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)
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.8

### Nationwide Hepatitis B Vaccination Program

Taiwan’s mass vaccination program against HBV was launched on July 1, 1984.2 Details of the program have been reported previously.2,5 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.7

### 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 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 ≤ 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.10

### 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,
.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, 0.5-4.6) 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. 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. 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. 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. 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. In Taiwan, perinatal mother-to-infant transmission of HBV accounts for 40% to 50% of HBsAg carriers. 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%). 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. 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.

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**REFERENCES**


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