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SEROLOGIC STATUS OF NEONATES BORN TO HEPATITIS B POSITIVE MOTHERS AND GIVEN HEPATITIS B VACCINE AT BIRTH IN A TERTIARY GOVERNMENT HOSPITAL FROM JANUARY 2007 TO JUNE 2008: A PILOT STUDY

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KEYWORDS
Seroconversion, Hep B vertical transmission, Hepatitis B vaccine,

ABSTRACT

BACKGROUND: Data evaluating effectiveness of the Newborn Hepatitis B Immunization program remains unavailable years after its implementation**.**

OBJECTIVE: This study describes the serologic status of infants nine-to-18 months, born to Hepatitis-Bs-Antigen-positive mothers and who received Hepatitis B vaccine at birth.

METHODOLOGY: Fifty-one infants with complete immunization data and whose parents consented to serologic testing for Hep Bs Ag and Anti HBs were included in the study. Venous blood was collected and tested using SD HBs Ag test kit (Intec) and SD Anti HBs test kit (Bioline).

RESULTS: One of 51 (1.9 %) infants tested was positive for HBs Ag; 22 (43.1%) had Anti HBs seroconversion; and 28 (54%) were non reactive to both Anti HBs and Hep Bs Ag. The infant reactive to Hep Bs Ag received three doses of Hepatitis B vaccine but did not receive HBIg.

CONCLUSION: Giving of Hepatitis B vaccine with or without HBIg conferred protection from vertical transmission in 98% of the study population. Only 1.9 % (n=1) tested positive for Hep Bs Ag and did not receive protection from Hep B vaccination. The seroconversion rate was only 43.1% even if majority of patients received two subsequent doses of vaccine before serologic testing. There is a need to review the dosing schedule of Hep B vaccination being implemented in our primary care setting to ensure seroconversion after vaccination.

INTRODUCTION

Hepatitis B is one of the world's serious and widespread chronic diseases that commonly cause chronic liver disease. It is estimated that 400 million people are chronic carriers of Hepatitis B virus (HBV).[1] The prevalence of chronic HBV infection is high at 8% to 15% in all socioeconomic groups in certain areas around the world, including, Southeast Asia. In the Philippines, the prevalence ranges from 2% to 16.5% or an average of 12%.[2] One or 2 million people per year or 4,500 people everyday die from Hepatitis-B-related complications.[2, 3, 4] Furthermore, 72.5% of liver cancer is associated with HBV with a mortality rate of 1%.[5] Approximately 9000 people are estimated of dying from chronic liver disease in the Philippines annually; a mortality rate comparable to that of Tuberculosis.[1, 2, 6].

Mode of transmission is horizontal when infection is thru exposure to infected blood, serologic preparations, needles and syringes of Hep Bs Ag positive contact and/or direct contact like oral-oral, sexual, or intimate physical contact like percutaneous wound exudate. Vertical transmission or perinatal exposure to Hep Bs Ag positive mothers, however, is the most important risk factor for infection, occurring in 70% to 90% of infants born to Hep Bs Ag and Hep Be Ag positive mothers and 5% to 20% of infants born to Hep Bs Ag positive and Hep Be Ag negative mothers. The risk for chronic infection is inversely related

to the age at the time of acute infection; so, if infection is acquired perinatally, the risk is >90% as against 25% to 50% if acquired at one-to-five years old, and 6% to 10% in older age group/adult.[2, 3, 4]

Several studies have shown that passive and active Hepatitis B immunization to newborns born to Hepatitis-B-positive mothers is 85% to 95% protective, while Hepatitis B vaccine administered alone is 70% to 95% effective in preventing perinatal HBV infection.[7,8,9] Through its rational vaccination program (1991-2001) which used three doses of Hepatitis B vaccine, Taiwan reduced the prevalence rate of Hepatitis B infection from 20.3% to 4.4% in males and from 14.3% to 2.4% in females who were born more than six years before the start of the program. A later study in 2003 further decreased prevalence to only 0.7%.[10]

Both the American Academy of Pediatrics and the Center for Disease Control and Prevention recommend the administration of monovalent Hepatitis B vaccine to all newborns before hospital discharge and the Hepatitis B Immunoglobulin (HBIg) within 12 hours of birth if the mother is Hepatitis Bs Ag positive. Hepatitis B series should be completed with either monovalent Hepatitis B or a combination vaccine containing Hepatitis B with the second dose administered at age one or two months and the final dose administered at an age not earlier than 24 weeks or six months. Administration of a fourth dose is encouraged when combination vaccines containing Hepatitis B are administered after the birth dose. Lastly, they recommend that infants born to Hep Bs Ag positive mothers be tested for Hep Bs Ag and Anti Hbs after the completion of at least three doses of the Hepatitis B series at the age of nine-to-18 months, or generally, at the next well-child visit.[4, 11]

The World Health Organization (WHO) recommends giving the first dose of vaccine within 24 hours of birth to prevent mother-to-child transmission of infection.[12] However, WHO does not have guidelines on when to test serologic status or response to vaccination.

Since 1992 and in accordance with WHO guidelines, Hepatitis B vaccination has been made available to Filipinos through the National Expanded Program on Immunization (EPI); it initially covered 40% of infants and had increased its coverage by 10% every year until it reached 100% coverage in 1999. However, the implementation was limited due to insufficient funding and because the first dose was scheduled at six weeks of age and not at birth. Pursuant to Republic Act No. 7846 or the "Compulsory Hepatitis B Immunization among infants and children less than 8 years old", a new Administrative Order No. 2006-0015 provides guidelines on Hepatitis B immunization for infants meant to improve effectiveness of management in the provision of three doses of routine Hepatitis B vaccine among infants including a birth dose".[13]

In the Northern Mindanao Medical Center (NMMC), a tertiary care government hospital, there is an average of 5000 deliveries a year. Mothers are routinely screened for Hepatitis Bs Ag prenatally. Since 24 January 2007 the hospital started giving Hepatitis B vaccination to all newborns right after birth and additionally HBIg, if the mother is Hep Bs Ag positive. However, HBIg was not always given to all babies of Hep Bs Ag positive mothers because this had to be procured separately by the parents who could not always afford to purchase it.

In the Philippine setting, the prevalence of reactivity to Hep Bs Ag among pregnant women is 8.5% according to Lingao, et al. Overall, seven out of 17 (41.2%) infants born to Hep Bs Ag positive mothers became Hep Bs Ag positive within the first 12 months of life. The risk of becoming infected with Hep Bs Ag positive was about 20 times higher for infants born to Hep Bs Ag positive mothers than for infants born to Hep Bs Ag negative mothers.[14]

In a study by Harma, et al in 2002, 48 infants born to Hep Bs Ag positive mothers were immunized with HBIg and a Hepatitis B

vaccine and were examined at approximately 28 months of age. In 44 or 91.6% of the infants, the vaccine with HBIg was found effective.[15] The superiority of giving HBIg in addition to the vaccine compared to Hepatitis B vaccine alone was proven by a meta analysis of 29 studies by Chuangfang Lee in 2000, wherein he found that this regimen was able to better prevent Hepatitis B associated diseases.[16]

On the other hand, without the administration of HBIg, the vaccine alone is also quite effective, as long as the first dose is given at birth. Snapavat S in 1992 reported that giving recombinant vaccine starting at birth suggested protective efficacy levels above 90% even without the use of additional HBIg at birth.[17]

If a baby born to a Hep Bs Ag positive mother received the birth dose and two more subsequent doses, the vaccine confers 98.87% protection against infection in the first year of life; this was seen in the study by del Cancho, et al wherein only eight out of 705 infants turned Hep Bs Ag positive during their first year of life.[18]

OBJECTIVE

The aim of this study is to describe the serologic status of infants born to Hepatitis B Antigen positive mothers and who received hepatitis B vaccine at birth, upon follow up at nine-to-18 months of life.

Currently, there are no data regarding rates of seroconversion or other indices of effectiveness of this newborn Hepatitis B immunization program. This is the first study to look into the serologic status of babies on follow up at nine-to-18 months of age after being given Hepatitis B vaccine at birth.

METHODOLOGY

Research Design: A cohort study at the Northern Mindanao Medical Center was performed.

Research Setting:

The study was carried out at a tertiary government training hospital in Cagayan de Oro City.

Subjects and Methods:

Hospital records were reviewed to identify infants who were born between January 2007 to June 2008 at the Northern Mindanao Medical Center (NMMC), who have mothers were prenatally diagnosed to be Hep Bs Ag positive, and who were given Hepatitis B vaccine at birth, with or without HBIg administration. These patients were contacted and their caregivers were asked to provide the investigator with an immunization record, like a baby book or EPI record book. Informed consent was administered for the collection of blood samples for Hep Bs Ag and Anti HBs determination at nine-to-18 months of age.

Excluded from the study were preterm infants born <37 weeks AOG; infants with birth weights < 2000 grams; infants diagnosed with liver disease, congenital anomalies, TORCH, and other chronic diseases, since said conditions may contribute to poor response to vaccination. Also excluded were those who received Hepatitis B vaccine in the last four weeks prior to serologic testing since immunologic response may not have manifested yet. Lastly, those who did not consent to participate in the study were also excluded.

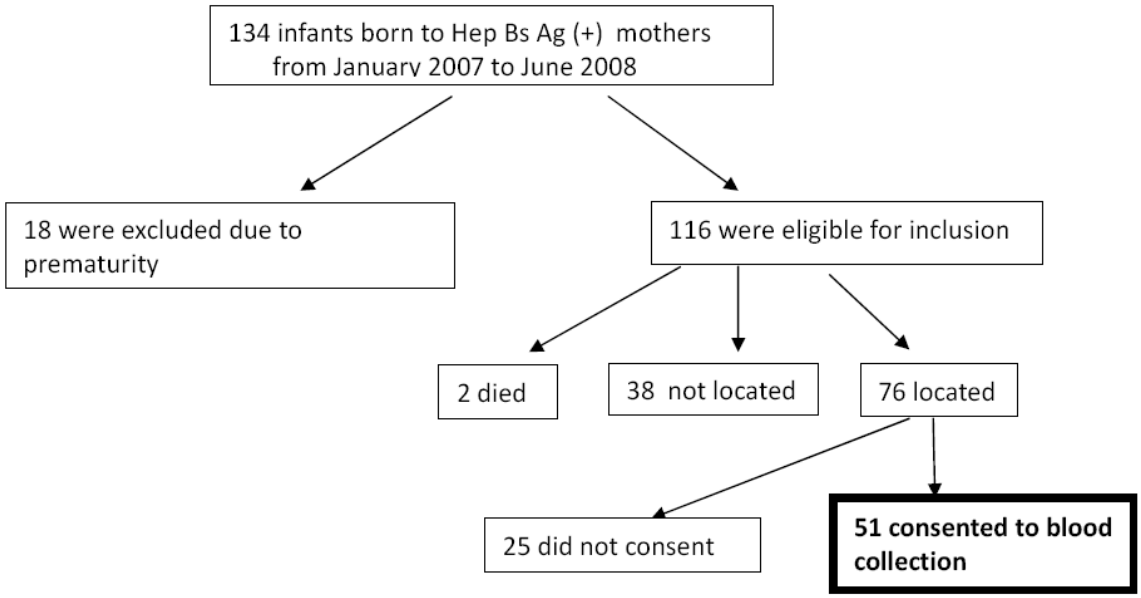
Statistical Analysis:

Descriptive statistics used were frequency in numbers, ratios, means, percentages and ranges.

Definition of Terms:

1. Hepatitis B infection – serologic test result showed Hepatitis Bs Antigen positive.
2. Responder – serologic test result showed Anti HBs positive.
4. Active immunization – giving of Hepatitis B vaccine.
5. Passive immunization – giving of Hepatitis B Immunoglobulin within 12 hours of birth.
6. Birth dose – giving of Hepatitis B vaccine within 24 hours of birth.

Figure 1: Number of eligible and actual study participants



RESULTS

A total of 134 neonates were born to Hep Bs Ag positive mothers from January 2007 to June 2008. All of these babies received Hepatitis B vaccine (0.5 ml), with or without HBIg at birth. There were 89 or 66% who were given HBIg at birth while 45 or 33% received Hepatitis B vaccine only. Out of the 134 infants, 18 were excluded due to prematurity, which left 116 eligible for inclusion in the study. Of the 116, two died of causes not related to Hepatitis B, and 38 were not located because of change in addresses or false information regarding their address on record. Out of the 76 babies who were located, only 51 consented to participate in the study (Figure 1).

Of the 51 study participants, only one (1.9%) was found to be infected with Hepatitis B, seen as Hep Bs Ag positive, Anti HBs negative status on follow up, despite being given the birth dose of Hepatitis B vaccine; this baby did not receive HBIg at birth (Table 1). Review of immunization record, however, showed that this baby also received two more subsequent doses of Hepatitis B at one month and two months of age. This baby was given a follow up schedule for monitoring of liver function.

Table 1. Distribution of study participants according to kind of immunization received at birth and subsequent protection from vertical transmission.

Protection from vertical transmission	Kind of immunization		
	Active immunization	Active + Passive immunization	Total
HBs (-)	29	21	50 (98.1%)
HBs (+)	1	0	1 (1.9%)

Twenty-two of the 51 study participants (43.1%) seroconverted and were seen as Anti HBs positive on follow up. All of them, except one, availed of the 2nd and 3rd doses at their Local Health Center which uses a 0-1-2 schedule of primary immunization. The one, who did not receive three doses, received only the birth dose at NMMC.

Twenty nine of the study participants, including the one infected, did not seroconvert. All of them received three doses at the Local Health Center (Table 2).

Table 2. Distribution of study participants according to vaccine doses received and immunization response.

Immunization response	Vaccine Dose Received		
	Birth dose only	Birth dose + 2 doses	Total
Responder	1	21	22 (43.1%)
Non-responder	0	29	29 (56.8)

Thus, of the 51 study participants, a total of 50 received three doses of Hepatitis B vaccine using a 0-1-2 schedule, and only one received just the birth dose.

DISCUSSION

In this study, one out of 51 infants (1.9%) was positive for Hep Bs Ag at 18 months of age and therefore was not protected by Hepatitis B immunizations at birth, at 1 month and at 2 months of age; this may be due to the inability to give HBIg at birth. In the ideal situation, government hospitals should also be able to provide free HBIg at birth in addition to the vaccine given to all babies born to Hep Bs Ag (+) mothers to ensure protection.

There is also the possibility that the mother may have been positive for Hep Be Ag. Previous studies have demonstrated increased risk of infection in babies born to mothers reactive to both Hep Bs Ag and Hep Be Ag, compared to those babies born to mothers reactive to Hep Bs Ag only. In a study by Jian-She Wang, et al in 2005, four out of 16 babies born to Hep Be Ag (+) and Hep Bs Ag carrier mothers and who received both Hepatitis B vaccine and HBIg at birth, still became persistently infected with HBV. The other 26 babies born to HBe Ag negative and Hep Bs Ag carrier mothers who also received Hepatitis B vaccine and HBIg at birth, were protected from HBV.[9] In another study by Boxall, EH in 1996, two of the 128 babies born to Hep Be Ag and Hep Bs Ag carrier mothers and who received Hepatitis B vaccine alone were infected with HBV, while, all the babies born to Hep Be Ag negative mothers and Hep Bs Ag carrier mothers were protected from HBV infection after receiving the vaccine.[19]

The presence of Hep Be Ag in mothers who are also Hep Bs Ag positive poses a greater risk of transmitting the infection to their babies. There has been no previous recommendations regarding Hep Be Ag testing among pregnant women, thus, this is not routinely done. This is most likely because screening for Hep Be Ag does not add to the recommended management of giving both HBIg and Hep B vaccine at birth. Furthermore, Hep Be Ag testing is also not routinely done in newborns. In a baby born to Hep Bs Ag and Hep Be Ag positive mother, the transplacental Hep Be Ag can be detected at one month of age but it would disappear before four months of age in uninfected babies. Only the babies with Hep Be Ag positive persistently detected after four months of age have HBV infection breakthrough.[9] Thus, reactivity to Hep Be Ag in a newborn does not always mean that the baby will be infected with Hepatitis B.

Only 22 or 43.1% of the 51 subjects responded. All, except one, received two or more doses of Hep B vaccine. Most studies show higher seroconversion rates after vaccination. Sunbul, et al showed 48.4% of cases who seroconverted after the first vaccination, 63.6% after the second vaccination and 90.9% after the third vaccination.[20] SR Sedonio-Jesena reported of an 83.8% seroconversion rate among 37 infants a year after receiving three doses of Hepatitis B vaccine.[21] Khukhlovich, et al reported seroconversion in 76.7% of children aged four-to-five months after the third Hepatitis B vaccine injection and in 95.7% for children aged five-to-16 months, with none of them receiving HBIg.[22] Cedena, et al reported that 74.5% of children remained reactive to Anti HBs for eight-to-15 years after primary immunization.[23] Possible reasons for the low seroconversion rate in this study compared to previous studies are ineffectiveness of the dosing schedule, vaccine failure and the emergence of HBV

mutants, which can potentially escape vaccine-induced immunity.[6]

All of the subjects in this study, except the one who received only the birth dose, were vaccinated in their respective Local Health Center following the recommended 0-1-2 schedule of the Department of Health. Lee, et al collected samples of 126 children and 111 adults who were immunized according to 0-1-2 and 0-1-6 schedule, respectively; Anti HBs were measured one month after the last dose. The results showed seroconversion rate after 0-1-2 vaccination schedule at 98.4% in children and 44.3% in adults. Seroconversion rate after 0-1-6 schedule were 100% in children and 93.4% in adults.[24] A study by Kumar in 2001 showed that 95% to 100% of children attain seropositive levels of Anti HBs after three doses given at birth and at one month and six months of age. Typically, this 0-1-6 schedule yields a higher seroconversion rate and relatively higher titers of Anti Hbs that will persist for an extended period of time compared to the levels of Anti HBs in 0-1-2 dosing schedule. Hence, a 4th dose at 12 months is recommended if the 3rd dose is given before six months of age in order to elicit a higher titer of Anti HBs.[25] The AAP and CDC recommend the 0-1-6 schedule due to high seroconversion rates compared to the 0-1-2 schedule.[4, 11] WHO recommends a 0-1-2 schedule in endemic countries[12] like the Philippines; thus, this is being followed by our Department of Health and the local health centers.

The 29 patients who failed to seroconvert may actually benefit from a fourth dose of Hepatitis B vaccine after the 0-1-2 schedule. Montazerifar SJ in 2006 reported on 94 of the 146 children (64.4%) given Hepatitis B vaccine at 0-1-6 schedule with low or nondetectable Anti HBs but seroconverted in 95.7% after receiving one booster dose of Hepatitis B vaccine.[26] In another study by Saffar et al in 2004, 191 of the 453 children did not seroconvert despite completing the routine universal three doses Hepatitis B immunization but 144 seroconverted after giving a booster dose.[27] However, our local health centers currently are unable to provide the 4th dose because it is not included in the EPI.

Vaccine failure is also a big issue especially in patients born to mothers positive for Hep Bs Ag like our subjects. Causes of vaccine failure include poor storage and poor cold chain maintenance. [28] A study by Hipgrave et al on immunogenicity of Hepatitis B vaccine with the birth dose stored outside the cold chain for up to one month in rural Vietnam compared to infants who received three doses stored within the cold chain, showed that the vaccine was protective in 80.3% of all infants. There was no difference in the prevalence of protective level of antibody or antibody titer among groups of infants according to storage strategy. The heat stability of Hepatitis B vaccine should enable its storage outside the cold chain, increasing access to the birth dose in areas lacking refrigeration.[29] Ideally, vaccine quality should also be investigated; however, this is not within the scope of the study.

Recent studies have shown proof that immunologic memory to Hepatitis B vaccine remains intact for at least 23 years and confers protection against clinical illness and chronic Hepatitis B virus infection. Even at the cellular level, studies have shown that cellular immunity appears to persist even though antibody levels might become low or decline below detectable levels.[26] The CDC in September 27, 2001 speculated that the majority of children with undetectable antibodies may be actually protected against HBV. Thus, a routine administration of booster doses of vaccine to children may not be necessary; but additional information is needed to assess whether the immunologic memory in children vaccinated as infants persist into the adolescence and adulthood, when the risk of infection, either by lifestyle or HBV professional exposure, becomes higher.[6]

CONCLUSIONS

Among the 51 babies born to Hep Bs Ag (+) mothers who participated in this study, 98.1%

were protected from vertical transmission. There was an infection rate of 1.9% despite being given birth dose of Hepatitis B vaccine and subsequent two doses at one and two months old. Seroconversion determined on follow up at nine-to-18 months of age was only 43.1% among the study participants. Majority of study participants received three doses of Hep B vaccine with the 2nd and 3rd dose administered at one and two months of age, respectively, at the local health center. There is a need to review the schedule of Hep B vaccination provided by the government-funded local health center and determine the need for a fourth dose, in light of the low seroconversion rate seen in this study.

RECOMMENDATIONS

This study can be extended to investigate the effect of a fourth dose on the study participants who failed to seroconvert. Further studies should ideally enroll participants at birth to ensure adequate follow up and include baseline data on the Hep Be Ag status of mothers around the time of birth. Additional investigation on the cost-effectivity of giving government-funded HBIg together with vaccine at birth should also be done.

REFERENCES

1. WHO. Global Health Situation and Projections and Estimates 1992. World Health Organization, Geneva, 1992.
2. Behrman R, Kliegman R, Jenson H, Stanton B. Nelson Textbook of Pediatrics.18ed.Philadelphia: W. B. Saunders; 2004.
3. Carandang E, Carlos C, Ong-Lim A. Handbook on Infectious Diseases. 10th ed. Philippines; 2004.
4. Pickering LK. Report of the Committee on Infectious Diseases.26th ed.2008.
5. Palmer, M. Hepatitis and Liver Disease: What You Need to Know. May 12, 2006.
6. US Center for Disease Control and Prevention Effectiveness of Hepatitis B Vaccination in Babies Born to HBs Ag Positive Mothers in Italy. Sept 27, 2001.
7. del Mundo F.,Estrada F, Santos Ocampo P, Navarro X. Textbook of Pediatrics and Child Health.5th ed. Philippines: JMC Press; 2000.
7. Greenberg, DP. Pediatric Experience with Recombinant Hepatitis B vaccines and Relevant Safety and Immunogenicity Studies. Pediatric Infectious Disease Journal 1993; 12:438-45.
9. Jian-She Wang et al. Transformation of Hepatitis B Serologic Markers in Babies Born to Hepatitis Bs Ag Positive Mother. World Journal of Gastroenterology. 2005; 1 (23):3582-3585.
10. Lingao, A., Domingo, E., Raymundo, D., Caragay, B., West, S. Incidence and Prevalence of Hepatitis B. American Journal of Epidemiology. Vol 123, No4 : 681-689.
11. Center for Disease Control and Prevention, Department of Health and Human Services. February 23, 1999.
12. Gitlin N. Hepatitis B: Diagnosis, Prevention, and Treatment. Clinical Chemistry, 1997, 43:1500-1506.
13. Implementing Guidelines on Hepatitis B Immunization for Infants. Department of Health. Administrative Order No.2006-0015. June 23, 2006.
14. Lingao AL, Torres NT, Lansang MA, West SK, Bosch FX, Domingo EO. Mother to Child Transmission of Hepatitis B Virus in the Philippines. UP-PGH. June 5, 1989.
15. Harma, Mehmet et al. Vaccination of Newborns from Chronically Infected Mothers is Effective in Preventing Hepatitis B in Infants. Department of Gynecology and Obstetrics, Faculty of Medicine, University of Harran, Turkey.
16. Chuangfang Lee. Effect of Hepatitis B Immunization in Newborn Infants of Mothers Positive for Hepatitis B surface Antigen: Systematic Review and Meta-analysis. BMJ 2006; 332:328-336.
17. Snapavat, S. Long Term Efficacy of Hepatitis B Vaccine in Infants Born to Hep Be Ag Positive Mothers. Pediatric Infectious Disease Journal.1992 Oct; 11(10):816-21.
18. Del Cancho R, Grosheide PM, Schalm SW, de Vries RR, Heijtink RA. Failure of Neonatal Hepatitis B Vaccination. Journal Hepatology 1994; 20:483-486.15.
19. Boxall, EH. Prevention of Hepatitis B in the Newborn, Children and Adolescent.Zucherman A., editor. London: Royal College of Physicians; 1996.
20. Sunbul M. Response to Hepatitis B vaccine in HBs Ag/Anti HBs Negative and Subjects. Scand J Infectious Diseases.2000; 32(3):315-6.
21. Sedonio-Jesena, SR. Immune Response of Infants One Year After Three Doses of Hepatitis B Immunization. Philippine Pediatric Research. 1997-2001.
22. Khukhlovich PA et al. The Vaccinal Prophylaxis of Hepatitis B Among Children Born to Mothers with Persistent HBs-antigenemia. Mikrobiol Epidemiol Immunobiology.1996; 2:55-59.
23. Cedena EB, de la Calzada GJ. The Antibody Response

of Children to Hepatitis B Vaccine 8-15Years After Primary Immunization. Philippine Pediatric Research.2002-2005.
24. Lee TH. Predictors of Poor Response to Hepatitis B Vaccine. Journal Watch General Medicine. January 7, 1994.
25. Kumar et al. Indian Journal of Medical Microbiology. 2001.
26. Montazerifar SJ. Persistence of Anti HBs Antibody and Immunological Memory in Children Vaccinated with Hepatitis B Vaccine at Birth. J Ayub Med Coll Abbottabad. 2006 Oct-Dec; 18(4):4-9.
27. Saffar, M.J. et al. Long-term Antibody Response and Immunologic Memory in Children
28. Immunized with Hepatitis B Vaccine at Birth. Indian Pediatrics 2004; 41: 1232-1237.Shah, Nitin MD. Indian Academy of Pediatrics. 1998-2001.
29. Hipgrave DB et al. Immunogenicity of a Locally Produced Hepatitis B Vaccine with the Birth Dose Stored Outside the Cold Chain in Rural Vietnam. AM J Trop Med Hyg.2006; 74:255-260.