversion	50%	91.60%	100%	100%
Seroprotection	16.60%	66.60%	100%	100%
GMT (mIu/mL)	8	18.6	72.55	173.6

Level of anti-HBs titer increases with age in vaccinated babies born to HBsAg positive mothers

Totally, 118 infants were followed up after full course of vaccination and among them only 68 were followed up to 12 mo. Among the 68 babies, 35 were administered with GeneVac-B®, 21 with Engerix B® and 12 with Shanvac B® vaccine. After the completion of 12 mo post vaccination at 0, 1 and 6 mo schedule, 100% of seroconversion and seroprotection were observed in all the three groups of vaccinees. The GMT values of anti-HBs titers were 226.7 mIU/mL with GeneVac-B®, 197.9 mIU/mL with Engerix B® and 173.6 mIU/mL with Shanvac B® vaccinees. No differences were found in the anti-HBs levels ($P > 0.05$) between Engerix B®, Shanvac B® and GeneVac-B®. Children who were followed up till 12th mo had high antibody response when compared to anti-HBs response on 7th mo follow up (Table 2).

Protective efficacy of the vaccines administered in infants

During the 9th mo follow up, tests for HBsAg, anti-HBs and anti-HBc were performed in all the babies. Infants in all the three groups had 100% of seroprotection (data not shown). Although all the mothers were HBsAg carriers, none of their children were HBsAg positive. However 7 infants, 3 from GeneVac-B® group and 2 each from Engerix B® and Shanvac B® group were positive for anti-HBc IgM. This test became negative in 4 of 7 who were followed for 12 mo, thus 1 in each vaccine group were positive for anti-HBc, however the percentages of infants with Protective anti-HBs concentrations did not decrease in any of the vaccine groups.

DISCUSSION

Hepatitis B virus vaccines provide highly effective protection against acute and chronic hepatitis B infection and the chronic carrier's status[20,21]. Immunization with hepatitis B vaccine for infants, children, adolescents and high-risk adults has been recommended by WHO and other international organizations[22,23]. Previous studies have shown that the risk of chronic HBV infection is higher in a younger age group and thus it is inversely correlated with age [24]. In South East Asia, chronic hepatitis B is often caused by maternal-infant transmission during the perinatal period[4] and this fact is reinstated in studies conducted in Egypt[25], Saudi Arabia[26] and Sub-Saharan Africa[27]. In endemic countries, effectiveness of universal vaccination has already been proven to reduce hepatitis B carriage leading to a decline of Hepatocellular Carcinoma in children[28]. Evidence is mounting to support the universal infant vaccination to control HBV-related diseases and is the best means of controlling disease in countries with intermediate or high levels of HBV endemicity.

In the present study, the prevalence of HBsAg among the pregnant women enrolled in the study was 5.9% which confirms that the HBV infection is endemic in Indian population. Prevalence of HBeAg positive mothers in our study was 17.7%, however the reported HBeAg positive rates among HBsAg-positive pregnant women in India varies between 8% and 47%; most studies show positive rates towards the lower end of this range[29-31]. Without prophylaxis, a very large proportion of infants born to HBV positive carrier mothers may become carriers of HBV[30,31]. Infection in this high risk setting is prevented most effectively by prenatal screening to identify carrier mothers[32,33], with administration of hepatitis B immunoglobulin at birth along with a course of vaccines to achieve both immediate and long lasting immunity to HBV. Many countries such as India lack the resources to implement such programs and must depend on vaccine alone to prevent the development of chronic HBV carriage in these babies. It is important that regimen of vaccination chosen for the use in a nationwide program should be highly immunogenic and cost effective. Previous studies about infants in several countries revealed that there were wide variations in the immunogenicity between different hepatitis B vaccines. Furthermore, the response of new born infants to vaccine varies and hence, it is important to evaluate the efficacy and immunogenicity of different vaccines that can widely be adopted for infants in India.

In this study, we found no significant difference in the immunogenicity between the three groups of recombinant vaccines after the third dose of vaccination. Most infants who received recombinant vaccines acquired the antibody levels to hepatitis surface antigen above 10 mIU/mL. Comparison of the geometric mean titers of anti-HBs levels achieved by the three vaccinees reveals that GeneVac-B® has achieved slightly higher anti-HBs titers compared to the other two vaccines. In addition this finding is similar to the results obtained in HBV vaccine along with DPT in babies born to HBsAg negative mothers in India with GeneVac-B® and Engerix B®[18]. Moreover in this study 97.5% of the vaccinated babies born to HBsAg positive mothers who were immunized with the three groups of vaccines at birth controlled the infection up to one year which is not often seen in babies born to HBsAg positive mothers. Our results indicate that administration of hepatitis B vaccines with in 24 h of birth prevents the occurrence of hepatitis B virus in the newborn infants who were born to HBsAg positive mothers. However, long-term follow up is needed to know the preventive efficacy of these vaccines.

This is the first study in India to test the effectiveness of the three different commercially available recombinant hepatitis B vaccines in babies born to HBsAg positive mothers without HBIG administration. Several studies report that the plasma and recombinant hepatitis B vaccines alone without HBIG can be quite effective in preventing chronic HBV infection among high risk infants of HBeAg-positive carrier mothers, with efficacy estimates ranging from 65%-95%. Here in our study, though 17.7% of the mothers were HBeAg positive, we have not seen any case of infection in the infants during our follow up period of 12 mo. This result clearly indicates that the vaccines administered immediately (24 h) after the births in babies born to HBsAg positive mothers are highly effective in high risk infants even without the coadministration of HBIG.

The safety and tolerability of hepatitis B vaccines under study has been extensively studied by several investigators including studies conducted in adults on GeneVac-B®, Engerix B® and Shanvac B® in our laboratory[14]. In summary, mild adverse effects as mentioned below seem to occur: (1) temperature greater than 37.7℃ in 1%-6%; (2) erythema in 3%; (3) swelling in 3%; and (4) rash in 3%, the observations made in the present study show slightly higher mild fever in 9.3%-7.8% of the infants and moderate fever was reported in 2%-3%. However, in the present study no other generalized symptoms were observed. The study has clearly shown that, all the three vaccines were well tolerated without significant difference in vaccine associated adverse effects.

In an effort to further reduce the cost involved in HBV vaccination which facilitate universal immunization against hepatitis B in all countries, studies are being conducted to find out whether a two dose schedule can replace the existing recommendation of three dose hepatitis B

vaccination regimens. These studies have also looked at the logistics of vaccine delivery given at varying intervals of time[34-36]. All these studies have shown that the two dose regimen of recombinant hepatitis B vaccine is highly immunogenic and induces effective immunological memory like the three dose regimen. If a similar study is also conducted in countries like India, the results may facilitate the policy planners to adopt the programme of universal hepatitis B immunization expediously with significant reduction in vaccine cost and the vaccine compliance rate also increase to the desired level. However, out of three vaccines compared in the present study, GeneVac-B® is less expensive hepatitis B vaccine available in the Indian market[13,19] which can be widely considered in India to prevent hepatitis B infection.

ACKNOWLEDGMENTS

The vaccines and finance for the clinical study were provided by Serum Institute of India Limited, Pune, India. The authors are grateful to Mr. David from UICIC for his outstanding administrative support.

COMMENTS

Background

Hepatitis B (HB) is a serious public health problem throughout the world and is responsible for more than 600 000 deaths every year. In high-incidence areas, perinatal transmission of hepatitis B virus (HBV) from carrier mothers to newborns appears to be the most important factor for the high prevalence of HBV infection. Around 70% to 90% of infants become chronically infected with HBV when a mother is positive for both HBsAg and HBeAg. It may be beneficial to administer vaccines to these babies at birth to prevent HBV incidence.

Research frontiers

The current recommendation for hepatitis B prophylaxis in babies born to HBsAg positive mothers is to co-administer vaccine and hepatitis B immunoglobulin (HBIG). Several studies have assessed the immunogenicity of vaccines along with HBIG in babies of known HBsAg positive mothers. However, screening for HBV among pregnant women is not a routine in India and HBIG is not affordable to most of the people. Universal neonatal vaccination is effective and has been shown to favorably alter the clinical course of HB in regions where the disease is endemic. To better understand the response of the vaccine alone in babies born to HBsAg positive mothers, we studied the immunogenicity and safety of three different vaccines without the co-administration of HBIG in this population.

Innovations and breakthroughs

Several studies have assessed the immunogenicity of hepatitis B vaccines along with the administration of HBIG in babies born to known HBsAg positive mothers. On the other hand, there is not much data on the immunogenicity of vaccine alone in this population. However, because of the two above-mentioned constraints, which limit the use of HBIG, we thought that it is valuable to assess the immunogenicity of the recombinant vaccine alone in these babies.

Applications

The results of this study demonstrate that, in the absence of the HBIG, babies born to HBsAg positive mothers can be administered the available hepatitis B vaccines and they mount a high immune response. This may prevent the occurrence of the HBV infection to a certain level. However, long term follow-up studies are needed for determining the clinical efficacy of the vaccines alone in this population.

Terminology

Tukey's multiple comparison tests: It is one of the several tests that can be used to determine which means amongst a set of means differ from the test.

Peer review

The authors compared three hepatitis B vaccines in terms of efficacy and safety. They demonstrated GeneVac-B as effective as and more cost-effective than other two vaccines. This is an important and useful finding.

REFERENCES

1 **Maddrey WC**. Hepatitis B: an important public health issue. *J Med Virol* 2000; **61**: 362-366
2 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745
3 **Yao JL**. Perinatal transmission of hepatitis B virus infection and vaccination in China. *Gut* 1996; **38** Suppl 2: S37-S38
4 **Stevens CE**, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 1975; **292**: 771-774
5 **Akhter S**, Talukder MQ, Bhuiyan N, Chowdhury TA, Islam MN, Begum S. Hepatitis B virus infection in pregnant mothers and its transmission to infants. *Indian J Pediatr* 1992; **59**: 411-415
6 **Okada K**, Kamiyama I, Inomata M, Imai M, Miyakawa Y. e antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. *N Engl J Med* 1976; **294**: 746-749
7 **Beasley RP**, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol* 1977; **105**: 94-98
8 **Beasley RP**, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, Chen CL. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet* 1983; **2**: 1099-1102
9 **Nayak NC**, Panda SK, Zuckerman AJ, Bhan MK, Guha DK. Dynamics and impact of perinatal transmission of hepatitis B virus in North India. *J Med Virol* 1987; **21**: 137-145
10 **Aggarwal R**, Ranjan P. Preventing and treating hepatitis B infection. *BMJ* 2004; **329**: 1080-1086
11 **Beasley RP**, Hwang LY. Postnatal infectivity of hepatitis B surface antigen-carrier mothers. *J Infect Dis* 1983; **147**: 185-190
12 **Nair PV**, Weissman JY, Tong MJ, Thursby MW, Paul RH, Henneman CE. Efficacy of hepatitis B immune globulin in prevention of perinatal transmission of the hepatitis B virus. *Gastroenterology* 1984; **87**: 293-298
13 **Kulkarni PS**, Raut SK, Patki PS, Phadke MA, Jadhav SS, Kapre SV, Dhorje SP, Godse SR. Immunogenicity of a new, low-cost recombinant hepatitis B vaccine derived from Hansenula polymorpha in adults. *Vaccine* 2006; **24**: 3457-3460
14 **Vijayakumar V**, Hari R, Parthiban R, Mehta J,Thyagarajan SP. Evaluation of immunogenicity and safety of GeneVac-B: a new recombinant hepatitis B vaccine in comparison with Engerix B and Shanvac B in healthy adults. *Ind J Med Microbiol* 2004; **22**: 34-38
15 **Vijayakumar V**, Shraddha M, Subhadra N, Saravanan S, Sundararajan T, Thyagarajan SP. Immunogenicity and safety of 10 mg and 20 mg doses of Genevac-B, a recombinant hepatitis B vaccine, in healthy adolescents. *Indian J Gastroenterol* 2004; **23**: 34-35
16 **Kakrani AL**, Bharadwaj R, Karmarkar A, Joshi S, Yadav S, Bhardwaj S, Kulkarni P, Kulkarni S. Immune responses induced by two dose strengths of an yeast-derived recombinant hepatitis B vaccine in adolescents. *Indian J Gastroenterol* 2003; **22**: 71-72
17 **Velu V**, Nandakumar S, Shanmugam S, Thyagarajan SP. Persistence of anti-HBs titers after two different doses of Genevac-B, a recombinant hepatitis B vaccine, in healthy adolescents. *Indian J Gastroenterol* 2007; **26**: 48
18 **Shivananda** V, Srikanth BS, Mohan M, Kulkarni PS. Comparison of two hepatitis B vaccines (GeneVac-B and Engerix-B) in healthy infants in India. *Clin Vaccine Immunol* 2006; **13**: 661-664
19 **Sapru A**, Kulkarni PS, Bhave S, Bavdekar A, Naik SS, Pandit

AN. Immunogenicity and Reactogenicity of Two Recombinant Hepatitis B Vaccines in Small Infants: A Randomized, Double-Blind Comparative Study. *J Trop Pediatr* 2007; Epub ahead of print

20 **Margolis HS**. Prevention of acute and chronic liver disease through immunization: hepatitis B and beyond. *J Infect Dis* 1993; **168**: 9-14

21 **Lemon SM**, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; **336**: 196-204

22 **Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination**. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep* 1991; **40**: 1-25

23 **Freed GL**, Bordley WC, Clark SJ, Konrad TR. Reactions of pediatricians to a new Centers for Disease Control recommendation for universal immunization of infants with hepatitis B vaccine. *Pediatrics* 1993; **91**: 699-702

24 **Hyams KC**. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995; **20**: 992-1000

25 **Hyams KC**, Osman NM, Khaled EM, Koraa AA, Imam IZ, el-Ghorab NM, Dunn MA, Woody JN. Maternal-infant transmission of hepatitis B in Egypt. *J Med Virol* 1988; **24**: 191-197

26 **Basalamah AH**, Serebour F, Kazim E. Materno-foetal transmission of hepatitis B in Saudi Arabia. *J Infect* 1984; **8**: 200-204

27 **Botha JF**, Ritchie MJ, Dusheiko GM, Mouton HW, Kew MC. Hepatitis B virus carrier state in black children in Ovamboland: role of perinatal and horizontal infection. *Lancet* 1984; **1**: 1210-1212

28 **Hsu HM**, Lu CF, Lee SC, Lin SR, Chen DS. Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999; **179**: 367-370

29 **Prakash C**, Sharma RS, Bhatia R, Verghese T, Datta KK. Prevalence of North India of hepatitis B carrier state amongst pregnant women. *Southeast Asian J Trop Med Public Health* 1998; **29**: 80-84

30 **Mittal SK**, Rao S, Rastogi A, Aggarwal V, Kumari S. Hepatitis B--potential of perinatal transmission in India. *Trop Gastroenterol* 1996; **17**: 190-192

31 **Gupta I**, Sehgal A, Sehgal R, Ganguly NK. Vertical transmission of hepatitis B in north India. *J Hyg Epidemiol Microbiol Immunol* 1992; **36**: 263-267

32 **Gill HH**, Majumdar PD, Dhunjibhoy KR, Desai HG. Prevalence of hepatitis B e antigen in pregnant women and patients with liver disease. *J Assoc Physicians India* 1995; **43**: 247-248

33 **Biswas SC**, Gupta I, Ganguly NK, Chawla Y, Dilawari JB. Prevalence of hepatitis B surface antigen in pregnant mothers and its perinatal transmission. *Trans R Soc Trop Med Hyg* 1989; **83**: 698-700

34 **Schiff GM**, Sherwood JR, Zeldis JB, Krause DS. Comparative study of the immunogenicity and safety of two doses of recombinant hepatitis B vaccine in healthy adolescents. *J Adolesc Health* 1995; **16**: 12-17

35 **Halsey NA**, Moulton LH, O'Donovan JC, Walcher JR, Thoms ML, Margolis HS, Krause DS. Hepatitis B vaccine administered to children and adolescents at yearly intervals. *Pediatrics* 1999; **103**: 1243-1247

36 **Heron LG**, Chant KG, Jalaludin BB. A novel hepatitis B vaccination regimen for adolescents: two doses 12 months apart. *Vaccine* 2002; **20**: 3472-3476

S- Editor Zhu LH **L- Editor** Alpini GD **E- Editor** Ma WH