Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China

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Abstract

China has one of the highest rates of hepatitis B virus (HBV) endemicity in the world. In a survey of five provinces, the overall HBV infection rate in the general population was found to be 42.6%, with 10.3% testing positive for hepatitis B surface antigen (HBsAg). Higher rates were found in rural than in urban areas. The prevalence of HBsAg among children under 1 year of age is quite low but increases rapidly thereafter, reaching a peak among 5 to 9 year olds. The pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood, and the proportion of chronic HBsAg carriage attributable to perinatal transmission has been estimated at only 13-20%. Contact with infected family members probably accounts for much of the horizontal transmission in children. In a nationwide survey, 27.2% of families were found to have one or more HBsAg positive members and a strong tendency for family clustering has been identified. The strategy for prevention of HBV infection includes vaccination of all newborns, whether their mothers are HBsAg positive or negative, together with vaccination of high risk populations, and improved control measures in clinics and blood transfusion centres.

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China has one of the highest rates of hepatitis B virus (HBV) endemicity in the world, with an estimated 150 million hepatitis B surface antigen (HBsAg) carriers nationwide. Most chronic carriers of HBsAg are infected during early childhood, emphasising the importance of both perinatal and horizontal transmission. Assessment of the routes of HBV transmission is essential for the establishment of an appropriate strategy for prevention and vaccination.

Prevalence of HBV infection in China

The reported prevalence of HBV infection and HBsAg carrier rates vary according to the particular population samples and ethnic groups studied, and the detection methods used. In a survey carried out in 1979, a total of 277 186 subjects (138 360 males and 138 826 females), sampled from 209 counties and cities in 29

provinces, municipalities, and autonomous regions, were investigated using the RPHA method.¹ The overall standardised prevalence of HBsAg positivity was reported to be 8.8% (range 3.8% to 16.8%), with a higher rate in rural (10.2%) than in urban (7.9%) areas. As the RPHA method is comparatively insensitive, a further study was carried out using RIA.² A total of 4039 serum samples taken from subjects in five provinces were investigated. The overall HBV infection rate was found to be 42.6% (range 35.5-61.6%), with an HBsAg carrier rate of 10.3% (range 7.4-15.4%).² Between 1984 and 1987, another seroepidemiological study of hepatitis B was carried out in four provinces.³ In total, 10 484 serum samples were collected and tested by RIA. Positivity rates for HBsAg and for any HBV marker were 10.1% and 58.2%, respectively (Table I).³ The highest carrier rate was found among children under 3 years of age, and the highest annual increase in HBsAg positivity also occurred in this age group. Two peaks of HBsAg positivity were recorded, in children aged 2 to 8 years and adults aged 35 to 40 years. The average positivity rate for anti-HBs antibodies was 32.2% and increased with age as a result of the combined impact of both perinatal and horizontal transmission. The lowest ratio of HBsAg to anti-HBs positivity was seen in children aged 3 years or less, who were therefore at the highest risk of infection and of becoming chronic carriers.

Perinatal versus horizontal transmission

According to a nationwide epidemiological survey in 1979 to 1980, the prevalence of HBsAg carriage among children under 1 year of age is comparatively low (3.2%). From 1 to 4 years of age, however, it increases rapidly to 8.9%, reaching of >10% among 5 to 9 year olds.¹ Similar results were shown in another study during 1984 to 1987.³ This pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood. The relative importance of horizontal and perinatal transmission has been investigated in a study carried out in four provinces.⁴ The study population comprised 4500 children and mothers, all of whom were tested for HBsAg positivity. The results showed that children born to HBsAg positive mothers ran a significantly higher risk of becoming HBsAg positive themselves than those born to HBsAg negative mothers, with a relative risk ratio (RR) of 5.3 (Table II). This could be attributed to the combined effects of

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TABLE I *HBV prevalence in inhabitants of four provinces*³

Age (y)	Number tested	HBsAg+ve n (%)	Anti-HBs+ve n (%)	Anti-HBc+ve n (%)	HBV+ve n (%)	HBsAg: anti-HBs ratio
0-	131	5 (3.8)	8 (6.1)	15 (11.5)	20 (15.3)	1:1.6
1-	229	20 (8.7)	22 (9.6)	37 (16.2)	50 (21.8)	1:1.1
2-	256	32 (12.5)	23 (9.0)	52 (20.3)	70 (27.3)	1:0.7
3-	286	31 (10.8)	27 (9.4)	57 (19.9)	80 (28.0)	1:0.9
4-	262	32 (12.2)	42 (16.0)	72 (17.5)	91 (34.7)	1:1.3
5-	244	28 (11.5)	49 (20.1)	80 (32.6)	97 (39.8)	1:1.8
6-	266	25 (9.4)	52 (19.6)	74 (27.8)	104 (39.1)	1:2.1
7-	285	36 (12.6)	75 (26.3)	109 (38.3)	147 (51.6)	1:2.1
8-	238	26 (10.9)	65 (27.3)	111 (46.6)	130 (54.6)	1:2.5
9-	231	22 (9.5)	74 (32.0)	98 (42.4)	128 (55.4)	1:3.4
10-	1289	127 (9.9)	422 (32.7)	554 (42.9)	725 (56.3)	1:3.3
15-	1113	126 (11.3)	399 (35.9)	555 (49.9)	698 (62.7)	1:3.2
20-	898	73 (8.1)	302 (33.6)	400 (44.5)	524 (58.4)	1:4.1
25-	887	91 (10.3)	310 (34.9)	412 (46.5)	565 (63.7)	1:3.4
30-	972	102 (10.5)	323 (33.2)	455 (46.8)	590 (60.7)	1:3.2
35-	672	85 (12.7)	242 (36.0)	365 (54.3)	457 (68.0)	1:2.8
40-	507	65 (12.8)	195 (38.5)	278 (54.8)	364 (71.8)	1:3.0
45-	131	48 (11.1)	192 (44.6)	243 (56.4)	316 (73.3)	1:4.0
50-	730	67 (9.2)	279 (38.2)	393 (53.8)	502 (68.8)	1:4.2
60-	557	34 (6.1)	201 (36.1)	321 (57.6)	383 (68.8)	1:5.9
Total	10484	1076 (10.3)	3302 (31.5)	4681 (44.7)	6041 (57.6)	1:3.1
Adjusted rate (%) [*]		10.1	32.2	45.5	58.2	1:3.2

^{*}Prevalence adjusted according to baseline age structure estimated in 1982 from national census statistics.

horizontal and perinatal transmission. It was estimated that the proportion of chronic HBsAg carriage attributable to perinatal transmission ranged from only 13% to 19.6%.^{4,5} Furthermore, HBsAg carrier children of HBsAg positive mothers accounted for only 32.3% of the entire carrier population. Horizontal transmission therefore seems to outweigh perinatal transmission as a risk for HBV infection in China. Attempts to prevent perinatal transmission of the virus should thus be combined with simultaneous strategies to prevent horizontal transmission.

Possible mechanisms of horizontal transmission

According to the study described earlier, at least 80% of chronic carriers of HBsAg are infected via horizontal transmission, with most being infected during early childhood.⁴ Close contact with infected family members, particularly the mother, is probably the major source of infection. Other important routes of infection in children include close contact with other HBsAg positive infants and injections with inadequately sterilised syringes. In young adults, medical procedures such as injections, dental treatments, surgery, and acupuncture may be important routes of HBV transmission. Sexual contact with infected spouses and blood transfusions are other possible sources.

TABLE II *Prevalence of HBsAg among children born to HBsAg positive or negative mothers*⁴

Region	Age (y)	Born to HBsAg-ve mothers		Born to HBsAg+ve mothers		RR
		Number tested	HBsAg+ve n (%)	Number tested	HBsAg+ve n (%)	
Shanghai	0-	186	10 (5.4)	23	5 (21.7)	4.0
	10-	89	3 (3.4)	25	9 (36.0)	10.7
	>20	472	51 (10.8)	39	20 (51.3)	4.8
Hebei	1-	478	49 (10.1)	49	17 (34.7)	3.4
	10-	694	35 (5.0)	53	12 (22.6)	4.5
	>20	353	16 (4.5)	24	6 (25.0)	5.5
Heilong-jiang	0-	489	24 (4.9)	44	18 (40.9)	8.3
	7-18	982	58 (5.1)	91	35 (38.5)	6.5
Sichuan	3-5	371	37 (9.8)	38	19 (50.0)	5.0

$X_{M-H} = 320.9$, $RR_{M-H} = 5.3$, $X_{M-H} = X_{Mantel-Haenszel} (\chi^2 \text{ test})$.

At present, neither homosexual activity nor intravenous drug abuse are responsible for HBV infection in China, but careful monitoring is advisable. The most likely routes of transmission are discussed in more detail below.

INTRAFAMILIAL TRANSMISSION

In a nationwide survey, 19 421 families were investigated, 5305 (27.2%) of which were found to have one or more HBsAg positive members.⁶ Analysis of the intrafamilial distribution of HBsAg using a binomial model suggested a strong tendency for family clustering.⁶ The overall family clustering rate of HBsAg in China was found to be 37%, with a higher rate in rural (37.8%) than in urban (33.6%) areas.⁶ The clustering rate was also found to be directly proportional to the general prevalence of HBsAg positivity in most provinces. Within families, the HBsAg carrier rate in children was closely related to their parents' HBsAg status, particularly in rural areas (Tables III and IV).

TRANSMISSION IN NURSERY AND KINDERGARTEN

HBV infection may be transmitted through close contact between carriers and non-infected children in nurseries and kindergartens. A report from Sichuan Province of 1167 children attending a seven day kindergarten during the period 1985 to 1986 indicated an HBV marker prevalence of 41.3% and an HBsAg positivity rate of 12.7%. After one year of follow up, the annual HBV infection rate among 448 susceptible children was found to be 13%, with 3.8% remaining HBsAg positive. The number of newly infected children was directly correlated to the number of HBsAg carriers present in each classes ($p < 0.05$).⁷

TRANSMISSION VIA INADEQUATELY STERILISED SYRINGES AND ACUPUNCTURE NEEDLES

An investigation into the relation between HBV infection and disinfection of needles and syringes was carried out in a six year study in a village in Hebei Province.⁸ This village, with 4000 inhabitants, has two small poorly equipped outpatient clinics where five private practitioners work. The investigators found that hypodermic needles were being changed between patients but not the syringes. During the period 1984 to 1986, positivity rates for HBV markers and HBsAg were 39.4% and 20.9%, respectively, in 1 year olds and 36.9% and 11.6% in 2 year olds. Besides mother to infant transmission, this high prevalence of HBV infection may also be attributed to frequent vaccinations and therapeutic injections using unsterilised syringes during early childhood. Between 1987 and 1990, stricter measures were taken to prevent HBV infection in these clinics, including training of medical personnel, provision of sterilised syringes, needles and transfusion sets, and the use of sterilised syringes and needles for single injections. After the introduction of these measures,

TABLE III Relation between HBsAg status of parents and that of their children⁶

HBsAg status of parent	No of children tested	Children HBsAg+ve n (%)	Children anti-HBs+ve n (%)	Total HBsAg+ve or anti-HBs+ve n (%)
Father and mother both positive	452	199 (44.0)	17 (3.8)	216 (47.8)
Mother only positive	2697	1035 (38.4)	129 (4.8)	1164 (43.2)
Father only positive	2979	536 (18.0)	173 (5.8)	709 (23.8)
Father and mother both negative	26173	2409 (9.2)	1179 (4.5)	3588 (13.7)
Total	32301	4179 (12.9)	1498 (4.6)	5677 (17.6)

the HBsAg carrier rate in infants born to HBsAg negative mothers fell from 15.4% to 3.3% in 1 year olds and from 11.6% to 2.1% in 2 year olds, a statistically significant difference in each case ($p < 0.001$).⁸ The results suggest that inappropriate use of needles and syringes is a major route of HBV transmission.

TRANSMISSION VIA TRANSFUSION OF BLOOD AND BLOOD PRODUCTS

Since 1973, blood donors and blood products have been screened for HBsAg. The standard method at present is an EIA kit incorporating national quality control reference panels. After the introduction of HBsAg screening, the incidence of post-transfusion hepatitis B fell considerably but has not yet been reduced to zero. In one study, for example, all 70 HBV negative transfusion recipients were given HBsAg negative blood (tested by RIA), yet one patient still developed acute hepatitis B three months later.⁹ Screening for anti-HBc would be of no practical value in preventing transmission of HBV because around 55–65% of the general population in China are anti-HBc positive.

TRANSMISSION BETWEEN SPOUSES

An interesting study has been carried out to determine the impact of sexual contact on HBV infection among newly married couples.¹⁰ Fifty seven couples comprising one HBsAg/anti-HBc positive partner and one HBV marker negative (that is, susceptible) partner were included in the study. A further 61 couples, all of whom were negative for HBV markers, were enrolled as a control group. The observation period ranged from 24 to 31 months (average 27 months). At the end of the study, the HBV infection rate was 62.6% among previously negative partners in the study group, with 14% remaining HBsAg positive. In contrast, the incidence of HBV infection in the control group was 16%, with an HBsAg positivity rate of only 1.6%. The RR between these two groups was 8.6 for HBsAg

and 3.1 for HBV infection, a statistically significant difference ($p < 0.01$).¹⁰

HBV INFECTION AMONG MEDICAL PERSONNEL

Medical personnel are considered to represent a high risk population for HBV infection. However, a number of surveys have shown that the prevalence of HBsAg is no higher among such people than among the general population, although more are anti-HBs positive. During a four year study of 667 medical and nursing students (two years in school and two years after graduation), the HBV infection rate increased from 3.8% at baseline to 11.2% at the end of the study and the HBsAg positivity rate increased from 0.5% to 4.0%.¹¹ The HBsAg positivity rate among those who had experienced medical injuries (for example, needle sticks) or undergone medical procedures (for example, intravenous infusion, acupuncture, and tooth extraction) was higher than in those without such a history and was directly related to the number of exposures.¹¹

Strategy for prevention of HBV infection in China

The basic strategy for the prevention of HBV infection in China is the introduction of HBV vaccination into the national Expanded Programme on Immunisation (EPI), and vaccination of certain high risk groups. In addition, strict sterilisation of all medical instruments, syringes, and needles (including acupuncture needles), together with screening of blood donors and blood products and control of iatrogenic infections are all important preventive measures. At present, there is no general policy for vaccination of adolescents or adults.

VACCINATION OF NEWBORNS

All newborns and young children are to be vaccinated against hepatitis B, whether their mothers are HBsAg positive or negative. Because less than 20% of all chronic HBV infection is reported to result from perinatal infection and only 32% of carriers born to HBsAg positive mothers are HBsAg positive due to the combined impact of perinatal and horizontal routes of infection,^{4,5} vaccination only of those infants born to HBsAg positive mothers is insufficient for complete control of HBV infection.¹² A trial hepatitis B vaccination programme was carried out in the southern district of Shanghai city, with a population of approximately 780 000 and an annual birth rate of around 10 000.¹³ Between 1986 and 1990, more than 95% of newborns in this area were vaccinated with plasma derived HBsAg vaccine. The HBsAg carrier rate among young children fell from 9.4% before vaccination to 0.9% after four years, with a protection rate of 89.6%.¹³ During the period 1988 to 1990, a nationwide hepatitis B vaccination programme was introduced, and was made possible by sufficient supplies of domestically produced plasma derived or recombinant hepatitis B

TABLE IV Relation between HBsAg status of parents and that of their children in urban and rural areas⁶

HBsAg status of parents	Urban		Rural		p Value
	No of families tested	Families with HBsAg+ve children n (%)	No of families tested	Families with HBsAg+ve children n (%)	
Father and mother both positive	24	10 (41.7)	129	97 (75.2)	<0.001
Mother only positive	163	87 (53.4)	839	505 (60.2)	>0.05
Father only positive	162	42 (25.9)	931	400 (43.0)	<0.001
Father and mother both negative	2161	360 (16.7)	7530	2034 (27.0)	<0.001
Total	2510	499 (19.9)	9429	3036 (32.1)	<0.001

vaccine.^{14 15} Anti-HBs responses to the vaccine are shown in the paper by Professor Yao Jilu (see pages S37–S38).

VACCINATION OF HIGH RISK GROUPS

For high risk groups, such as medical or laboratory workers, blood centre and blood products workers, and newly married people with HBsAg positive spouses, a full course of hepatitis B vaccine should be given. There are convincing data for the efficacy of hepatitis B vaccine in protecting newly employed medical personnel.¹⁶ Among 220 HBV negative student nurses given three doses of hepatitis B vaccine, not one developed HBV infection or became HBsAg positive during the 24 month follow up period. In contrast, two of 234 non-vaccinated students became positive for HBsAg and anti-HBc (one experiencing acute hepatitis) and nine became anti-HBs or anti-HBc positive, or both, giving a total infection rate of 5.8%.¹⁶ As yet, there is no evidence that vaccination has had much impact for the newly married.

Conclusion

Both perinatal and horizontal transmission play important parts in the transmission and persistence of HBV infection. In China, horizontal transmission seems to be more important. Vaccination for all neonates, young children, and high risk population groups is therefore the fundamental strategy for hepatitis

B prevention. Prevention of iatrogenic infection is also essential.

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