

# Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan

Jia-Horng Kao, MD, Hsu-Mei Hsu, MPH, Wen-Yi Shau, MD, Mei-Hwei Chang, MD, and Ding-Shinn Chen, MD

**Objectives:** To assess the annual mortality rate associated with fulminant hepatitis in infants before and after the mass immunization program that was launched in Taiwan in July 1984.

**Study design:** From the National Mortality Registry System, the data on the mortality from fulminant hepatitis in infants from 1975 to 1998 were retrieved. Poisson regression analysis was used to assess the difference in average mortality from fulminant hepatitis in infants before (1975-1984) and after (1985-1998) the implementation of the mass hepatitis B vaccination program.

**Results:** The ratio of yearly mortality from 1975 to 1998 was 1.10 ( $P < .001$ ), representing a progressive decrease in the number of the cases. The average mortality associated with fulminant hepatitis in infants from 1975 to 1984 and from 1985 to 1998 was 5.36 and 1.71 per 100,000 infants, respectively. The ratio of the average mortality in the period from 1985 to 1998 to that in the period from 1975 to 1984 was 0.32 ( $P < .001$ ).

**Conclusions:** These data indicate that since the institution of a program of mass hepatitis B vaccination in Taiwan, the mortality associated with fulminant hepatitis in infants has declined significantly. (*J Pediatr* 2001;139:349-52)

Hepatitis B virus (HBV) infection is a global health problem; more than 350 million of the world population are chronically infected with the virus.<sup>1</sup> HBV infection is associated with a wide spectrum of clinical manifestations, ranging from acute or fulminant hepati-

tis to various forms of chronic infection including asymptomatic carrier state, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). In Taiwan, HBV infection is prevalent, and we have already shown that universal vaccination in infants is feasible and effec-

tive in reducing the number of hepatitis B surface antigen (HBsAg) carriers.<sup>2</sup> Most importantly, a trend of declining incidence of childhood HCC was observed, suggesting that universal hepatitis B vaccination in infants can effectively control childhood HCC.<sup>3</sup>

See editorial, p 343.

Fulminant hepatitis is uncommon in children and is associated with a high mortality rate.<sup>4</sup> Fulminant hepatitis has been documented in infants of HBV carrier mothers, especially those positive for antibodies against hepatitis B e antigen.<sup>5,6</sup> We have previously shown that HBV causes most of the fulminant hepatitis in infants in Taiwan.<sup>7</sup> A nationwide hepatitis B vaccination program, aimed at all newborn babies, was launched in Taiwan in July 1984.<sup>2</sup> To assess the possible effect of the vaccination, we analyzed the annual mortality associated with fulminant hepatitis in infants in Taiwan from 1975 to 1998.

HBsAg Hepatitis B surface antigen  
HBV Hepatitis B virus  
HCC Hepatocellular carcinoma

From the Graduate Institute of Clinical Medicine, Department of Pediatrics, and Hepatitis Research Center, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan; and Center for Disease Control, Department of Health, Executive Yuan, Taipei, Taiwan.

Supported by grants from the Department of Health and the National Science Council, Executive Yuan, Taiwan.

Submitted for publication Dec 12, 2000; revisions received Feb 2, 2001, and Mar 26, 2001; accepted Apr 5, 2001.

Reprint requests: Ding-Shinn Chen, Hepatitis Research Center, National Taiwan University Hospital, 1 Chang-Te St, Taipei 100, Taiwan.

Copyright © 2001 by Mosby, Inc.

0022-3476/2001/\$35.00 + 0 9/21/116277

doi:10.1067/mpd.2001.116277

## METHODS

### Population Data

Taiwan has a current population of over 22 million, and the health care system changed little in the study period from 1981 to 1998. All births, deaths, marriages, and divorces must

**Table.** Annual mortality (1975-1998) from fulminant hepatitis in infants in Taiwan

Year	Population (0-1 y of age)	Mortality from fulminant hepatitis* [No. (rate per 100,000)]
1975	331,760	20 (6.0)
1976	359,611	16 (4.4)
1977	370,443	24 (6.5)
1978	366,345	19 (5.2)
1979	376,966	20 (5.3)
1980	376,970	23 (6.1)
1981	374,254	25 (6.7)
1982	368,901	14 (3.8)
1983	359,022	24 (6.7)
1984 <sup>†</sup>	345,625	10 (2.9)
1985	325,084	15 (4.6)
1986 <sup>‡</sup>	302,342	6 (2.0)
1987	289,687	5 (1.7)
1988	300,777	6 (2.0)
1989	304,541	9 (3.0)
1990	309,435	13 (4.2)
1991	315,568	2 (0.6)
1992	307,460	9 (2.9)
1993	306,815	4 (1.3)
1994	299,810	1 (0.3)
1995	297,261	2 (0.7)
1996	303,000	1 (0.3)
1997	305,622	3 (1.0)
1998	281,091	1 (0.4)

\* $P < .001$  for the comparison of values before 1985 with those after 1985 (average mortality was 5.36 vs 1.71, respectively, with a mortality ratio of 3.11 [95% CI: 2.37-4.09]).

<sup>†</sup>Mass immunization against HBV launched on July 1, 1984, for HBsAg-carrier mothers' newborns.

<sup>‡</sup>All newborns have been included in the immunization program since July 1, 1986.

be registered with the government's household registration offices. Information on education, employment, and migration is also recorded. These records are double-checked annually by registration officers, who conduct home visits. Demographic data obtained from household registration offices are complete and accurate. The year-end population statistics for infants used in the present study were obtained from the annual reports on health and vital statistics published by the Department of Health.<sup>8</sup>

### **Nationwide Hepatitis B Vaccination Program**

Taiwan's mass vaccination program against HBV was launched on July 1,

1984.<sup>2</sup> Details of the program have been reported previously.<sup>2,3</sup> The primary targets are newborn babies. In the first 2 years, only HBsAg-carrier mothers' infants were vaccinated. From July 1986, all newborns were vaccinated. The program has been implemented smoothly and successfully, and the vaccine coverage has been >90% of the targeted population.

### **Definition of Fulminant Hepatitis**

Fulminant hepatitis was defined as severe acute hepatitis, with profound impairment of hepatic function associated with progressive mental changes occurring within 4 weeks of the onset of symptoms.<sup>7</sup>

### **Trends in the Annual Mortality from Fulminant Hepatitis in Infants**

To look for changes in the mortality from fulminant hepatitis in infants after the vaccination program was implemented, we used the National Mortality Registry System to study the mortality associated with this disease from 1975 to 1998, spanning the years before and after the start of the program. Death certificates, which must be registered in the household registration offices, are routinely reviewed and submitted to the national death certification system by local health bureaus. By law, a certificate must be registered within 1 month of any death. All certificates are reviewed and coded by medical registrars according to the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*<sup>9</sup> in the central office of the national death certification system, Department of Health.

### **Statistical Analysis**

The annual mortality rate from fulminant hepatitis in infants was determined by dividing the annual number of cases in children aged  $\leq 1$  year by the year-end population of the same age. In order to assess the effect of the nationwide vaccination program on the mortality rate from fulminant hepatitis in infants, the statistical significance of the difference for the 2 periods under comparison was examined by using Poisson regression analysis.<sup>10</sup>

## **RESULTS**

The annual mortality associated with fulminant hepatitis in infants from 1975 to 1998 is shown in the Table. Poisson regression analysis was used to calculate the average ratio of consecutive years across the interval of time. Our results showed that the ratio of yearly mortality from 1975 to 1998 was 1.10 (95% CI: 1.07-1.11,  $P <$

.001), representing a progressive decrease. The average mortality associated with fulminant hepatitis in infants from 1975 to 1984 was 5.36 per 100,000 infants (range, 2.9-6.7). The average mortality declined to 1.71 per 100,000 infants (range, 0.3-4.6) for the period from 1985 to 1998. The ratio of the average mortality in the period from 1985 to 1998 to that in the period from 1975 to 1984 was 0.32 (95% CI: 0.24-0.42,  $P < .001$ ). In other words, the mortality rate for fulminant hepatitis in infants in Taiwan decreased 3-fold after implementation of the hepatitis B vaccination program, and the change was statistically significant.

Of interest was the distribution of cases in 1984; of the 10 fatal cases, 7 occurred before July 31, and 3 occurred afterward.

## DISCUSSION

Taiwan is one of the first countries in the world to implement a universal vaccination program against hepatitis B.<sup>2</sup> Subsequent surveys have shown that the HBsAg seroprevalence rate in Taiwan declined from 10% to <1% 10 years after the initiation of mass immunization in children <10 years of age.<sup>11</sup> Most importantly, the average annual incidence of HCC in Taiwanese children aged 6 to 14 years declined from 0.70 per 100,000 children in 1981 to 1986 to 0.57 in 1986 to 1990, and further to 0.36 in 1990 to 1994.<sup>3</sup> These data indicate that an HBV mass vaccination program is not only effective in preventing perinatal and early horizontal transmission of HBV but also in controlling childhood HCC in Taiwan, a disease almost exclusively caused by HBV.<sup>3</sup> A similar decrease in the incidence of HCC will very likely be seen in young adults within the next few years. Accordingly, the World Health Organization has recommended that hepatitis B vaccination should be integrated into the routine Expanded Program of Immunization, and more than

100 countries worldwide have followed this recommendation.

Fulminant hepatitis, a rare but disastrous complication of HBV infection in infants, usually occurs in those born to asymptomatic HBsAg-carrier mothers, especially those negative for HBeAg and positive for antibodies against hepatitis B e antigen.<sup>5,6</sup> In Taiwan, perinatal mother-to-infant transmission of HBV accounts for 40% to 50% of HBsAg carriers.<sup>12</sup> We have previously shown that fulminant hepatitis in children occurs mainly during infancy, especially before 6 months of age, with HBV infection as the major cause (~76%).<sup>7</sup> Although the incidence of fulminant hepatitis is low, these perinatally infected infants are at risk for this acute, severe form of hepatitis. The average mortality associated with fulminant hepatitis in infants dramatically declined from 5.36 per 100,000 infants in the 1975-1984 period to 1.71 per 100,000 infants in the 1985-1998 period, coinciding with the implementation of the hepatitis B immunization program in 1984. This association was further supported by the stepwise decline in the number of infants who died of fulminant hepatitis. The first decline occurred in 1984 after hepatitis B vaccination for HBsAg-carrier mothers' infants was launched. Of interest, 7 of the 10 fatal cases in 1984 occurred before the end of July, when the infants did not receive hepatitis B vaccination. The second decline was observed in 1986 when all newborns were vaccinated, beginning in July of that year. After 1986, the cases per year decreased to single digits almost without exception. Although management of fulminant hepatitis has improved in recent years, the mortality rate for such a catastrophic illness remains unchanged in Taiwan.<sup>13</sup> Liver transplantation, an effective treatment for fulminant hepatic failure, has never been performed in infants for this indication in Taiwan. Thus, the evident decline in mortality from fulminant hepatitis in infants in

our study can be reasonably attributed to the effect of Taiwan's mass hepatitis B vaccination program.

In conclusion, our study strongly suggests that universal hepatitis B vaccination is effective in preventing fulminant hepatitis in infants in Taiwan. A nationwide hospital-based study with a better-defined etiology of fulminant hepatitis in infants is ongoing to further address this interesting and important issue.

*We thank Mr Shiuh-Ming Huang at the Office of Statistics, Department of Health, Taiwan, for his assistance with the vital statistics.*

## REFERENCES

1. Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;337:1733-45.
2. Hsu HM, Chen DS, Chuang CH, Lu JC, Jwo DM, Lee CC, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface antigen-carrier mothers. *JAMA* 1988;260:2231-5.
3. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997;336:1855-9.
4. Dulac O, Dupuy JM, Hadchouel M, Alagille D. Severe viral hepatitis in children. *Arch Fr Pediatr* 1978;35:230-41.
5. Sinatra FR, Shah P, Weissman JY, Thomas DW, Merritt RJ, Tong MJ. Perinatal transmitted acute icteric hepatitis B in infants born to hepatitis B surface antigen-positive and anti-hepatitis B e-positive carrier mothers. *Pediatrics* 1982;70:557-9.
6. Delaplane D, Yogev R, Crussi F, Shulman ST. Fatal hepatitis B in early infancy: the importance of identifying HBsAg-positive pregnant women and providing immunoprophylaxis to their newborns. *Pediatrics* 1983;72:176-80.
7. Chang MH, Lee CY, Chen DS, Hsu HC, Lai MY. Fulminant hepatitis in children in Taiwan: the important role of hepatitis B virus. *J Pediatr* 1987; 111:34-9.
8. Department of Health, the Executive Yuan, Republic of China. Republic of China Health and Vital Statistics, 1975-1998.

- 9. Manual of the international statistical classification of diseases, injuries, and causes of death. 1975 Rev. Vol 1. Geneva: World Health Organization; 1977.
- 10. Poisson regression analysis. In: Selvin S. Practical biostatistical methods. Belmont (CA): Duxbury Press; 1995. p. 455-90.
- 11. Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. JAMA 1996;276:906-8.
- 12. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771-4.
- 13. Liu CJ, Kao JH, Lai MY, Chen PJ, Chu JS, Chen W, et al. Minimal role of GB virus-C/hepatitis G virus in fulminant and subfulminant hepatitis in Taiwan. J Gastroenterol Hepatol 1999;14:352-7.

# **O** ***N THE MOVE?***

**Send us your new address at least six weeks ahead**

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

*Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.*

**JOURNAL TITLE:**

Fill in the title of the journal here. \_\_\_\_\_

**OLD ADDRESS:**

Affix the address label from a recent issue of the journal here.

**NEW ADDRESS:**

Clearly print your new address here.

Name \_\_\_\_\_

Address \_\_\_\_\_

City/State/ZIP \_\_\_\_\_

**COPY AND MAIL THIS FORM TO:**

Mosby  
 Subscription Customer Service  
 6277 Sea Harbor Dr  
 Orlando, FL 32887

**OR FAX TO:**

407-363-9661



**OR PHONE:**

800-654-2452  
 Outside the US, call  
 407-345-4000