EVALUATION OF THE PROGRAM FOR PREVENTION OF VERTICAL TRANSMISSION OF HEPATITIS B INFECTION

IN

KANIYAMBADI BLOCK AND CHAD HOSPITAL

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CERTIFICATE

This is to certify that the dissertation titled **"Evaluation of the program for prevention of vertical transmission of Hepatitis B infection in Kaniyambadi block and CHAD hospital"** is a bonafide work of Dr. Anu Mary Alexander in partial fulfillment of the requirements for M.D. branch XV (Community Medicine) Examination to be held in March 2009.

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Contents

ABBREVIATIONS

ACIP	**Advisory Committee on Immunization Practices**
Anti HBs	**Anti body to Hepatitis B surface antigen**
Anti HBc	**Anti body to Hepatitis B core antigen**
CHAD	**Community Health and Development Program**
CMC	**Christian Medical College**
HBsAg	**Hepatitis B surface antigen**
HBIG	**Hepatitis B Immunoglobulin**
HBV	**Hepatitis B Virus**
INASL	**Indian Association for the Study of the Liver**
IAP	**Indian Academy of Pediatrics**
PCR	**Polymerase Chain Reaction**
UIP	**Universal Immunization Program**

1. INTRODUCTION AND JUSTIFICATION

Hepatitis B infection which has been listed among the top ten leading causes of death worldwide is one of the few vaccine preventable causes of a cancer[1]. It is estimated that one in three persons worldwide show evidence of current or past infection with Hepatitis B. There are around 350 million chronic carriers of Hepatitis B infection of which a fourth will progress to have either cirrhosis of the liver or hepatocellular carcinoma[2].

Although there are many approaches to prevent transmission of Hepatitis B infection, Hepatitis B vaccine is the most effective method for the same. The vaccine has an efficacy of 95% when used as a pre-exposure prophylaxis [3].

Perinatal transmission of Hepatitis B which is an important route of infection is believed to be responsible for a third of adult chronic carriers in India [4,5]. Prevention of perinatal transmission of Hepatitis B is an effective method of reducing the prevalence of chronic HBsAg carriers, in areas where a large proportion have acquired infection through this route. Studies have shown that a combination of Hepatitis B immunoglobulin and Hepatitis B vaccine is 92-100% effective in preventing perinatal transmission of Hepatitis B from HBsAg positive mothers to their infants [6]. However, in view of the high costs of Hepatitis B immunoglobulin, this strategy may not be possible in resource poor countries like India. The Hepatitis B vaccine alone when given soon after birth also has a remarkable efficacy ranging from 72%-100%, when given as a post exposure prophylaxis to infants born to HBsAg positive mothers [6,7].

One strategy followed at national levels is universal immunization of all infants. When this scheme involves routine administration of the first dose of vaccine within 24 hours, it is the ideal way to prevent both vertical and horizontal transmission. The other strategy involves screening of all pregnant women during the antenatal period and selectively immunizing the infants born to the HBsAg positive mothers. Although universal immunization may be more cost effective in the long run it is not feasible in places where the rate of institutional deliveries is low [8]. Thus the selective immunization strategy is an option in places where resources are limited and the prevalence of Hepatitis B is also very low.

In India the Hepatitis B immunization program which was initially introduced as a pilot project, followed a schedule of immunization at 6, 10 and 14 weeks along with the three DPT immunizations, with the aim to prevent early horizontal transmission [9]. The effectiveness of this strategy has not been studied to prove lower transmission of Hepatitis B in the pilot areas.

It has been argued that it is very difficult to routinely screen all pregnant women, offer counseling services for test positive women and ensure delivery of the birth dose of vaccine for these women. The Community Health Department of Christian Medical College has been providing such a screening program for antenatal women through services at the village level as well as at the base hospital, since 2002. Children born to mothers who tested positive for HBsAg were offered immunization commencing at birth, in order to prevent perinatal transmission. This study was an evaluation of the effectiveness of this program of antenatal screening and selective immunization of the infants born to HBsAg positive mothers.

2. AIMS AND OBJECTIVES

Aim:

To evaluate a program to prevent vertical transmission of Hepatitis B in Kaniyambadi block and CHAD hospital

Primary objective:

To evaluate the effectiveness of the program in reducing the vertical transmission of Hepatitis B among children born to HBsAg positive mothers who received three doses of the Hepatitis B vaccine commencing at birth

Secondary objectives:

1. To assess the effectiveness of the Hepatitis B immunization program in providing the planned immunization schedule commencing at birth

2. To determine seroprotection among children who received three doses of the Hepatitis B vaccine

3. To determine the prevalence of HBsAg among children born to HBeAg positive mothers, who received three doses of Hepatitis B vaccine commencing at birth

3. REVIEW OF LITERATURE

3.1 The Magnitude of the problem of Hepatitis B infection

The World Health Organization (WHO) estimates that two billion people worldwide have serologic evidence of past or current infection with Hepatitis B. The number of chronic carriers who are test positive for Hepatitis B surface antigen (HBsAg) for a period of at least 6 months is around 350 million. Every year, globally, around 600,000 people die of Hepatitis B related diseases such as cirrhosis of the liver and hepatocellular carcinoma [(10)].

The epidemiology of Hepatitis B virus infection has been described according to three categories of high, intermediate and low endemicity. Countries with high endemicity are those where HBsAg seroprevalence rate is 8% or more; countries with intermediate endemicity are those with seroprevalence of 2-7%; and those with low endemicity are those with seroprevalence of less than 2 %[(11)]. Regions with high endemicity include South-East Asia, China and the Amazon basin while regions with intermediate endemicity are parts of Eastern and Southern Europe, the Middle East, Japan and parts of South America. Developed countries in Northern America, Western and Northern Europe and Australia have low endemicity [(12)].

3.2 Prevalence of Hepatitis B carriers in India

Indian studies show wide variations in the prevalence of Hepatitis B surface antigen positivity based on whether they were done among antenatal women, blood donors (voluntary, replacement or professional donors), children, general population, groups at

high risk for sexually transmitted infections, tribal populations etc. For a long time it was believed that the national average carrier rate was 4.7% according to the consensus statement of the Indian Association for the Study of the Liver (INASL). India was said to be an intermediate prevalence country for chronic carriers of Hepatitis B. One of the flaws with this estimate was that all the studies were one time cross sectional surveys of prevalence of Hepatitis B infection and not of the chronic carrier rate, which would have required a second test to be positive after 6 months. Many of the studies included individuals belonging to high risk groups which have a higher prevalence compared to the general population. Another limitation was that the estimate of test positivity of 4.7% was not a weighted average, but a simple average of the prevalence in different studies [13].

There are very few estimates of prevalence of HBsAg infection in India from community based surveys. A community cluster study done in Tamil Nadu, estimated that the prevalence of Hepatitis B infection was 5.7% (95% CI: 4.7%-6.8%) in the general population [14]. However it was later found that the area in which the study was carried out was a zone with a high prevalence of commercial sex workers. A community based study done among women in the reproductive age group in an urban slum of migrant workers in Delhi, showed a prevalence of 5.8%. This study showed increasing prevalence with age, as the prevalence was 9.7% among older women (more than 30 years) as compared to 3.1% among younger women (15-29 years) [15]. Another community based study of the prevalence of reproductive tract infections among young married women, showed a prevalence of 2% for Hepatitis B surface antigen in Kaniyambadi block, Tamil Nadu [16].

A review done by Anant Phadke et al using data from 19 studies, excluding those from high risk groups, stated that the prevalence of chronic carriers of Hepatitis B was 1.42% challenging the previously accepted figure of 4.7% [13]. Further a systematic review of literature by Lodha et al in 2001, estimated the prevalence of Hepatitis B positive carriers to be between 1 to 2 % which also suggested that India was a low prevalence country [17].

In 2007 a meta-analysis done under the guidance of the Indian Medical Association was published as an improvement over the systematic review done by Lodha et al. This study showed that the true prevalence of Hepatitis B was 2.4 % (95% CI: 2.2%-2.7%) in non-tribal populations and 15.9 % (95% CI: 11.4%-20.4%) in tribal populations. Assuming that 80% of those who are test positive for HBsAg will continue to be test positive after 6 months of the initial test, the prevalence of chronic carriers among non tribal populations was 1.9% according to this meta-analysis[18]. This was consistent with the earlier finding of the systematic review by Lodha et al.

The prevalence of HBeAg is highly variable among different populations. According to the review by Lodha R et al, the HBeAg positivity rate among chronic carriers of Hepatitis B surface antigen was 7.8-47.8%, with most studies showing 18% or less[17].

3.3 Hepatitis B virus structure and serology

The Hepatitis B virus is a DNA virus with an outer lipoprotein envelope containing the ‘surface antigen' protein (HBsAg) and a nucleocapsid core (Hepatitis B core antigen). The nucleocapsid core also includes the viral DNA genome and enzymes. There is another protein which is found independently as a soluble antigen secreted from

infected cells, called the Hepatitis B e Antigen (HBeAg) whose function is largely unknown but which serves as a marker of active viral replication. The persistence of HBeAg beyond a period of 10 weeks indicates chronic infection and infectiousness. HBV DNA which can be detected by hybridization assays or Polymerase chain reaction (PCR), is used to detect mutant forms of the virus which escape detection by conventional methods[(2)].

The antibodies associated with HBV infection include antibody to HBsAg (anti-HBs), antibody to HBcAg (anti-HBc) and antibody to HBeAg (anti-HBe). In persons who recover from HBV infection, HBsAg is eliminated from the blood, usually within 3-4 months, and anti-HBs develops during convalescence. The presence of anti-HBs indicates immunity from HBV infection. The majority of persons who recover from natural infection will be positive for both anti-HBs and anti-HBc IgG, whereas persons who respond to immunization have only anti-HBs. Anti HBs levels of more than or equal to10 mIU/ ml, tested 1-3 months after the primary vaccine series is considered to be indicative of adequate seroconversion (also called seroprotection). In persons who become chronically infected, HBsAg and anti-HBc IgG persist for more than 6 months and typically for life [(19)].

3.4 Transmission of Hepatitis B

Hepatitis B is transmitted through perinatal transmission, household (non-sexual) contact, sexual contact, blood transfusions, needle sharing and occupation/health-care related events. The routes of transmission depend upon the endemicity of HBsAg in the region. In high prevalence areas, transmission is mainly perinatal and horizontal (exposure to chronically infected household members). In low endemicity areas, it is

mostly among young adults who acquire the infection sexually or by injection drug use. In intermediate endemicity countries like India, there is a mix of perinatal, health-care related, sexual and horizontal routes of transmission but relative contributions of perinatal, sexual and horizontal transmission in childhood are not known[17].

3.4.1 Perinatal transmission of Hepatitis B

Perinatal transmission is believed to account for 35-50 % of Hepatitis B carriers in high endemicity countries[20]. Although there is no definite estimate for India, some studies have estimated the proportion of chronic carriers who have acquired the infection vertically to be around 33% [4,5]. It has been suggested that since there was no progressive increase in prevalence of chronic carriers among children, it was unlikely that horizontal transmission played a major role in India. [21-23]. However, perinatal transmission may be responsible for up to 15% HBV related deaths even in low endemicity areas[3].

Studies done in the 1970s first suggested a link between the presence of HBeAg among carrier mothers which led to higher transmission of HBsAg to their children [24]. A study done by Beasley et al in Taiwan found that 85% of children born to HBeAg positive mothers were HBsAg positive, compared to 31% of children born to HBeAg negative mothers. Further studies done later also confirmed the findings that if the mother was both HBsAg and HBeAg positive, 70-90% of the children become chronically infected[25-27]. If the mother was HBsAg positive but HBeAg negative the risk of perinatal infection was only 5-20%[25]. The overall risk of acquiring infection through this route was 18.6-50% depending on the proportion of HBeAg positive

mothers [5]. Another risk factor found to be associated with perinatal transmission was high levels of HBV DNA in the mothers [28].

The possible routes for perinatal transmission are trans-placental (intra-uterine) infection and transmission at the time of delivery. It has been found that the time of acquiring Hepatitis B infection from the infected mothers is more often at birth rather than during pregnancy, in-utero transmission accounting for less than 2% of all perinatal transmission [25,26]. Hepatitis B vaccine and immunoglobulin cannot protect against trans-placentally acquired infection which occurs in-utero, which can be detected by the presence of IgM anti HBc antibodies in the cord blood. One of the suggested mechanisms for trans-placental infection was hematogenous transfer of infection when there is some factor like a threatened abortion which causes a break in the placental microvasculature. The other route could be cellular transfer, when the placenta is infected because of a high titre of the virus in the maternal blood which enters the fetal circulation [12].

There is no clear evidence to suggest that breast feeding increased the risk of acquiring HBV infection from HBsAg positive mothers [29,30].

3.4.2 Horizontal transmission

Horizontal transmission or early childhood transmission can also occur among children through exposure to infected family members or contacts through cuts, bruises, bites etc [25].

3.5 Morbidity and mortality due to Hepatitis B infection

Hepatitis B viral infection can lead to acute Hepatitis, chronic HBV infection, cirrhosis of the liver or hepatocellular carcinoma. While acute infection is more likely with increasing age, the chances of infection remaining chronic are greater among infants.

The proportion of affected persons who develop signs of acute infection are 1% among those affected perinatally, 5-15% among those affected between 1-5 years and 20-50% among those affected after 5 years of age. The proportion of infections which become chronic is 90% among those affected through vertical transmission; 25-50% among those affected between 1-5 years and 6% among those infected later [(25)].

There are three phases of chronic Hepatitis B when infection is acquired perinatally. The first is an immunotolerant phase when there is a lack of immune response owing to tolerance to the virus. There are either mild symptoms or none at all despite a high level of viremia. In the second immune clearance phase, clinical remission occurs with clearance of the virus due to activation of the immune response. In the residual phase there is minimal viral and immunological activity. Cirrhosis of the liver can occur due to damage occurring in the immune clearance phase and hepatocellular carcinoma can occur even when there is apparent clearance of the virus [(31)].

The association between Hepatitis B infection and hepatocellular carcinoma was proved by several case-control and prospective studies in Taiwan and China [(12,32)]. Around 25% of those who acquire chronic HBV infection die of cirrhosis of the liver or hepatocellular carcinoma and 1% clear the virus every year [(3)]

In India, according to the National Cancer Registry Program of the Indian Council of Medical Research, there are 5000 deaths every year due to hepatocellular carcinoma associated with Hepatitis B, constituting 1.6% of all cancers in India. There are undoubtedly many more cases of cirrhosis, but there is no registry maintained for the same [33].

3.5.1 Economic burden of Hepatitis B

Hepatitis B infection causes ill health through acute hepatitis B, liver cancer or cirrhosis of the liver. Assuming that the life expectancy in India in 2040 when future benefits of immunization are expected, will be 66 years, and that hepatocellular carcinoma (HCC) occurs at 45 years, 21 years of life are lost per case [34].

A South Korean study estimated that the annual cost of treatment and prevention of Hepatitis B was USD 1 billion. The direct medical costs of treatment accounted for 65.9 % of the total cost, indirect costs for 20.9% and preventive strategies for 13.2% of the total cost. Indirect costs included transportation, loss of wages, reduced work productivity, and premature death. The mean duration of hospitalization per year was 15.25 days for acute hepatitis, 16.73 days for chronic hepatitis, 33.83 days for cirrhosis, and 38.84 days for liver cancer [35].

3.6 Prevention of transmission of Hepatitis B

3.6.1 Prevention of sexual and horizontal transmission

In countries with low endemicity of infection where the majority of chronic carriers acquire infection through sexual contact or injection drug abuse, counseling and behavior change communication will be useful in reducing transmission. Screening

blood and blood products for HIV, Hepatitis C antibody and Hepatitis B surface antigen as well as observing universal precautions in the practice of healthcare are other methods used to prevent transmission.

3.6.2 Prevention of perinatal transmission of Hepatitis B

3.6.2.1 Elective Caesarean section

In view of the conflicting evidence regarding effectiveness of elective caesarean section as a measure to reduce perinatal transmission of Hepatitis B, a recent systematic review was conducted to analyze the evidence from randomized controlled trials. It was found that elective caesarian section before rupture of membranes reduced the risk of perinatal transmission of Hepatitis B. However the trials included in this meta analysis had high possibilities for bias and therefore there was no convincing evidence that caesarian section should be routinely recommended to reduce perinatal transmission of Hepatitis B [(36)].

3.6.2.2 Active and Passive Immunization

Although safe injection practices and promotion of safe sex are important in reducing transmission, universal immunization of newborns commencing at birth is considered to be the most effective strategy in reducing the prevalence and transmission of Hepatitis B. The Hepatitis B vaccine available from 1982 is the world's first cancer prevention vaccine and the first vaccine against a sexually transmitted disease.

There are two types of vaccine, the plasma derived and recombinant DNA vaccines. The recombinant DNA vaccines which are either yeast derived or mammalian cell derived have largely replaced the plasma derived vaccines. India has developed an

indigenous yeast derived recombinant vaccine called Shanvac-B (Santha Biotechnics, 1997). Both the plasma derived and recombinant vaccines have similar effectiveness and withstand temperatures of up to 45 degrees Celsius for a week and 37 degree Celsius for a month [7,37]. The vaccine must be stored at 2-8 C but never frozen as freezing destroys the potency of the vaccine by dissociation of the antigen from the adjuvant alum.

Prevention of perinatally transmitted infection from Hepatitis B surface antigen positive mothers depends on whether the carrier mother is HBeAg positive or not. Infants born to mothers who are both HBsAg and HBeAg positive are advised to be given both Hepatitis B immunoglobulin and active immunization within 12-24 hours [19]. This is followed by two more doses commencing at least a month after the first dose. The third dose acts as a booster which increases anti HBs to several times above the protective level of 10 mIU/ml. Various studies have demonstrated seroprotection rates at one year after immunization, to range from 58.8% to 95 % [38,39].

The Hepatitis B vaccine without Hepatitis B immunoglobulin (HBIG) has also been found to be very effective in preventing perinatal infection, when given within 24 hours of birth. A randomized double blind controlled trial was done by Beasley et al in Taiwan which showed a vaccine efficacy of 75% when the vaccine was used alone to prevent perinatal transmission, which was also seen in an Indian study in Delhi [26] , [5]. Further randomized trials of administration of the Hepatitis B vaccine in a 3 or 4 dose schedule without HBIG, beginning within 12 hours after birth, have demonstrated prevention of 70%-95% of perinatal HBV infections among infants born to women who are positive for both HBsAg and HBeAg [38]. A systematic review showed that

protective effect of recombinant DNA vaccines when used without HBIG was 90-100% and when used with HBIG was 92%-100%[6]. Based on this, it was concluded that vaccine alone may be used in national immunization programs, at the meeting of the Viral Hepatitis Prevention Board organized in conjunction with CDC/Atlanta, the WHO and UNICEF[25].

A review done by the Cochrane Collaboration showed a vaccine efficacy of 72% (RR 0.28 95% CI: 0.20-0.40) when the Hepatitis B vaccine was given alone at birth, to infants born to HBeAg positive mothers. Subgroup analyses did not find a difference based on the mother's HBeAg status or time of vaccine administration (within 12, 24 or 48 hours of birth) [7]. The use of the vaccine alone is especially important in areas where cost makes the use of hepatitis B immune globulin impractical.

3.7 Immunization schedules for Hepatitis B vaccine

The Hepatitis B vaccine can be given in different schedules as shown in Table No 1. The WHO classifies the various schedules as those having a birth dose and those not having one.

Table No.1 Immunization schedules for Hepatitis B immunization

Organization	with birth dose	without birth dose
WHO, IAP	birth, 6 and 14 weeks	6, 10 and 14 weeks
	birth, 6, 10 and 14 weeks	
ACIP	birth, 1-2 months, 24 weeks	
IAP	birth, 1 and 6 months	
UIP, India	not recommended	6, 10 and 14 weeks

Universal immunization at birth is recommended by the WHO, for areas with high endemicity or with high chances of perinatal transmission. In this situation the first dose must be given as soon as possible after birth (within 24 hours), followed by a second dose at 6 and another at 14 weeks. The other schedule is a birth dose followed by three doses along with the three DPT doses. Although some studies do show added benefit with Hepatitis B immunoglobulin, on operational and cost-effectiveness grounds, the WHO does not recommend HBIG in places where there is no antenatal screening for HBsAg. When there is no administration of the birth dose the three doses of the vaccine may be given at 6, 10 and 14 weeks [(3)].

Both the Indian Academy of Pediatrics (IAP) and the Advisory Committee on Immunization Practices (ACIP) which provides guidance to the Centers for Disease Control and Prevention (CDC) recommend screening of all antenatal women for HBsAg in each pregnancy. This is to be followed by administration of Hepatitis B vaccine and Hepatitis B Immunoglobulin within 12-24 hours of birth to the infants born to the infected mothers. The IAP also recommends routine immunization of all infants at birth ,6 and 14 weeks or birth,1 and 6 months. In case the mother is HBsAg negative or the birth dose has been missed for some reason, it is recommended to give the three doses at 6, 10 and 14 weeks[(40)].

3.8 National Policy on Hepatitis B vaccine

In any country there are different reasons for choosing immunization schedules. These include data on magnitude, mortality, mortality which in turn depends on adequate disease surveillance mechanisms and judgments regarding incidence levels which qualify for commencement of mass immunization programs. Other factors to be

considered are immunological appropriateness of the strategy, economical viability and technical feasibility. There is also the choice of giving the vaccine to selected high risk groups or providing it as part of the Universal Immunization Program (UIP) to all children. [41]

The Government of India launched a pilot project for the introduction of Hepatitis B in a phased manner throughout the country, beginning with 15 selected cities and 32 districts in 17 states in 2002. In this program it was decided to give the Hepatitis B vaccine starting at 6 weeks along with DPT, to children living in slums in areas having at least 80% coverage for the third dose of DPT, under the UIP [9]. Studies have shown that such accelerated schedules of 0, 1, 2 months starting at 6 weeks achieved high seroconversion although mean GMT was lower compared to schedules of 0, 1, 6 months and 2, 4, 6 months[42-45]. According to the government, Hepatitis B vaccine coverage was 69% in 2007 in these project areas. However since the program does not insist upon the birth dose and instead gives the vaccine at 6, 10 and 14 weeks it will not be able to tackle the problem of perinatal transmission.

A sub-committee on immunization formed by the Indian Medical Association evaluated the status of the pilot project and reported that there was inadequate evidence of success of the pilot project in bringing down the carrier rates in the project areas. Although it was planned to conduct a serological survey of 3-5 year olds, 5 years after the implementation of the program, there are no reports available of any final evaluation of the prevalence of HBsAg among those children who have been immunized [33]. In spite of this lack of data regarding evaluation of the pilot project the Government of India decided to include the Hepatitis B vaccine in a phased manner throughout the country.

The Government of Tamil Nadu launched Hepatitis B as part of the universal immunization program in January 2008.

One reason for not including a birth dose was that perinatal transmission was not considered to be the major form of transmission. This was because the proportion of women who are HBeAg positive among those who are HBsAg positive, varies from 8 to 47%, with most studies showing 18% or less [46]. The other reason was the low rate of antenatal care and institutional deliveries. The proportion of antenatal mothers who had at least 3 antenatal care visits for their last birth was only 50.7% in India while it was 96.5% in Tamil Nadu [47]. Also since institutional deliveries in India was only about 40% and deliveries conducted by health personnel 48%, it has been argued that it was not feasible to give the birth dose to all children [48].

In Tamil Nadu however, the proportion of institutional deliveries was 90% and deliveries conducted by skilled personnel was 93% [47]. However, only 64.2% of the deliveries occur in the government facilities, 39.7 % occurring at government hospitals, 20.6% at primary health centers and 4.5% at health sub centers [49]. Testing all pregnant women for HBsAg and giving selective immunization would be difficult in other parts of the country where there is a lack of adequate antenatal services as available in Tamil Nadu.

One community based study conducted in Delhi showed the feasibility of this 'screen and vaccinate' strategy, giving Hepatitis B immunization at birth using community health workers, but the effectiveness of reducing transmission was not shown[34,50]. There is a lack of community based studies showing the effectiveness of selective immunization.

3.9 Hepatitis B immunization coverage worldwide

In 1991, the Global Advisory Group of the Expanded Program on Immunization recommended integration of the Hepatitis B vaccine into immunization programs by 1995, in countries with a HBV carrier prevalence of 8% or higher. It also set 1997 as the target for all other countries to achieve this goal. In 1994 the World Health Assembly set the goal of achieving an 80% decrease in new Hepatitis B child carriers by 2001. As of December 2007, 171 countries have incorporated Hepatitis B immunization in their national immunization schedules and 139 countries have vaccine coverage of at least 80 %[10]

Most countries which have intermediate to highly endemic hepatitis B have now achieved 65-100% coverage with the vaccine. Some low endemic Northern European countries immunize only groups at higher risk while other low endemic countries have universal infant or adolescent programs.

3.10 Vaccine efficacy and effectiveness

Vaccine efficacy refers to the protective effect of the vaccine against a disease or infection under idealized conditions. Before a vaccine can be introduced in an immunization program other factors besides efficacy, e.g. costs, logistics, secondary effects, adverse effects, herd immunity also need to be considered [51]. These characteristics taken together comprise what is referred to as vaccine effectiveness or the vaccine efficacy under program conditions. Effectiveness is best estimated in evaluative studies (like randomized control trials) in which the unit of intervention and analysis are populations and not individuals. Ideally effectiveness of the vaccine should be measured in terms of the protection it offers against disease. Most trials measure

surrogate outcomes i.e. HBsAg positivity and anti HBs due to the difficulty and long follow up period required, if one were to study clinical outcomes like chronic hepatitis, cirrhosis of the liver or hepatocellular carcinoma.

In spite of active immunization and administration of Hepatitis B immunoglobulin within 24 hours of birth, 5-10% of the children suffer from immunoprophylaxis failure, i.e. they become carriers of HBsAg. The main risk factors which have been found to be significantly associated with failure of immunization were HBeAg seropositivity and HBV DNA seropositivity in the mothers [52].

Another explanation for vaccine failures is the theory of 'vaccine escape mutants'. Some infants may be infected with HBV variants which bear single point mutations in the HBV surface antigen. Due to this mutation binding of anti HBs to the antigen is blocked, which explains why the antigen is not cleared in spite of the presence of circulating anti HBs [53,54]. Both immunization as well as treatment may be reasons for selection and amplification of these variants in anti HBs positive hosts. Some studies have shown that a part of these HBV mutant variants are maternally derived and that as good immunization practices with regard to Hepatitis B immunization increase, there are higher chances of these variant forms emerging.

The prevalence of vaccine escape mutants is low in most studies [54]. In India, a study from Chennai showed a prevalence of 2.9% of Hepatitis B virus variants among 68 children followed up for 2 years, who were successfully vaccinated at birth, 1 and 6 months and [55]. Although the problem of vaccine escape mutants has not yet evolved into a public health problem it is recommended to monitor the emergence of these

variants [56]. Another factor contributing to failure of immunization is the presence of high levels of HBV DNA in the mother [57].

3.11 Anti HBs concentration after immunization and factors associated with persistence

A study comparing the antibody levels achieved by three different types of recombinant DNA vaccines showed GMT values of 226.7, 193.9 and 173.6 mIU/ ml one year after completion of three doses[58]. A higher prevalence of antibodies has been found with DNA recombinant vaccines as compared with plasma derived vaccines and with four doses as compared with three doses of the vaccine [59]. The immunization schedule, age at receiving first dose of vaccine, amount of HBsAg present in the vaccine, administration of Hepatitis B immunoglobulin, higher peak antibody response are all shown to be associated with persistence of anti HBs levels [60]. Studies have also shown that increase in the duration between the first two doses does not significantly affect immunogenicity or effectiveness[61]. Accelerated schedules like 0, 1, 2 months increase the proportion of those who complete the course of immunization, but require a fourth dose to reach antibody levels comparable to other schedules[45].

Follow up studies years after immunization have shown that anti HBs levels progressively decline with age [62]. It has been shown that the anti HBs concentration decreases 10 years after immunization, to less than 10 mIU/ml, in 10-50% of vaccinees. However although antibody levels decline to undetectable levels, it has been shown that adequate immune memory exists after the primary vaccine series as seen by an anamnestic response to a repeat exposure to the antigen many years later. This is because immunization induces B and T memory cells which proliferate rapidly

producing antibodies and cytokines during the repeat exposure to a booster leading to a more rapid, larger and qualitatively different response. This response is also effective when there is exposure to the disease agent even after antibody level declines to undetectable levels. This anamnestic response is seen in more than 95% vaccinees even after 10 years of primary immunization [63]. Thus a booster dose is not considered to be necessary.

Studies have shown that one dose of Hepatitis B immunoglobulin (HBIG) given at birth does not interfere with the active production of anti HBs and the combination produces immediate and sustained high levels of the antibody [7]. However, since there is not much of an added benefit of Hepatitis B immunoglobulin in comparison to administration of the vaccine alone, the consensus at the meeting of the Viral Hepatitis Prevention Board was that national policies of administering vaccine alone were justifiable [25].

Although there is no need to routinely test everyone who receives the Hepatitis B vaccine for antibody levels, the WHO specifies certain conditions where testing may be done. This includes infants born to HBsAg positive mothers and sexual partners of HBsAg positive persons. The time period at which testing is recommended is at 8-15 months of age, after completion of the vaccine series which is expected to be latest around 6 months. [3]

According to the ACIP, post immunization testing for anti-HBs and HBsAg should not be performed before age 9 months, to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti HBc transferred trans-placentally may persist till 24 months of age [19].

3.12 Impact of Hepatitis B immunization programs

The long term impact of integrating Hepatitis B immunization in national immunization schedules is best studied in those countries which have a long history of running such programs. One such example is Taiwan, where the effectiveness of the immunization after 20 years has been proved [32]. The carrier rate of Hepatitis B in Taiwan was 15-20% in the era prior to immunization. Some of the landmark studies by Beasley et al were done in Taiwan assessing the effectiveness of Hepatitis B immunization and the Hepatitis B immunoglobulin the association between HBsAg and hepatocellular carcinoma [26]. Based on the findings of these studies a nationwide immunization program was launched in 1984. During the first two years of the program only infants born to HBsAg positive mothers were offered immunization. Immunization was gradually extended to all newborns, preschool children, elementary school children, health workers, and finally to teenagers and adults on a fee-for-service basis.

To assess the effectiveness of the immunization program a study was done using 3,464 randomly selected vaccinees tested at 18 months of age. Among the children born to HBeAg positive mothers the HBsAg positivity rates were 14% for those who received the vaccine and immunoglobulin on schedule, as compared to 20% among those who received only the vaccine on schedule. The overall protective effect was found to be 85%. Among infants born to mothers who were HBeAg negative the rate of HBsAg positivity was 3% for those who received the vaccine on schedule and 7% for those who did not receive the vaccine on schedule ($p < 0.003$). Studies were conducted at different times and places in the post immunization era, which showed significant

decreases in the prevalence of HBsAg carrier state as well as infant mortality due to fulminant hepatitis and hepatocellular carcinoma [32].

There were many reasons which contributed to the success of the program in Taiwan [32]. These included a motivated government, an efficient public health care system, extensive research and involvement of the public. There was also a robust system of registration of patients with any type of cancer, reporting of deaths and a complete and accurate national immunization registry which provided the individualized data needed to evaluate the program.

Based on the success of the Hepatitis B immunization program in Taiwan it was suggested that when available, individualized data among recipients of the immunization program should be analyzed as part of a post immunization surveillance program. This should incorporate data from cancer and death registries, immunization registries, immunization records etc. Such data would help in conducting effectiveness and cost-effectiveness studies on the Hepatitis B immunization program.

3.13 Number Needed to Screen

Number Needed to Screen (NNS) is defined as the number of people that need to be screened for a given duration to prevent one death or adverse event. This measure provides a chance to compare efficacies of screening strategies.

$$NNS = \frac{\text{Number Needed to Treat for risk factors}}{\text{Prevalence of unrecognized disease}}$$

Number Needed to Treat (NNT) is defined as the number of people that need to be treated for a given duration to prevent one death or one adverse event.

NNT = 1/ Absolute Risk Reduction (ARR)

A positive value for NNS implies that screening prevents an adverse outcome and a negative number implies that screening increases the adverse outcome [64].

3.14 Cost effectiveness of alternate programs for Hepatitis B immunization

3.14.1 Universal Immunization

Universal immunization beginning at birth would be the ideal method of reducing the prevalence of the HBsAg carrier state as it would be effective in preventing perinatal transmission as well as early childhood transmission. However difficulties in developing countries include a lack of institutional deliveries, unavailability of the vaccine in small health facilities and costs involved in universal immunization. As there are around 25 million surviving live births per year approximately 75 million doses of the vaccine are required. The government estimated that the cost of universal immunization would be Rs. 525 crores [65].

3.14.2 Selective Immunization

Selective immunization by screening antenatal women and immunizing the children born to Hepatitis B positive mothers is an alternative strategy to reduce perinatal transmission. In certain European countries like the UK with a prevalence of 0.14% among antenatal women, this strategy is followed for childhood Hepatitis B immunization [66].

In India there are conflicting data regarding cost effectiveness of universal versus selective immunization. In order to calculate cost effectiveness of selective versus universal immunization it is necessary to obtain data on magnitude of morbidity and mortality associated with the disease, which is lacking in India [41]. Thus the estimates that are possible with the current data are mostly based on some form of mathematical modeling.

A community based study conducted in Delhi by the St. Stephen's Hospital, found the true prevalence of HBsAg positive antenatal women to be 1.47%. Antenatal screening for HBsAg was followed by selective immunization of the children born to HBsAg positive mothers starting at birth or within 48 hours. The cost of selective immunization was calculated as the costs of testing all women during the first pregnancy; costs of salary and travel for a health worker to administer the birth dose and the cost of three doses of the vaccine. Given that the cost of the vaccine was Rs. 70 and the HBsAg test Rs.30, the projected cost for the country to implement universal immunization commencing at birth was calculated to be Rs. 5000 million. Assuming the number of deaths due to HBV related carcinoma to be 5000, the cost per life saved was estimated to be Rs. 1,000,000. As the cost per Quality Adjusted Life Years saved was found to be Rs. 48,540 which was more than twice the value of India's Gross National Product, it was stated that the cost-benefit ratio of universal immunization was high [34]. One of the criticisms of this study was that the benefits of universal immunization were underestimated, as the number of deaths related to HBV would be higher if deaths from cirrhosis were included to those from hepatocellular carcinoma. Since this study did not measure the success of the program in delivering the birth dose or the effectiveness of

the selective immunization strategy, a cost benefit ratio could not be calculated for selective immunization [50].

A cost minimization analysis done in Delhi calculated the cost of universal immunization starting at 6 weeks to be twice as much as the cost for selective immunization, assuming that the proportion of carriers due to vertical transmission was 50%. Assuming that 66% carriers were due to horizontal transmission, it was estimated that universal immunization would be as cost-effective as selective immunization if the carrier rate was 1.1%[67].

Other studies have shown that universal immunization was more cost effective compared to selective immunization strategies [8]. A review of economic evaluations of different strategies revealed that universal immunization was cost effective in areas of low, intermediate and high endemicity but data from areas of low endemicity were controversial[68]. One of the reasons for the cost effectiveness of universal immunization was that the cost of the Hepatitis B vaccine has fallen dramatically since the early 1980s to less than 1 USD per dose. Also the effectiveness of selective immunization strategies depended to a large extent on the capability of the program to screen a high proportion of the target group and successfully vaccinate those at risk.

3.15 Importance of the birth dose and difficulties involved in administration

Reduction in deaths due to Hepatitis B is much greater with administration of the birth dose than without it. A flexible mathematical model was developed by Goldstein et al which allowed predictions to be made on mortality and morbidity related to Hepatitis B,

as well as estimation of the reduction in mortality achieved by different immunization strategies.

According to this model, universal immunization without the birth dose would prevent up to 75% of global Hepatitis B Virus (HBV) related deaths, depending on coverage for the complete series. As coverage for the third dose increases from 50% to 90%, the reduction in HBV related deaths is expected to increase from 38% to 68% respectively.

Administration of a birth dose to 50% and 90% of the vaccinated cohort would increase the proportion of HBV related deaths prevented from 77% to 84%, when the coverage for the third dose of the vaccine is 90%. With 100% immunization coverage and all of the immunized children receiving the birth dose, it would be theoretically possible to prevent 95% of HBV related deaths [(69)].

Administration of the birth dose depends largely on the place and provider of maternity care, the coordination between the National Immunization Program and maternal health care services. Institutional deliveries occur in public or private health facilities with or without access to a continuous cold chain. Although it is more feasible to administer the birth dose in the case of institutional deliveries as compared to home deliveries, studies from developing countries have shown that the birth dose may be delayed or missed even when the delivery takes place in the hospital. This can occur due to lack of coordination between maternity staff and those involved in immunization, non availability of the vaccine 24 hours of the day or referral to a different centre for Hepatitis B immunization [(37)]. This is especially true in the case of deliveries occurring at lower level health facilities where the cold chain may not be available.

The WHO has suggested a few common guidelines irrespective of place of birth, for improving the coverage of the birth dose [37].

1. The planning stage for incorporation of the birth dose in the Hepatitis B immunization schedule should include a situation analysis of perinatal health services. It must also involve the maternity staff, besides nurses or pediatricians who are usually involved in immunization services.

2. There must be a high priority accorded to increasing the proportion of deliveries conducted by trained personnel. A health worker must be designated to provide the first dose at home for home deliveries after receiving information about the birth. The program must also progress gradually from ensuring 100% coverage among institutional deliveries to increasing coverage among home deliveries.

3. The availability of the vaccine for maternity staff must be ensured at all times even if it means keeping the vaccine out of the cold chain for a short while.

4. There should be adequate recording and reporting of the birth dose. This step may involve modification of the immunization card for entering the date and time of receiving the first dose of Hepatitis B vaccine.

3.16 New methods of Vaccine delivery

One of the difficulties in achieving universal immunization is the non availability of the vaccine when the delivery occurs either at home or at a health facility without access to the cold chain. As the Hepatitis B vaccine remains stable at room temperature even up to one month, the WHO allows for storing and using the vaccine even out of the cold

chain. This is subject to certain conditions being fulfilled, such as the vaccine having remained in the cold chain but never frozen, at all other points before reaching the lowest point of use and the presence of a vaccine vial monitor.

The use of pre-filled syringes for immunization is another strategy which has been used to improve the coverage of Hepatitis B immunization. In India a study using Shanvac-b showed that a single use pre filled device Uniject when used in infants at 0, 1, 2 months gave 100% seroprotection and a GMT of 385.4 mIU/ml, 4-6 weeks after the third dose [70]. These may be future options for the Indian government, to enable introduction of the birth dose in the Hepatitis B immunization schedule.

4. METHODOLOGY

4.1 Study Design

The study was an evaluation of the program for prevention of vertical transmission of Hepatitis B. The program was an intervention study without a control group. The prevalence of Hepatitis B infection among the antenatal women and the effectiveness of the program in delivering the specified vaccine schedule, including the birth dose were estimated. A cross sectional serological survey of the children born to the women who tested positive for HBsAg was also carried out. Thus the overall effectiveness of the program in preventing vertical transmission of Hepatitis B under field settings was determined.

4.2 Background of the study and description of the program

The Community Medicine department of the Christian Medical College (CMC Hospital) is situated in Kaniyambadi a rural block in Vellore district. The department also called CHAD (Community Health and Development program), runs a secondary hospital and has been serving this area for the past 50 years. The block consists of 88 villages and a population of 1, 04,832 with a crude birth rate of 13.9/1000 population. The referral centre for CHAD hospital is a multi-specialty tertiary hospital, the Christian Medical College, Vellore. Antenatal women with complications during pregnancy or delivery are referred to this hospital.

The CHAD program provides primary health care to the people of Kaniyambadi in a form similar to the government services. At the village level is a part-time community health volunteer who is an elderly lady selected by the community and lives in the

village itself. The next level is a 'health aide', a trained health worker similar to the Village Health Nurse in the government services, who supervises 4-5 part time community health volunteers and covers a population of around 5000. A public health nurse supervises 3-4 health aides and a doctor is appointed for every 30,000 population. The health team of the doctor, public health nurse, the health aide and the community health volunteer conduct a mobile clinic every month in each village.

The services provided are antenatal care, Hepatitis B immunization, treatment of minor ailments and chronic diseases. A home based antenatal card is provided at the first visit. The women who receive antenatal care at the mobile clinics are categorized as 'permanent' residents or 'temporary' residents, the latter being those women who previously belonged to families in the service area and who come back for the first delivery to their own mother's house.

In May 2002 it was decided to screen antenatal women for HIV and Hepatitis B. This involved administration of a written consent form by the doctor at the first visit, followed by collection of 5 ml of blood. At the time of blood collection consent was also obtained for storing and using any residual sample for further studies in the future. The collected samples were transported back to the base hospital on the same day and the sera separated. The kit used for testing for Hepatitis B was a rapid one step immunoassay, Hepacard (sensitivity 99.8% and specificity >99% according to manufacturer), manufactured by J.Mitra and Co.Pvt.Ltd, New Delhi in collaboration with Program for Appropriate Technology in Health. Residual sera from all patients were stored in a deep freezer at -20 degrees C, irrespective of the result of the tests.

At the base hospital CHAD conducts a weekly antenatal and immunization clinic where women and children from Vellore and surrounding areas are registered. In 2004, antenatal screening for HIV and HBsAg was extended to all the women who came to CHAD hospital for antenatal care. At the first visit there was a group teaching on the importance of screening, modes of transmission and prevention of Hepatitis B and HIV following which consent was obtained for testing.

Women who tested positive for HBsAg through either system of antenatal screening (peripheral or base hospital), received post test counseling by a senior doctor in the special clinic for high risk antenatal women at CHAD. During the post test counseling, Hepatitis B surface antigen positive mothers were advised hospital delivery and Hepatitis B immunization for the children commencing at birth. In case a woman delivered at home, the family was advised to bring the child for the first dose of the vaccine within 24 hours of birth. The need for Hepatitis B vaccine for the child was mentioned on the mother's card but the fact of the mother being HBsAg positive was not highlighted for the sake of confidentiality. The schedule followed for immunization was a birth dose of Hepatitis B vaccine, followed by two more doses at 1 and 2 months. The second and third doses were administered in the mobile clinics and all the three doses were provided free of cost to the children born to Hepatitis B positive mothers. There was no administration of a booster dose.

The data regarding vital events, antenatal care and immunization which were collected every week by the health aides with the help of the community health workers, were verified by the nurse and doctor. This information was entered in the computerized health information system, from which information is available on all pregnancies in the block since 1986.

4.3 Study Population

The database of all the antenatal women who were registered with CHAD during the study period was obtained. This included both women from the service area, Kaniyambadi block, as well as those who were from other areas who registered at the base hospital CHAD. All children 6 months of age and above born to women who tested positive for HBsAg during the study period were eligible for the serological study.

4.4 Sample Size

Sample size was calculated as the sample size for difference between proportions

$$n = \left[Z_{\alpha} + Z_{1-\beta}\right]^2 \frac{p1(1-p1) + p2(1-p2)}{(p1-p2)^2}$$

p1 (proportion of children becoming chronic carriers without immunization) = 18.6 x 90 % = 17 % and p2 (proportion of children becoming chronic carriers with immunization) = 25% x 17 = 4 %

The assumptions made were a perinatal transmission rate of 18.6 % according to Nayak et al in 1987, 90 % rate of chronic infection among newborns infected with Hepatitis B and vaccine efficacy of 75% [5,26]

For the significance level α =0.05, the two tailed deviate Z= 1.96; and for power (1-β) = 0.80, Z = 0.842

$$n = \left[1.96 + 0.842\right]^2 \frac{0.17(1-0.17) + 0.04(1-0.04)}{(0.17-0.04)^2}$$

The sample size was 84 in each of two groups, one of which received and the other which did not receive the immunization and therefore the total number required was 168 children born to Hepatitis B positive mothers.

4.5 Collection of data

4.5.1 Recruitment of study subjects:

The names and addresses of women who had tested positive for HBsAg during the antenatal screening were obtained from the CHAD database. Children of mothers, who tested positive for Hepatitis B surface antigen, were eligible for this study if at least two months had elapsed since the last dose of vaccine. The age group of the eligible children was taken as above 6 months to ensure this. Female health workers from the service area were asked to refer the HBsAg positive women and their children for the study. Letters were sent to women who were from the non service areas informing them about the study. Home visits were made for those who did not respond to the mail, for patients residing either in Kaniyambadi block or in Vellore town. All the women and children were asked to come on a scheduled day of the week bringing their antenatal cards and the immunization cards.

4.5.2 Obtaining consent

Written consent in the local language was obtained (see Annexure 2) from the mother. In case the mother could not be interviewed due to unavoidable reasons, the father or other relative who brought the child gave consent.

4.5.3 Questionnaire

The questionnaire was administered to the mother/guardian of the study child. The questionnaire covered details of delivery, immunization of the child, as well as acceptance and compliance to the program protocol (Annexure 1). The timing of the birth dose was confirmed from the in-patient records for those born in either CHAD or CMC hospital. Information on 2nd and 3rd doses was obtained from patient retained immunization cards or hospital records.

4.5.4 Serological testing

As part of the evaluation 5 ml samples of blood were obtained from the study child. The separated sera were sent to the Virology laboratory of the Christian Medical College for the tests. The test kits used were the DIASORIN HBsAg kit, AXSYM AUSAB, a micro particle enzyme immunoassay (MEIA) for the quantitative determination of anti HBs and AXSYM CORE (Abbott Laboratories) an MEIA for anti HBc. When the titre of the neat serum sample was above 1000 mIU/ml, the sera were tested after diluting the sample in human sera which was negative for anti-HBs and HBsAg. The stored sera of the mothers were retrieved and HBeAg testing was done in order to determine if higher infectivity interfered with the protective effect of the vaccine. HBV DNA testing could not be done as the samples were not cryo preserved and the cost involved would have been high.

Study children were tested for HBsAg, to check for carrier status of the child; anti HBs to check for seroconversion after immunization and total anti HBc to look for other evidence of infection. Only children above 24 months were tested for anti HBc in order to avoid detection of maternally derived antibodies.

4.5.6 Non-respondents

The information regarding delivery and immunization status of the children was obtained from hospital records for children from the service area who could not be contacted. Similar data on immunization was not available for those children born to women who had registered at the base hospital but could not be contacted for the present evaluation.

4.6 Data entry and analysis

The data was entered using EpiData version 3.1.The software used for analysis of the data was SPSS for Windows version 12. The primary outcome analyzed was occurrence of HBsAg among the children who were tested and subgroup analyses were done according to the type of immunization schedule followed and the mother's HBeAg status. The other outcome measures for vaccine effectiveness were occurrence of anti HBc and presence of antiHBs of more than or equal to10 mIU/ml at the time of testing. Calculation of Geometric means Titres (GMTs) involved logarithmic transformation of the values of anti HBs.

5. RESULTS

5.1 Antenatal screening for Hepatitis B surface antigen (HBsAg)

Women from the service area Kaniyambadi block, registered for antenatal care with CHAD through the services offered at the village level. Since May 2002 routine screening for HIV and HBsAg infections was offered to all the antenatal women who were registered. From the month of May 2002 till December 2007 there were 12,977 pregnancies in Kaniyambadi block. Of all the pregnancies in the block 12,038 women who registered for antenatal care with CHAD were offered antenatal screening for HIV and HBsAg. There was only one woman who refused consent for antenatal testing. The rate of screening for HBsAg was 93% among all the pregnancies in the block between May 2002 to December 2007 and 99.9% among those who registered with CHAD for antenatal care.

Since April 2004, antenatal screening for HBsAg and HIV was started for all the antenatal women who attended CHAD hospital for antenatal care. Since the beginning of the program till December 2007, 9130 women registered for antenatal care and only one refused blood testing for HBsAg. Thus 9129 were screened during this period.

5.2 Prevalence of Hepatitis B surface antigen

5.2.1 Point prevalence of HBsAg infection among antenatal women in Kaniyambadi block:

Analysis of the data from the CHAD service from 2002 showed that, of the 12,037 pregnancies that had been tested, 190 had been detected to be HBsAg positive. Of all

the women who tested positive for HBsAg, 40 women had been tested again in a subsequent pregnancy during this period. Thus the number of women who were identified to be HBsAg positive was 150 out of 11997 women who had been tested. The prevalence of HBsAg positive women ranged from 1.31% to 1.78% as shown in Table No.2. The overall point prevalence of HBsAg infection was 1.25% (95% CI 1.05%-1.45%) among antenatal women of Kaniyambadi block during this period.

Table No. 2 Prevalence of HBsAg in Kaniyambadi block

Year	No. of pregnancies who were tested	No. of test positives	HBsAg Prevalence %	95%CI	
				Lower	Upper
2002	1513	27	1.78	1.12	2.45
2003	2043	36	1.76	1.19	2.33
2004	2204	29	1.32	0.84	1.79
2005	1997	29	1.45	0.93	1.98
2006	2077	29	1.40	0.89	1.90
2007	2203	40	1.82	1.26	2.37
Total	12037	190			

Chi-square for trend = 0.037, p = 0.847

5.2.2 Point prevalence of HBsAg infection among antenatal women attending CHAD hospital:

From April 2004, there were 9130 pregnancies registered at the base hospital, CHAD from places both in and around Vellore. All of them were offered antenatal screening for HIV and HBsAg and only one refused screening. Thus the number of positive samples among the 9129 pregnancies which were screened was 148. Of these 148 pregnancies, 18 were women who had been tested again during subsequent pregnancies.

The yearly prevalence of HBsAg positivity ranged from 1.40% to 1.82% as shown in Table No. 3. The overall prevalence of HBsAg among women from non service areas attending CHAD hospital for antenatal care was 1.43 % (95% CI: 1.18%-1.67%) which was 130 out of 9111 women screened.

Table No. 3 Prevalence of HBsAg among antenatal women attending CHAD hospital

Year	No. of pregnancies	No. of test positives	HBsAg Prevalence %	95%CI	
				Lower	Upper
2004	1562	26	1.66	1.03	2.30
2005	2186	35	1.60	1.07	2.13
2006	2629	37	1.40	0.96	1.86
2007	2752	50	1.82	1.32	2.32
Total	9129	148			

Chi-square for trend = 0.12, p value = 0.729

5.3 Description of pregnancies in Kaniyambadi block (May 2002-December 2007)

During the study period there were 12,977 pregnancies in Kaniyambadi. The description of pregnancies and their outcomes were available in the CHAD database for 12,016 women out of the 12,037 who underwent screening for HBsAg. The number of HBsAg positive women for whom complete information was available for analysis was 183 out of the 190 women who were test positive. Of the remaining, two aborted; one woman committed suicide; two moved out and two who were temporary residents lost to follow up during the antenatal period, were later found to have delivered live children. Table No. 4 is a comparison of prevalence of HBsAg among women of different residence statuses and obstetric scores. It was found that there was no

significant difference between the prevalence of HBsAg by residence or obstetric scores (gravida, parity, number of living children and number of abortions).

Table No 4 HBsAg prevalence by selected characteristics of antenatal women

Residence	Total	HBsAg positive (No)	HBsAg positive (%)	p value (Chi-square)
Temporary	3711	64	1.72	0.228
Permanent	8305	119	1.43	
Gravida				
1st	5250	80	1.52	0.995
2nd or more	6766	103	1.52	
Parity				
1	4549	73	1.6	0.549
2 or more	1788	25	1.4	
Living children				
0	5904	87	1.47	0.664
1 or more	6112	96	1.57	
Abortions				
0	10766	164	1.52	0.993
1 or more	1250	19	1.52	

Table No 5 describes the outcomes of 12,016 pregnancies among those who underwent antenatal screening for HBsAg from Kaniyambadi block , excluding abortions.

Deleted:

Table No. 5 Outcomes of pregnancies in Kaniyambadi block

	HBsAg positive N=178		HBsAg negative N=11664	
Place of delivery	**No**	**%**	**No**	**%**
CHAD	117	65.7	7305	62.6
CMC	19	10.7	671	5.75
Other Institutions	22	12.4	2587	22.2
Home	20	11.2	1101	9.3
Mode of delivery				
Vaginal delivery	166	93.3	10380	89
Caesarian Section	12	6.7	1284	11
Outcome of delivery				
Alive at day 7	172	96.6	11316	97
Stillbirths	4	2.3	202	1.7

There was no significant difference between the proportion of home deliveries between the groups of HBsAg positive and negative women (p = 0.379).There was also no significant difference between the proportions of vaginal and caesarian deliveries between the two groups (p = 0.07).

The mean birth weight of the children born to the HBsAg infected women was 2.810 kg (SD 0.477) which was comparable to the mean birth weight of 2.805 kg (SD 0.479) among the children born to uninfected mothers. The perinatal mortality rate among the children born to HBsAg positive women was 34/1000 live births, compared to 31/1000 live births among children of HBsAg negative women (p = 0.764 for perinatal deaths vs. healthy children).

5.4 Children eligible for the prospective serological study

The number of pregnancies which were HBsAg positive was 338 from May 2002 till December 2007 (190 from the service area and 148 from among the women who attended CHAD hospital). For the present evaluation children who were less than 6 months old were excluded. Thus children who were born after 30th December 2007 were not eligible at the time of testing. The number of children who were eligible for the current study was 269. Among the 269 children, 109 were from non service areas and 160 from the service area.

Figure 1 shows the overall outcomes and eligible children of all the HBsAg positive pregnancies in Kaniyambadi block

Figure No: 1 Pregnancy outcomes and eligible children - Kaniyambadi block:

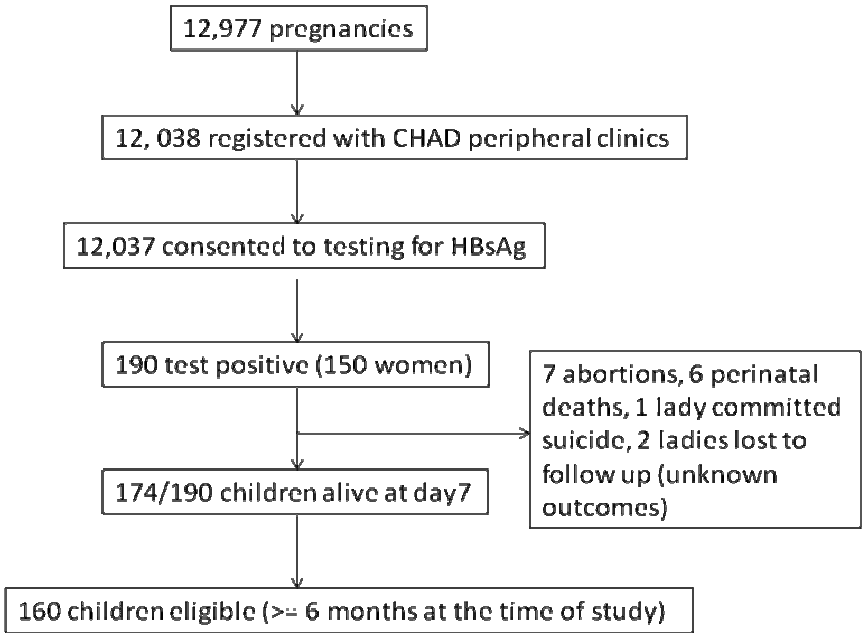
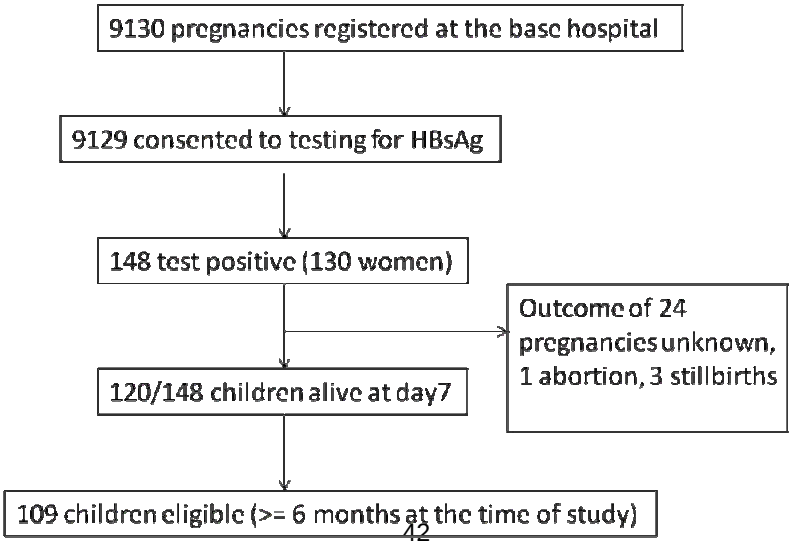


Figure 2 shows the overall outcomes of all the HBsAg positive pregnancies registered at CHAD hospital.

Figure No: 2 Pregnancy outcomes and eligible children - CHAD hospital:



5.5 Types of immunization schedules followed (Kaniyambadi block)

The immunization schedule as advised by the program was a dose of Hepatitis B vaccine at birth, followed by two further doses after one and two months.

Immunization schedules followed by the children were available for 154 of the children born to HBsAg positive mothers from the service area. The data on immunization for those children who could not be contacted for the evaluation was obtained from immunization records. Table No 6 depicts the various schedules which were followed for immunization of the children born to the HBsAg positive mothers in the service area. The 'birth dose' in these schedules was given on the date of birth or the next day (within 48 hours).

Table No: 6 Immunization schedules of children born to HBsAg positive mothers

Type of vaccine schedule	No.	Percent
Birth,1 month,2 months	81	52.6
Birth,1 month,3 months	14	9.0
Birth,1 month,4-6 months	7	4.5
3 doses, including dose at birth	17	11.0
3 doses, no birth dose	27	17.53
Birth dose, Incomplete immunization	0	0
No dose at birth, incomplete immunization	6	3.9
No dose received	2	1.3
Total	154	100

Overall, the coverage for the birth dose was 77.2% among the 154 children in the service area for whom data was available. The proportion of children who received the vaccine according to the schedule advised by CHAD was 52.6%. Among the 154 children 102 (66%) received any one of the standard schedules.

5.6 Descriptive statistics of the study population

Of all the eligible 269 children, (160 children from the service area and 109 children from the CHAD hospital group), 131 children were available for the present evaluation. Thus the population evaluated constituted 112 women and 131 children, some of the women having had more than one child.

Of the 131 children who came for the present evaluation, 98 (75%) were from the service area. Among the 160 children from Kaniyambadi block eligible for this study, 70 of the 104 permanent residents (67%) and 30 of the 56 temporary residents (53.5%) participated in the evaluation. The family of one child refused to give consent and six permanent residents who had migrated out of the block could not be contacted. The proportion of eligible children who could be contacted from among the population served by CHAD hospital was 30% (33/109 eligible children).

The age group of the 131 children who were tested ranged from 6 to 66 months (median 28 months). First born children constituted 44.3 % (58/131) of the children who were screened. Of the 131 children tested, 92.4% were born in hospitals (80% were born in CHAD).

Table No.7 shows the place of birth for children born to mothers registered either at the peripheral services in Kaniyambadi or at the CHAD hospital. Of the women who were available for the evaluation, 77% from Kaniyambadi block and 85% of women who registered at CHAD hospital from non-service areas delivered in CHAD.

Table No 7 Place of delivery

Place of delivery	CHAD	CMC	HOME	Other HOSPITALS	Total
Kaniyambadi group	76	8	9	5	99
CHAD hospital group	29	2	1	1	34
Total	105	10	10	6	131

5.7 Immunization coverage among study children

5.7.1 Hepatitis B immunization schedules followed by the study children

The exact dates of receiving the 3 vaccine doses were checked using immunization card or hospital records for 129 children. Two mothers had lost the immunization cards and hence parental recall of immunization doses was used. Table No.8 shows the immunization schedules followed by the 131 children who were available for the evaluation.

Table No. 8 Immunization schedules followed by the study children

Type of vaccine schedule	Number	percent
Birth,1 month,2 months	72	55.0
Birth,1 month,3 months	17	12.9.
Birth,1 month,4-6 months	3	2.3
3 doses, including dose at birth	16	12.2
3 doses, no birth dose	15*	11.4
Birth dose, Incomplete immunization	7	5.3
No dose at birth, incomplete immunization	1	0.8
Total	131	100

*3 of these children received Hepatitis B immunoglobulin at birth

The birth dose of the vaccine was received by 115 (87.8 %) of the study children. The number of children who followed the schedule as advised by the CHAD program (birth, 1 and 2 months) was 72 out of the 131 children (55%). Overall 92 children (70%) were immunized according to any one of the accepted schedules i.e. birth, 1 and 2 months; birth, 1 and 3 months or birth, 1, 4 to 6 months. Among the study children 123 (93.9%) received 3 or more doses of the vaccine. There were 5 children who received only a single dose, which was given at birth.

Of the 16 children who did not receive the birth dose, 4 were born at home; 3 were born in health centres out of the service area where the vaccine was not available; 3 received Hepatitis B immunoglobulin at birth followed by the vaccine later and 6 were born in CHAD but were not given the first dose of the vaccine on time.

The study population included 98 children from the service area. Of the remaining 62 eligible children who did not come for the study, information regarding Hepatitis B immunization status was available for 54 children. The proportion of children who came for the study among those who received a birth dose of the vaccine was 72.3 % (86 out of 119). Of the 81 children who followed the schedule advised by CHAD, 56 (69%) were available for the evaluation. Data on immunization status was not available for 6 children who were temporary residents and 2 children who were permanent residents who had moved out of the area.

5.7.2 Time of receiving first dose of vaccine

The information regarding exact time of receiving first dose of vaccine was available from hospital records for 89 of the 131 children. Median time of receiving the first dose was 65 minutes for these 89 children. The program was able to deliver the first dose of

the vaccine within 24 hours to 111 children (85%) and within 48 hours of birth to 115 children (87.8%).

5.8 Results of serological survey of the study children

5.8.1 HBsAg positivity among the tested children

Of the 131 children who were contacted for the evaluation, 8 were test positive for HBsAg giving an overall prevalence of 6.1% (95% CI: 1.92%-10.28%). Among the 115 children who received the first dose of vaccine within forty eight hours, HBsAg was detected in 7 children (prevalence: 6 %, 95% CI: 1.57%-10.43%). HBsAg was positive in 5 of the 92 children who received three doses of the vaccine according to standard schedules (prevalence: 5.4%, 95% CI: 0.69%-10.1%).

5.8.2 Results of anti HBc tests

Anti HBc was tested only among the 74 children in the study who had completed two years of age and 6 were positive for anti HBc (8.1%). However only 59 of these 74 children had received three doses of the vaccine including the birth dose and 5 of these (8.47%) were positive for either anti HBc or HBsAg.

Table No.9 shows the immunized children who tested positive for either or both the two markers of infection namely, HBsAg and anti HBc.

Table No. 9 Markers of infection among immunized children aged above two years

	Anti HBc		**Total**
HBsAg	**positive**	**negative**	
Positive	2	2	4
Negative	1	54	55
Total	3	56	59

5.8.3 Immunization schedule vs. HBsAg status of the study children

In the present evaluation, 7 out of 115 (6.0%) children who received the first dose of the vaccine within 48 hours of birth tested positive for HBsAg compared to 1 out of 16 children (6.25%) who did not receive a birth dose (Table No. 10). This difference was not found to be statistically significant (S.E. for difference between the proportions = 7.55, p value = 0.976). The difference in rates of children with positive HBsAg tests was not significantly different even when the definition for birth dose was taken as having received it within 24 hours (p value=0.88).

Table No 10: Immunization schedule and HBsAg status of study children

Type of schedule	No. of HBsAg positive children	Percentage of HBsAg positive children	Total no of children
Birth,1 month,2 months	2	2.7	72
Birth,1 month,3 months	3	1.8	17
Birth,1 month,4-6 months	0	0	3
3 doses, including dose at birth	1	6.3	16
3 doses, no birth dose	1	6.6	15
Birth dose, Incomplete immunization	1	1.4	7
No dose at birth, incomplete immunization	0	0	1
Total	8		131

Of all the 92 children who had received any of the accepted schedules, 5 children (5.4%) tested positive for HBsAg. Among those children who received non-standard or incomplete immunization schedules the rate of HBsAg positivity was 3 out of 39 children (7.69%). This difference was not statistically significant (S.E. for difference between the proportions = 5.55, p = 0.681).

Out of the 8 HBsAg positive children, 7 had received the first dose of vaccine within 24 hours but one finally received only two doses of the vaccine. Of all the 8 HBsAg positive children 7 had received three doses of the vaccine (Table No 10).

5.8.5 Type of delivery and HBsAg status

The proportion of children born by vaginal delivery was 91.6%. Among the 120 children in the study group who were born by vaginal delivery, 8 children were found to be HBsAg positive. None of the 11 children born by LSCS were HBsAg positive.

5.8.6 Anti HBs titres

The Geometric Mean Titre (GMT) for children between 6-12 months who received three doses of the vaccine was 345.9 mIU/ml (95% CI: 91.8-568.9 mIU/ml).

Among the 123 children who received three doses of the vaccine the seroconversion rate was 91% (children with detectable antibody levels). Anti HBs level of at least 10mIU/ml is considered to be evidence of adequate seroprotection. Among the children between 6-24 months who received 3 or more doses of the vaccine, the seroprotection rate was 92.4% (49 out of 53 children). Of all the 123 children who received 3 or more doses of the vaccine, 93 (75.7%) were found to have antiHBs levels of greater than or equal to 10mIU/ml at the time of testing.

Table No.11 shows the proportion of children in each age group who had protective antibody levels at the time of testing.

Table No. 11 Age in months vs. Anti HBs levels

Age of children in months	Children with antiHBs >=10 mIU/ml		
	No.	Sero protection (%)	Total
<=12	17	89	19
13-24	32	94	34
25-36	19	68	28
37-48	10	63	16
49-60	8	53	15
61-72	7	64	11
Total	93	75.7	123

Of the remaining 30 children who did not have protective anti HBs levels at the time of testing 26 children (87%) were above two years of age.

5.8.7 Effect of Hepatitis B Immunoglobulin on titres of anti HBs

There were six children who were born in CMC who received Hepatitis B Immunoglobulin (HBIG) at birth. The average GMT of the 6 children who received HBIG (42.26 mIU/ml, 95% CI: 13.38-133.56) was not significantly different from that of children who did not receive HBIG (77.23 mIU/ml, 95% CI: 50.42-118.30).

5.8.8 Anti HBs concentration and HBsAg positivity of the tested children

There were 3 children who tested positive for HBsAg despite having antiHBs values of more than 10 mIU/ml at the time of testing. Table No 12 represents the HBsAg status of the study children and their anti HBs antibody levels.

Table No. 12 AntiHBs level vs. HBsAg status of the study children

Anti HBs	HBsAg positive		Total
mIU/ml	No.	%	
<10	5	13.5	37
10-100	2	4.5	44
101-500	1	2.6	38
501-999	0	0	6
>=1000	0	0	6
Total	8	6.1	131

5.8.9 Relationship between Anti HBs values and type of immunization schedule

Table 13 shows the Geometric Mean Titres of anti HBs values for the children who received three doses of vaccine according to different vaccine schedules. The GMT was calculated for the 112 children who seroconverted out of 123 children who received three doses of the vaccine. The numbers of children who had taken different vaccine schedules in different age groups was small and some of the age groups had only one child who received a particular vaccine schedule.

Table 13 shows that children who received the immunization at birth, 1 month and 3-6 months of age had apparently higher antibody levels as compared to those who received the vaccine at birth,1 and 2 months except in the age group 6-12 months. In this age group (6-12 months) GMT of children who received the birth dose, 1 and 2 months schedule was 208 mIU/ml (95% CI: 65-668 mIU/ml) compared to 161 mIu/ml (95% CI: 56-458 mIU/ml) among those who received a birth dose followed by two doses at 1 month and 3-6 months.

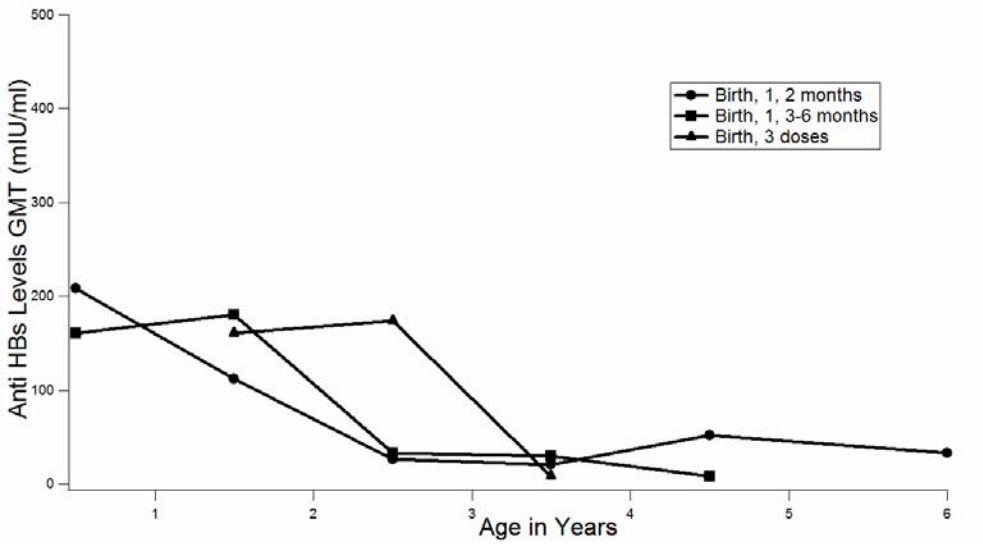
Table No 13 : Mean Anti HBs values by age group and immunization schedule

Age in months and Geometric Mean titre(mIU/ml)												
Vaccine schedule	**<=12**		**13-24**		**25-36**		**37-48**		**49-60**		**61-72**	
	GMT	**no**	**GMT**	**no**	**GMT**	**no**	**GMT**	**no**	**GMT**	**no**	**GMT**	**no**
birth,1,2 months	208	13	112	17	26	12	21	9	52	9	33	5
birth,1, 3-6 months	161	4	180	5	33	2	30	4	8	4	203	1
3 doses, birth dose given		0	53	8	52	5		0			86	1
3 doses, no birth dose	3090	1	161	3	174	5	8	2	1	1	72	1
Total	346	18	104	33	45	24	20	15	23	14	51	8

However, on analyzing using ANOVA for the log transformed values of anti HBs, there were no significant differences between the anti HBs values achieved by different vaccine schedules in each age group. Antibody levels decreased with increasing age of testing as expected.

Figure 3 is a line diagram which shows the mean anti HBs values in mIU/ml of different age groups according to the type of vaccine schedules. Some of the age groups in which there was only child who received a particular schedule were not represented on the graph.

Figure No 3: Comparison of mean anti HBs for different vaccine schedules



5.9 HBeAg status of the mothers

There were 129 stored samples collected during the antenatal period, from mothers whose children were available for the study with the rate of HBeAg positivity being 16.3% (95% CI: 9.8% - 22.8%).

5.9.1 HBeAg status of mothers vs. HBsAg status of children

Of 115 children who received the birth dose of the vaccine HBeAg status was available for 113 of the mothers (Table No.14). The prevalence of HBsAg was more among those children whose mothers were HBeAg positive compared to those whose mothers were HBeAg negative (RR = 2.1 ,95% CI: 1.05-9.09).

Table No. 14 HBsAg prevalence among children vs. HBeAg status of the mothers

HBeAg status of mothers	HBsAg status of children		Total
	positive	negative	
positive	2	16	18
negative	5	90	95
Total	7	106	113

The transmission of infection overall from mothers who were HBeAg positive, to their children was 12.5 % (2/16) among children who received three doses of the vaccine starting at birth and 4.5 % (4/88) from HBeAg negative mothers (p=0.20). The relative risk was 2.77 (95% CI: 1.24- 9.63) for acquiring HBsAg if the mother was HBeAg positive.

5.9.2 HBeAg status of mothers vs. markers of infection among the children

There were 73 children greater than two years of age for whom anti HBc was tested and maternal HBeAg status was also done as part of the study. Of these children 59 were immunized with three doses of the vaccine including the birth dose. Table No. 15 shows the perinatal transmission of hepatitis B virus infection among these children with respect to maternal HBeAg status.

Table No 15: HBeAg status of mothers vs. Hepatitis B infection among the children.

HBeAg status of mothers	Anti HBc status of children	HBsAg status of children		Total
		positive	negative	
positive	positive	2	0	2
	negative	0	4	4
negative	positive	0	1	1
	negative	2	50	52
	Total	4	55	59

Of the 6 immunized children born to mothers who were HBeAg positive, 2 (33.3%) children showed signs of infection. Among the 53 children born to mothers who were HBeAg negative, 3 children (5.7%) showed evidence of infection (RR 5.8, 95% CI: 1.58-21.11).

5.10. Vaccine efficacy

Assuming 18.6% as the rate of vertical transmission and 90% as the rate of chronicity of infection, the rate of chronic HBsAg infection among the unvaccinated children = 17% [17]**.** The prevalence of HBsAg among vaccinated children (present study) was 5.4% (5 out of 92 children who received the birth dose of the vaccine and standard immunization schedules)

$$\text{Vaccine efficacy} = \frac{\text{HBsAg rate among unvaccinated- HBsAg rate among vaccinated}}{\text{HBsAg rate among unvaccinated}}$$

Vaccine efficacy = (17-5.4 /17) x 100 = 68 %

6. DISCUSSION

6.1 Screening of antenatal women for HBsAg infection

There are many studies from India on prevalence of HBsAg but very few are community based. These studies are based on different types of subjects like voluntary or replacement blood donors, children, antenatal women, special clinic attendees etc. Of all these groups the prevalence among antenatal women which is easier to obtain is often taken as being representative of the general population. However, even community based studies of HBsAg prevalence among antenatal women are not always representative of the prevalence in the general population, as often only a few women who receive antenatal care at a particular clinic are included. A few of these community based studies were actually based on high risk communities [14,15].

The prevalence of HBsAg infection in the present study has been obtained by screening 93% of all the pregnancies in one rural block (service area) between May 2002-December 2007. This high rate of coverage was possible by actively identifying and registering antenatal women through services provided at the village level and was facilitated by the long standing relationship between the CHAD program with the people of the service area, Kaniyambadi.

Of the remaining 7% of the women who could not be screened through this program, a few had antenatal care from other service providers, e.g. the government services, CMC hospital and private practitioners while others had gone with their husbands to different places to work during the antenatal period.

A similar program of screening women for HBsAg would be successful only in places where the rate of women registering for antenatal care is high. According to the National Family Health Survey 3, the proportion of women who had three antenatal

care visits was only 50.7% in India while it was 96.5% in Tamil Nadu[47].Thus screening for HBsAg may not be feasible in states where the antenatal care is not as widely available or utilized.

Even among the antenatal women who came to the base hospital the acceptability for antenatal screening for HBsAg was high (99.9%), only one woman having refused the screening tests.

6.2 Prevalence of HBsAg infection among antenatal women

The point prevalence of HBsAg infection was 1.25% (95% CI: 1.05%-1.45%) among the antenatal women screened from the service area and 1.43% (95% CI: 1.18%-1.67%) among the antenatal women screened at CHAD.

Although ideally the HBsAg test must be positive on two occasions 6 months apart before labeling a person as being a HBsAg carrier, this is not feasible in pregnancy. By the time the second test is done the patient may deliver and the chance to prevent perinatal transmission may be lost as not all women register in the first trimester of pregnancy. It is possible that if the women had been screened a second time 6 months later the prevalence of antenatal women who were HBsAg positive would have been around 80% of the present estimate[71]. However, even if the vaccine were to be given to a few children who were actually not at risk for perinatal transmission, they would still be protected from horizontal transmission later on in life. Therefore in the CHAD program women were tested only once and as early as possible in their pregnancy, so that even if they did not come to CHAD for the delivery they would be aware of the need for Hepatitis B immunization for their children at birth.

The data obtained on prevalence from this study is that of point prevalence of HBsAg positivity and not of the HBsAg carrier state. This result was significantly lower than the estimated true prevalence of HBsAg positivity in India of 2.4% (95% CI: 2.2%-2.7%) according to the meta-analyses done by Batham et al. This meta-analysis had shown that the chronic carrier rate in India was 1.9%, assuming that follow up testing after 6 months reveals 80% of persons who are HBsAg positive at initial testing to be chronic carriers [18]. However, the data present from Kaniyambadi block was a community based study of a high proportion (93%) of antenatal women from a defined area, whereas the populations included in the meta-analyses included groups like voluntary and replacement blood donors.

6.2.1 Trend of prevalence of HBsAg

There was no significant trend of declining prevalence of Hepatitis B among the antenatal populations of both the service area (chi-square for trend= 0.037, p = 0.847), and the population served by the base hospital (chi-square for trend = 0.12, p value = 0.729). However, the prevalence of HIV among antenatal women in the service area was found to have decreased from 0.59% in 2002 to 0.24% in 2006 (unpublished data). This was similar to data for Tamil Nadu where HIV prevalence decreased from 0.82% in 2003 to 0.58% in 2006. [72]

It has been estimated that perinatal transmission contributes to 35-50% of chronic carriers in high endemicity countries and around 33% in India with the remaining 67% of chronic carriers in India acquiring the infection horizontally in childhood or sexually[5,20] . The exact contribution of each method of transmission is not known [17].The absence of a declining trend for HBsAg infection in an area where the HIV

prevalence has been found to be decreasing possibly due to concerted efforts in decreasing the sexual transmission of HIV, may be partly because a large proportion of HBsAg positive antenatal women may have been infected through either vertical transmission or horizontal transmission in early childhood. Therefore unless measures are taken to control perinatal transmission by ensuring Hepatitis B immunization at birth, it will be a long time before any significant decline in prevalence can be expected.

Various studies from Taiwan conducted at different intervals after the start of the immunization program, have shown the impact of universal immunization commencing at birth with the effect of reduction in HBsAg prevalence seen as early as 5 years later. A follow up study from Taipei showed a decrease in the prevalence of HBsAg among children under 5 years of age from 9.3% in 1984 to 2% in 1989[32]

6.3 HBeAg positivity rates

During the present evaluation HBeAg was tested among the women who were HBsAg positive and whose children were available for the serological evaluation. The rate of HBeAg positivity among the 129 women available for the study was 16.28% (95% CI: 9.8% - 22.8%) which was similar to other Indian studies where the range was between 7.8% - 47.8 % with most studies showing around 18% prevalence[17]. This was considerably lower than the prevalence of HBeAg in East Asian countries like Taiwan [73].

6.4 Strategies for prevention of HBsAg carrier state

There are different strategies which are being followed worldwide for the prevention of transmission of Hepatitis B infection. These are universal immunization, selective immunization of high risk groups and a combination of both strategies.

6.4.1 Universal immunization

Ideally universal immunization starting at birth would be the best way to prevent both vertical transmission as well horizontal transmission of Hepatitis B in early childhood.

For preventing vertical transmission it is recommended to administer the first dose as soon as possible, preferably within 24 hours [19]. This method of universal immunization commencing at birth has been shown to be the most cost effective method for preventing Hepatitis B carrier state [8,68].

In India the recommended immunization schedule is three doses of Hepatitis B vaccine at 6, 10 and 14 weeks [9]. Universal immunization without the provision of the birth dose does not help in reducing vertical transmission. This schedule was adopted because it was considered to be difficult to provide the birth dose to all newborns in the country. The other reason was that since the prevalence of HBeAg ranges from 8-47% with most studies showing estimates less than 18%, perinatal transmission was not considered to be a major contributing factor in transmission of HBsAg infection[46].

6.4.1.1 Problems and Issues involved in universal immunization

The WHO (Western Pacific Region) field guidelines for the administration of the birth dose of the Hepatitis B vaccine, has identified key issues involved in this process and suggested methods to ensure administration of the birth dose[37]. One of the main problems was a lack of institutional deliveries or deliveries in low level health facilities where cold chain facilities are unavailable.

However administration of the first dose of the Hepatitis B vaccine at birth is not unconceivable although it does require coordination between the maternity staff involved in the birth process and those involved in immunization. The practice of

administering injections to newborns is not a novel idea as most newborns receive Injection Vitamin K at birth and BCG vaccine is also given before discharging the mother from the place of delivery. For successful and timely administration of the birth dose of the Hepatitis vaccine either the maternity staff can be trained to give the vaccine or the staff in charge of immunization should be able to coordinate administration of the birth dose.

Thus although it is theoretically possible to universally immunize all children at birth with the Hepatitis B vaccine, the difficulties include lack of the cold chain at lower level health facilities like primary health centers, where a large proportion of deliveries occur and home deliveries. The other difficulty is the cost of universal immunization, which would be hard to justify given the increasing evidence that the prevalence of HBsAg infection is less than 2% making India a low endemicity region[18]. The government of India has estimated the cost of universal immunization to be Rs. 525 crores [65].

6.4.2 Selective Immunization

An alternative strategy to prevent perinatal transmission is screening antenatal women for HBsAg infection and ensuring immunization for their children commencing at birth. This strategy was employed by the CHAD program. This strategy of selective immunization is expected to prevent most of the perinatal transmission provided the coverage for antenatal screening is high. This strategy also relies on a high rate of institutional deliveries similar to universal immunization starting at birth. However in this case as the women who are HBsAg positive are few it would be easier to counsel them and ensure a high rate of institutional deliveries among these women. In countries like the United Kingdom where the prevalence of Hepatitis B among antenatal women

is only 0.14% this has been followed as the only strategy for childhood Hepatitis B immunization [66].

The success of the CHAD program depended partly on ensuring institutional deliveries for women who were HBsAg positive. Therefore these women were advised specifically to deliver at CHAD or at any hospital where the vaccine could be given within 24 hours of birth.

The proportion of all the antenatal women who had institutional deliveries during May 2002-December 2007 was 93% in the service area (Kaniyambadi block). This was similar to the figure for Tamil Nadu (90%) and much higher as compared to 40.7% institutional deliveries for the country[47]. The proportion of deliveries conducted by skilled personnel was 98 % in the service are as compared to 93% for Tamil Nadu. There was also no significant difference between the proportions of Hepatitis B positive and negative women who delivered in hospitals. In Tamil Nadu there has been a substantial increase in deliveries occurring at Primary Health Centers and childhood immunization is also being given in the PHCs rather than in health sub centers as was the practice earlier. Hence if this strategy under the National Rural Health Mission continues to work well in Tamil Nadu, it should be possible to give a dose of Hepatitis B vaccine at birth, especially if all carrier mothers were to be identified earlier.

6.5 Compliance to the immunization schedule

The children born to the HBsAg positive women were advised Hepatitis B immunization at birth, 1 and 2 months. The Indian Academy of Pediatrics recommends the first dose at birth, followed by two further doses one and three months later[48]. The Advisory Committee on Immunization Practices (ACIP), CDC recommends a dose at

birth, second dose at 1-month and the third at 6 months [19]. The recommendation is to give the first dose within 24 hours of birth, preferably within 12 hours of birth.

The effectiveness of the program was 77% (102/154) in providing the birth dose to children of HBsAg positive mothers in the service area and 66 % in providing three doses as per standard schedules. Overall 94.8% of the children received three doses of the vaccine.

Only the antenatal women who tested HBsAg positive and their husbands were informed about the need for immunization for their children during the post test counseling. In order to maintain confidentiality health aides of the service area were not informed about the results of antenatal screening and home visits were not made to follow up the children.

6.6 Serological evaluation

Of all the eligible 269 children born to HBsAg positive mothers from the service area as well as those who attended CHAD hospital for antenatal care, 131 were available for the evaluation and serological testing.

From the service area 67% of the children of permanent residents and 53% of the children of temporary residents were available. This is because the temporarily resident mothers were women who grew up in the service area, married and were now living elsewhere. They had registered with the CHAD peripheral services in order to have antenatal care and delivery at their maternal homes, as is the practice in this part of the country. Although attempts were made to inform all these women through their relatives residing in the service area, only a few of them were able to come for the

study. It was possible to contact only 30% of the children born to women who had antenatal care at CHAD hospital from non-service areas, since they resided over a wide area both within and outside the district.

The sample size calculated was 168, of which 84 were expected to be in each group of those who accepted the immunization program and those who did not. Since there were only 8 children in the study group who did not receive the complete vaccine series and none who were completely unvaccinated, the rate of HBsAg infection among the unvaccinated children was taken from other studies for calculating vaccine efficacy.

6.6.1 Coverage for the birth dose among the study children

Among these 131 children available for the serological survey, the proportion who received the birth dose of vaccine was significantly less among those born at home (60%, 109 out of 121 children) compared to those children born in hospitals (90% coverage for birth dose, 6 out of 10 children), p value for chi-square=0.02. Studies have shown that even in hospitals there is a chance of not receiving the birth dose [37]. The reasons for this problem in the present study included children being sick after birth; being born in health centers where the vaccine was unavailable or the health care providers were unaware of the HBsAg status of the mother. As the availability of the vaccine in public health facilities has increased it is less likely that in future the birth dose will be missed, due to non availability of the vaccine.

6.6.2 Prevalence of HBsAg among the tested children

Among the 92 children who received the three doses of the vaccine commencing at birth, the prevalence of HBsAg (failure of immunization) was 5.4%. Overall there were

8 children who were found to be HBsAg positive among the 131 tested children (6.1%). These children who were found to be HBsAg positive could have got the infection either perinatally from their mothers or through horizontal transmission later on in life. In either case this was an indication of failure of immunization. In order to determine the vertical transmission alone it would have been necessary to measure prevalence of IgM anti HBc in cord blood, which was not done as part of the present study.

Transmission of infection to unvaccinated children could not be defined from our study as there was no child among the 131 tested children who was totally unvaccinated.

The presence of HBeAg which is a sign of higher infectivity, has been shown to be a significant risk factor in perinatal transmission [24,73]. In the present study children born to women who were HBeAg positive were twice as much at risk of acquiring HBsAg infection in spite of receiving a birth dose, as compared to those whose mothers were HBeAg negative (RR = 2.1 , 95% CI: 1.05-9.09). Thus HBeAg positivity of the mother was one of the significant factors associated with immunization failure.

Presence of anti HBc which is also a sign of natural infection was tested only among the children who were above 2 years of age to avoid detection of maternally derived antibodies [19]. There were 59 children above 2 years of age who received three doses of Hepatitis B vaccine including the birth dose, for whom maternal HBeAg was tested. The risk of the child becoming either HBsAg or anti HBc positive was significantly higher for children born to HBeAg positive mothers (RR 5.8, 95% CI: 1.58-21.11).

Ideally women who are HBsAg positive should undergo testing for HBeAg and if positive their children must receive Hepatitis B immunoglobulin (HBIG) at birth [40]. However HBeAg testing is not feasible in smaller level health facilities and the high cost of HBIG makes it impractical for use in developing countries. Besides, a review by

André and Zuckerman showed a protective efficacy of vaccine alone to be 90-100%, which was a difference of only 2-5% from efficacy of immunization as well administration of HBIG (92-100% efficacy)[6]. Based on these factors, national policies of administering vaccine alone were considered to be justifiable at the meeting held by the Viral Hepatitis Prevention Board [25]. Considering the above reasons the CHAD program did not do HBeAg testing for HBsAg positive mothers or administer Hepatitis B immunoglobulin to the newborns.

6.6.3 Presence of both anti HBs and HBsAg

The presence of anti HBs implies immunity which is acquired through natural infection, immunization or passive administration of Hepatitis B immunoglobulin. Immunity acquired through natural infection is evidenced by the presence of anti HBs as well as anti HBc whereas immunity acquired through immunization is indicated by the presence of anti HBs alone [19]. It has been seen that occasionally there occurs the emergence of mutant forms of hepatitis B virus which can replicate in the presence of circulating anti HBs[53]. It has been suggested that with increase in the immunization coverage there may be an increase in the development of these mutant form and therefore it is recommended to monitor the emergence of these forms [56].

There were 3 children who were HBsAg positive despite having adequate antiHBs. The ages of these children were 5 months, 17 months and 45 months and all of them had received three doses of the vaccine staring at birth,1 and 3 months. HBsAg positivity in the presence of adequate anti HBs in these children implies infection by mutant forms of the virus which are not cleared by the circulating anti HBs.

The prevalence of children with both HBsAg and anti HBs was 3.3% in this study as compared to a prevalence of 2.9% mutant forms in the study from Chennai [55].It is planned to retest these children 6 months later to check for persistence of HBsAg positive status. Further testing by Polymerase Chain Reaction (PCR) amplification and HBV DNA sequencing for identification of mutants was not done due to lack of cryopreserved specimens and high costs involved.

6.6.4 Risk factors for Vaccine failure

The most significant risk factor for immunization failure was the HBeAg positive status of mothers (RR was 5.8; 95% CI: 1.58-21.11) for infection among children greater than two years. HBV DNA is another significant risk factor for transmission of infection, with a study from Taiwan showing odds ratio for carrier state among children born to HBeAg negative mothers to be 19.2 (95% CI: 2.3-176.6) and a significant increase in odds ratio for HBsAg carrier state among children born to HBeAg positive mothers as well[28]. This could not be studied in the present study in CHAD as the samples were not cryopreserved. The type of delivery (vaginal or Caesarian Section) was not a significant risk factor for the development of HBsAg among the children. A recent meta-analysis of randomized controlled trials showed that elective caesarian sections were protective although the evidence was not convincing due to a lack of good quality trials [36].

6.6.5 Seroprotection among the immunized children

The different vaccine schedules are known to produce different levels of antibody to HBsAg. Accelerated schedules which incorporate a birth dose (e.g. birth,1 and 2 months) achieve lower final antibody levels compared to those where the second and

third doses are further apart which was also seen in the present study among children of all ages except those between 6-12 months [42,43].

The data from the present study showed that the sero protection rate (anti HBs more than or equal to 10 mIU/ml) was 92.4% among children between 6-24 months of age which is similar to rates found in other Indian studies[39]. The Geometric Mean Titre (GMT) of anti HBs for children aged 6 to 12 months was 345.9 mIU/ml which was also comparable to data available from other Indian studies [58].

6.7 Vaccine efficacy

Various studies have calculated the vaccine efficacy of Hepatitis B vaccine when used as post exposure prophylaxis to prevent perinatal transmission to be 70-95% [5,7,26].Our study showed the vaccine efficacy to be 68% in preventing HBsAg infection among children who received three doses of the vaccine according to standard schedules.

6.8 Number Needed to Screen

Assuming that the rate of vertical transmission rate to newborns is 18.6% [17] and the rate of chronic infection at one year to be 90% of this rate, the rate of Hepatitis B carriers would be 17%. The rate of transmission of HBsAg infection to vaccinated children in the present study was 5.4% and vaccine efficacy 68%.The Absolute Risk Reduction was 11.6% and the Number Needed to Treat (NNT) was 8.6. This implied that 8.6 children would have to be vaccinated to prevent one child from becoming a carrier.

The Number Needed to Screen was 688 [64]. In order to prevent one child from acquiring Hepatitis B infection from an infected mother, 688 antenatal women would

have to be screened in a program of selective immunization for children born to HBsAg positive mothers.

6.9 Cost of preventing one case of Vertical Transmission

The unit cost for preventing a single child born to an infected mother from becoming HBsAg positive was calculated assuming different strategies.

1. Strategy of screening for Hepatitis B surface antigen and administering vaccine to children born to mothers who are Hepatitis B positive. Table No 16 shows the cost of preventing one case of perinatal transmission of HBsAg from infected mothers to their children. This was excluding the costs of counseling and direct non medical costs such as travel to place of testing/immunization.

Table No. 16 Selective immunization strategy (administering vaccine alone)

	Number	Unit Cost (Indian Rs.)	Total cost
Cost of testing for HBsAg (Hepacard)	688 (number needed to screen)	30	20,640
Cost of 3 doses of the vaccine	8.6 (NNT)	60 x 3 (doses)	1,548
Total			Rs 22,188

2. Strategy of screening for Hepatitis B surface antigen, followed by HBeAg for HBsAg positive mothers; administering vaccine to children born to mothers who are Hepatitis B positive and additional Hepatitis B immunoglobulin if the mother is HBeAg positive. Table No 17 shows the cost of preventing one case of HBsAg infection by this strategy.

Table No. 17 Selective immunization (vaccine and immunoglobulin)

	Number of individuals	**Unit Cost (Indian Rs.)**	**Total cost**
Cost of testing for HBsAg (Hepacard)	688 tests (number needed to screen)	30	20,640
Prevalence of HBsAg	1.25% of 688 = 8.6 women		
Prevalence of HBeAg	16.3% of 8.6 = 1.4 women		
Cost of testing for HBeAg	8.6 women	485	4,171
Cost of 3 doses of the vaccine	8.6 (NNT)	60 x 3 (doses)	1,548
Cost of hepatitis B immunoglobulin	1.4 children	4800	6,720
Total			33,079

3. Strategy of universal immunization starting at birth followed by two doses.

Table No 18 shows the cost of universal immunization without antenatal testing, for the 688 children born to the women who would have to be screened in the above strategies.

Table No. 18 Cost of Universal immunization

	Number of individuals	**Unit Cost (Indian Rs)**	**Total cost**
Cost of 3 doses of the vaccine	688 children	60 x 3	20,640

The present study did not show much difference between the costs of preventing one HBsAg positive carrier among the children born to Hepatitis B positive mothers by selective or universal immunization strategies. Studies worldwide have shown that universal immunization was more cost effective than selective immunization [8,68]. However in view of the difficulties involved in administering the birth dose to all newborns due to lack of hospital deliveries and a large proportion of institutional deliveries occurring in low level health facilities, selective immunization may be a more

feasible alternative strategy of reducing Hepatitis B transmission until such a time when institutional deliveries become commoner in PHCs where the vaccine is also stored.

The current strategy of the government of India of universal immunization starting at 6 weeks would be ineffective in tackling vertical transmission. An expenditure of Rs. 525 crores is also difficult to justify, given the low prevalence of HBsAg (1.25%) from our community based study as well as similar findings from other studies [65].

Until the time when the strategy of universal immunization at birth (without antenatal screening) is possible, the option of selective immunization of infants born to carrier mothers (with the vaccine alone) can be considered in areas where the rate of institutional deliveries is reasonably high. A combined strategy of selective immunization commencing at birth, for children born to HBsAg positive mothers and universal immunization of other children along with the routine immunization schedule, would prevent both vertical as well as early childhood transmission.

7. LIMITATIONS OF THE STUDY

As the study was done five years after the program had started, the children were followed up at different ages, with some being over 5 years at the time of testing. The children who were HBsAg positive were also between 15-64 months, thus making it possible that some of them may have escaped perinatal transmission and acquired the infection horizontally due to an inadequate immune response. In order to evaluate vertical transmission alone HBsAg status of children born to infected mothers should have been checked at an earlier age before there could be chances of having acquired the infection horizontally. Analysis of cord blood for IGM anti HBc would have helped to make the diagnosis of infection acquired in-utero, against which immunization does not work.

The follow up rate was only 67% for permanent residents, 53% for temporary residents from the service area and 30% for women who had registered at CHAD, although attempts were made to contact all of them.

Detectable maternal HBV DNA which has been shown to be a significant risk factor for perinatal transmission could not be studied as the samples had not been cryopreserved and the costs involved were high. DNA extraction and sequencing to study mutant viral forms also could not be done due to the high costs.

Prevalence of HBsAg infection among unvaccinated children could not be calculated from the study as none of the children available for serological testing were totally unvaccinated. Cost calculations were only analyzed with respect to the service provider and did not include the cost for the family in attending counseling and immunization sessions.

8. CONCLUSIONS AND RECOMMENDATIONS

The CHAD program for the prevention of vertical transmission of HBsAg was successful in screening 93% of the pregnancies in the service area, which was one rural block in Tamil Nadu. The prevalence of HBsAg positivity among the antenatal women in the service area was 1.25 % (95% CI: 1.05%-1.45%) which falls into the category of low endemicity according to the WHO [3]. Evaluation of the program showed coverage of 70% for immunization with three doses of the Hepatitis B vaccine on schedule, commencing at birth. The program was able to administer birth dose to 77% of children born to HBsAg positive mothers in the service area and three doses of the vaccine to 94.8%.

Presence of HBeAg in the mother was found to be significantly associated with immunization failure (RR of 5.8; 95% CI: 1.58-21.11). The seroprotection rate (anti HBs of at least 10 mIU/ml) of children between 6-24 months was 92.4%. The vaccine efficacy was found to be 68% which was similar to other studies [5,7].

As the NNT was 8.6, this implied that 8.6 children would have to be immunized in order to prevent one case of vertical transmission. The NNS being 688, this was the number of women who would have to be screened in order to prevent one case of vertical transmission of HBsAg by a program of selective immunization.

The cost of preventing one case of HBsAg infection among children born to HBsAg positive mothers was Rs. 22,188 by the selective immunization strategy and Rs. 20,640 by universal immunization. Considering the fact that many deliveries occur in lower level health facilities without a cold chain even in places where the rate of institutional deliveries may be high, universal immunization may not always be feasible and selective immunization may be a viable alternative.

Thus instead of completely omitting the birth dose as is being done under the current government program, it would be useful to administer the birth dose of the Hepatitis B vaccine to infants identified to be at risk for perinatal transmission and to make the vaccine available to other children along with the DPT vaccines, in states where universal immunization at birth is not feasible. In Tamil Nadu with a high proportion of pregnant women receiving antenatal care and a high rate of institutional deliveries, provision of the birth dose to all newborns seems to be a feasible intervention to prevent perinatal transmission of Hepatitis B. As there has been a move to increase deliveries occurring at primary health center rather than at health subcentres, the availability of the vaccine also should not be a hindrance as the vaccines are available at the Primary Health Centre level. It is hoped that the government would consider introducing the birth dose of the Hepatitis B vaccine in regions like Tamil Nadu where it would be feasible to do so.

Annexure 1

Questionnaire

A. **Demographic details**

1. Name
2. Age
3. Village Antenatal No
4. Hospital No/ID No.
5. Date of Last child birth
6. Obstetric score G P L A

B. Antenatal period

1. When was blood collected for testing for Hepatitis B during your pregnancy?
2. Was consent taken at the time of testing for Hepatitis B? Yes/No
3. Did you understand why it was necessary to have yourself checked for Hepatitis B? Yes/No
4. Did you receive adequate post test counseling after being informed that you were Hepatitis B positive? Yes/No
5. Did you ever feel that confidentiality was not maintained by the health staff, causing you discomfort? Yes/No

C. Details of delivery

Where did you have your last delivery?

CHAD/ CMC Vellore/ Vellore Medical College/ Home/ other Health centre

When did your child receive the first dose of Hepatitis B vaccine?

1. Within the first 12 hours
2. Within 24 hours of birth
3. After 24 hours of birth

Date of receiving first dose:-
Date of receiving second dose:-
Date of receiving third dose:-

If any dose was not given, or given late, was there any specific reason for the delay?
If your child has not been immunized for Hepatitis B at all, can you tell us why you chose not to get your child immunized?

Checklist:

Birth dose timing checked: Yes/No
Immunization card verified: Yes/No
Hospital's immunization record checked: Yes/No

Annexure 2

Consent form

The Department of Community Health, CMC Vellore, (CHAD), is conducting a study on all the children, who were born to mothers whose blood tested positive for jaundice (Hepatitis B).

During your antenatal period you were tested for Hepatitis B and HIV after being informed of the need for the same. You were then offered intervention with 3 doses of Hepatitis B vaccine, commencing at birth.

Some of you accepted the intervention and some of you chose not to do so.

We now need to test your child and check whether the vaccine has protected your child from Hepatitis B. We also need to check if the virus has stayed on or been removed from the blood.

This means that we will have to collect 5 ml of the child's blood on which three tests will be done to obtain the above information.

I, Mrs. _____, wife of Mr._____, having read/been explained the above, give my consent for including my child in the study and for giving blood for testing him/her for the above mentioned tests.

Signature/Thumb impression

Witness Date

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Evaluation of a program for the prevention of vertical transmission of Hepatitis B in Kaniyambadi block and CHAD hospital

Background:

Hepatitis B is one of the few vaccine preventable causes of a cancer. A third of chronic carriers acquire infection through perinatal transmission. However immunization at birth is not a part of the newly launched government program. Community Health Department of Christian Medical College, Vellore has been running a program of antenatal screening and selective immunization of children born to HBsAg positive mothers. Other children receive Hepatitis B vaccine along with routine vaccines.

Objectives:

The primary objective was to evaluate the effectiveness of the program in preventing HBsAg among immunized children born to infected mothers. Secondary objectives included assessing the coverage for the immunization schedule commencing at birth, effect of maternal HBeAg on immunization failures as well as seroconversion to the vaccine series.

Methodology:

Evaluation of the program was done by assessing immunization coverage achieved, vaccine efficacy and seroconversion to three doses of the vaccine by following up of the children of HBsAg positive women.

Results:

The prevalence of HBsAg among antenatal women was 1.25 % (95% CI: 1.05%-1.45%). The coverage for three doses of the vaccine on schedule including a dose at birth was 70%. Vaccine efficacy was 68% and seroconversion was 92.4 % in children aged 6-24 months. HBeAg was a significant risk factor for immunization failure.

Conclusions:

The prevalence of HBsAg was very low and a program of selective immunization is a feasible alternative to universal immunization. Coverage of immunization along with a birth dose was higher than the coverage achieved in the pilot areas under the government's strategy of universal immunization starting at 6 weeks. This strategy of screening and vaccination can be used in places where the rate of institutional deliveries is low while states with a high rate of institutional deliveries can give immunization at birth to all children.