MAJOR ARTICLE

Effect of Age on the Incidence of Acute Hepatitis B After 25 Years of a Universal Newborn Hepatitis B Immunization Program in Taiwan

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(See the editorial commentary by Schwarz, on page 702.)

Background. Raising concerns about the waning immunity of cohorts receiving hepatitis B virus (HBV) vaccination in infancy persuaded us to identify the changing incidence of acute hepatitis B (AHB) in children and young adults.

Methods. Data on AHB surveillance through the National Notifiable Disease Surveillance System from July 2001 to June 2009 were collected and described. Cases were divided into 2 cohorts according to their birth year: before or after the universal newborn HBV vaccination program. Age-specific incidence was compared for the 2 birth cohorts with diagnosis at age 15–24 years.

Results. In total, 2226 patients with AHB were identified. AHB rates varied by age; the highest rates occurred among unvaccinated individuals aged 25–39 years (2.33/100 000). Due to breakthrough HBV infection from mother-to-infant transmission, vaccinated infants (0.78/100 000) had higher rates than those aged 1–14 years (0.04/100 000), who had the lowest rates. The incidence in vaccinated birth cohorts was significantly lower than in unvaccinated birth cohorts among patients 15–24 years old, with an adjusted-relative risk of 0.42.

Conclusions. Implementation of universal-at-birth HBV immunization programs has effectively reduced the occurrence of AHB among adolescents and young adults in Taiwan for >25 years, making infants and the 25–39-year-old cohort additional targets for preventing AHB.

Hepatitis B virus (HBV) infection remains an important global health threat and could be eliminated through an effective immunization program. Based on epidemiological conditions in different regions of the world, universal immunization has been endorsed and aimed at preventing chronic HBV infection during early childhood and reductions in acute HBV infection in adolescents and young adults [1, 2].

The universal hepatitis B vaccination program in Taiwan has been well described [3, 4]. Beginning in July 1984, pregnant women were screened for serum hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Only infants born to high-risk mothers with positive HBeAg and HBsAg results received 0.5 mL of hepatitis B immunoglobulin (HBIG) within 24 hours after birth, in addition to the routine HBV vaccination [5]. Newborns born to HBsAg-positive mothers were the initial target group for vaccination. Since July 1986, an extensive immunization program has enrolled all newborns regardless of their maternal HBsAg status to receive 4 doses of plasma-derived HBV vaccine, which changed to 3 doses of recombinant yeast vaccine after 1 November 1992. A catch-up vaccination program was also conducted for preschool children and extended to all elementary school children from 1987 to 1990. Since July 1984, such programs have successfully demonstrated efficacy for preventing chronic HBV infection, fulminant hepatitis, and hepatocellular carcinoma in infants and children [1, 6–8].

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Raising concerns about the waning immunity and the need for a booster vaccine for cohorts who received the HBV vaccination in infancy led us to think about the health impact of acquiring HBV infection in hosts of different ages and immunity statuses [9–11]. Thus, disease surveillance and seroepidemiological surveys of hepatitis B immunity and carrier prevalence could help reevaluate the national hepatitis B vaccination program, which has been implemented for >25 years [11]. In this study, we identified the changing incidence of acute hepatitis B (AHB) in Taiwan through notifiable disease surveillance data collected from July 2001 to June 2009. Additionally, we compared the age-specific incidence among vaccinated and unvaccinated birth cohorts 15–24 years of age to understand the impact of the mass infant hepatitis B immunization program on AHB.

METHODS

Data Sources

AHB cases were identified by clinical physicians and were requested by law to be reported to the Taiwan Centers for Disease Control via the National Notifiable Diseases Surveillance System (NNDSS) within 1 week. NNDSS is a passive surveillance system that serves as an informative platform for public health sectors to collect demographic data, such as the patient identification number, address, sex, birth date, and nationality, date of disease onset, and contact information of reporting physicians to conduct case investigations and to control and prevent disease transmission. Regarding the clinical manifestation of AHB cases, the detailed medical data were inadequate for the comparison of the difference depending on physicians reported these cases in the NNDSS database. In this study, Taiwanese confirmed with AHB from July 2001 to June 2009 were enrolled, because the acute viral hepatitis surveillance data has demonstrated stable reporting rates since 2001. For investigating cases of perinatal HBV infection, identification numbers of cases with AHB diagnosed in children <1 year old were further linked to the National Immunization Informative System database to obtain the HBV immunization records and prenatal maternal HBV screening results. This study was approved by the institutional review board at the Taiwan Centers for Disease Control, Department of Health.

Definition of AHB

AHB was defined as an acute illness with symptoms of nausea, anorexia, fever, malaise, or abdominal pain, and elevation of the levels of serum bilirubin or aminotransferase above the upper normal limit, and was confirmed by laboratory criteria, which included positive results for HBsAg and immunoglobulin M (IgM) antibody to hepatitis B core antigen and negative results for IgM antibody to hepatitis A virus [2, 12]. Patients who were not jaundiced may have undergone liver function or HBV serologic testing owing to the other above-mentioned symptoms or their contact histories.

Before reporting cases with AHB to NNDSS, physicians were requested to rule out a diagnosis of chronic hepatitis B with acute exacerbation, which is defined as an abrupt increase in alanine aminotransferase levels to >5 times of the upper normal limit in patients with chronic HBV infection [13]. However, it might be misdiagnosed as AHB in those with negative history of hepatitis or had never been examined for hepatitis B seromarkers in the past. Physicians would consider the possibility of reactivation of chronic hepatitis B when liver histology documented chronic hepatitis and/or when low index values of IgM antibody to hepatitis B core antigen were detected [14, 15].

Vaccinated and Unvaccinated Birth Cohorts

We defined those who were born after 1 July 1986 as the vaccinated birth cohort. More than 86.9% of these subjects received ≥3 doses of hepatitis B vaccine in their infancy regardless of maternal HBsAg status (Supplementary Table 1). The unvaccinated birth cohort was born before June 1984 and was not covered by the neonate mass-vaccination program against hepatitis B. To avoid confusion, we excluded the AHB data of the 2-year birth cohorts for the birth years between 1 July 1984 and 30 June 1986, because the neonatal HBV vaccination program was selectively applied to infants born to HBsAg-positive mothers. With regard to the study period starting from 15 years after the universal newborn HBV vaccination program, the age-specific incidences were compared between vaccinated and unvaccinated birth cohorts only for those whose AHB was diagnosed at age 15–24 years, to evaluate the impact of the mass infant hepatitis B immunization program on AHB. Vaccine coverage of vaccinated cohorts was determined through the National Immunization Information System of the Taiwan Centers for Disease Control and data on live births from the Census Bureau.

Statistical Analysis

Crude rates (per 100 000 population) of AHB were calculated on a yearly basis and divided by age groups of 0, 1–14, 15–24, 25–39, and ≥40 years of age. The *P* value for the trend test was measured at the level of significance of the regression coefficient for each ordinary variable in the logistic regression model. Excluding the 2-year birth cohorts between July 1984 and June 1986, the age-specific incidence per 100 000 person-years of AHB was calculated in those aged 15–19 or 20–24 years at onset and divided into 2 strata according to whether they were born before or after July 1986. Follow-up person-years were derived from the birth cohort-specific population taken from the Taiwan National Household Registration on a yearly basis [7].

The effect of the universal newborn hepatitis B immunization program on AHB was illustrated by the rate ratio by

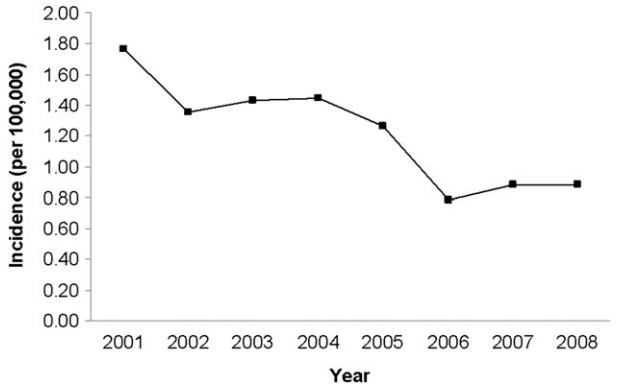

Figure 1. Annual incidence (per 100 000 population) of acute hepatitis B in Taiwan between July 2001–June 2002 and July 2008–June 2009 (n = 2226) (trend test, $P < .0001$).

comparing the age-specific incidence of the vaccinated cohort with that of the unvaccinated cohort. A Poisson regression model was conducted to estimate multivariable-adjusted rate ratios with 95% confidence intervals (CIs) for categories specified by age and birth year. Differences were considered statistically significant at $P < .05$ (2-tailed tests). All statistical analyses were performed using Microsoft Excel and SAS version 9.1 software (SAS).

RESULTS

Hepatitis B Vaccine Coverage in Infants

In total, 86.9%–98.0% of the vaccinated cohorts received ≥3 doses of the hepatitis B vaccine in their infancy regardless of maternal HBsAg status (Supplementary Table 1). Additionally, the vaccine coverage reached to 95% above for those born after January 2001.

Crude Rates of AHB

From July 2001 to June 2009, 2226 patients with AHB were identified through NNDSS. Among them, 80.6% (n = 1794) were reported by internists, 2.3% (n = 52) by family physicians, 1.6% (n = 36) by pediatricians, and 15.5% (n = 344) by other physicians. Gastroenterology/hepatology specialists and infection specialists accounted for 68.3 % (n = 1521) and 2.9% (n = 64) of reporting, respectively. The overall incidence declined steadily during the 8 years, from 1.76 per 100 000 population in July 2001–June 2002 to 0.89 in July 2008–June 2009, representing a decline of 50% and a decreasing trend ($P < .0001$) since July 2001 (Figure 1).

Patterns of Change in AHB Rates Among Different Age and Birth Cohorts

AHB rates varied by age. Table 1 shows the mean rate of AHB cases per 100 000 population for the 5 age groups, from July 2001 to June 2009. The highest rates occurred among individuals aged 25–39 years, the second highest in those aged 15–24 years, and the third highest in those aged ≥40 years. Infants had higher rates than those aged 1–14 years, who had the lowest rates. Considering the annual rates for each age group, the rate of AHB in 2001 was highest in those aged 25–39 years, second highest in those aged 15–24 years, and third highest in those aged ≥40 years for the unvaccinated birth cohorts (Figure 2). In 2005 and later, those aged 15–24 and ≥40 years had similar AHB incidences when the 15–24-year age group was composed of the vaccinated cohort. The AHB rates showed a decreasing trend since July 2001 for the 15–24-, 25–39-, and ≥40-year age unvaccinated groups (trend test, $P < .0001$) but not for the vaccinated young age groups of 0 years (trend test, $P = .61$) and 1–14 years (trend test, $P = .57$). This is because the AHB rates in 0–14-years had already declined to a low level before 2001 (data not shown). The greatest rates of decline occurred among adolescents and young adults aged 15–24 years (77.3 %), and 48% and 35% decreases were also observed in the 25–39- and ≥40-year age groups, respectively.

Table 1. Mean Rates of Acute Hepatitis B (AHB) by Age Groups, July 2001 to June 2009

Age Group, years	AHB Cases, No.	Population, No.	Mean Rate (per 100 000)
0	13	1 675 267	0.78
1–14	14	32 794 739	0.04
15–24	416	27 958 857	1.49
25–39	1057	45 299 250	2.33
≥40	726	74 134 204	0.98
Total	2226	181 862 317	1.22

Incidence by the 2 Birth Cohort Strata

We conducted a further analysis of the 2 birth cohorts, with 362 cases of AHB diagnosed at age15–24 years. The incidence in patients aged 15–19 years was lower than that in those aged 20–24 years for both unvaccinated and vaccinated cohorts (Table 2). The AHB incidence for those who were born after July 1986 (vaccinated birth cohorts) was significantly lower than that in unvaccinated birth cohorts among children aged 15–24 years, showing an adjusted rate ratio of 0.42 (95% CI, .28–.62) (Table 3). Furthermore, the risk of acquiring AHB was higher among those aged 20–24 than among those aged 15–19 years, demonstrating an cohort-adjusted relative risk of 2.33 (95% CI, 1.63–3.33).

Special Pattern of AHB Infection in Infants

A total of 13 infants acquired AHB, and the median age at diagnosis was 5.6 months (range, 2.1–8.4 months). All of these infants were born to an HBsAg-positive mother,

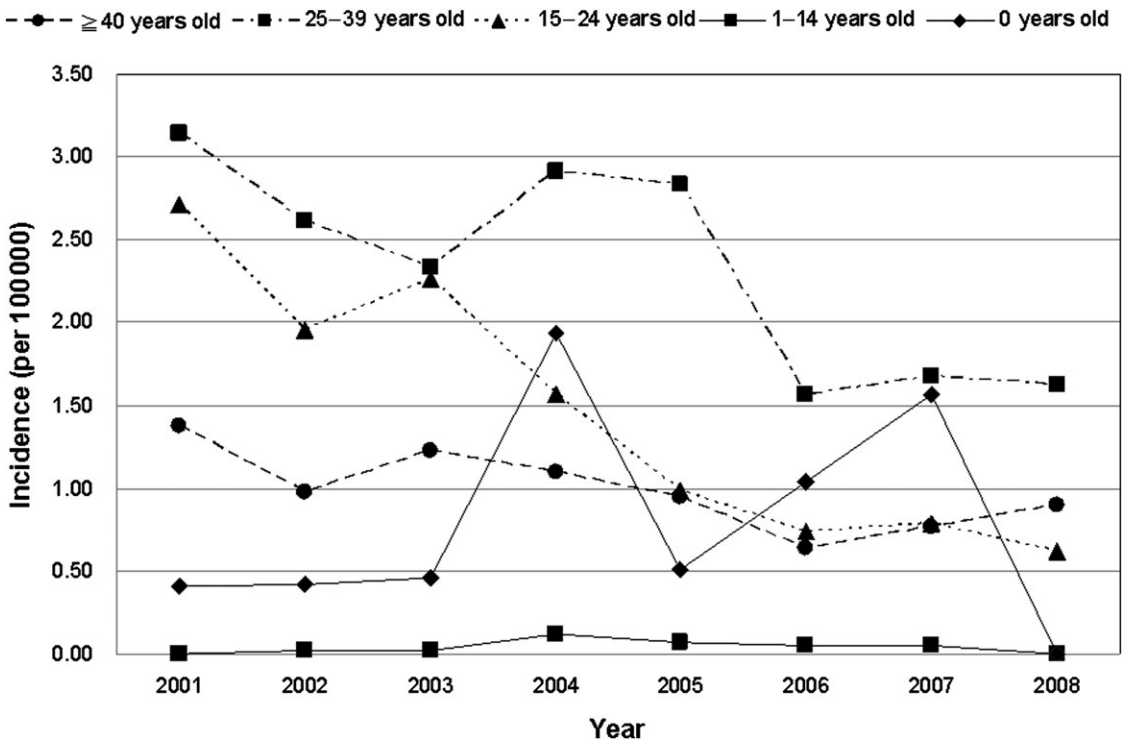

Figure 2. Incidence (per 100 000 population) of acute hepatitis B by age groups and year in Taiwan, July 2001–June 2009 (n = 2226) (trend test, $P = .61$, $.57$, $<.0001$, $<.0001$, and $<.0001$ for those aged 0, 1–14 , 15–24 , 25–39 , or ≥40 years, respectively).

a status that could be regarded as a perinatal HBV infection (Supplementary Table 2). Ten had available maternal HBeAg status information. HBIG was given to 5 infants born to HBeAg-positive mothers, but not administered to the others born to HBeAg-negative mothers according to Taiwan's HBV immunization policy. One additional infant who was born in the United States with unknown maternal HBeAg status and received HBIG there. With regard to HBV vaccination history, 5 patients (38.5%) acquired AHB after completing the 3 vaccination doses. Eight (61.5%) of the 13 acquired AHB by 6 months, and the HBV vaccination history was not completed on schedule.

DISCUSSION

Our findings demonstrated different age-dependent patterns of AHB in the era of the universal newborn hepatitis B immunization program in Taiwan. Reduced occurrence of AHB among adolescents and young adults (15–24 years old) was observed by comparing the age-specific incidence among the vaccinated and unvaccinated birth cohorts.

An extremely low incidence of AHB in vaccinated children aged 1–14 years and a continuing decreasing trend of AHB for those aged 15–24 years might imply that there is no urgent

Table 2. Age-Specific Incidence of Acute Hepatitis B (AHB) Diagnosed at Age 15–24 Years Between 1 July 2001 and 30 June 2009 for both vaccinated and unvaccinated cohorts (n = 362)

Age at Diagnosis and Birth Years[a]	AHB Cases, No.	Person-Years	Incidence Density (per 100 000 Persons-Years)	Rate Ratio (95% CI)	*P*
15–19 y					
July 1981–June 1984	27	2 227 536	1.21	1.00 (referent)	
July 1986–June 1994	33	8 042 153	0.41	0.34 (0.20–0.56)	<.0001
20–24 y					
July 1976–June 1984	289	11 655 636	2.48	1.00 (referent)	
July 1986–June 1989	13	953 241	1.36	0.55 (0.32–096)	.03

[a] We excluded the data for those born between 1 July 1984 and 30 June 1986.

Abbreviation: CI, confidence interval.

Table 3. Multivariate-Adjusted Relative Risk of Acquiring Acute Hepatitis B (AHB) at Age 15–24 Years Between July 2001 and June 2009 (n = 362)

Birth Cohort and Age	Person-Years	AHB Cases, No.	Rate Ratio (95% CI)	*P*
Birth cohort				
Nonvaccinated	13 883 172	316	1.00 (referent)	
Vaccinated	8 995 394	46	0.42 (0.28–0.62)	<.0001
Age, y				
15–19	10 269 689	60	1.00 (referent)	
20–24	12 608 877	302	2.33 (1.63–3.33)	<.0001

Abbreviation: CI, confidence interval.

need to consider booster hepatitis B vaccinations for the vaccinated cohorts [10].

The vaccinated cohort in this study could reach the age of 14 and 22 years old in 2001 and 2008, respectively. In 2001, the age groups of 15–24, 25–29, and ≥40 years were not vaccinated; the highest incidence occurred in the 25–39-year-old cohort, the second highest in the 15–24-year-old cohort, and the third highest in the ≥40-year-old cohort. However, the age-related incidence pattern changed after the 15–24-year age group joined the vaccinated cohort. Since 2005, the incidence in 15–24-year-old patients has declined to a level similar to that in the ≥40-year-old cohort, leading to a changed pattern, with the highest incidence rate in the 25–39-year-old cohort and the second highest in the 15–24- and ≥40-year-old cohorts. Therefore, the decline in AHB was observed mostly in those aged 15–24 years.

Compared with decreased trends of AHB in patients aged 15–24 years, those aged 25–39 years and ≥40 years revealed a similar trend, but with less of a reduction in AHB. A possible explanation could be the indirect protection or herd immunity gained from high hepatitis B vaccine coverage in the young cohorts, a decreasing infection burden of HBV carriers in the general population, or effective public health measures to eliminate HBV transmission [11, 16, 17].

AHB in infants is another age-dependent unique phenomenon, even after the immunization era. The incidence of AHB in patients <1 year of age was higher than that in the older vaccinated cohorts. The reason that vaccinated infants still have a high incidence of AHB is breakthrough mother-to-infant transmission of HBV. Regimens combining the hepatitis B vaccine and/or HBIG are 85%–95% effective in preventing HBV infection when administered at birth to infants born to HBsAg-positive mothers [3]. It remains a challenges to eliminate all possibilities of maternal-infant transmission, because certain infants born to HBsAg-positive mothers were not protected by postnatal HBV vaccines, with or without HBIG. Perinatal HBV infection in newborns may range from asymptomatic to fulminant hepatitis [8]. Therefore, the incidence of AHB in patients <1 year old could have been underestimated. A close follow-up program of infants born to HBsAg-positive mothers was conducted in the United States to ensure the completeness of on-schedule HBV vaccination, the presence of protective antibody to hepatitis B surface antigen (anti-HBs), the need for revaccination with anti-HBs < 10 mIU/ml, and the diagnosis of possible perinatal HBV infection [18, 19]. The Taiwan Centers for Disease Control have endorsed a similar program targeting infants born to HBeAg-positive mothers since 2010 as part of the goal to eliminate HBV. Some other choices may be available to combat perinatal HBV infection, including development of a better immunogenic HBV vaccine, prenatal prophylaxis for high-risk pregnant women with chronic hepatitis B, and medical referral for infants who fail to respond to postnatal HBV immune prophylaxis [19, 20].

A previous study demonstrated the efficacy of reducing AHB through effective routine HBV immunization targeting of not only infants but also adolescents [21, 22]. Furthermore, general improvements in quality of living standards and hygiene as well as the introduction of public health measures, such as blood screening for hepatitis virus infection, the use of universal precautions in the medical setting, health education for safe sexual behaviors, and avoidance of all potential risk behaviors for HBV infection, play crucial roles [11]. The decline in AHB infection was greatest among children <15 years old in the United States and Italy, which was attributed to the vaccinated cohorts through adequate observation periods in pre- and postvaccination campaigns. In this study, we discovered that children aged 1–14 years had a steady and extremely low incidence from July 2001 to June 2009, and the incidence in this age group did not show a decreasing trend. This is because the study period began in July 2001, 15 years after the universal newborn HBV vaccination program.

This study has provided a quick and efficient method to generate a protective-effect hypothesis for a universal immunization program through databases already established in public health sectors. Further results regarding the direct or indirect protective effect of HBV vaccination could be demonstrated via observation studies, seroepidemiology surveys, and continuing surveillance of vaccine-preventable diseases, which are important for developing prevention strategies and monitoring immunization programs.

In conclusion, the declines in AHB in adolescent and young adults in Taiwan were attributed to a successful universal newborn HBV vaccination program. A unique age effect on AHB after 25 years of the HBV vaccination program was noted in the 15–24-year-old age group or younger, making 25–39-year-olds and infants the main future target of AHB prevention. Considering the epidemiology of AHB based on surveillance data and high coverage of the 3-dose HBV vaccine in infants, there might not be an urgent need to

consider booster HBV vaccination for the members of the vaccinated 15–24-year-old cohort who were immunized against HBV at birth.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Disclaimer. This manuscript has not been published or been considered for publication elsewhere in any language. All authors have participated sufficiently in the study and approved the manuscript.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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