EFFICACY AND SAFETY OF VACCINATION AGAINST HEPATITIS B VIRUS WITHOUT PRIOR SCREENING TEST

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Abstract:
Hepatitis B virus infection is a major global health problem. There is no specific treatment for acute hepatitis B infection. A safe and effective vaccine, which has been available for more than 30 years, is 95% effective in preventing the development of chronic infection. The employee of Bangladesh Bank and their family member had received 4 doses of Engirex B according to schedule 0, 1,6,12 months without any prior screening test. They received 4th booster dose in 2009.The goal of this study to find out and compare the efficacy and safety of vaccination against HBV without prior screening test. The employee (more than 50years old) underwent annul health check up and their serum HBsAg and Anti-HBs (quantative) were measured in the Immunology department of Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) and Popular diagnostic center. HBsAg is measured by MEIA method. Anti-HBs (quantative) are measured by chemiluminescence EIA method. 491 subjects have been studied. Among them 480(97.76%) are HBsAg negative and 11(2.24%) cases are HBsAg positive. Ten out of eleven HBsAg positive cases are male. The average anti-HBs titer of the employee is 610.9958(0- >2000 m IU/ml). The average anti-HBs titer of female (n=90) employee is 713(10- >2000 mIU/ml) and average anti-HBs titer of male (n=390) employee is 587.77(0 - >2000 m IU/ml). Female employee developed higher immunity (73.33%) than male employee (56.41%). So it is presumptive that vaccine is safe and effective and we can continue vaccination without prior screening test.

Key word: *HBsAg, Anti-HBs, HBV vaccine.*

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Introduction:

Hepatitis B virus infection is a major global health problem .Worldwide it is the 10th leading cause of death. In Western countries, the disease is relatively rare and acquired primarily in adulthood, whereas in Asia and most of Africa, chronic HBV infection is common and usually acquired perinatally or in childhood. Prevalence of Hepatitis B in Bangladesh is yet to be ascertained by a reliable study. Data available from different studies show that it is ranges between 0.8 and 5.4% [1, 2,3,4,5] based on the detection of HBsAg antigen. Relying on these statistics Bangladesh can be categorized as an intermediate endemic zone for HBV [6,7].Globally, variation in prevalence depends on age, sex, country, income, education, life style and co-morbidity. Lifetime risk of infection is 20%-60% and infections occur in all age groups.[8] The estimated lifetime risk of HBV infection in the United States varies from almost 100% for the highest-risk groups to less than 5% for the population as a whole.[9]

The virus is transmitted through contact with the blood or other body fluids of an infected person. The most important routes of transmission are perinatal and sexual contact, either heterosexual or homosexual, with an infected person. In the past two decades, outbreaks of hepatitis B have occurred in long-term care facilities (e.g., assisted living facilities and nursing homes) as the result of lack of infection control practices related to blood glucose monitoring. Hepatitis B virus remains infectious for at least 7 days on environmental surfaces and is transmissible in the absence of visible blood. Direct percutaneous inoculation of HBV by needles during injection-drug use is an important mode

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of transmission. Breaks in the skin without overt needle puncture, such as fresh cutaneous scratches, abrasions, burns, or other lesions, may also serve as routes for entry. Nosocomial exposures such as transfusion of blood or blood products, hemodialysis, use of meters and lancets for glucose monitoring, insulin pens, and needle-stick or other "sharps" injuries sustained by hospital personnel have all resulted in HBV transmission.[8]

An estimated 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen positive for at least 6 months). An estimated 2 billion persons worldwide have been infected with HBV, and more than 350 million persons have chronic, lifelong infections. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 50% of hepatocellular carcinomas (HCC). The World Health Organization estimated that more than 600,000 persons died worldwide in 2002 of hepatitis B-associated acute and chronic liver disease.[8] Hepatitis B is an important occupational hazard for health workers. The role of the HBV carrier is basic to the epidemiology of HBV transmission. A carrier is defined as a person who is HBsAg positive on at least 2 occasions, at least 6 months apart. Although the degree of infectivity is best correlated with HBeAg positivity, any person with a positive test for HBsAg is potentially infectious. The likelihood of developing the carrier state varies inversely with the age at which infection occurs. During the perinatal period, HBV transmitted from HBeAg-positive mothers results in HBV carriage in up to 90% of infected infants, whereas 6%-10% of acutely infected adults become carriers[7]. HBV is about 100 times more infectious than HIV.[10]

HBsAg is the most commonly used test for diagnosing acute HBV infections or detecting carriers. HBsAg can be detected as early as 1 or 2 weeks and as late as 11 or 12 weeks after exposure to HBV when sensitive assays are used. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic.

There is no specific treatment for acute hepatitis B infection. Treatment is supportive. However, those who develop antibody to HBsAg (anti-HBs) during convalescence after acute HBV infection or following hepatitis B vaccination ,are usually protected against subsequent infection. Hepatitis B viral infection is a preventable disease. A safe and effective vaccine, which has been available for more than 30 years, is 95% effective in preventing the development of chronic infection. A titer of at least 1mIU/ml or more was interpreted as seroconversion and a titer above 10 mIU/ml was considered as seroprotection.[11] The vaccine produces neither therapeutic nor adverse effects in HBV carrier[12]. When primary vaccination produces anti-HBs (Hepatitis B surface antibody) level >100 m IU/ml, it is considered to be adequate response or the vaccine is called responders. If between 10-100 m IU/ml, then hypo responders and if it is <10 m IU/ml, then there is no response or non responder.

In 1991, the World Health Organization (WHO) recommended that all countries introduce a policy of universal hepatitis B vaccination to prevent and control HBV infection and its long term sequelae on a global scale.. Hepatitis B vaccine for infants had been introduced nationwide in 184 countries by the end of 2014. Global coverage with 3 doses of hepatitis B vaccine is estimated at 82% and is as high as 92% in the Western Pacific[13]

Bangladesh (since late 2004) has started incorporating the HBV vaccination into national immunization program with the schedule of immunizing babies at 6, 10 and 14 weeks of birth.

In the mid 1980s, recombinant DNA hepatitis B vaccines containing HBsAg expressed in HBV transfected yeasts (i.e. *Saccharomyces cerevisiae*), the so-called "second" generation hepatitis B vaccine, were commercialized. This new technology offered the potential of unlimited production, which allowed the hepatitis B vaccine to become one of the most widely used in the world. Several hundred million doses of hepatitis B vaccine have been administered worldwide with an excellent record of safety and efficacy.[14]

Bangladesh Bank is an autonomous body situated in Dhaka, Bangladesh. A mixture of highly educated and educated people is working in this institute. They enjoy some medical facility. Considering the seriousness of HBV infection, the employee and their family member were vaccinated against HBV in 2000-2001 and they had received 4 doses Engirex B according to schedule 0, 1,6,12 months without any prior screening test. They received 4th booster dose in 2009.The goal of this study to find out and compare the efficacy and safety of vaccination against HBV without prior screening test.

Methodology: This is a large, prospective, longitudinal, descriptive and opportunistic type study carried out in Bangladesh Bank Medical Center, Motijheel, and Dhaka. The employee (more than 50years old) underwent annul health check up in 2013-2014 and their serum HBsAg and Anti-HBs (quantative) were measured in the Immunology department of Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) and Popular diagnostic center. HBsAg is measured by MEIA method. Anti-HBs (quantative) is measured by chemiluminescence EIA method. Data were collected from employee's digital medical records. All data were checked for completeness and consistencies. Then data were complied and appropriate statistical analysis was done using computer based Microsoft Excel windos7 professional.

Observation and results:

For the purpose of the study, 491 subjects have been studied. Table-I showed age sex and HBsAg status of the employee. Out of 491employee, 91 (18.53%) are female and 400(81.47%) are male employee. Median age of the employee is 55.78(51-59) years. Average age of female employee is 56(50-59) years and of male employee is 55.64(50-59) years. Among them 480(97.76%) are HBsAg negative and 11(2.24%) cases are HBsAg positive. Ten out of eleven HBsAg positive cases are male.

Table-II showed antibody titer (anti-HB) 4 to 5 years after vaccination. The average antibody titer of the employee is 610.9958(0- >2000 m IU/ml). The average antibody titer of the healthy employee is 875.5(0- >2000 m IU/ml). The average antibody titer of the diseased employee is 618.58(0- >2000 m IU/ml).The average antibody titer of female (n=90) employee is 713(10- >2000 mIU/ml). The average antibody titer of healthy female (n=15) is 977.69(103- >2000 m IU/ml). The average antibody titer of diseased female (n=75) is 652.82(0- >2000 m IU/ml). The average antibody titer of male (n=390) employee is 587.77(0 - >2000 m IU/ml). The average antibody titer of healthy male (n=121) is 594.39(0- >2000 m IU/ml). The average antibody titer of diseased male (n=269) is 585(0- >2000 m IU/ml). Seroconversion (antibody titer >1 m IU/ml) occur among 432(87.98%) and Seroprotection (antibody titer >10 m IU/ml) seen among 380(77.39%). Female employee developed higher immunity (73.33%) than male employee (56.41%). Among the positive cases, 6 (1.23%) are diseased and all are male .They continued treatment and remaining 5(1.02 %) are carrier .They continue follow up procedure and needs no treatment.

Table-III showed distribution of total HBsAg negative employee (n=480) according to level of immunity. 286(59.58%) employee have good protection against HBV. Among them 220 (56.4%) are male and 66(73.33%) are female. 94(19.58%) employee have low protection. Among them 80(20.51%) are male and 14(15.55%) are female. 100(20.83%) employee have no protection against HBV. Among them 90(23.07%) are male and 10(11.11%) are female.

Table-IV, figure 1 and 2 showed that 136(28.33%) employee are disease free and 344(71.67%) employee are suffering from different diseases. It also showed distribution of total HBsAg negative diseased employee and comparison between male and female employee. Data showed that female employee is more diseased than male employee. Total 136 (28.33%) employee are diseases free. Among them 121(24.59%) are male and 15(2.87%) are female employee. 38(9.22%) male are disease free and they have no immunity.

272(56.67%) employee are suffering from *hypertension*. Among them 210(53.85%) are

male and 62(68.89%) are female employee. 179(37.29%) employee are suffering from *diabetes*. Among them 134(34.36%) are male and 45(50%) are female employee.81 (16.88 %) employee suffering from *heart disease*. Among them 69(17.69 %) are male and 12(13.33 %) are female. 59(12.29 %) employee are suffering from *bronchial asthma*. Among them 40(10.26%) are male and 19(21.11%) are female. 26(5.41%) employee suffering from *chronic kidney disease* .Among them 19(4.87%) are male and 7(7.78%) are female. 16(3.33%) employee suffering from *hypothyroidism*. Among them 9(2.3%) are male and 7(7.78%) are female. Table-V showed comparison between employee those who fail to develop immunity (n=100) and seroprotective group (n=380).Regarding disease prevalence, there is no significant difference. 100(20.83%) employee are failing to develop immunity. Among them 38 male employee are disease free. 62% employee is suffering from different diseases. Among them 52% are male, 10% are female. Among the seroprotective group, 300(75%) are male employee and 80 (88.88%) are female employee. Seroprotection found more among female than male.

Table-I

Age, sex and HBsAg status of the employee (n=491)

Sex	Total no	Age (years)	HBsAg -ve	HBsAg +ve	Percentage
Female	91	56(51-59)	90	1	18.53%
Male	400	55.64(50-59)	390	10	81.47%
Total	491	55.78(50-59)	480(97.76%)	11(2.24%)	

Table-II

Anti-HBs titer 4-5 years after 4th booster dose

Sex	Healthy/ Diseased	Number of employee	Antibody titer
Female	Healthy	15	977.69 (103-2000) mIU/ml
	Diseased	75	652.82 (0-2000) mIU/ml
	Total /Average	90	713 (0-2000) mIU/ml
	Seroprotection	80	88.88%
Male	Healthy	83	774 (10-2000) mIU/ml
	Healthy but no immunity	38	(0-9) mIU/ml
	Diseased	269	585 (0-2000) mIU/ml
	Total /Average	400	587.77 mIU/ml
	Seroprotection	300	75%
Average antibody titer			610.9958(0-2000) mIU/ml
Average antibody titer for healthy employee			875.5mIU/ml
Average antibody titer for diseased employee			618.5mIU/ml
Seroconvertion (antibody titer >1 mIU/ml)			432(87.98%)
Seroprotection (antibody titer >10 mIU/ml)			380(77.39%)

Table-III

Distribution of total HBsAg negative employee(n=480) according to immunity

	Male(n=400)	Female(n=91)	Total(n=491)
HBsAg Positive	10(2.5%)	1(1.1%)	11(2.24%)
HBsAg Negative	390 (97.5%)	90 (98.9 %)	480 (97.76%)
Good immunity	220 (56.4%)	66(73.33%)	286(59.58%)
Low immunity	80(20.51%)	14(15.55%)	94(19.58%)
No immunity	90(23.07%)	10(11.11%)	100(20.83%)

Table-IV

Distribution of total HBsAg negative Diseased employee (n=480)

	Male(n=390)	Female(n=90)	Total(n=480)
Disease free	121(31%)	15(16.67%)	136(28.33%)
No immunity, no disease	38(9.74 %)	0	38(7.9 %)
Diseased	269(68.97%)	75(83.33%)	344(71.67%)
HTN	211(54%)	64 (71%)	275(57.29%)
DM	132(33.84%)	45(50%)	177(36.87%)
IHD	69(17.69 %)	12(13.33 %)	81(16.88 %)
BA	40(10.26%)	19(21.11%)	59(12.29 %)
CKD	19(4.87%)	7(7.78%)	26(5.41%)
Hypothyroidism	9(2.3%)	7(7.78%)	16(3.33%)

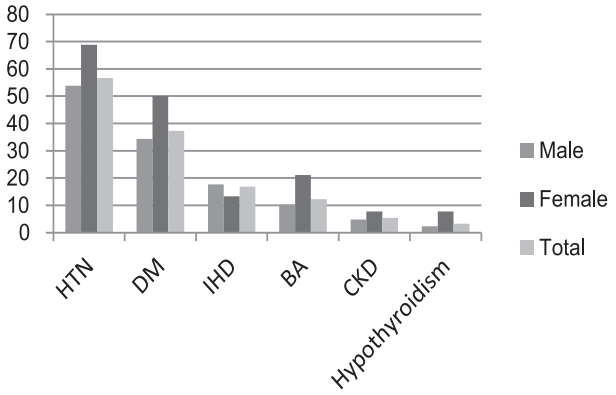
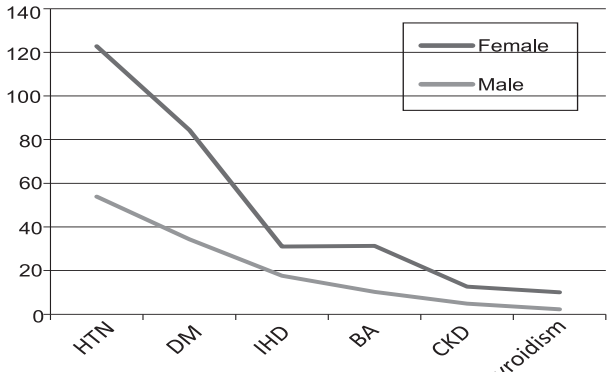


Fig.-1: *Distribution of total HBsAg negative Diseased employee (n=480)*



HTN-Hypertension, CKD- Chronic kidney disease, Hypothyroid-Hypothyroidism

Fig.-2: *Comparison of total HBsAg negative Diseased employee (n=480)*

Table-V

Comparison of patients between those who fail to produce immunity (N =62) and seroprotective group (n=380)

Name of diseases	Seroprotective Male (n=300)	No immunity Male (n=90)	Seroprotective Female (n=80)	No immunity Female (n=10)	Total N=480
HTN	173(57.67%)	38(42.22%)	56(70%)	8(80%)	275(57.29%)
Diabetes	107(35.66%)	25(27.78%)	37(46.25%)	8(80%)	177(36.87%)
Heart disease	56(18.67%)	13(14.44%)	11(13.75%)	1(10%)	81(16.88 %)
Bronchial asthma	30(10%)	10(11.11%)	18(22.5%)	1(10%)	59(12.29 %)
CKD	16(5.33%)	3(3.33%)	7(8.75%)	0	26(5.41%)
Hypothyroid	7(2.33%)	2(2.22%)	7(8.75%)	0	16(3.33%)

Discussion:

South East Asia experienced a strong reduction in HBsAg prevalence between 1990 and 2005,particu-larly in the young age groups of 0–14 years that had prevalence levels of 1.2–1.4% in 2005. In contrast, South East Asian adult s appeared to continuously have higher-intermediate HBsAg prevalence of 5% to over 6% in 2005.[7] Declines in HBV infection prevalence may be related to expanded immunization.[7]The hepatitis B vaccine is the mainstay of hepatitis B prevention. From the study it was found that 97.76% employee are HBsAg negative. Only 2.24% employee is HBsAg positive and among them 90% is male. Same findings are seen in different studies.[2-7] There is a study done in VNC[1] in 1997, the study showed that the prevalence of HBsAg among healthy female school age children was 2.3% by the screening method and 0.8% by the confirmatory method.

Seroconversion rate of Hepatitis B vaccine globally ranges from 85-90 %[15] A k Jain et al found seroconversionrate of 98.45 %. [16] Kruman.S et al found 99% of subjects developed protective level of Anti-HBs after vaccination with Recombivax HB (Merck) after 1 month of last dose in his study.[17] Sunita Tripathy et al found 100% seroconversion in medical students and among them 80% had high response (HBsAb > 1000 mIU/ml) after primary vaccination with Engerix -B vaccine.[18] In this study seroconversion were seen among 432(87.98%) employee 5 years after 5th dose of vaccination with Engerix -B vaccine. But we could not evaluate seroconversion rate among the employee after 3rd dose of vaccination with Engerix -B vaccine because there is no such opportunity.

The US Public Health Service Advisory Committee On Immunization Practice (ACPI) recommendation issued in 1987 defined the protective level of anti HBs as greater than or equal to 10 mIU/ml, measured 1-2 months after completion of hepatitis b vaccine series.[19,20]An Indian study conducted by Kunal Das showed that among seroprotected individuals there were 32.4% hyporesponders (Anti-HBs level 10 -99 mIU/ml) and 52.9% were responders (anti HBs >100mIU/ml).[21] Sunita Tripathy et al found only 5% hyporesponder and rest 95% were responders.[18] From the study it was found that 58.2% employee achieved good (responders)and 18.65% employee achieved low protective immunity (hyporesponders) against HBV 5 years after vaccination. Brian J Mac Mohan reported males had higher antibody level than females .[22] Whereas Jane W.S Fang et al found that female children responded with a significantly higher antibody level than male children.[23] In the study conducted by Mohd. Abdul in Bangladesh found protective level of anti HBs antibody in 85.88% male and 92.31 % of female.[24] Glaser et al found in his study that antibody level becomes less in persons undergoing more stress than less stress one.[25] In this study 344(71.67%) employee are suffering from hypertension, diabetes ,heart disease, chronic kidney disease, bronchial asthma and hypothyroidism. Anti- HBs level is lower among(anti-HB 618mIU) them than healthy(anti-HB 875.5mIU) employee. Dr Hayley Willecy also found that those above 40 years, obese and smokers are more likely to fail to respond. [26] In the study conducted by Ann P. Winter, higher proportion of smokers failed to seroconvert after 3 doses of hepatitis vaccine.[27] In this study , higher antibody level were found among female employee than male.

In this study, no antibody titers or immunity found (<10mIU/mL) among 20.83 %(100/480) employee. They were vaccinated previously with 5 dose of Engirex B. Among them 38 male employee are disease free and remaining 62 are diseased. Only 10(11.11%) out of 90 female employee are failing to show immunity. Incase of male employee, 100(23%) out of 400 fail to show immunity. The reason of this no response, most probably due to long interval(the study done 13-14 years after vaccination), male employee, smoking habit and all employee are more than 50 years old[1,8,9] .It has been reported that antibody response decreases with age. R. John Looney found that antibody response was dramatically different between young and elderly group.

Study conducted by Kunal das et al [21], Seroprotection (Anti-HBs >10mIU/ml) after

primary vaccination was achieved in 85.3% volunteers who were more than 40 years of age. Surg Cdr C N Choudhury et al concluded in his study that higher age at vaccination is a risk factor for low antibody response.[28] we could not compare elderly group for seroconversion with young because participants of less than 25 years had their primary vaccination 15 years back are not available. There are few long term studies which suggest that hepatitis B vaccine protects an individual for more than 15 years.[29] Jafar zadeh et al evaluated persistence of antibody level in healthy Iranian children at 10 years after primary vaccination and found that 47.9% of children had protective level of HBsAb >10 m IU/ml.[30] It has been seen that approximately 20% geometric mean titer decay occurs per year.[31] In this study, there is no chance to estimate geometric mean titer decay. We found persistence of antibody level in both sexes and antibody level less among male .In this study mean antibody titer was 610.99 m IU/ml 5years after forth booster dose. Although initially it was thought that Hepatitis B vaccination does not provide indefinite protection. This is no longer considered. Previous reports suggested that primary vaccination would provide protection between 5-7 years.[32, 33] But subsequently it has been appreciated that protection may be provided for at least 25 years due to long term immunity derived from immunological memory in those individuals who showed adequate response to primary Hepatitis vaccination.[34] .Our study suggested that DNA recombinant vaccine maintains protective level of anti-HBs for more than 10 years. Although, after vaccination the levels of antibody to hepatitis B surface antigen may decline over time, the necessity to maintain anti-HBs concentrations above a certain titer is not widely accepted, since long term immune memory remains intact even in the absence of detectable antibodies. [35] Gabbuti et al suggested that booster dose is not required in immunocompetent individuals.[36]

Duration of vaccine- induced immunity: After three intramuscular doses of hepatitis B vaccine, more than 90% of healthy adults and more than 95% of infants, children, and adolescents (from birth to 19 years of age) develop adequate antibody responses. However, there is an age-specific decline in immunogenicity.[8,37,38] But immune memory remains intact for more than 20 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes).[6,8,39,40] In this study good immunity(>100mIU/mL) found among 58.2% employee.

Vaccine Failure: A small percentage of adults fail to mount an immunological response despite completion of the immunization schedule. Several factors have been associated with nonresponse to hepatitis B vaccine. These include vaccine factors (e.g., dose, schedule, injection site) and host factors are older age (40 years and older), male sex, obesity, smoking, and chronic illness have been independently associated with nonresponse to hepatitis B vaccine. [8,18,41,42] Preterm babies <2Kgs are also known to show insufficient responses.[41]

Cost-effectiveness: Cost is an important issue for a resource poor country like Bangladesh. Cost analysis done in countries with low endemicity shows that routine vaccination against HBV costs about $6.9x3= $207 (542*3=1626/taka) per life saved, compared with over $228-3184.71(17972- 250000 taka) yearly for HBsAg positive chronic hepatitis or HCC per patient.[43] In 2014-15,$13516 (1182652/taka)were spent for the management 17 HBsAg positive patient. On the other hand, to reduce the risk of ischemic heart disease, myocardial infarction and brain stroke $86817.32 (6815159.99/taka)were consumed (as cost of lipid lowering drugs) and it will be continued life long.[43] Economic analysis of vaccinating Asian Americans in Philadelphia was found to be cost-effective and even cost-beneficial with a benefit-cost ratio of 4.4:1[44] However Bangladesh is a medium income country(per capita income is$1314) , literacy rate is 60%, safe drinking water is 95% , purchase capacity increased more than previous ,vaccine is available and price is affordable and community clinic is available everywhere. All children are vaccinated against HBV since 2004 by EPI schedule. So all adult

person can be vaccinated with 3 dose schdule to protect future generation. There is no need of screening test and measurement of antibody titer for general public .[8, 45]

HBV infection is uncommon among adults in the general population (the lifetime risk of infection is less than 20%) [8], it is highly prevalent in certain groups. Risk for infection varies with occupation, lifestyle, or environment. Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. Pregnancy is a risky condition for women and regular shaving, field work is a risky condition for men. It has been found that about 1.2-3.5% of the pregnant ladies in Bangladesh are HbsAg positives and that 22-38% of them is also HBeAg positives.[3] The risk of perinatal transmission is about 10% if the mother is positive only for HBsAg. Pregnancy is not a contraindication to vaccination.[8] As many as 90% of infant HBV infections will progress to chronic infection.[8] Delaying vaccination for the first six weeks will put 70-90% babies at risk of acquiring perinatal infection. [3] If couple is vaccinated one by one, it will be economic for the family and beneficial both for society and country.

Conclusion:

The vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete vaccine series. For adults and children with normal immune status, booster doses of vaccine are not recommended. Serologic testing is not recommended before routine vaccination of infants, children, or adolescents. Routine serologic testing to assess immune status of vaccinees is not recommended.

These data helps to justify economic analysis of HBV vaccination in Bangladesh. To analyze cost benefit/cost effectiveness, present study is a guide for Bangladesh, as its infrastructure of health care and disease prevalence are improving than previous. Bangladesh needs an effective vaccination strategy against HBV. So it is presumptive that vaccine is safe and effective and we can continue vaccination without prior screening test. Healthy life style and good behavior increase immune protection.

Limitation: We cannot compare Anti-HBs level with body weight and smoking.

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Competing interests: I declare that I have no conflict of interest.

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