Hepatitis B Virus in Bangkok Families
Study Sample and Analysis of Infections

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OBJECTIVE : To determine when urban Thai children are first exposed to hepatitis B virus (HBV) and to search for the factors that influence transmission to infants during the first year of life.

BACKGROUND : This is a report of the long-term follow-up of the offspring of mothers who have Hepatitis B surface Antigen (HB_SAg), antibody to HB_SAg (anti-HB_S), or are negative for both.

DESCRIPTION : The study design was described earlier (1). To the basic tests for HB_SAg and anti-HB_S was added an immunodiffusion test of serum for e-antigen and antibdy (2). Antibody to Hepatitis B core Antigen (anti-HB_C) was determined on selected mothers' sera by radioimmune assay at WRAIR. The family follow-up period was extended to 24 months in order to detect HBV infections of infants during the second year of life.

PROGRESS : From 1 February 1974 to 31 January 1975, there were 2450 live births at Phra Mongkutklao Hospital, 1040 mothers (42.4%) were interviewed and bled. In order to describe the overall population of mothers who delivered babies at Phra Mongkutklao, all mothers with study numbers ending with 0, 3, 5, and 6 were tested for HB_SAg by counterimmunoelectrophoresis and RIA and anti-HB_S by PHA. The results of these tests were compared to females of similar age from Huay Khwang who were (previously) tested with these methods (3). In general, the prevalence of HB_SAg was similar to that of Huay Khwang but antibody was less frequently found (Table 1).

Study Sample

Although the intention was to follow the infants of 30 mothers with HB_SAg, 30 with anti-HB_S and 60 negatives, this was not possible due to mistaken original classifications and study dropouts. Several mothers who were negative for anti-HB_S by RIA and PHA were later found to have anti-HB_S at the time of delivery by AUSAB RIA. In addition, of 154 families selected for follow-up, 22 (14%) could not be adequately followed. The final study group consisted of 31 mothers with HB_SAg, 52 with anti-HB_S and 49 negatives. The final distribution was not considered detrimental to the interpretation of the results.

HBV Infections of Infants

During the first 12 months of follow-up, only infants of HB_SAg positive mothers became infected. Of the 31 infants with antigenemic mothers, 15 (48%) developed HB_SAg and/or anti-HB_S by the age of nine months (Figure 1). Two infants had high concentrations of HB_SAg in their umbilical cord serum and remained persistently positive thereafter. Seven and five other infants were infected by ages three and six months, respectively. Nine of the infected infants (60%) developed persistent antigenemia. None of the infected infants developed overt signs of acute hepatitis.

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Of the 52 infants of mothers with anti-HB_S, all but one had detectable antibody in the cord blood. The frequency of anti-HB_S declined steadily throughout the 12 month period (Figure 1). None of these infants had detectable HB_SAg or had lost and regained anti-HB_S during the first year. Similarly, none of the 49 infants of negative mothers showed evidence of infection with HBV.

At the beginning of the study, the mothers were divided into three groups on the basis of their serological test results. After the period of follow-up, four groups were differentiated : HB_SAg positive mothers with non-infected infants (16) ; anti-HB_S positive mothers (52) ; and negative mothers (49). Analysis of factors influencing HBV transmission was based on these four study groups.

HBV Infections of Other Family Members

HBV infections among the family contacts of the infants included persons infected before, during, and after the birth of the infant (Table 2). Family contacts included anyone living in the home, such as relatives, maids or friends. Persons having no detectable HB_SAg or anti-HB_S at the time of the infant's birth were considered susceptible to infection. The greatest frequency of antigen carriers and fewest susceptible contacts were found in the families of the infants infected.

New infections of family contacts were infrequent and only occurred in four members of two families (Table 3). In one family (No. 97) there were 10 members. The mother had anti-HB_S at delivery and for 12 months, the infant had anti-HB_S until age 39 weeks. At the time of the infant's birth, an uncle was antigenemic and had elevated serum transaminase valnes. During the following 12 months, a 7 year-old sister and a 2 year-old brother developed anti-HB_S. A 22 year-old sister-in-law developed hepatitis with HB_SAg and elevated serum transaminase values.

In another family (No. 89), with five members, the mother and infant were negative for HB_SAg and anti-HB_S. A 3 year-old brother had persistent asymptomatic antigenemia. Another brother seroconverted at the age of 2 years. Although the only infants to be infected in this study had antigenemic mothers, older siblings were sometimes infected when other persons in the family had HB_SAg. Thus, horizontal transmission of HBV occurred occasionally in older siblings.

Environmental Factors

The 132 families lived in homes scattered widely throughout the city in a distribution that was more representative of the maternity patients of the hospital than of the total population of Bangkok (Figure 2). Eighty two percent of the families lived in houses, 17% in apartment buildings (Table 4). Seventy one percent of the homes had one or two rooms, 27% had three or four rooms. Houses were usually wooden and had one or two floors and no basements. Apartments tended to be less than five stories high and were made of concrete block construction and wood.

No statistical differences were found between the groups with regard to the use of electricity, bottled gas, charcoal cooking fuel, source of drinking water, storage and preparation of drinking water, the number of indoor toilets and the type of sewage disposal. In addition there were no apparent differences in the method of food preparation, or cleaning of eating utensils. The most typical household description was as follows. The family lived in a house (82%) with less than three floors (71%) that had electricity (61%), bottled gas (31%), and cooked over charcoal (70%). City tap water was used for drinking (83%) and was boiled before consumption (96%) The families had an indoor toilet (92%) The mother prepared the food (81%) and washed vegetables with tap water (77%). The mother washed the dishes (84%) with tap water which was not previously treated (98%)

The mother provided the principal care for the baby in 83% of all families and 93% of the babies that were infected. Nearly all of the mothers (95%) indicated an intent to breast feed their babies.

Antigenemic mothers were more apt to breast feed for shorter periods and less frequently per day than those without antigenemia (Table 5). By the age of six weeks, most infants received supplemental baby food (51%), liquid formula (60%) and drank boiled water (94%)

None of the characteristics studied of the physical home environment were associated with HBV infections of infants.

Personal Contacts of Infants

Although the families were nearly equal in size, there were striking differences in the frequencies of HB_SAg carriers (Table 6). In families of infants who were infected, 60% of the household contacts were antigenemic. In families where the mother had antigen but the infant was not infected, only 45% of the household contacts had antigen. The difference was due to a larger number antigenemic siblings in the first group.

In families of mothers with anti-HB_S, antigen carriers were four times as frequent as in the families of negative mothers. This difference suggests that children born with maternal antibody may be at greater risk of infection after they lose the antibody than children of negative mothers.

The study was based on the assumption that, regarding infection of infants with HBV, the mother was the most important contact for the infant. This assumption was supported by the relative frequency of infant infections when individual relatives were considered (Table 7). The results suggest that an antigenemic mother is more important than an antigenemic father and that antigenemic siblings may indicate the infants at greatest risk.

Mothers with HB_SAg

Sixteen mothers with HB_SAg were tested for anti-HB_C; all were positive (Table 8). In addition, one of 12 negative mothers had anti-HB_C. The infant of the HB_SAg negative mother with anti-HB_C did not become infected.

Twenty-eight mothers with HB_SAg were tested for e-antigen (Table 9). e-Antigen was more frequently found in mothers with infected infants although two mothers with e-antigen did not have infected infants. The mother's serum CF titer of HB_SAg at the time of delivery was closely associated with infection of the infant (Table 10).

Predictability of HBV Infection in Infants

The following factors are associated with HBV infection during the first nine months of life:

1. Mothers with HB_SAg
2. Mothers with serum titers of HB_SAg 1:64
3. Mothers with detectable e-antigen
4. HB_SAg positive siblings
5. Concentrations of HB_SAg in the umbilical cord blood detectable by counterimmunoelectrophoresis.

Impact of Infant Infections on the Adult Carrier Population

Any estimate of the contribution of infant infections to the adult carrier population must be based on three assumptions. First, that over the period of at least one generation approximately the next 25 years) the factors affecting the transmission of HBV within the Bangkok population will remain constant, so that the prevalence of adult carriers of HB_SAg will remain the same. Secondly, all infants who become chronic carriers will remain antigenemic until they reach child-bearing age. Thirdly, the mortality rates of children and young adults with HB_SAg are the same as for those without antigen.

Using these assumptions and the observations from this study, it is apparent that HBV infections during the first year of life can not account for more than 28% of the adult carriers (Table 11). Conversely, up to 72% of the adult carriers in Bangkok are due to infections after the age of one year. Infections after the age of one year may be prevented by an effective vaccination program in the future.

SUMMARY : An analysis has been completed of the effect of HBV infections on infants and the factors influencing infection during the first year of life. All of the infected infants were asymptomatic and 60% developed persistent antigenemia. The factors most closely associated with infant infection were: an antigenemic mother; antigenemic siblings; e-antigen in the mother's serum; and a high CF titer of HB_SAg in the mother's serum. Evidence was found of horizontal HBV transmission among members of two families in which neither the mother nor the infant were infected. Only a minority of adult female antigen carriers can be accounted for by infant infections. The family follow-up period has been extended to two years to more clearly determine the frequency of HBV infections in youngsters.

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Table 1. Frequency of HB_SAg and Anti-HB_S in Bangkok Females

Source	Age Group	HB_SAg			Anti-HB_S		
		No. Tested	RIA +		No. Tested	PHA +	
			No.	%		No.	%
PMKH	15 - 19	96	6	6.3	59	20	33.9
	29 - 29	282	17	6.0	206	66	32.0
	30 - 39	23	0	0.0	20	7	35.0
	40 - 49	1	0	0.0	1	0	0.0
	Total	402	23	5.7	286	93	32.5
Huay Khwang[1]	15 - 19	54	3	5.6	52	21	40.4
	20 - 29	71	4	5.6	67	28	41.8
	30 - 39	53	4	7.5	51	31	60.8
	40 - 49	56	3	5.4	52	33	63.5
	Total	234	14	6.0	222	113	50.9

[1]Data abstracted from Grossman, et al. Amer. J. Epidemiol. 101:144 - 159, 1975

Table 2. Frequency of HB_SAg and Anti-HB_S in Family Contacts of Study Infants

Mother's Category	No. Families	Family Members							
		No.	Mean	HB_SAg		Anti-HB_S		Negative	
				No.	(%)	No.	(%)	No.	(%)
HB_SAg-I*	15	42	2.8	25	(60)	15	(36)	2	(4.8)
HB_SAg	16	47	2.9	21	(45)	10	(21)	16	(34)
Anti-HB_S	52	166	3.2	21	(13)	99	(60)	46	(28)
Negative	49	167	3.2	4	(2.5)	58	(37)	100	(64)
Total	132	412	3.1	71	(17)	177	(43)	164	(40)

* HB_SAg carrier mothers who transmitted to their infants

Table 3. New HBV Infections in Family Contacts

Family Number	No. Members	Mother's Category	Person Infected (Age)	Time of Follow up	HB_SAg	Anti-HB_S	SGOT* / SGPT
97	10	Anti-HB_S	Uncle (35)	At birth	Yes	NF**	305/95
			Sister (7)	28 weeks	No	Yes	39/15
			Brother (2)	56 weeks	No	Yes	29/10
			Sister-in-law (22)	56 weeks	Yes	Yes	402/294
89	5	Negative	Brother (3)	At birth	Yes	No	107/28
			Brother (1)	52 weeks	No	Yes	49/18

* Transaminase values at time seroconversion noted
** NF - not followed

Table 4. Type of Dwelling

Mother's Category	Number of Dwellings	House	Apartment	Shop
HB_SAg-(I)	15	.87*	.13	.00
HB_SAg	16	.88	.13	.00
Anti-HB_S	52	.79	.19	.02
Negative	49	.82	.16	.02
Combined	132	.82	.17	.02

*Proportion of dwellings

Table 5. Diet of Infants at Age 6 Weeks

Questionnaire	HB_SAg-I	HB_SAg	Anti-HB_S	Negative
Number of Infants	15	16	52	49
Intent to Breast Feed				
Yes	87%	94%	96%	96%
Duration Breast Feeding				
(O or 6 wk)	46%	50%	31%	31%
No. Breast Feedings per day				
1-5	51%	62%	43%	49%
6 or more	47%	38%	58%	52%
No. Formula Feedings per day				
None	27%	25%	37%	29%
1-5	20%	25%	25%	30%
6 or more	46%	50%	38%	40%
Other Baby Food				
Yes	47	32	60	49
No	53	69	40	51

Table 6. Household Contacts of 132 Infants

Mother's Category	No. of Families	Household Contacts		HB_SAg+ Contacts	
		No.	Mean	No.	(%)
HB_SAg - (I)	15	42	2.8	25	(60)
HB_SAg	16	47	2.9	21	(45)
Anti - HB_S	52	165	3.2	21	(13)
Negative	49	157	3.2	4	(3)
Combined	132	411	3.1	71	(17)

Table 7. Frequency of Infant HBV Infections Related to Family Contacts

Family Member with HB_SAg	Infants at Risk*	Infants Infected	
		No.	(%)
Father	8	2	(25)
Mother	31	15	(48)
Sibling	6	4	(67)
Mother and Sibling	5	4	(80)

*Infants with maternal antibody are excluded

Table 8. Frequency of Hepatitis B Core Antibody* in Mothers

Mother's Category	No. Tested	Anti - HB_C	
		No.	%
HB_SAg - (I)	9	9	(100)
HB_SAg	5	5	(100)
Anti - HB_S	1	0	(0)
Negative	12	1**	(8)

* Tests performed by Dr. G.R. Irwin, WRAIR, Washington, D.C.

** Infant did not become infected

Table 9. Frequency of e Antigen in Mothers with HA_SAg

e Antigen	Mothers No.	Infected Infants	
		No.	(%)
Positive	8	6	(75)
Negative	20	8	(40)
Total	28	14	(50)

Table 10. Complement Fixation Titers of HB_SAg Positive Mothers

Serum HB_SAg CF Titer*	Mothers No.	Infected Infants	
		No.	(%)
$\leq$ 1:32	15	2	(13)
$\geq$ 1:64	13	12	(92)
Total	28	14	(50)

* At time of delivery of infant
Chi square = 14.35
$p < .001$

Table 11. Estimation of the Proportion of Adult HB_SAg Carriers that are Due to Infection During Infancy

Frequency of HB_SAg + mothers at PHMH	5.7%
Frequency of HBV infection in infants	48%
Frequency of infected infants becoming chronic carriers	60%
Prevalence of chronic HB_SAg carriers among children of mothers delivering at PMKH:	
$5.7\% \times .48 \times .60 =$	1.6%
Proportion of adult HB_SAg carriers caused by infant infections	
$\frac{1.6\%}{5.7\%} = 0.28 =$	28%

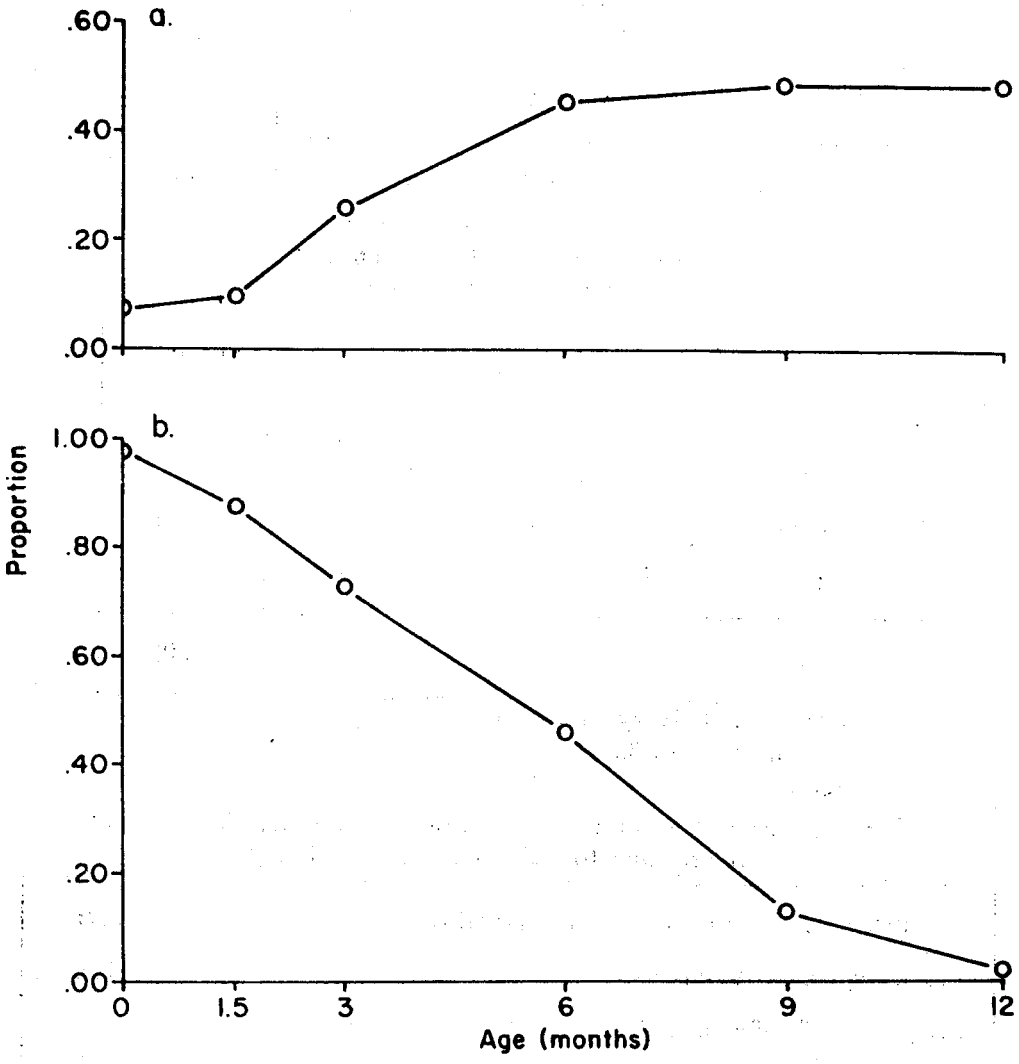

Figure 1. Infants with HB_sAg or anti-HB_s during the first year of life.
a. 31 Infants of HB_sAg positive mothers.
b. 52 Infants of anti-HB_s positive mothers.

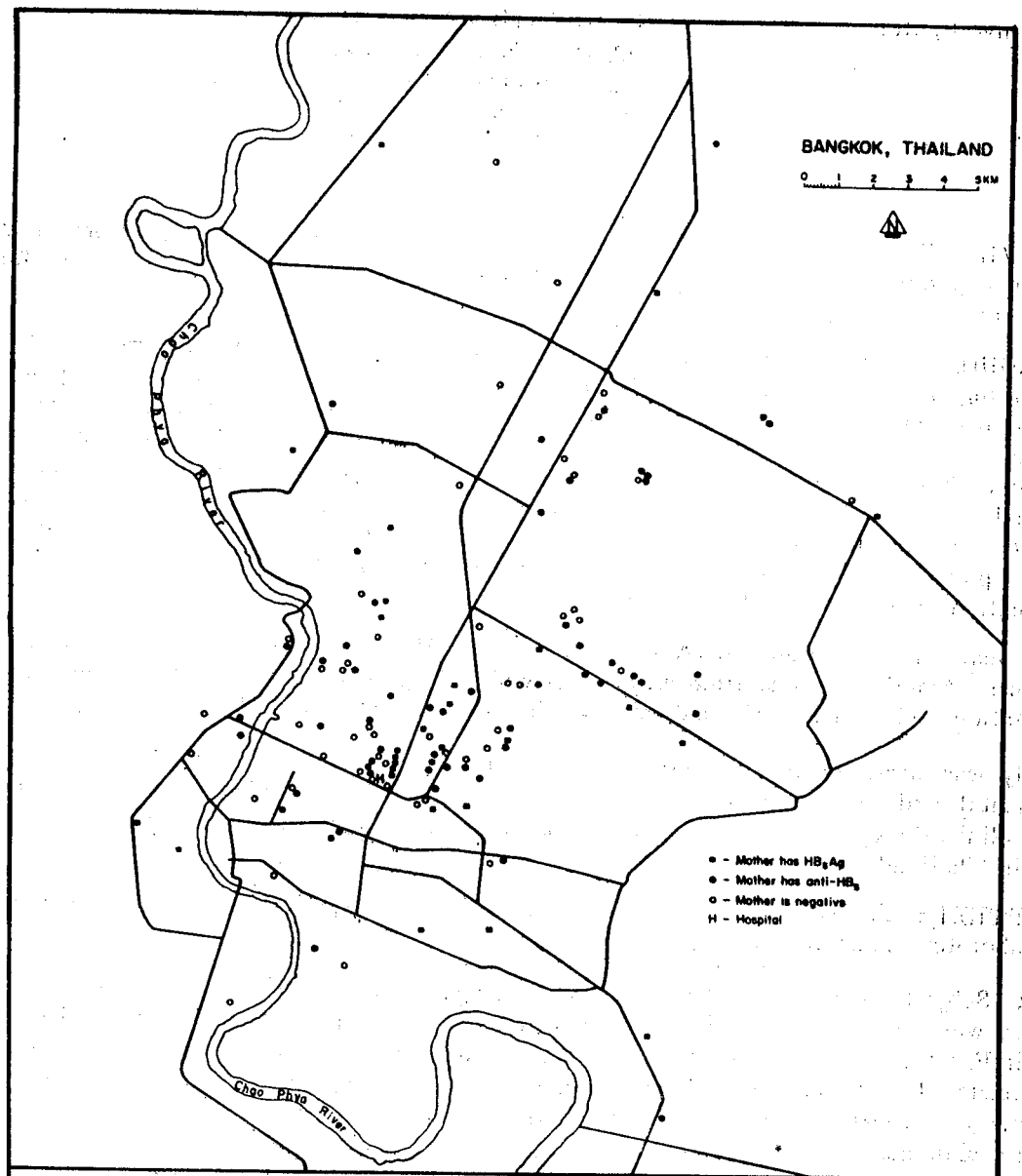

Figure 2 Map of Bangkok showing the locations of houses of 131 study families. One additional family with a negative mother was located to the east of the area shown.