Vaccine 29 (2011) 2956–2961

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Change in hepatitis A epidemiology after vaccinating high risk children in Taiwan, 1995–2008

Tsung-Pei Tsou[a,b,*], Cheng-Chung Liu[c], Ji-Jia Huang[c], Kun-Ju Tsai[c], Hsiu-Fang Chang[c]

[a] Field Epidemiology Training Program, Centers For Disease Control, Department of Health, 2F, No. 6 Linsen South Road, Taipei City 100, Taiwan
[b] Research and Diagnostic Center, Centers for Disease Control, Department of Health, No. 161, Kunyang Street, Taipei City 115, Taiwan
[c] Second Division, Centers for Disease Control, Department of Health, 10F, No. 6 Linsen South Road, Taipei City 100, Taiwan

ARTICLE INFO

Article history:
Received 30 November 2010
Received in revised form 31 January 2011
Accepted 1 February 2011
Available online 15 February 2011

Keywords:
Hepatitis A
Hepatitis A vaccines
Herd immunity
Population surveillance
Epidemiology

ABSTRACT

Taiwan started to immunize children in 30 indigenous townships against hepatitis A since June 1995. The program was further expanded to 19 non-indigenous townships with higher incidence or increased risk of epidemic in 1997–2002, covering 2% of total population. Annual incidence of hepatitis A decreased from 2.96 in 1995 (baseline period) to 0.90/100,000 in 2003–2008 (vaccination period). The incidence in vaccinated townships and unvaccinated townships declined 98.3% (49.66–0.86/100,000) and 52.6% (1.90–0.90/100,000). In 2003–2008, incidence doubled in people aged >=30 years, mostly in unvaccinated townships (0.42–0.92). During 2003–2008, travel to endemic countries was the most commonly reported risk factor (13.5%). First dose vaccine coverage was 78.8% in 1994–2005 birth cohort. Taiwan's experience demonstrates the great, long-term efficacy of hepatitis A vaccine in disease control in vaccinated townships, and out-of-cohort effect in unvaccinated townships. Further reduction can be achieved by improving vaccination coverage of adults at risk.

1. Introduction

Hepatitis A is an acute illness caused by the hepatitis A virus (HAV). It is transmitted by the fecal-oral route through person-to-person contact or ingestion of contaminated food or water [1]. In children less than 6 years of age, >70% of infections are asymptomatic. Beyond that age, infection is usually symptomatic with jaundice occurring in >70% of the patients [2]. With more than 1.5 million cases annually worldwide as estimated by the World Health Organization (WHO), this generally self-limiting disease imposes considerable direct and indirect economic burden on society [3]. Epidemiology of the disease differs in different countries and countries can be categorized as to have high, intermediate or low endemicity [3,4]. In countries with high endemicity, infection is usually acquired during early childhood as asymptomatic or mild infection with limited mortality and morbidity [3]. In countries with intermediate endemicity, children escape infection in early childhood because of improved environmental hygiene and socioeconomic conditions. The reported rates of symptomatic hepatitis A are higher and the morbidity/mortality can be increased as infection occurs later in life [4].

Safe and effective killed HAV vaccines were licensed in the 1990s [5]. Pre- and post-exposure vaccinations are effective for decreasing the incidence or outbreak control [3]. Because of the difference in disease incidence, vaccine cost and availability among countries, vaccination policies vary from universal childhood immunization to targeting at-risk groups, namely travelers, people with chronic liver diseases, intravenous drug users (IDU) and men who have sex with men (MSM) [6]. Since the introduction of the vaccine, the epidemiology has changed in several countries [6]. In Israel, a universal immunization program for toddlers has decreased the incidence of hepatitis A by more than 95% [7]. In the United States (US), a stepwise, nationwide vaccination program also decreased the incidence to a historically low level in 2007 [8].

Taiwan was endemic for hepatitis A until the 1980s, when the economic boom led to improved hygiene [9]. Among the population of 23 million, 2% are indigenous of which, 53% lives in indigenous townships mainly located in the mountainous areas [10]. Previous seroepidemiological studies in Taiwan showed that the hepatitis A prevalence has declined significantly in the metropolitan areas since the 1980s [11,12]. However, the prevalence of hepatitis A remained high in indigenous townships until the mid 1990s because of the unique lifestyle and less than ideal hygiene conditions among the people. This included decreased use of flush toilet, frequent use of underground water or spring water and use

* Corresponding author at: Centers for Disease Control, Department of Health, No. 161, Kunyang Street, Taipei City 115, Taiwan. Tel.: +886 2 26517303; fax: +886 2 27850288.
E-mail addresses: tsungpei@cdc.gov.tw, tsungpei1106@gmail.com (T.-P. Tsou).

0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.02.001

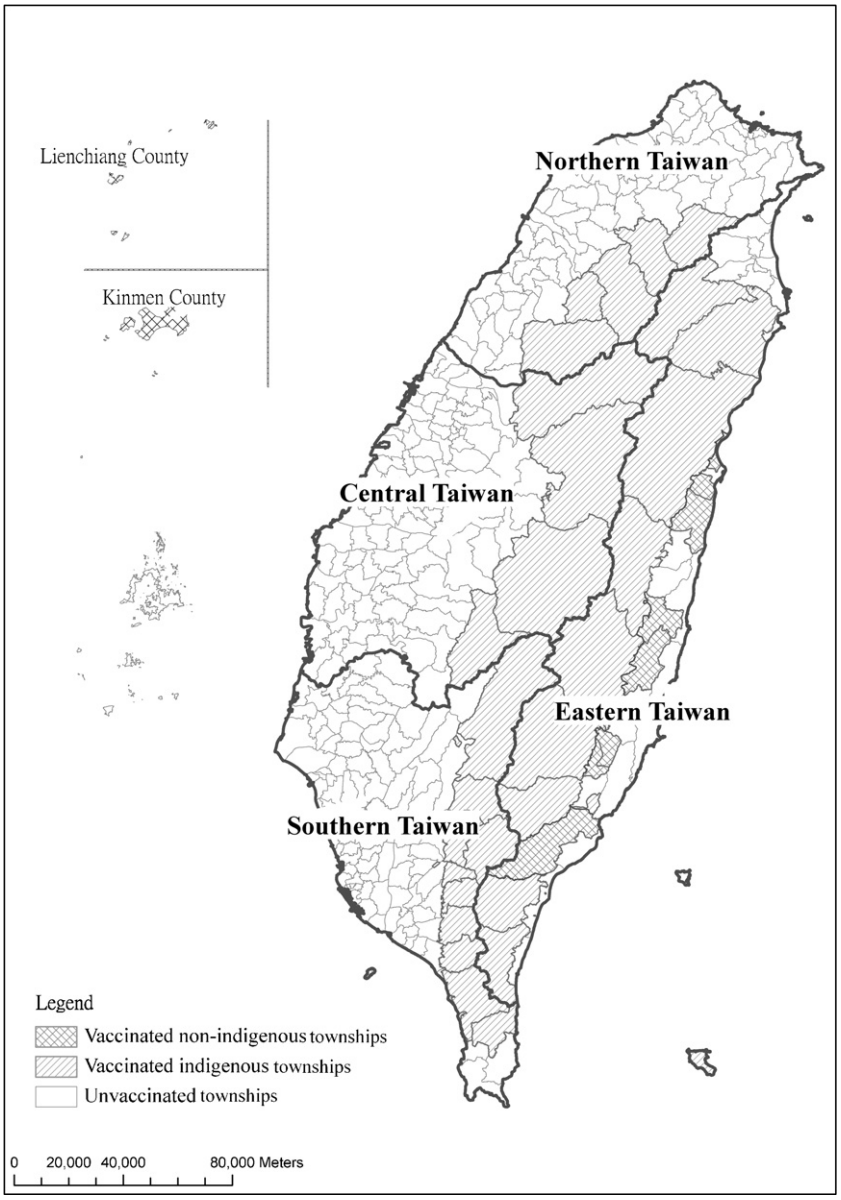

Fig. 1. Distribution of hepatitis A vaccinated and unvaccinated townships in Taiwan.

of human waste as fertilizer [13]. The prevalence odds ratio for indigenous townships was 2.97 when compared to metropolitan areas [11]. This geographic disparity in disease endemicity is the basis of our immunization policy.

Using data from a nationwide passive surveillance system, we report the impact of a vaccination program targeting high risk children on the epidemiology of hepatitis A in Taiwan.

2. Material and methods

2.1. Vaccination program and evaluation

Three doses of hepatitis A vaccines with 360 enzyme-linked immunosorbent essay (ELISA) units were administered at months 0, 1 and 6 free of charge to children aged 15 months to 12 years living in 30 indigenous townships (total population of 199,000) since June 1995 [14]. The vaccine was offered to eligible toddlers during routine vaccination clinics or school based vaccination program for 7–12 year-olds. Since November 1998, nine townships (total population of 219,000) nearby the indigenous ones, which also had higher incidence for hepatitis A, were included in the expanded vaccination program. At the same time, the three-dose regimen was changed to two doses of hepatitis A vaccines with 720 ELISA units given 6–12 months apart. Following the implementation of the "Mini Three Links" between two offshore island counties of Kinmen and Lien-Chiang and Mainland China in January 2001, the risk of importing hepatitis A was thought to be increased through increased travel and trade. Therefore, children in the ten townships of Kinmen and Lien-Chiang counties (total population of 60,000) were included in the vaccination program in February 2002. The minimum age for first-dose vaccine was changed to 24 months in November 2002.

Vaccinated townships include 30 indigenous townships, 9 nearby non-indigenous townships plus 10 townships in Kinmen and Lien-Chiang counties (Fig. 1). Because of the gradually expanding program and the changing population covered in 1996–2002, we compared the incidence in 1995 (baseline period) with the average incidence of 2003–2008 (vaccination period). Incidence of vaccinated townships were compared with the rest of Taiwan (unvaccinated townships).

A computer-based system – Primary Health Information System (PHIS) – had been used in 1993–2001 for immunization registry in Taiwan. All local health centers were equipped with computers to record demographic data of individual vaccinees, date and place of all routine immunizations, type of vaccine given and batch number of vaccines. Since 2002, a web-based, nationwide registration system, the National Immunization Information System (NIIS), replaced PHIS. NIIS is accessible by all local health bureaus and linked to the National Household Registration System. Information collected by PHIS was later integrated with NIIS and formed the immunization registry in Taiwan, in which information of all routine immunizations given after 1993 is readily available. Hepatitis A vaccines given by school-based immunization program were not recorded in PHIS. First-dose and complete series (three or two doses) vaccination coverage of hepatitis A vaccine in the 1994–2005 birth cohort was calculated using NIIS data. Private sales estimate of vaccines beyond routine immunization was provided by the vaccine manufacturer.

2.2. Hepatitis A surveillance

Since 1985, HAV infection can be reported to the health authority but it was not mandated by law. Acute hepatitis A was made a notifiable disease in 1999 and people with positive serum anti-HAV IgM and symptom/signs of acute hepatitis such as fever, malaise, abdominal pain, nausea, jaundice or elevated liver function should be reported within 24 h of diagnosis via the web-based National Notifiable Diseases Surveillance System (NNDSS) to Taiwan Centers for Disease Control (TCDC). Before 1999, only demographic data and laboratory result were collected. Since 2000, health departments collect information of patients by filling a structured questionnaire including demographics, ethnicity, symptom, date of onset, travel and contact history, occupation, laboratory results and disposition. The questionnaire should be completed within 72 h after diagnosis and sent to TCDC via NNDSS. Only cases with positive serum anti-HAV IgM were classified as confirmed cases. Those with negative serum anti-HAV IgM were excluded, and those with undetermined or unavailable result of serum anti-HAV IgM are classified as undetermined. All confirmed cases in 1995–2008 were included for further analysis. Because structured questionnaire was used since 1999, only cases reported in the vaccination period (2003–2008) were included for risk factor and disease severity analysis. Cases with travel history to foreign countries two months before disease onset were classified as imported cases.

The data analyzed here are collected as part of the routine disease surveillance activities of TCDC, and are exempt from institutional board review. Informed consent is not required for investigating cases of nationally notifiable diseases.

2.3. Statistical analysis

The incidence is expressed as annual incidence per 100,000 people. Annual age- and population group-specific rates were calculated using the annual population size provided by the Taiwan Directorate General for Budget, Accounting, and Statistics. Rate in 2003–2008 were compared with baseline rate in 1995 by the calculation of a normal z statistic [15]. To be more conservative about the statistical significance of the large denominators in these comparisons, a p-value <0.01 was chosen for statistical significance. Statistical analysis was performed using Microsoft Excel and SPSS 14.0.

3. Results

From January 1, 1995 to December 31, 2008, there were 3513 cases of acute hepatitis A reported to NNDSS. Among them, 440 had no laboratory result available, 30 had negative anti-HAV IgM and 11 were duplications. A total of 3032 cases were confirmed and included for analysis.

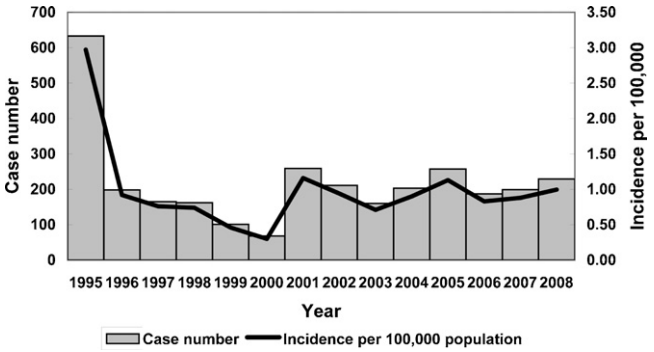

Fig. 2. Number and incidence of reported hepatitis A cases in Taiwan, 1995–2008 (n = 3032). *Decrease in incidence over time is statistically significant (p = 0.045, exponential regression).

3.1. Trends in overall incidence

In 1995, there were 663 confirmed cases and the annual incidence was 2.96 per 100,000. During 1995–2008, the annual number of cases decreased two-thirds to around 200. The incidence fluctuated between 0.3 and 1.2 in 1996–2008 and remained low in the vaccination period (Fig. 2).

In 1995, incidence decreased with age and was the highest in children and adolescents younger than 20 years (Table 1). Cases aged 0–9 years and 10–19 years accounted for 34.4% (n = 218) and 34.8% (n = 220) of all patients, respectively. Number of cases in children and adolescents decreased markedly in 1996, accounting for 29.3% (n = 58) and 26.3% (n = 52) of all cases, respectively. Since 1997, more than half (51–61%) of the cases were aged 20–39 years. During the vaccination period, incidence decreased most markedly in persons <20 years and was the highest in adults aged 20–29 years. Comparing baseline and vaccination periods, incidence of hepatitis A doubled in persons aged ≧ 30 years (0.46–0.91/100,000, $p < 0.001$) especially among those aged 30–39 years (0.55–1.55/100,000, $p < 0.001$). This age shift was reflected in the median age of cases. The median age of all cases were 18 years in 1995 and increased to 34 years in 2008 ($p < 0.05$, linear regression).

There is a gender difference in hepatitis A incidence. Although incidence was markedly decreased in both sexes in the vaccination period, rates among men are consistently higher than among women (Table 1). The relative risk of men having the disease was 2.17 (95% CI 1.83–2.57) in 1995 and decreased to 1.25 (95% CI 1.11–1.40) in 2003–2008.

3.2. Comparison of trends in vaccinated and unvaccinated townships

In 1995, the mean incidence in vaccinated townships was 26.2 times higher than unvaccinated townships (49.66 vs. 1.90/100,000) (Table 1). Among all cases, 29% were from the 30 indigenous townships (median incidence 90.68 per 100,000, range 0–316) and 7.4% were from other vaccinated townships (median incidence 17.38 per 100,000, range 0–88). In vaccinated townships, incidence was highest in children <10 year-old; in unvaccinated townships, children aged 10–19 year-old had the highest incidence. Incidence in vaccinated and unvaccinated townships both decreased in 1996 (Fig. 3), and compared to 1995, the difference in incidence between vaccinated and unvaccinated townships decreased from 26.2 to 14.9 times (10.47 vs. 0.70/100,000). After initiation of the vaccination program, no case was reported in vaccinated townships in 1998, 2000 and 2005.

Table 1
Hepatitis A incidence by demographic characteristics: overall and by region, 1995 and 2003–2008[a].

	All			Vaccinated townships			Unvaccinated townships		
	1995	2003–2008	Incidence change[b] (95% CI)	1995	2003–2008	Incidence change[b] (95% CI)	1995	2003–2008	Incidence change[b] (95% CI)
Overall	2.96	0.90	−2.06 (−2.30, −1.82)	49.66	0.86	−48.80 (−55.14, −42.45)	1.90	0.90	−1.00 (−1.19, −0.80)
Age, y									
0–9	6.80	0.22	−6.57 (−7.48, −5.67)	240.57	0.29	−240.28 (−276.51, −204.05)	1.57	0.22	−1.35 (−1.79, −0.90)
10–19	5.65	0.57	−5.09 (−5.84, −4.33)	61.21	0.51	−60.69 (−77.50, −43.88)	4.44	0.57	−3.87 (−4.55, −3.19)
20–29	3.69	1.62	−2.07 (−2.71, −1.42)	10.29	2.21	−8.08 (−14.93, −1.23)	3.53	1.61	−1.92 (−2.56, −1.28)
>=30	0.46	0.91	+0.46 (+0.32, +0.59)	3.05	0.68	−2.37 (−4.66, −0.08)	0.42	0.92	+0.50 (+0.37, +0.63)
Sex									
M	4.01	1.00	−3.01 (−3.39, −2.63)	50.99	0.99	−50.00 (−58.71, −41.29)	2.88	1.00	−1.88 (−2.21, −1.55)
F	1.85	0.81	−1.05 (−1.32, −0.77)	48.06	0.71	−47.35 (−56.60, −38.10)	0.87	0.80	−0.06 (−0.25, +0.13)

[a] Incidence is expressed as annual (1995) or average annual (2003–2008) incidence per 100,000 population.
[b] *p*-Value < 0.001 for all change in incidence except for that of female in unvaccinated townships.

Fig. 3. Incidence of hepatitis A in vaccinated and unvaccinated townships in Taiwan, 1995–2008. *Decrease in incidence is statistically significant in vaccinated townships ($p = 0.003$, exponential regression) but not in unvaccinated ones ($p = 0.246$).

During the vaccination period, overall incidence decreased significantly both in vaccinated (49.66–0.86, 98.3% decrease) and unvaccinated (1.90–0.90, 52.6% decrease) townships. Age-specific incidence decreased in both geographic regions among those < 30 years, but increased in adults ≧30 years living in unvaccinated townships (Table 1). Incidence decreased significantly in both sexes except for women in unvaccinated townships, which the decrease is only minimal (0.87–0.80/100,000, $p = 0.25$) (Table 1). Overall, age- and gender-specific incidence was similar in vaccinated and unvaccinated townships in the vaccination period.

3.3. Incidence by region

Incidence of hepatitis A in Taiwan varied geographically, with higher rates reported in eastern Taiwan where most of the indigenous townships were (Fig. 1). As our vaccine policy was to vaccinate children with the highest risk of infection, the percentage of population covered by the hepatitis A immunization program varied greatly between different regions. Based on the population in 2000, 24.14% of the population in eastern Taiwan was covered by the vaccination program. The percentage of population covered was 0.36%, 1.07% and 1.04% in northern, central and southern Taiwan, respectively.

In 1995, the incidence was highest in eastern (14.74/100,000), followed by northern (3.97/100,000), central (1.18/100,000) and southern Taiwan (0.91/100,000). Since 1996, the decrease in incidence was island-wide but most evident in eastern and northern Taiwan. During 2003–2008, the incidence per 100,000 population in eastern, northern, central and southern Taiwan decreased 14.36 (95% C.I. 12.07–16.65, $p < 0.001$), 2.36 (1.99–2.82, $p < 0.001$), 0.55 (0.25–0.84, $p < 0.001$) and 0.29 (0.01–0.57, $p < 0.01$), respectively.

3.4. Vaccination coverage in vaccinated townships

During the study period, 64,756 children in the 1994–2005 birth cohort living in vaccinated townships were considered eligible for vaccination. Among them, 78.8% had received at least 1 dose of vaccine and 73.9% had completed 3 or 2-dose vaccination series. Vaccination coverage in 1994–2005 birth cohorts and number of newborns are shown in Fig. 4. First dose vaccine coverage increased from 60 to above 80 and remained high after initiation of the program. Children of the 1980s birth cohort vaccinated by school-based immunization program were not recorded in NIIS so no data on vaccination coverage of these cohorts was available. However, based on our previous experience of school-based vaccination program, coverage above 80 was expected.

Records of yearly pediatric and adults doses of hepatitis A vaccine distributed in the private market since 2000 were obtained from one of the two companies offering hepatitis A vaccine in

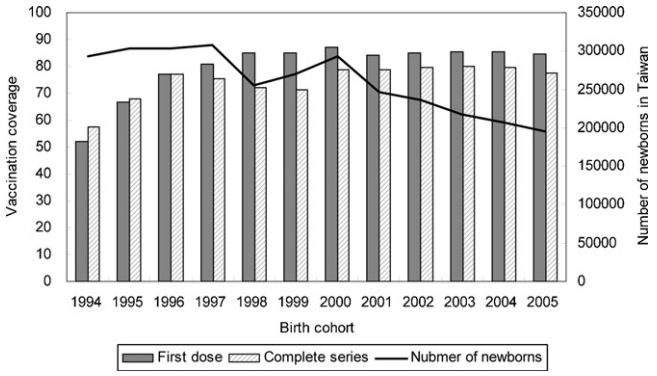

Fig. 4. Hepatitis A vaccination coverage of birth cohorts in vaccinated townships and annual number of newborns in Taiwan, 1994–2005.

Taiwan, which owns approximately half of the private market share. During 2000–2008, a total of 148,280 pediatric doses and 27,220 adult doses were distributed, meaning that 74,000–148,280 children ≦18 years and 13,610–27,220 adults were vaccinated for the first dose beyond the routine immunization program. Given that Taiwan had 5,500,000 children ≦18 years and 17,500,000 adults in 2008, and the company owned half of the market share, the estimated first dose hepatitis A vaccination coverage in unvaccinated townships was no more than 2.7–5.3% in children ≦18 years and <0.1% in adults.

3.5. Severity of illness and risk factor analysis in the vaccination period (2003–2008)

During the vaccination period, 1235 patients of hepatitis A were reported. No outbreak involving more than 5 patients had been reported. Among the 1235 patients 1177 had information about disposition available in NNDSS. Sixty percent ($n = 702$) were hospitalized for hepatitis A. Percentage of patients hospitalized differs in different age groups. Patients aged 0–9 years and >=60 years were most likely to be admitted (70%). There were eight persons who died. Mean age of these patients (60.1 years, SD 19.9) was significantly older than those who lived (35.1 years, SD 15.9).

Ninety-two percent of the 1235 patients had travel history available in NNDSS. Among them, 167 (13.5%) had traveled to foreign countries two months before disease onset and were classified as imported cases. Imported cases accounted for 9, 18, 24, 8, 12 and 15 percent of all cases in 2003–2008, and were most common in adults aged 30–39 years, accounting for 21.5% of all cases in that age group. Among the imported cases, the top three source countries were China (including Hong Kong, 35.9%), Indonesia (14.6%) and the Philippines (11.1%). More than half (50.2%) had source country in South-East Asia.

4. Discussion

Previous studies have shown profound effect of vaccinating children against HAV in reducing the disease burden. Protection beyond the immunized people, also known as herd protection, was the main reason for the high effectiveness [7]. Protection beyond the age group vaccinated is well-documented in several countries. In Israel, incidence of hepatitis A decreased in all age groups after initiating universal immunization of toddlers, demonstrating profound, sustainable herd protection in adults [7]. Studies in Spain and the US also showed 20–50% decline in incidence in adults >18 years after immunizing toddlers [16,17]. These results are evidence that children are the main distributors of hepatitis A in the community and form the basis of universal childhood vaccination. In countries where vaccines were only given to toddlers in a confined area, protection beyond the geographical region had also been evident. In the US, hepatitis A vaccine was first given to children in 11 states with the highest incidence since 1999. Besides the 88.2% incidence decline in vaccinated states, which accounts for 33% of the US population, non-vaccinated states also had a 52.6% decrease in incidence in 2003, compared to 1990–1997 [15]. In Queensland, Australia, immunization targeting indigenous children living in a confined community decreased cases reported in the non-indigenous community [18].

The magnitude of herd protection is the result of interaction between vaccine efficacy, vaccination policy, vaccination coverage, population dynamics and the presence of high risk population. In previous studies, vaccination coverage was either estimated by sampling or pharmaceutical records of yearly doses distributed, both of which are only the best estimate available [7,15]. Our nationwide registry system provides accurate information on vaccination coverage. First dose vaccination coverage of 78.8% effectively decreased the incidence in vaccinated townships by 98.3%. After 14 years of implementation of the vaccination program, we found that the effect is significant and sustainable and vaccine effectiveness is likely to be maintained in vaccinated townships by adding immunized cohort year by year. As vaccine coverage remains high, the risk of future outbreaks in vaccinated townships is low and catch-up vaccination is not considered necessary so far.

With a childhood vaccination program covering 2% of the overall population and coverage of 73.9%, the incidence in unvaccinated townships decreased 52.6%, showing herd protection beyond the vaccinated population. Given the low vaccination coverage in unvaccinated townships (no more than 2.7–5.3% in children and <0.1% in adults), the decrease is more likely to be caused by herd protection rather than direct effect of vaccination. Children living in indigenous townships may serve as hubs of hepatitis A transmission, both inside and outside these townships. Vaccination interrupts the chain of transmission and offers protection to the broader community [18].

As the incidence of hepatitis A can be decreased following economic boom and improved environmental hygiene, at least some of the incidence reduction after initiation of vaccination is likely attributable to other non-vaccine factors. However, we consider vaccination the main reason for the incidence decline because of the following reasons. 1. Taiwan's per capita national income was 3037 USD in 1985, 11,838 USD in 1995 and 14,383 in 2005 [19]. The increase of per capita national income was more abrupt in 1985–1995, but the change of hepatitis A epidemiology took place only since 1996, after initiation of the vaccination program. 2. The coverage of piped water supply in Taiwan was 41.3% in 1974, 74.5% in 1986, 88.0% in 1995, and 92.2% in 2008 [20], showing that improvement of water supply system was only marginal after 1995. 3. The epidemiology of other diseases transmitted by the fecal-oral route, such as shigellosis and typhoid fever, has not been changed during the same period, indicating the presence of other factors affecting the epidemiology of hepatitis A [21].

Besides the great effect of vaccinating children, transmission among adults with specific risk factors can be sustained in the absence of transmission among children and international travelers, IDU and MSM are considered especially risky [15]. In a hospital-based study on HIV positive patients in Taiwan, IDU and MSM have been documented to have higher prevalence of anti-HAV antibody [22]. However, among all these risk factors, only travel history is routinely collected during our investigation. Mainland China and Southeast Asian countries are the most commonly reported source of infection and are endemic for hepatitis A [23]. According to the Tourism Bureau, in 2008, 35.9% of outbound tourists are heading for Mainland China (including Hong Kong) and 26.7% are heading for South-East Asian countries [24]. Among all the outbound tourists, 78.3% of them are ≧30 year-old [24]. In 2002–2008,

the number of outbound tourists ≧30 years heading for Asian countries increased from 4.8 to 5.4 million per year ($p < 0.05$) [24]. These information suggests that imported hepatitis A may be an important cause of the increased incidence in adults ≧30 years. Further efforts must be taken on more detailed risk factor collection and phylogenetic analysis of the virus, which can help to evaluate the impact of imported cases on epidemiology.

Because of the nature of passive surveillance, under-reporting is a major limitation of our study. As reporting was not mandatory before 1999, under-reporting is truly a concern for cases in 1995–1998. As the method of data collection did not change during 1999–2008 and no means of active surveillance was ever used, the percentage of case not reported should be consistent and would not change the trend in incidence. Furthermore, it is possible that the incidence in 1995 is one of the cyclic peaks and the impact of vaccination is overestimated [15]. However, reports of outbreaks virtually disappeared after 1996 [25,26], suggestive of a fundamental change in hepatitis A epidemiology in the past decade.

In conclusion, Taiwan's experience demonstrates the great, long-term efficacy of hepatitis A vaccine in disease control in vaccinated townships, and out-of-cohort effect in unvaccinated townships. The age and geographic disparity of hepatitis A epidemiology has been eliminated and Taiwan has shifted from intermediate to low endemicity country. Vaccination strategy targeting high risk adults, especially travelers, can further decrease hepatitis A incidence and prevent future outbreaks.

Acknowledgments

The authors would like to thank Ms. Shu-Fang Chen and Ms. Christine Ding-Ping Liu for their help on data collection and interpretation, Mr. Hsu-Wen Yang for graphic works, Dr. Donald Dah-Shyong Jiang and Dr. Hwa-Jen Teng for help on statistical analysis and Angela Song-En Huang members of Taiwan FETP for their support and helpful discussions.

References

[1] Koff RS, Hepatitis A. Lancet 1998;351(May (9116)):1643–9.
[2] Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. Am J Epidemiol 1985;122(August (2)):226–33.
[3] Hepatitis A vaccines. Wkly Epidemiol Rec 2000;75(February (5)):38–44.
[4] Wasley A, Fiore A, Bell BP. Hepatitis A in the era of vaccination. Epidemiol Rev 2006;28:101–11.
[5] Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, et al. Protection against hepatitis A by an inactivated vaccine. JAMA 1994;271(May (17)):1328–34.
[6] FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Hepatitis A and E: update on prevention and epidemiology. Vaccine 2010;28(January (3)):583–8.
[7] Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA 2005;294(July (2)):202–10.
[8] Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis – United States, 2007. MMWR Surveill Summ 2009;58(May (3)):1–27.
[9] Wu JS, Chen CH, Chiang YH, Lee YC, Lee MH, Ko YC, et al. Hepatitis A virus infection in Taiwan. Taiwan Yi Xue Hui Za Zhi 1980;79(August (8)):694–9.
[10] Population statistics of the indigenous people. In: Concil of Indigenous Peoples EY, editor. Taipei, 2010. http://www.apc.gov.tw/main/docDetail/detail_TCA.jsp?isSearch=&docid=PA000000003035&cateID=A000296&linkSelf=160&linkRoot=4&linkParent=49&url= [last accessed November 2010].
[11] Wang LY, Cheng YW, Chou SJ, Hsieh LL, Chen CJ. Secular trend and geographical variation in hepatitis A infection and hepatitis B carrier rate among adolescents in Taiwan: an island-wide survey. J Med Virol 1993;39(January (1)):1–5.
[12] Tseng HY, Lu CY, Lee CY, Yeh CC, Lin SC, Shih WY, et al. Hepatitis A virus infection in Taipei in 1999. J Formos Med Assoc 2001;100(September (9)):604–7.
[13] Lin HH, Li YH, Yu JH, Wang YW, Lua AC, Huang LC, et al. Ethnic and geographic variations in the prevalence of hepatitis A, B and C among aboriginal villages in Hualien, Taiwan. Infection 2000;28(July–August (4)):205–8.
[14] Lee WT, Chang MH, Lee CY, Chen DS, Safary A, Andre FE. Immunogenicity of an inactivated hepatitis A vaccine in healthy children: two years' follow-up. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1995;36(September–October (5)):331–5.
[15] Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA 2005;294(July (2)):194–201.
[16] Dominguez A, Oviedo M, Carmona G, Batalla J, Bruguera M, Salleras L, et al. Impact and effectiveness of a mass hepatitis A vaccination programme of preadolescents seven years after introduction. Vaccine 2008;26(March (14)):1737–41.
[17] Averhoff F, Shapiro CN, Bell BP, Hyams I, Burd L, Deladisma A, et al. Control of hepatitis A through routine vaccination of children. JAMA 2001;286(December (23)):2968–73.
[18] Hanna JN, Hills SL, Humphreys JL. Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland. Med J Aust 2004;181(November (9)):482–5.
[19] Key Economic and Social Indicator. Taipei, Taiwan: Directorate-General of Budget, Accounting and Statistics; 2010.
[20] Number and Percentage of Subscribers in Served Area. Taipei, Taiwan: Taiwan Water Corporation; 2010.
[21] Centers for Disease Control DoH, R.O.C. (Taiwan). CDC Annual Report 2009. Centers for Disease Control, Department of Health, R.O.C. (Taiwan); 2009.
[22] Sun HY, Kung HC, Ho YC, Chien YF, Chen MY, Sheng WH, et al. Seroprevalence of hepatitis A virus infection in persons with HIV infection in Taiwan: implications for hepatitis A vaccination. Int J Infect Dis 2009;13(September (5)):e199–205.
[23] Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010;28(41):6653–7.
[24] Outbound Departures of Nationals of the Republic of China by Age. Tourism Bureau, Ministry of Transportation and Communications, R.O.C. (TAIWAN), 2009. http://admin.taiwan.net.tw/indexc.asp [last accessed Jan 2011].
[25] Chao DYWYS, Lu CW, Chen KT, Chu CL, Hsu HM, Horng CB. An investigation of risk factors in a hepatitis A outbreak in a college in Tamshui. Taiwan Epidemiol Bull 1997;13(4):17.
[26] Hsu NH, Lin SR, Hsu ST, Liu JY, Sun HC, Yang BS, et al. An outbreak of hepatitis A in Lin-Kou Taipei County in 1982. Taiwan Yi Xue Hui Za Zhi 1984;83(December (12)):1222–31.