

## The evidence of mother to child transmission of hepatitis B virus infection in Pakistan and the need for hepatitis B immunization policy change

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### Abstract

**Objective:** To establish the hepatitis B surface antigen and hepatitis B 'e' antigen seroprevalence of mothers and their children aged 6-36 months and to assess the risk of hepatitis B transmission occurring in infants born to hepatitis B surface antigen positive mothers in Pakistan.

**Methods:** Mothers and their children were selected from eight districts of three provinces that have been identified as high hepatitis B prevalence areas between May 2010 to February 2011. Ages of the children and their vaccination status were obtained from the lady health workers' registers and also verified from the mothers. Five ml of blood was drawn from all the children and their mothers for testing. All sera were tested for anti-hepatitis B. Those found negative were run for HBsAg the surface antigen and those positive for it were further run for hepatitis B 'e' antigen. All tests were run on Abbott machine using chemiluminescence method. EPI-info 12 was used for statistical purposes.

**Results:** A total of 1561 mothers and their 1612 children were tested. Among the mothers, 590 (37.8%) were hepatitis B antibody positive. Remaining 971 (62.2%) samples were tested for surface antigen and 123 (12.7%) were found positive of which 27 (22%) showed HBeAg positivity. Out of 1612 children tested, 975 (60.5%) were positive. Remaining 637 (39.5%) were tested for surface antigen and 49 (8%) were found positive of which 24 (49%) were HBeAg positive with a perinatal hepatitis B virus transmission rate of 5.4% by 12 months of age. Of the 123 surface antigen positive mothers, 18 (14.6%) had children who were also positive, while of the 1489 children born to the 1438 surface antigen negative mothers, 31 (2.1%) were positive. Children born to surface antigen positive mothers had eight times higher risk of getting hepatitis B virus infection and the risk rose to 17 times if the mother was also HBeAg positive. Hepatitis B vaccination record showed that 1229 (76.25%) children were vaccinated at six weeks with pentavalent vaccine, but despite vaccination 33 (2.6%) became surface antigen positive. No vaccination was received by 320 (19.9%) children and out of these 16 (5%) became surface antigen positive. Moreover, the vaccinated and unvaccinated children born to surface antigen positive mothers were nine and 11 times respectively more likely to be exposed to the risk of hepatitis B virus transmission relative to vaccinated children born to surface antigen negative mothers.

**Conclusions:** Hepatitis B vaccination given at 6, 10 and 14 weeks of birth is not sufficiently protective, indicating a strong need for the introduction of birth dose into the national immunisation system.

**Keywords:** Hepatitis B surface antigen, Infants, Mothers. (JPMA 64: 403; 2014)

### Introduction

Hepatitis B is a vaccine-preventable disease.<sup>1,2</sup> Globally the rate of chronic infection of Hepatitis B ranges from 0.1%-20%.<sup>1-4</sup> The prevalence of hepatitis B world over is divided into three categories i.e. high (>8%), intermediate (2-7%) and low (<2%).<sup>5,6</sup> Considering Hepatitis B 'e' antigen (HBeAg) prevalence as a major indicator of mother-to-child-transmission (MTCT), the highest rates were detected among young females from East Asia, like China, where the perinatal transmission is the most common route of infection, and the lowest in Sub-Saharan Africa, where the horizontal transmission is the

predominant mode of transmission.<sup>7-9</sup> Accordingly, in countries having high and intermediate endemicity of hepatitis B, early childhood infection accounts for most chronic infections, while in low prevalence countries sexual and other horizontal routes of transmission are predominant.<sup>5-7,10</sup> In low prevalence countries, infection predominantly spreads through unprotected sex and intravenous drug use.<sup>11</sup> The risk of progression to chronic infection is inversely related to the age at acquisition of infection and among the newly infected, approximately 90% of perinatal infections, 25-50% of infections amongst toddlers and about 5% of adult life infections become chronic carriers of the virus.<sup>5,7,12</sup>

In Pakistan, only 54% of the eligible children have received all the three doses of hepatitis B vaccine.<sup>13</sup> Blood transfusions are still not fully screened and medical devices are not properly disinfected/sterilized. Therefore,

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transmission of hepatitis B virus (HBV) is seen all the year round both as acute viral infections and chronic liver disease in children and adults.<sup>14,16</sup> The national prevalence study of Pakistan showed hepatitis B surface antigen (HBsAg) positivity to be 2.5% with wide variations seen within the provinces and districts.<sup>16</sup> HBeAg positivity in the sampled population was 14.5%. The prevalence of HBsAg in children under 5 years was 1.3%.<sup>16,17</sup> The study thus indicates a large pool of highly infectious cases that are transmitting the disease to their close contacts.<sup>11</sup>

The MTCT risk is related to the HBV deoxyribonucleic acid (DNA) status or HBeAg positivity of the mother, where a mother who is HBeAg positive has a 90% chance of transmitting this disease to her newborn but this figure drops to 20% if the mother is HBeAg negative.<sup>18,19</sup> Globally, hepatitis B vaccine has been incorporated in the Expanded Programme on Immunisation (EPI) to protect all newborns irrespective of mother's HBV status. Hepatitis B vaccine is currently an integral part of the national EPI of many countries as pentavalent formulation in combination with Diphtheria, pertussis, tetanus (DPT) and Haemophilus influenzae type b (Hib) vaccines.<sup>20</sup> These combined vaccines sustain their efficacy, safety and tolerability and provide the opportunity of effecting a unified promotion and acceleration strategies, while immediately raising the coverage of HBV vaccine to that of other EPI vaccines.<sup>21,22</sup>

Hepatitis B vaccine was first incorporated in Pakistan's EPI in 2001 as a tetravalent vaccine (with DPT) and later replaced with the pentavalent vaccine (DPT, HBV, Hib) given at 6, 10 and 14 weeks without a birth dose. The hepatitis B prevalence data is showing a 1.3% prevalence of HBsAg in children <5 years of age<sup>17</sup> and is pointing towards a possibility of vertical transmission as most of these children were vaccinated through EPI at around 6 weeks without a birth dose of HBV vaccine.

The present study targeted mothers and their infants, residing in high hepatitis B prevalent districts of three provinces of Pakistan, namely Balochistan, Sindh and Punjab and aimed at establishing the HBsAg and HBeAg seroprevalence and to assess the risk of hepatitis B MTCT.

## Subjects and Methods

The hepatitis survey data has identified Balochistan, Sindh and Punjab as high prevalence provinces for hepatitis B infection with high prevalence districts within these Pakistan provinces.<sup>16</sup> Two districts with highest prevalence were selected between May 2010 and February 2011 from each province using the same survey data, while from Balochistan four districts were chosen as

the HBsAg carrier rate was the highest there. From Sindh, Ghotki and Khairpur were selected; from Balochistan, Jafarabad, Dera Murad Jamali, Musakhail and Loralai; and from Punjab, Dera Ghazi Khan and Islamabad were selected. The study was descriptive analytical to find the hepatitis B transmission occurring in infants born to HBsAg positive mothers. A stratified two-stage sampling design was adopted. Selection of Primary Sampling Units (PSUs) i.e. enumeration blocks in urban domain, and villages/mouzas/dehs in rural domain. Second selection of Secondary Sampling Units (SSUs) i.e. household from each urban and rural sample PSUs were selected within equal probability using systematic sampling technique with a random start. There was collaborative effort between the Pakistan Medical Research Council (PMRC) and the Federal Bureau of Statistics (FBS) for household identification.<sup>17</sup>

Using the HBsAg prevalence figures of 2.5% (47043 screened subjects) in the population,<sup>17</sup> a sample size of 1419 mothers and their children was calculated with 95% confidence interval and 0.8% margin of error. The sample size was increased 10% (i.e. 1561 mothers and their children) to cover for inadequate or lost samples. After obtaining the consent of the federal and provincial health authorities, the Executive District Officer Health (EDO-Health) was approached in each district and informed about the project, who assigned Lady Health Workers (LHWs) to identify the females residing in their catchment area localities who had a child aged 6-36 months. LHWs using their birth registers identified the relevant households for inclusion in the study.

After informed verbal and signed consent, a questionnaire was filled for both mother and the child, where apart from the basic demographics of name, age, gender, the HBV vaccination status was also noted. About 5 ml of whole blood was taken from the mother and the child and was placed in gel bottles after labelling. Both mother and child tubes were adhered together using a paper tape for easy identification. Samples were transported to the main laboratory in a cool box. Sera were separated and frozen in 2 aliquots each for further testing. Chemiluminescent microparticle immunoassay (CMIA) kits from Abbott were used and the tests were run on ARCHITECT by Abbott. All samples were initially tested for hepatitis B antibodies (anti-HBs). Those found negative were run for HBsAg and those found positive were run for HBeAg. Data was entered in Microsoft Excel sheet and statistical software EPI-Info version 12.0 was used for calculating descriptive statistics, Odds ratio (OR) and 95% confidence intervals (CI).

## Results

A total of 1561 mothers and their 1612 children were tested from the 8 selected sites (Table-1). Some were twins, while some households had 2-3 children within the relevant age bracket.

Out of the 1561 mothers, 590 (37.8%) had anti-HBs, indicating immunity/protection against the virus. Remaining 971 (62.2%) samples were tested for HBsAg and 123 (12.7%) were found positive, and of these 27 (22%) were HBeAg positive. The protective level of anti-HBs among the children population cohort was significantly higher than that of the mothers' cohort, despite the unsatisfactory EPI coverage in the country [OR(95% CI): 2.48 (2.15-2.87)] (Table-2).

A total of 1612 children were tested for anti-HBs, and 975 (60.5%) were found positive, indicating immunity. Remaining 637 (39.5%) children who were negative for anti-HBs were tested for HBsAg and 49 (7.7%) were found

**Table-1:** Distribution of Mothers and Children according to districts.

	No. of Mothers	No. of Children
Overall	1561	1612
Districts of Punjab		
Dera Ghazi Khan	192	193
Islamabad	280	327
Districts of Sindh		
Ghotki	194	194
Khairpur	186	189
Districts of Baluchistan		
Lorali	164	164
Musakhail	201	201
Jafarabad	190	190
Dera Murad Jamali	154	154

**Table-2:** Frequency of Anti HBs, HBsAg and HBeAg in mothers (n=1561).

	Anti HBs	HBsAg	HBeAg
Overall	37.8% (590 / 1561)	12.7% (123 / 971)	22.0% (27/123)
<b>Districts of Punjab</b>			
Dera Ghazi Khan	37.0% (71 / 192)	6.6% (8 / 121)	- (0 / 8)
Islamabad	15.0% (42 / 280)	5.5% (13 / 238)	15.4% (2 / 13)
<b>Districts of Sindh</b>			
Ghotki	61.9% (120 / 194)	5.5% (4 / 74)	25.0% (1 / 4)
Khairpur	35.5% (66 / 186)	18.3% (22 / 120)	9.1% (2 / 22)
<b>Districts of Baluchistan</b>			
Lorali	33.5% (55 / 164)	13.8% (15 / 109)	13.3% (2 / 15)
Musakhail	39.8% (80 / 201)	33.1% (40 / 121)	37.5% (15 / 40)
Jafarabad	46.3% (88 / 190)	9.8% (10 / 102)	40.0% (4 / 10)
Dera Murad Jamali	44.2% (68 / 154)	12.8% (11 / 86)	9.1% (1 / 11)

Anti-HBs: Hepatitis B Antibody. HBsAg: Hepatitis B Surface Antigen. HBeAg: Hepatitis B 'e' Antigen.

**Table-3:** Frequency of AntiHBs, HBsAg and HBeAg in children (n=1612).

	Anti HBs	HBsAg	HBeAg
Overall	60.5% (975 / 1612)	7.7% (49 / 637)	48.9.0% (24/49)
<b>Age groups</b>			
Upto 12 months	58.9% (290 / 492)	5.4% (11 / 202)	18.2% (2 / 11)
13-36 months	61.2% (685 / 1120)	8.7% (38 / 435)	57.9% (22 / 38)
<b>Districts of Punjab</b>			
Dera Ghazi Khan	65.3% (126 / 193)	1.5% (1 / 67)	- (0 / 1)
Islamabad	82.3% (269 / 327)	12.1% (7 / 58)	28.6% (2 / 7)
<b>Districts of Sindh</b>			
Ghotki	72.2% (140 / 194)	1.8% (1 / 54)	100% (1 / 1)
Khairpur	62.9% (119 / 189)	- (0 / 70)	-
<b>Districts of Baluchistan</b>			
Lorali	52.3% (89 / 164)	1.3% (1 / 75)	100% (1 / 1)
Musakhail	26.4% (53 / 201)	17.6% (26 / 148)	61.5% (16 / 26)
Jafarabad	51.0% (97 / 190)	10.7% (10 / 93)	40.0% (4 / 10)
Dera Murad Jamali	53.2% (82 / 154)	4.2% (3 / 72)	- (0 / 3)

Anti-HBs: Hepatitis B Antibody. HBsAg: Hepatitis B Surface Antigen. HBeAg: Hepatitis B 'e' Antigen.

**Table-4:** The risk of maternal-child transmission assessed by HBsAg and HBeAg in children in relation to mothers' hepatitis B (HBsAg and HBeAg) virus status.

Mothers' hepatitis BHBsAg and HBeAg status of the offspring virus infection status				
HBsAg	HBsAg +ve	HBsAg -ve	Total	OR (95% CI)
Children born to HBsAg -ve mothers	31	1458	1489	1
Children born to HBsAg +ve mothers	18	105	123	8.1 (4.2-15.5)
Total	49	1563	1612	
HBeAg	HBeAg +ve	HBeAg -ve	Total	
Children born to HBsAg-ve Mothers	11	1478	1489	1
Children born to HBsAg+ve Mothers	13	110	123	17.3 (7.2-41.8)
Total	24	1588	1612	

Anti-HBs: Hepatitis B Antibody. HBsAg: Hepatitis B Surface Antigen. HBeAg: Hepatitis B 'e' Antigen.

positive and of these 24 (49%) were HBeAg positive. Of the 202 children up to 12 months of age, 11 (5.4%) were HBsAg positive compared to 38 (8.7%) among those between 13-36 months of age (Table-3).

Out of 123 HBsAg positive mothers, 18 (14.6%) children were HBsAg positive and 105 (85.4%) negative, while of the 1489 children born to 1438 HBsAg negative mothers, 31 (2.1%) were HBsAg positive and of these 11 (35%) were HBeAg positive, indicating other routes of viral transmission. Children born to HBsAg positive mothers had eight times higher risk of getting hepatitis B virus infection and the potential of this risk rose to 17 times when the mother was also HBeAg-positive, relative to children born to HBsAg-negative mothers respectively (Table-4).

Using the vaccination cards or mother's recall, a total of

**Table-5:** HBV transmission among the offsprings in relation to mother's HBsAg status and children's vaccination outcome.

Mothers' HBsAg and child vaccination status	Number of children	Children HBsAg +ve	Children HBsAg -ve	OR(95% CI)
Mother HBsAg +ve and child vaccinated	93	13	80	9.07 (4.09-19.95)
Mother HBsAg +ve and child not vaccinated	30	5	25	11.16 (3.36-34.93)
Mother HBsAg -ve and child vaccinated	1136	20	1116	1
Mother HBsAg -ve and child not vaccinated	320	11	309	1.99 (0.88-4.41)

HBV: Hepatitis B Virus. HBsAg: Hepatitis B Surface Antigen.

1229 (75.26%) children were vaccinated of which 33 (2.7%) were HBsAg positive; while of the 320 (19.95) who did not receive any vaccination 16 (5%) were HBsAg positive. Both the vaccinated and non-vaccinated children born to HBsAg positive mothers were nine and 11 times more likely to get HBV infection relative to vaccinated children born to HBsAg negative mothers respectively. On the other hand, no difference was found in children's HBsAg carrier rate among those born to HBsAg negative mothers irrespective of their vaccination status, indicating the low levels of horizontal transmission of HBV infection in young children [OR(95% CI): 1.99 (0.88-4.41)] (Table-5).

## Discussion

The high prevalence rate of HBsAg among mothers (12.7%) in our study was associated with an increased HBeAg seroconversion rate (27%); a situation known to correlate with relatively high levels of viral replication, enhance vertical transmission of HBV infection and pose a significant risk for MTCT.<sup>8,23-27</sup> The most important objective of hepatitis B immunisation strategies is the prevention of chronic hepatitis B infection, which can be achieved by routine infant vaccination, prevention of perinatal HBV transmission and catch up vaccination of older age group.<sup>1</sup> In 1992, the World Health Assembly (WHA) passed resolution 45.17 that called member states for the integration of hepatitis B vaccine into the national immunisation programmes by 1995 for countries with HBsAg prevalence of 8% or more, and by 1997 for all other countries, irrespective of their level of HBV endemicity. It was subsequently reaffirmed by the resolution WHA63.18.<sup>28-30</sup>

According to the crude birth rate reflected by the 2010 Pakistan report, issued by the Ministry of Population Welfare, approximately 4.85 million children are born in the country each year.<sup>31</sup> Considering the nationwide prevalence of HBV infection estimated at 2.5% among pregnant women, with a similar reported countrywide overall prevalence rate of HBsAg, about 121,000 expecting mothers are anticipated being HBsAg positive every year.<sup>16,17,32</sup> The latter confirms the imperative of advancing the necessary control strategies that include

introducing the hepatitis B vaccine birth dose as an integral component and cardinal measure of the national EPI to prevent MTCT, eliminate the prevailing high rate of HBV chronic infection among infants and young children and reduce the high burden of chronic liver disease in the country.<sup>8,26</sup> The relatively low anti-HBs prevalence of about 61% in 13-24 months old children reflects, as reported earlier, inadequate vaccination coverage and a need for its acceleration to avert HBV transmission and the flare-ups of outbreaks of other vaccine-preventable diseases.<sup>33</sup> Yet, it is evident that the current protective level of Anti-HBs among the children population cohort is significantly higher than that of the mothers' cohort, indicating the progressive trend of increasing population immunity against the burden of chronic liver disease.

In the present study, the risk of MTCT is revealed by the eight-fold increase in HBV infection among infants born to HBsAg positive mothers relative to infants born to HBsAg negative mothers and by the rise of this risk to 17 folds if the mother was also HBeAg positive. The perinatal transmission of HBsAg at 5.4% and the relatively high proportion of HBeAg positive mothers corroborate the reported imminent risk of these mothers to pass the infection to their offspring.<sup>8,23,24,26,27,33</sup> This epidemiological situation is aggravated by the absence of a hepatitis B vaccine birth dose policy in the country. The effect of this epidemiological situation has been described by other research studies, confirming that in HBsAg positive women without proper preventive measures against the risk of vertical transmission, 40%-90% of their offspring will acquire HBV infection, approximately 90% of these will develop chronic HBV infection with a 15%-25% risk for premature death from chronic liver disease, including hepatocellular carcinoma (CDC).<sup>34</sup> To prevent this high burden of HBV infection, the federal and provincial governments of Pakistan ought to consider the revision of the national hepatitis B vaccination policy with the major public health imperative of promptly preparing for the universal and timely administration of a free birth dose of hepatitis B vaccine.

Screening for maternal HBsAg and a birth dose for

children born to HBsAg positive mothers with the addition of hepatitis B immunoglobulin (HBIG) within 24h of birth was considered to be the most effective way to prevent HBV infection.<sup>7,27,34</sup> However, it is important to recognise that in Pakistan the logistical challenges and cost implications inherent to prescreening and HBIG administration are immense. Moreover, HBV infection cannot be viably prevented by identifying infants born to HBsAg positive mothers and giving them a birth dose of hepatitis B vaccine or by screening pregnant women for HBsAg as many children still get infected with the virus despite their mother being HBsAg negative.<sup>23-25,35</sup> The latter is corroborated by our findings, where in children born to HBsAg negative mothers, no significant difference was found in HBV infection rate between the vaccinated and the unvaccinated infants. This substantiates the need for the birth dose even if a pregnant woman does not have hepatitis B. Universally a free hepatitis B vaccine birth dose is to be provided to every newborn in addition to the three-dose hepatitis B vaccination currently administered through the national immunisation system. This vaccination strategy is required in order to achieve optimal prevention of HBV infections in the country as alternative strategies targeting adolescent and adult risk groups have failed to control hepatitis B adequately.<sup>1</sup>

A major factor impeding the effective implementation of this strategy and the timely coverage of a large number of infants with hepatitis B vaccine birth dose is the fact that close to 60% of the mothers in Pakistan choose to give birth at home as well as the weak EPI management capacity at the district level. Accordingly, specific provincial and district level supported strategies will be required to address the emerging logistical challenges that include the creation of sufficient cold chain storage facilities for the coverage and timely delivery of the vaccine to remote rural communities and populous poor urban slums. The national health system of Pakistan should take advantage of the service delivery capacities of the over 100,000 LHWs, strongly imbedded in the communities and providing direct antenatal services at the grassroot level.<sup>36</sup> The LHWs engagement in the EPI in general and in the administration of the hepatitis B vaccine birth dose in particular is a necessary step to be taken to create a reliable system capable of delivering the timely scheduled birth dose to the target population. This strategy is operationally viable as many LHWs have been effectively trained in conducting vaccination sessions, while many others are in the course of being inducted in district and sub-district level training programmes. Moreover, hepatitis B vaccine being stored in the EPI cold chain at 2-8 degrees°C and having reliable heat stability can effectively be used even after its exposure to the

ambient temperature during the home-visits of the LHWs to the newborns of their catchment area communities.<sup>37</sup>

Hepatitis B viral infection is endemic in Pakistan and the risk of perinatal transmission cannot be ignored as it leads to high rates of chronic HBV infection and complications of chronic liver disease. In view of the corroborated significant MTCT in Pakistan, the health sector has to introduce a universal and timely coverage with hepatitis B birth dose vaccination administered soon after birth and within the first 24 hours. This proposal was recommended in 2010 by the World Health Organisation (WHO) Eastern Mediterranean Regional Committee to its member states including Pakistan.<sup>38</sup> In all rural and remote population settlements, the hepatitis B birth dose strategy may be pursued as this will ease vaccine related logistic challenges, minimise wastage and enable the LHWs to timely vaccinate every newborn. This effort should be an integral part of an accelerated national programme of routine immunisation, with strong policy commitment and advocacy at federal, provincial and district levels. The government has to promote inter-provincial equity and inter-sectoral co-ordination and collaboration in the fight against vaccine-preventable diseases. Serious efforts are also required to re-engage local communities and families in the planning, implementation, surveillance and monitoring of the EPI services for ensuring the universal coverage and timely administration of the hepatitis B vaccine birth dose. With these combined efforts the vertical transmission of hepatitis B virus infection will effectively be controlled and the goal towards the elimination of HBV infection in Pakistan shall be made possible.

## Conclusion

Hepatitis B vaccination at 6, 10 and 14 weeks of birth is not sufficiently protective. The situation indicates a strong need for the introduction of birth dose into the overall immunisation mechanism.

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