RESEARCH PAPER

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Revaccination of non- and low- responders after a standard three dose hepatitis B vaccine schedule

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Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; WHO, world health organization; EPI, Expanded Programme on Immunization; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; GMT, geometric mean titres; LBW, low birth weight; anti-HBc, hepatitis B core antibody; RR, risk ratio

Background: Guangdong province of China is HBV high endemicity and 1.6 million neonates are administrated 5 μg yeast recombinant anti-HBV vaccine each year. But few studies are performed to evaluate the immunogenicity and revaccination effect on non- and low- responders.

Results: Of 1,814 subjects, 3.1% were non-responders (anti-HBs titer < 10 mIUml^{-1}) and 28.9% were low-responders (anti-HBs ≥ 10 mIUml^{-1} and < 100 mIUml^{-1}). Low birth weight (LBW) was a risk factor for non- and low- responders (RR = 1.6, 95%CI = 1.2–2.0). After revaccination, of the 34 non-responders, 14.7% became low-responders and 85.3% became responders. Of the 74 low-responders, 21.6% remained at the same level and 78.4% shifted into responder category.

Methods: A total of 2,199 children were administered intramuscularly with 5 μg vaccine at 0, 1 and 6 mo after birth. A 3 ml blood sample was drawn from each infant 1 mo after the third dose for determination of anti-HBs level. Three additional doses (10 μg each) were given to non- and low- responders.

Conclusions: Based on the lower responding rate after the primary immunization cycle and the higher responding rate after the additional cycle, measurement of anti-HBs level should be considered for people who had been immunized with three-dose 5 μg HB vaccine in Guangdong, especially for specific populations including LBW infants, healthcare workers, and patients with immunodeficiency disorders. An amount of 10 μg vaccine should be revaccinated to any non- and low- responders to provide adequate seroprotection.

Introduction

Hepatitis B virus (HBV) infection is a constant and serious threat in the world. China is a HBV high endemic country. More than 700 million adults (about 30% of the worldwide) show evidence of prior infection and nearly 120 million individuals are chronic hepatitis B surface antigen (HBsAg) carriers.[1] In China, over 300,000 deaths per year are due to HBV-related liver diseases.[1] Guangdong province is a HBV high endemic area in China with 13.55% of the HBsAg positive rate in 2006, the second highest in the country.[2]

During the past three decades, prophylactic hepatitis B immunization has been firmly established as an effective method for reducing the incidence of HBV infection, the HBsAg carrier state and hepatocellular carcinoma.[3] Mass vaccination of neonates and pre-school children has been strongly recommended by the WHO Expanded Programme on Immunization (EPI).[4] The Ministry of Public Health of China introduced the techniques of manufacturing plasma-derived and recombinant hepatitis B (HB) vaccines with internationally accepted quality control in domestic plants through technology transfer from Merck and Co. Plasma-derived HB vaccine was available in late 1980s, and the recombinant vaccine was manufactured in early 1993 in China. Plasma-derived vaccine was used first, gradually supplemented, and finally replaced by recombinant vaccine in 1997 for nationwide use.[5] Not all vaccinees, however, respond to vaccination. Levels of Hepatitis B surface antibody (anti-HBs) at or exceeding 10 mIUml^{-1} 4–8 weeks after the last vaccine injection have been considered to be protective since the early 1980s.[6] The 10 mIUml^{-1} level of anti-HBs associated with protection was originally established from passive immunization studies with immune globulin,[7,8] and received subsequent confirmation from a long-term protective efficacy study in a high-risk group.[9] Non-responders (anti-HBs titer < 10 mIUml^{-1}) remain susceptible to HBV and are at risk of becoming chronic carriers after the infection.[10,11] Further research find breakthrough infections have occurred in vaccinees whose anti-HBs titers are low (< 100 mIUml^{-1}) after a hepatitis B vaccine schedule.[12,13] HBV infection was much more severe with clinical sign of disease in non- and low-responders than in responders.[13] In a number of countries, anti-HBs values

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Table 1. Chi-square test of factors influencing anti-HBs titers after primary immunization with 5 μg HB vaccines, Guangdong, China 2006

	Total	Anti-HBs titer < 100 mIUml^{-1}		RR(95%CI)
		n	%	
Infant months				
7	1789	572	32	0.89(0.52–1.5)
8	25	9	36	
Infant Sex				
Male	1006	314	31	0.94(0.83–1.08)
Female	808	267	33	
LBW				
Yes	62	31	50	1.6(1.2–2.0)
No	1728	548	32	
Premature				
Yes	69	25	36	1.1(0.82–1.6)
No	1734	553	32	
Mother HBsAg-positive				
Yes	118	40	34	1.0(0.78–1.3)
No	1316	438	33	
Mother HBeAg-positive				
Yes	34	12	35	1.1(0.66–1.7)
No	1372	461	34	

determination 4–8 weeks after the end of the basic immunization series ≥ 100 mIUml^{-1} are regarded as a surrogate marker for successful vaccination.[13-15] Persons with an anti-HBs concentration of ≥ 100 mIUml^{-1} are protected against disease, especially for health care workers who with, only antibody levels ≥ 100 mIUml^{-1} could give adequate protection against occupational exposure.[16] Once the children have antibody levels < 100 mIUml^{-1}, they will be at similar risk of infection and reversion.[10]

Different vaccination schedules have been adapted by the health authorities in different countries. The hepatitis B immunization program has been introduced by the Guangdong province since 1992 as the rest of the country. Newborns were immunized at 0, 1, and 6 mo with 5 μg or 10 μg dosage HB vaccine which were both paid by their families. From 2002 on, universal vaccination of 5 μg dosage for newborns has been paid by the government. However, people could select 10 μg dosage at their own expense mainly due to the huge vaccination population, high expense and limited governmental funding. Indeed, both different dosages of early plasma-derived and current recombinant HB vaccine have shown excellent records of safety, immunogenicity, protective efficacy. And they have a significant impact on the problem of HBV infection. Recent studies in China[17,18] found that seroprotection rate of 3 doses 5 μg HB vaccine is significantly lower than 3 doses 10 μg at the time of one month and one year after immunity, and the 3 doses 5 μg HB vaccine seroprotection rates are also high (85–100%). But most of the research use ≥ 10 mIUml^{-1} as the cutoff of anti-HBs positive conversion and their study objectives are mostly adults or children. Newborns are seldom studied because of the difficulties in collecting blood samplings.

Now 1.6 million neonates each year and more than 18 million people who were born from 1997 to 2011 are administrated 5 μg yeast recombinant anti-HBV vaccine in Guangdong while most of other countries perform recombinant anti-HBV vaccine with 10 μg dosage, even 20 μg dosage. Few studies have been performed to evaluate the immunogenicity of 5 μg HBV vaccine and to analyze the influence factors though so many neonates are administrated each year. The primary objective of this study is to identify the number of non- and low-responders to the vaccine and then appraise the influence of host factors [age, sex, LBW, premature, mother HBsAg-positive and HBeAg (hepatitis B e antigen)-positive] on the immune response. Secondary objective is to evaluate the response to supplementary doses of the vaccine in the identified group of non- and low-responders.

Results

We obtained data on the anti-HBs titer in 1,814 subjects, representing 82.5% of the enrolled cohort. 263 (12%) subjects refused to be taken blood sample. 122 (5.5%) neonates tested positive for anti-HBc or HBsAg after the primary immunization circle were excluded from the study. Among the 122 neonates, 113 neonates were anti-HBc positive, and they might be infected or transmitted transplacentally from mothers. Three were positive for HBsAg, and 6 were positive for both HBsAg and core antibody. The 9 infants might be infected by HBV. Among 140 HBsAg or/and HBeAg positive mothers, 36 infants were detected HBsAg or anti-HBc positive and the vertical transmission rate could be calculated as about 25.7%.

At the end of the primary immunization cycle, only 56 infants out of 1,814 infants (3.1% of the sample) were found to be non-responders (anti-HBs titer < 10 mIUml^{-1}), whereas 1,233 babies (68.0%) were responders (anti-HBs titer ≥ 100 mIUml^{-1}). There were 525 low-responders (anti-HBs ≥ 10 mIUml^{-1} and < 100 mIUml^{-1}; 28.9% of the total). The mean GMT was 169.5 ± 115.3 mIUml^{-1}. The minimum GMT was 0.78 and the maximum was 705.8 mIUml^{-1}.

To analyze host factors that could confound immune response, non- and low- responders to the primary immunization cycle were compared with the others. Among 62 LBW neonates, 31 (50%) were found to be unprotected (anti-HBs titer < 10 mIUml^{-1}) after primary immunization, 1.6 times the risk (RR = 1.6, 95%CI = 1.2–2.0) among normal birth weight neonates (548/1728, 32%). Other factors, such as age, sex, premature, mother HBsAg-positive, mother HBeAg-positive, were not associated with immune response (**Table 1**).

Limited by the vaccine provision and fund, not all low-responders were administrated with additional anti-HBV vaccine. One hundred and five low-responders were randomly sampled from 525 low-responders by systematic sampling. We compared demographic characteristics (months, sex, gestational ages and birth weight) between 101 revaccination and 424 non-revaccination infants among 525 low-responders. There was no significant

difference between the two groups and the subset was representative for the entire study (**Table 2**). Following administration of the three additional doses of anti-HBV vaccine, the 108 infants in the non- and low-responder groups demonstrated a redistribution of the antibody titer. Of the 34 infants with an antibody titer < 10 $mIUml^{-1}$ at the time of seroconversion, 5 (14.7%) were shifted to the low-responder group and 29 (85.3%) became responders. Of the 74 low-responders, 16 (21.6%) remained at this level and 58 (78.4%) moved into responder category (**Table 3**). The mean GMT was 218.6 ± 181.0 $mIUml^{-1}$. The minimum GMT was 11.0 and the maximum value was 1435.4 $mIUml^{-1}$. A total of 324 revaccination vaccine doses were given, and adverse events were investigated in 318 (98.2%) of the cases. No complication was found after 318 vaccine doses, but a lower proportion of fever and local adverse events were found. Mild fever was found in 26 (8.2%) of the cases and 8 (2.5%) were found swelling. All adverse events were slight and largely resolved without treatment. Most adverse events were reported during the first 24 h in all doses.

Table 2. Comparison of demographic characteristics between revaccination and non-revaccination infants among 525 low-responders, Guangdong, China 2006

	Revaccination infants		P[a]
	Yes (n = 101)	No (n = 124)	
Months	7(7,7)	7(7,8)	0.165
Gestational weeks	37.8(30,45)	38.1(28,45)	0.130
Birth weight	3.3(2.3,4.2)	3.2(1.7,4.7)	0.203
Males, no. (%)	50(49.5)	237(55.9)	0.246

Note: Data are median (range) of subjects, unless otherwise indicated. [a]Exact χ^2 or nonparametric Kruskal-Wallis test for differences among treatment arms.

Table 3. Anti-HBs response in non- and low- responders after three additional hepatitis B revaccination: Guangdong, China 2006

	Booster low-responders		Booster responders		Total
	n	%	n	%	
Primary non-responders	5	14.7	29	85.3	34
Primary low-responders	16	21.6	58	78.4	74
Total	21	19.4	87	80.6	108

Discussion

Our results confirmed the efficacy of vaccination against HBV in infants and highlighted the fact that 3.1% were non-responders and 28.9% were low-responders. The percentage of responders in our study (68%) was lower than those of other studies (ranging between 80% and 97%).[19-21] The subjects of these studies were also neonates and the procedures were consistent with our study, except the dosage. Previous studies used 10 μg vaccine while 5 μg vaccine was used in this study, indicating that vaccine dosage influenced antibody response to anti-HBV vaccine.[22] The effect of vaccine might also be influenced by technology of different companies and epidemiology of different districts.

Furthermore, we analyzed the factors that may influence the antibody response to anti-HBV vaccine. The outcome of primary vaccination were influenced by neonate birth weight. We found non- and low- responders were more in LBW neonates (50%) than normal birth weight neonates (32%), which is consistent with other studies. For example Feratis et al. found that the seroprotection rate of LBW neonates was lower than normal weight neonates, especially for the neonates weight less than 1,700 g.[23] Hassan et al. observed low-response rate in LBW subjects was higher than that in normal birth weight neonates.[24] The seroprotection response rate after three doses of vaccine increased with birth weight. Infants weighing < 1,500 g at birth (< 1,000 g, 1,000 to 1,500 g) had lower rates of response (52% and 68%, respectively) than did infants weighing > 1,500 g at birth (84% response rate).[25]

Sex was not associated with the immunological response to HBV, which were consistent with other studies.[22,26-34] Because most of the subjects of our study were 7 and 8 mo newborns, we did not find the association between age and responsiveness. Our results were in agreement with studies that the frequency of preterm infants producing protective antibody levels was as high as that of full term infants.[35-39] As the aforementioned studies, our study infants had a higher gestational age Our study neither found the relation between mother HBsAg-positive and non-responses, nor did mother HBeAg-positive. The result was similar to other research result.[40] In the present study, 122 neonates tested positive for anti-HBc or HBsAg were excluded. And most of them were given birth by mothers identified as HBsAg- or HBeAg-positive. Some studies found that mother HBsAg- or HBeAg-positive contributed to the non-responses after vaccination.[41,42] However, they did not exclude anti-HBc or HBsAg positive neonates whose mothers were HBsAg- or HBeAg-positive.

Long-term protection against HBV after a primary immunization course has been shown in vaccinees with antibodies to HBV (anti-HBs > 10 mIU/ml).[43,44] And loss of antibodies does not necessarily mean loss of immunity to HBV. Protection against infection is not an all or nothing phenomenon but is a probability function. Therefore there cannot be an absolute protective level of antibody against infection. On the other hand, breakthrough infections had occurred in vaccinees whose anti-HBs titers were low (< 100 mIU/ml) or deficient (< 10 mIU/ml) after a hepatitis B vaccine schedule.[18,45] Hoffman et al. found that[10] the risk of HBV infection increased not only in non-responders who had undergone a complete vaccination series but also in low-responders. Base on a much higher number of vaccines, we can carry out a more precise conclusion. In recent years, there are about 1.6 million neonates who are born in Guangdong province per year. The non- and low- responding neonates are predicted to be 0.51 million per year who are still under the threat of HBV. Almost 80% of non- and low-responders developed anti-HBs titer > 100 mIU/ml after three additional 10 μg booster doses of recombinant anti-HBV vaccine.

Our research had some limitations. First, the initial sample size of non- or low-responders was sufficient initially, but attrition was large for the booster dose sample size for the low- and non-responders, thus limiting the generalizability of the data. Second,

we did not have different dose-dependent and time-dependent antibody responses for the specific revaccination to test how many additional doses were required to push the non-responsers and low-responders into the higher titer range. Third, there were still some argues about whether the low responders group (10–100 mIU/ml) was at significant risk for hepatitis B carrier, infection, disease or liver cancer and that this group was relevant for booster dosing.

The result of our study had important practical consequence. Probably 0.4 million non- and low- responders per year and almost 4.6 million in recent 15 y in Guangdong would become responders if additional immunization cycle was administrated. Based on the lower responding rate after the primary immunization cycle and the higher responding rate after the additional cycle, measurement of anti-HBs level should be considered for people who had been immunised with three-dose 5 μg HB vaccine, especially for specific populations including LBW infants, healthcare workers, and patients with immunodeficiency disorders. An amount of 10 μg vaccine should be revaccinated to any non- and low- responders to provide adequate seroprotection.

Based on our study result about high non- and low- responding rate of 5 μg HB vaccine and other studies result about higher non- responding rates of 5 μg HB vaccine comparing with 10 μg HB vaccine,[17,18] 5 μg yeast recombinant HB vaccine is fully considered to be replaced by 10 μg vaccine by the Guangdong health authority now. Further research is required to evaluate the revaccination immunogenicity induced by different vaccine dosages and different number of doses. Of course, further study sample size should be large enough to be sufficiently representative. Longer follow up of currently 5 μg immunized people and future 10 μg immunized people is also needed to understand antibody levels, HBV infection and carrier rates. These issues are important for the evaluation and optimization of vaccination policies.

Materials and Methods

Subjects and immunization schedule. The initial cohort consisted of 2199 children who received anti-HBV vaccine from six counties (Nanshan, Dalang, Shijie, Qingxi, Wanjiang, Houjie) of Guangdong province. All children were born from March 2005 to January 2006. Following the informed consent of at least one parent, 5 μg yeast recombinant anti-HBV vaccine was administered intramuscularly at 0, 1 and 6 mo. A 3 ml blood sample was drawn from each infant 1 mo after the third dose of vaccine for determination of hepatitis B core antibody (anti-HBc), HBsAg and the anti-HBs level. Variables associated with poor response were sought prospectively by collecting demographic and clinical data. We obtained data on anti-HBs titer in 1,814 subjects of the enrolled cohort. On the basis of the magnitude of the antibody response achieved at seroconversion, three groups of subjects were identified:

(1) non-responders, with anti-HBs levels < 10 mIU/ml.

(2) low- responders, with anti-HBs levels ≥ 10 mIU/ml and < 100 mIU/ml.

(3) responders, with anti-HBs levels ≥ 100 mIU/ml.

108 infants were studied after primary vaccination schedule. The 108 children group consisted of 34 out of 56 non-responders and 74 out of 105 low-responders.[22] non-responders parents and 31 low responders parents did not allow their children to receive further treatment. Three additional doses (10 μg each) of yeast recombinant HBV vaccine were given at 8, 9 and 14 mo of life.

Test of anti-HBs, HBsAg and anti-HBc. During the whole study period, serological tests were administrated in the same laboratory and the analysis kits were purchased from Beijing North Institute of Biological Technology.

At each time point, serum samples collected were stored at -20°C. Anti-HBs, HBsAg and anti-HBc were all quantitatively measured by radioimmunoassay. Seroprotection for anti-HBs was defined as an anti-HBs level of ≥ 10 $mIUml^{-1}$. Seroconversion for HBsAg as a radioimmunological count per minute (cpm) of sample over mean cpm of negative controls (S/N) of ≥ 2.1, and seroconversion for anti-HBc according to the instructions of the manufacturer.

Statistics. The data were processed using SPSS 17.0 software. All tests were performed two-sided at the 5% significance level. The dependency of the seroprotective rate on the host factors was assessed by using the x^2 test. The mean level of anti-HBs was expressed as GMT.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Wang LD. Vaccination practice and management. Beijing: People's medical publishing house 2006:187.
2. The report of seroepidemiological survey on hepatitis B in Chinese people. Ministry of health of the people's republic of China, Centers for disease control and prevention of China. Beijing: People's medical publishing house 2011: 79.
3. Assad S, Francis A. Over a decade of experience with a yeast recombinant hepatitis B vaccine. Vaccine 1999; 18:57-67; PMID:10501235; http://dx.doi.org/10.1016/S0264-410X(99)00179-6.
4. World Health Organization. Expanded Program on Immunization, Global Advisory Group. Wkly Epidemiol Rec 1992; 3:11-6.
5. Sun ZT, Ming LH, Zhu X, Lu JH. Prevention and control of hepatitis B in China. J Med Virol 2002; 67:447-50; PMID:12116043; http://dx.doi.org/10.1002/jmv.10094.
6. Goudeau A, Coursaget P, Barin F, et al. Prevention of hepatitis B by active and passive active immunization. Viral Hepatitis 1982: 509-525.
7. Redeker AG, Mosley JW, Gocke DJ, McKee AP, Pollack W. Hepatitis B immune globulin as a prophylactic measure for spouses exposed to acute type B hepatitis. N Engl J Med 1975; 293:1055-9; PMID:1101065; http://dx.doi.org/10.1056/NEJM197511202932101.
8. Seeff LB, Wright EC, Zimmerman HJ, Alter HJ, Dietz AA, Felsher BF, et al. Type B hepatitis after needle-stick exposure: prevention with hepatitis B immune globulin. Final report of the Veterans Administration Cooperative Study. Ann Intern Med 1978; 88:285-93; PMID:343678.
9. Hadler SC, Francis DP, Maynard JE, Thompson SE, Judson FN, Echenberg DF, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986; 315:209-14; PMID:2941687; http://dx.doi.org/10.1056/NEJM198607243150401.
10. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis 1999; 179:489-92; PMID:9878036; http://dx.doi.org/10.1086/314578.
11. Whittle H, Jaffar S, Wansbrough M, Mendy M, Dumpis U, Collinson A, et al. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. BMJ 2002; 325:569-73; PMID:12228132; http://dx.doi.org/10.1136/bmj.325.7364.569.
12. Whittle HC, Inskip H, Hall AJ, Mendy M, Downes R, Hoare S. Vaccination against hepatitis B and protection against chronic viral carriage in The Gambia. Lancet 1991; 337:747-50; PMID:1672389; http://dx.doi.org/10.1016/0140-6736(91)91367-4.
13. Hofmann F, Kralj N. Criteria for successful hepatitis B vaccination in adults: results of a case study. Infection 2009; 37:266-9; PMID:18854934; http://dx.doi.org/10.1007/s15010-008-7410-y.

14. STIKO. Empfehlung der standikegen impfkommission (STIKO) am Robert Koch-Institut/Stand: Juli 2002 Epid Bull 2002; 28:227-42.
15. Heermann KH, Goldmann U, Schwartz W, Seyffarth T, Baumgarten H, Gerlich WH. Large surface proteins of hepatitis B virus containing the pre-s sequence. J Virol 1984; 52:396-402; PMID:6492255.
16. Tedder RS, Zuckerman M, Brink N. Hepatitis B vaccination. Non-responders must be detected .... BMJ 1993; 307:732; PMID:8401100; http://dx.doi.org/10.1136/bmj.307.6906.732.
17. An S, Jia H, Han Y, et al. Meta-analysis of the immunogenicity of different dosages of yeast recombinant hepatitis B vaccine. Chinese journal of health statistics 2009; 26:398-399.
18. Chen B, Liu L, Zhang JY, et al. Meta-analysis of the immunogenicity of 5 μg and 10 μg dosages of a recombinant hepatitis B vaccine. Mod Prev Med 2010; 37:611-4.
19. Belloni C, Tinelli C, Orsolini P, et al. Revaccination against hepatitis B virus of non-responding and low responding infants immunized at birth. A parallel evaluation of rubella and tetanus vaccine. Vaccine 1998; 6:399-402; http://dx.doi.org/10.1016/S0264-410X(97)80917-6.
20. Cook IF, Murtagh J. Comparative immunogenicity of hepatitis B vaccine administered into the ventrogluteal area and anterolateral thigh in infants. J Paediatr Child Health 2002; 38:393-6; PMID:12174003; http://dx.doi.org/10.1046/j.1440-1754.2002.00013.x.
21. Junqueira AL, Tavares VR, Martins RM, Frauzino KV, da Costa e Silva AM, Minamisava R, et al. Safety and immunogenicity of hepatitis B vaccine administered into ventrogluteal vs. anterolateral thigh sites in infants: a randomised controlled trial. Int J Nurs Stud 2010; 47:1074-9; PMID:20189173; http://dx.doi.org/10.1016/j.ijnurstu.2010.01.009.
22. Hollinger FB. Factors influencing the immune response to hepatitis B vaccine, booster dose guidelines, and vaccine protocol recommendations. Am J Med 1989; 87(3A):36S-40S; PMID:2528297; http://dx.doi.org/10.1016/0002-9343(89)90530-5.
23. Freitas da Motta MS, Mussi-Pinhata MM, Jorge SM, Tachibana Yoshida CF, Sandoval de Souza CB. Immunogenicity of hepatitis B vaccine in preterm and full term infants vaccinated within the first week of life. Vaccine 2002; 20:1557-62; PMID:11858862; http://dx.doi.org/10.1016/S0264-410X(01)00493-5.
24. Hassan S, Ziba F. Antibody titer in Iranian children 6 years after hepatitis B vaccine administration. Vaccine 2007; 25:3511-4; PMID:17400337; http://dx.doi.org/10.1016/j.vaccine.2005.09.037.
25. Losonsky GA, Wasserman SS, Stephens I, Mahoney F, Armstrong P, Gumpper K, et al. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics 1999; 103:E14; PMID:9925860; http://dx.doi.org/10.1542/peds.103.2.e14.
26. Ghebrehewet S, Baxter D, Falconer M, Paver K. Intradermal recombinant hepatitis B vaccination (IDRV) for non-responsive healthcare workers (HCWs). Hum Vaccin 2008; 4:280-5; PMID:18398298; http://dx.doi.org/10.4161/hv.4.4.5687.
27. Yu AS, Cheung RC, Keeffe EB. Hepatitis B vaccines. Clin Liver Dis 2004; 8:283-300; PMID:15481341; http://dx.doi.org/10.1016/j.cld.2004.02.010.
28. Chang MH. Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. Liver Int 2003; 23:309-14; PMID:14708890; http://dx.doi.org/10.1034/j.1478-3231.2003.00865.x.
29. Viviani S, Jack A, Hall AJ, Maine N, Mendy M, Montesano R, et al. Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. Vaccine 1999; 17:2946-50; PMID:10462228; http://dx.doi.org/10.1016/S0264-410X(99)00178-4.
30. Ding L, Zhang M, Wang Y, Zhou S, Kong W, Smego RA Jr. A 9-year follow-up study of the immunogenicity and long-term efficacy of plasma-derived hepatitis B vaccine in high-risk Chinese neonates. Clin Infect Dis 1993; 17:475-9; PMID:8218692; http://dx.doi.org/10.1093/clinids/17.3.475.
31. Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. JAMA 1985; 254:3187-9; PMID:2933532; http://dx.doi.org/10.1001/jama.1985.03360220053027.
32. Shaw FE Jr., Guess HA, Roets JM, Mohr FE, Coleman PJ, Mandel EJ, et al. Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. Vaccine 1989; 7:425-30; PMID:2530717; http://dx.doi.org/10.1016/0264-410X(89)90157-6.
33. Malekzadeh R, Khatibian M, Rezvani M. Viral hepatitis in the world and Iran. J Iran Med Council 1997; 15:183-200.
34. Szmmuness W, Stevens CE, Harlay EJ, et al. Hepatitis B vaccine: demonstration of efficacy in the United States. N Engl J Med 1980:303.
35. Chirico G, Belloni C, Gasparoni A, Cerbo RM, Rondini G, Klersy C, et al. Hepatitis B immunization in infants of hepatitis B surface antigen-negative mothers. Pediatrics 1993; 92:717-9; PMID:8414862.
36. Belloni C, Chirico G, Pistorio A, Orsolini P, Tinelli C, Rondini G. Immunogenicity of hepatitis B vaccine in term and preterm infants. Acta Paediatr 1998; 87:336-8; PMID:9560044; http://dx.doi.org/10.1111/j.1651-2227.1998.tb01448.x.
37. Faldella G, Alessandroni R, Magini GM, Perrone A, Sabatini MR, Vancini A, et al. The preterm infant's antibody response to a combined diphtheria, tetanus, acellular pertussis and hepatitis B vaccine. Vaccine 1998; 16:1646-9; PMID:9713941; http://dx.doi.org/10.1016/S0264-410X(98)00060-7.
38. Huang FY, Lee PI, Lee CY, Huang LM, Chang LY, Liu SC. Hepatitis B vaccination in preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77:F135-8; PMID:9377137; http://dx.doi.org/10.1136/fn.77.2.F135.
39. Belson A, Reif S, Peled Y, Bujanover Y. Immune response to hepatitis B virus vaccine in 1-year-old preterm and term infants. J Pediatr Gastroenterol Nutr 1996; 23:252-5; PMID:8890074; http://dx.doi.org/10.1097/00005176-199610000-00008.
40. Amani A, Shoekri F. Immunogenicity of a recombinant hepatitis B vaccine inI ranian neonates: high frequeney of unresponsiveness in dependent of the carrier state of mothers. Iran J Med Sci 1995; 20:87-92.
41. Tian C, Li J, Han CZ, et al. Immunization effectiveness and influence factors of hepatitis B vaccination of newborns in China. Chin J Publ Health 2007; 23:678-9.
42. Deng XQ, Xu ZY, Ouyang PY, et al. Relationship between titre of maternal serum hepatitis B surface antigen, e antigen and failure of neonatal hepatitis B immunization. Chinese. J Infect Dis 2000; 18:232-5.
43. American Academy of Pediatrics Committee on Infectious Diseases. Universal hepatitis B immunization. Pediatrics 1992; 89:795-800; PMID:1557285.
44. Orsolini P, Belloni C, Klersy C, Campisi D, Chirico G, Togni C, et al. Anti-HBV neonatal immunization with recombinant vaccine. Part I. Critical appraisal for a long-lived antibody course. Vaccine 1995; 13:551-4; PMID:7483775; http://dx.doi.org/10.1016/0264-410X(94)00043-M.
45. Windebank KP, Faux JA, Chapel HM. ELISA determination of IgG antibodies to pneumococcal capsular polysaccharides in a group of children. J Immunol Methods 1987; 104:143-8; PMID:3680953; http://dx.doi.org/10.1016/0022-1759(87)90498-4.