AN ECONOMIC EVALUATION OF UNIVERSAL INFANT VACCINATION STRATEGIES AGAINST HEPATITIS B IN THAILAND: AN ANALYTIC DECISION APPROACH TO COST-EFFECTIVENESS

Thosporn Vimolket[1] and Yong Poovorawan[2]

[1]Department of Preventive Medicine; [2]Center of Excellence in Viral Hepatitis Research, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract. To evaluate the cost-effectiveness of four infant vaccination strategies aimed at protecting the Thai population against hepatitis B virus (HBV) infection, vaccination and giving hepatitis B immunoglobulin (HBIg) to high-risk infants were compared with universal vaccination of infants and no vaccination. An analytic decision model was used to estimate the clinical and economic consequences of HBV for a hypothetical cohort of newborns for each of the immunization strategies. The model focused on the numbers and the costs of cases prevented. The decision model examined four different HBV management strategies: 1. screening for HBsAg, and vaccination; 2. screening for HBsAg, then HBeAg, and vaccination; 3. universal vaccination of all neonates; and 4. no vaccination. The cost-effectiveness per case prevented for Strategy 1 was 292.79 baht; for Strategy 2, 264.34 baht; for Strategy 3, 151.05 baht; and for Strategy 4, 0 baht. The incremental cost comparing Strategy 3 to Strategy 4 was 6,521 baht; comparing Strategy 2 to Strategy 3, 20,000 baht; and comparing Strategy 1 to Strategy 2, 95,000 baht. There is no socially acceptable threshold value for cost per case prevented to guide decisions on funding health care interventions. Strategy 3 should certainly be continued. Nevertheless, based on these results, Strategy 2 may be considered, despite the incremental cost being about 2 times that of Strategy 3, as it might represent a worthwhile investment of public funds.

INTRODUCTION

Hepatitis B virus (HBV) is one of the world's most widespread infectious agents and is the most common cause of chronic liver disease worldwide. The prevalence of hepatitis B carriers globally varies between regions. In North America and Western Europe, the prevalence is less than 0.5%; while in South America, the Middle East, and Eastern Europe, it ranges 2-7%; and in tropical Africa and Southeast Asia, it ranges 8-20% (Andre *et al*, 1994). The transmission of hepatitis B can occur horizontally, via sexual contact, the parenteral route, or skin lesions; or vertically, from mothers to infants. Vertical transmission is thought to be secondary to mucous membrane penetration around the time of delivery (Goudeau *et al*, 1983).

In countries highly endemic for HBV, such as in Southeast Asia, perinatal transmission of HBV from infected mothers to their infants often leads to severe long-term sequelae. The rate of hepatitis B transmission from mother to child is increased if the mother has had acute hepatitis B infection in the last trimester of pregnancy, or if she is carrying the hepatitis B 'e' antigen (HBeAg) in addition to HBsAg. The transmission rates are 85%, if HBeAg positive, and 15-20%, if HBeAg negative; 85-95% of infected infants become chronic carriers (Beasley *et al*, 1977, 1983; Stevens *et al*, 1979, 1985). Most neonatal infections are asymptomatic or mild. The risk for these carrier children to die in adulthood of primary hepatocellular carcinoma (HCC) or cirrhosis is approximately 25% (Shiraki *et al*, 1977; Beasley *et al*, 1982, 1984). Their deaths always coincide with maximum familial and financial responsibilities, and these children become car-

Correspondence: Prof Yong Poovorawan, Viral Hepatitis Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Tel: +66 (0) 2256-4909; Fax: +66 (0) 2256-4929
E-mail: YongP@chula.ac.th

rier mothers themselves, perpetuating the cycle of perinatal transmission (Kane *et al*, 1988).

Prevention of perinatal transmission is possible if immunoprophylaxis is administered to babies-at-risk, shortly after birth (Beasley *et al*, 1981, 1983; Tada *et al*, 1982; Wong *et al*, 1984; Stevens *et al*, 1985). The vaccine, as well as the simultaneous administration of the vaccine and HBIg, have proven to be highly immunogenic and effective in preventing vertical transmission (Poovorawan *et al*, 1989, 1992). Prenatal HBsAg screening would identify infected mothers, thus allowing for immunization of their newborns with hepatitis B immunoglobulin (HBIg) and hepatitis B vaccine – a regimen that is 85-97% effective in preventing the development of a chronic HBV carrier state (Beasley *et al*, 1983; Wong *et al*, 1984; Stevens *et al*, 1985, 1987; Poovorawan *et al*, 1989, 1992). Use of vaccine alone can prevent the chronic carrier state in 70-95% of such infants (Wong *et al*, 1984; Xu *et al*, 1985; Poovorawan *et al*, 1990).

The Global Advisory Group of the Expanded Program on Immunization has recommended, with World Health Assembly endorsement, that countries with a prevalence of HBV carriers exceeding 2% should add hepatitis B vaccine to their routine infant immunization schedules (World Health Assembly, 1992). Universal immunization remains the only strategy capable of efficiently reducing the numbers of acute hepatitis patients and chronic carriers; hence, decreasing the long-term disease burden, such as with HCC. In addition, universal hepatitis B vaccination, as an integral part of the national Expanded Program on Immunization (EPI), has been found to provide long-term protective immunity (Poovorawan *et al*, 2002). In countries with high prevalence and evidence of HBV vertical transmission, such as China, Southeast Asia, and the Far East, the first dose of hepatitis B vaccine needs to be administered as soon as possible after birth, preferably within 24 hours. The Thai Ministry of Public Health (MoPH) has included the control of HBV infection as part of the EPI since 1992. HB vaccine is given, along with the other EPI vaccines, at birth and at the age of 2 and 6 months.

Universal immunization of all neonates in Thailand has markedly reduced the carrier rate to 0.7% (Poovorawan *et al*, 2000). However, cost-effectiveness studies of maternal HBsAg screening and the vaccination of babies at risk have never been undertaken in the context of health care service in Thailand. Routine HBsAg screening of all pregnant women may be initiated as part of regular antenatal checkups, where the facilities are available. However, selective passive-active immunization also requires a supply of HBIg. This study was carried out to estimate an economic rationale for introducing routine prenatal HBsAg screening and prescribing combined passive-active immunization to babies-at-risk.

MATERIALS AND METHODS

Models and strategies

We developed an analytic decision model, to estimate the clinical and economic consequences of HBV, for a hypothetical cohort of newborns with respect to each of the immunization strategies from the health care provider's perspective. The model focused on the number and the cost of cases prevented. The decision model examined four different HBV management strategies as follows (see details in Fig 1).

Strategy 1. Screening for HBsAg, then vaccination: a mixed-population strategy of screening all pregnant women, before or during labor, for evidence of active HBV infection (HBsAg positive); then administering HBV vaccine and hepatitis B immunoglobulin (HBIg) to those HBsAg positive, but administering only HBV vaccine to those negative for HBsAg.

Strategy 2. Screening for HBsAg then HBeAg if HBsAg positive, and vaccination: a mixed-population strategy of screening all pregnant women, for evidence of active HBV infection (HBsAg positive) then for evidence of HBeAg (HBeAg positive) if HBsAg positive; and administering HBV vaccine and hepatitis B immunoglobulin (HBIg) to those positive for HBeAg, but administering only HBV vaccine to those negative for HBsAg, or those HBsAg positive but HBeAg negative.

Strategy 3. Universal vaccination: vaccination of all neonates.

Strategy 4. No vaccination.

Since universal vaccination has now been implemented in Thailand and the risk of HBV infection is high, the 'no vaccination' strategy was considered in the decision tree for comparison purposes. The target population was a representative cohort of the 800,000 neonates that are born annually in Thailand. The decision model used in this analysis was developed after a critical review of the literature, with input from HBV experts to ensure accuracy and validity.

Cost

Data for 2004 on actual average payments of patients for outpatient hospital care, diagnostic tests, and HBIg were obtained from King Chulalongkorn Hospital (a publicly funded university hospital in Bangkok). Costs of HBV vaccines were obtained from the Disease Control Department, Ministry of Public Health, where the vaccine was bought and supplied to the hospitals in the EPI. The details of the cost are shown in Table 1.

The model was based on the perspective of the health care provider and was confined to direct medical costs. Direct non-medical costs, such as travel costs incurred in the course of receiving medical care, and indirect costs were excluded from the analyses.

Incremental outcome effectiveness and cost-effectiveness

Incremental cost-effectiveness was calculated to compare each alternative management strategy (Strategies 1-3) to Strategy 4 (no vaccination) and was expressed as the difference in cost (Thai baht) incurred per additional case prevented.

Table 1
Cost components for HBV prevention.

Item	Unit cost (baht)
Venous blood test for HBsAg	80
Venous blood test for HBeAg	180
HB vaccine (three doses)	150
Hepatitis B immunoglobulin (0.5 ml)	1,250

(40 baht = 1 US$)

RESULTS

Expected cost, health outcomes expressed as percent cases prevented, cost per case of HBV prevented, and incremental cost per incremental case prevented are shown in Table 2 for each strategy. Strategies 1-3 are all more effec-

Table 2
Cost effectiveness and incremental cost effectiveness of various strategies for HBV prevention.

Strategy	Expected cost	Expected case prevented	Cost effectiveness	Incremental cost-effectiveness
1. Screen for HBsAg, then vaccination	29,250	99.90	292.79	95,000
2. Screen for HBsAg then HBeAg, & vaccination	26,400	99.87	264.34	20,000
3. Universal vaccination	15,000	99.30	151.05	6,521
4. No vaccination	0	97.00	0	-

Table 3
Estimated annual cost of each strategy for 800,000 newborns.

Strategy	Annual cost	Incremental cost	Incremental cases prevented
1. Screen for HBsAg, then vaccination	234,000,000	22,800,000	240
2. Screen for HBsAg then HBeAg, & vaccinate	211,200,000	91,200,000	4,560
3. Universal vaccination	120,000,000	120,000,000	18,400
4. No vaccination	0	-	-

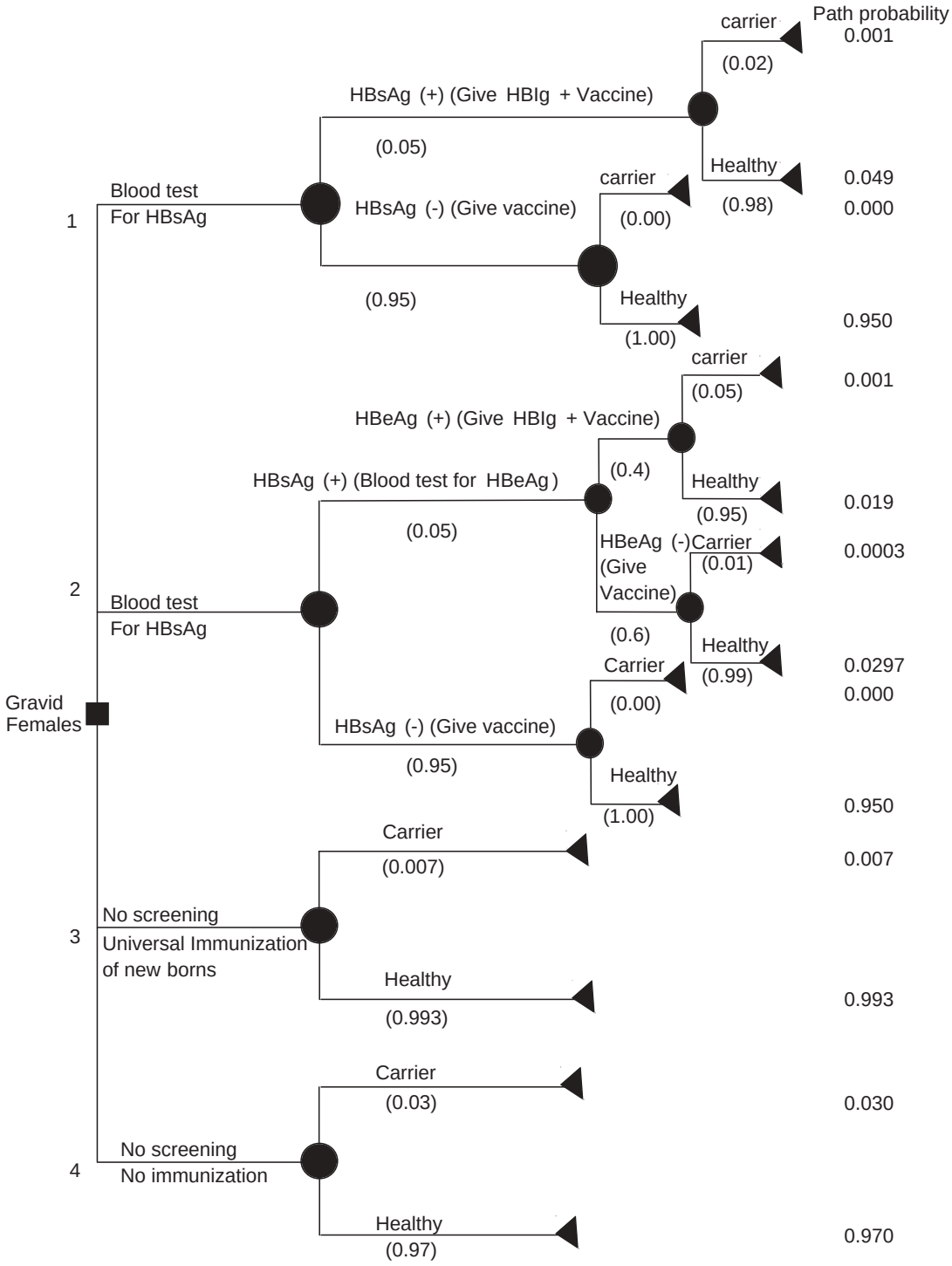

Fig 1–Decision tree analysis depicts the outcomes for Strategies 1-4 HBsAg = hepatitis B surface antigen, HBeAg = hepatitis B e antigen, HBIg = hepatitis B immunoglobulin. Square = decision node, Circle = chance node, Triangle = end node. Probability of each branch is shown in parenthesis.

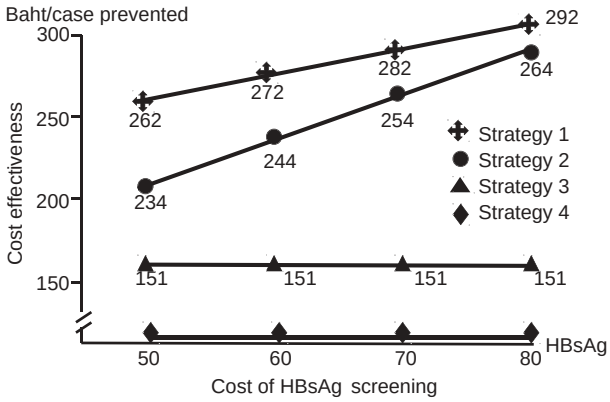

Fig 2–Sensitivity analysis of cost effectiveness for various costs of HBsAg screening test.

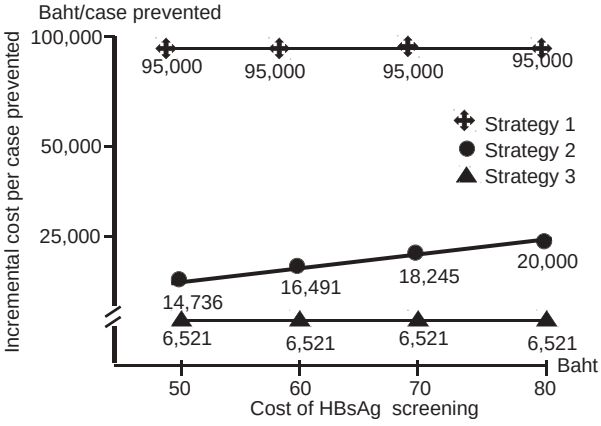

Fig 3–Sensitivity analysis of incremental cost per prevented case for various costs of HBsAg screening test.

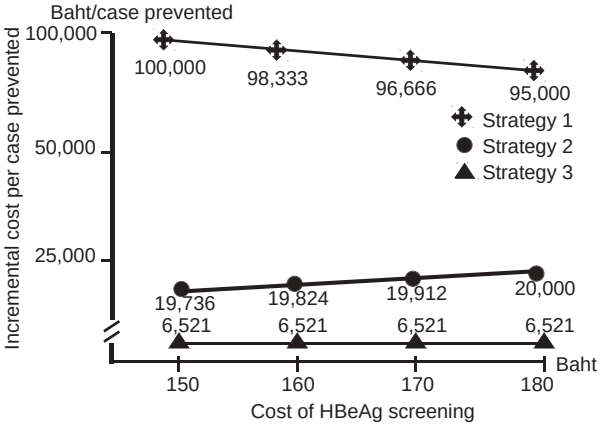

Fig 4–Sensitivity analysis of incremented cost effectiveness for various costs of HBeAg screening test.

tive and, because of the higher costs of screening tests and prophylactics, more expensive than Strategy 4, no vaccination in newborns. The cost-effectiveness for Strategy 1 is 292.79 baht per case prevented; while for Strategy 2, it is 264.34 baht per case prevented. For Strategy 3, it is 151.05 baht per case prevented; while for Strategy 4, it is 0 baht per case prevented. The incremental cost-effectiveness of Strategy 3 relative to Strategy 4 is 6,521 baht per case prevented; of Strategy 2 relative to Strategy 3, it is 20,000 baht per case prevented; of Strategy 1 relative to Strategy 2 it is 95,000 baht per case prevented.

Sensitivity analysis

We varied the HBsAg and HBeAg screening-test costs to determine the cost-effectiveness (Fig 2) and the incremental cost-effectiveness (Figs 3-4) of the four strategies. By decreasing the HBsAg and the HBeAg screening test costs, the cost-effectiveness for Strategies 1 and 2 could be lowered to 262 baht and 234 baht per case prevented, respectively, while the Strategy 3 remained unchanged at 151 baht per case prevented (Fig 2). The corresponding incremental cost-effectiveness differences of Strategy 2 relative to Strategy 3 are 14,736 and 19,736 baht per case prevented when HBsAg and HBeAg screening costs, respectively, are decreased (Figs 3-4).

DISCUSSION

A decade ago when HB vaccine was first added to our routine infant immunization schedules, it was considered cost-effective to vaccinate all neonates without screening. As the four alternative Strategies, there has not been any study to evaluate the cost-effectiveness, the incremental outcome effectiveness in the context of cost per case prevented, or the incremental cost per case prevented.

The analytic model would provide health policy makers with a basis to choose among the alternative Strategies 1-4, considering the long-term sequelae of HBV carriers, given that the incremental cost-effectiveness would be 95,000 per case prevented comparing Strategy 1 to Strategy 2, 20,000 baht comparing Strategy 2

to Strategy 3, and 6,521 baht comparing Strategy 3 to Strategy 4.

According to the sensitivity analysis, the incremental cost-effectiveness for Strategy 2 compared to Strategy 3 could be lowered to 14,736 baht and 19,736 baht per case prevented if the HBsAg screening test costs were to decrease to 50 baht per test and the HBeAg screening test costs to 150 baht per test, respectively.

The annual cost to the EPI in Thailand, for 800,000 neonates (approximate number of births per year), amounts to 234 million baht for Strategy 1, 211.2 million baht for Strategy 2, 120 million baht for Strategy 3, and 0 baht for Strategy 4, as shown in Table 3. There would be an incremental cost of 22.8 million baht for Strategy 1 compared to Strategy 2, 91.2 million baht for Strategy 2 compared to Strategy 3, and 120 million baht for Strategy 3 compared to Strategy 4. The incremental cost per case prevented (Table 3) is 240 baht for Strategy 1 compared to Strategy 2, 4,560 baht for Strategy 2 compared to Strategy 3, and 18,400 baht for Strategy 3 compared to Strategy 4.

There is no socially acceptable threshold value for cost per case prevented to guide decisions on funding health care interventions. Nevertheless, based on these results, Strategy 2 (screening for HBsAg and HBeAg, with vaccination may be considered, despite the incremental cost being about 2 times that of Strategy 3 (universal vaccination), as it might represent a worthwhile investment of public funds. To conclude, based on funds presently available in Thailand, universal vaccination should certainly be continued. If twice this funding could be assured, we would recommend that pregnant women be screened for both HBsAg and HBeAg, followed by high-risk newborns being given both HBIg and HB vaccine, while administering vaccine alone to low-risk neonates. To that end, we would require extensive logistical support from all health care workers.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Center of Excellence Research Fund, Chulalongkorn University; and the Thailand Research Fund, Senior Research Scholar. The authors would like to thank Ms P Hirsch for reviewing the manuscript.

REFERENCES

Andre FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. *J Med Virol* 1994; 44: 144-51.

Beasley RP, Hwang LY. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral hepatitis and liver disease. Orlando, FL: Grune & Stratton 1984: 209-24.

Beasley RP, Hwang LY, Lee GYC, *et al*. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet* 1983; ii: 1099-102.

Beasley RP, Hwang LY, Lin CC, *et al*. Hepatitis B immune globulin (HBIg) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state: initial report of a randomized double-blind placebo-controlled trial. *Lancet* 1981; ii: 388-93.

Beasley RP, Shiao IS, Wu TC, Hwang LY. Hepatoma in an HBsAg carrier-seven years after perinatal infection. *J Pediatr* 1982; 101: 83-4.

Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol* 1977; 105: 94-8.

Goudeau A, Yvonnet B, Lesage G, *et al*. Lack of anti-HBc IgM in neonates with HBsAg carrier mothers argues against transplacental transmission of hepatitis B virus infection. *Lancet* 1983; ii: 1103-4.

Kane MA, Hadler SC, Magnolis HS, Maynard JE. Routine prenatal screening for hepatitis B surface antigen. *JAMA* 1988; 259: 408-9.

Poovorawan Y, Sanpavat S, Pongpunlert W, *et al*. Comparison of a recombinant DNA hepatitis B vaccine alone or in combination with hepatitis B immune globulin for the prevention of perinatal acquisition of hepatitis B carriage. *Vaccine* 1990; S56-9; discussion S60-2.

Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *JAMA* 1989; 261: 3278-81.

Poovorawan Y, Sanpavat S, Pongpunglert W, *et al*. Long term efficacy of hepatitis B vaccine in infants born to hepatitis B e antigen-positive mothers. *Pediatr Infect Dis J* 1992; 11: 816-21.

Poovorawan Y, Sanpavat S, Theamboonlers A, *et al*. Long term follow-up (11-13 years) or high risk neonates, born to HBeAg positive mothers and vaccinated hepatitis B. In: Margolis H, Alter MJ, Liang TJ, Dienstag JL. eds, Viral hepatitis and liver disease. Atlanta: International Medical Press, 2002: 263-6.

Poovorawan Y, Theamboonlers A, Vimolket T, *et al*. Impact of hepatitis B immunisation as part of the EPI. *Vaccine* 2000; 19: 943-9.

Shiraki K, Yoshihara N, Kawana T, Yushi H, Sakurai M. Hepatitis B surface antigen and chronic hepatitis in infants born to asymptomatic carrier mothers. *Am J Dis Child* 1977;131: 644-7.

Stevens CE, Neurath RA, Beasley RP, Szmuness W. HBeAg and anti-HBe detection by radioimmunoassay: correlation with vertical transmission of hepatitis B virus in Taiwan. *Med Virol* 1979;3:237-41.

Stevens CE, Taylor PE, Tong MJ, *et al*. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. *JAMA* 1987; 257: 2612-6.

Stevens CE, Toy PT, Tong MJ, *et al*. Perinatal hepatitis B virus transmission in the United States: prevention by passive-active immunization. *JAMA* 1985; 253:1740-45.

Tada H, Yanagida M, Mishina J, *et al*. Combined passive and active immunization for preventing perinatal transmission of hepatitis B virus carrier state. *Pediatrics* 1982; 70: 613-9.

Wong VCW, Ip HMH, Reesink HW, *et al*. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis B vaccine and hepatitis B immune globulin: double-blind randomized placebo-controlled study. *Lancet* 1984; i: 921-6.

World Health Assembly. Immunization and vaccine quality. Proceeding of the Forty-Fifth World Health Assembly (Resolution WHA 45.17). Geneva: World Health Organization, 1992.

Xu ZY, Liu CB, Francis DP, *et al*. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. *Pediatrics* 1985; 76: 713-8.