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ORIGINAL ARTICLE

Hepatitis A virus seroepidemiology of elementary school children in New Taipei City in Taiwan

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Background: To establish the seroepidemiologic data of hepatitis A virus (HAV) vaccine-preventable HAV diseases among school children (7–12 years old) attending elementary schools in New Taipei City, Taiwan. This is a pilot study of an ongoing nationwide study, and will be the reference for a national immunization program.
Methods: The school children were selected for samplings, based on a multistage stratified sampling method that included 14 variables (4 socioeducational variables, 4 socioeducational variables, and 6 medical facilities' variables). The 29 administrative districts of New Taipei City were categorized into five strata. In total, 936 school children from 14 schools were recruited and bled for the serologic tests of HAV by enzyme-linked immunosorbent assay method.
Results: The seropositive rate for HAV was 8.33% among the 936 children. From each school, the difference in the seropositive rate for HAV ranged 0–18.75%. There was no significant difference between each stratum ($p = 0.059$) or grade ($p = 0.570$); however, there was a difference between schools in the first stratum ($p = 0.033$) that was associated with different vaccination rates. This study also revealed a significantly greater seropositive rate in the vaccination group ($p < 0.001$) and in females ($p = 0.02$).
Conclusion: The seropositive rate for the HAV was <10% and was mostly associated with the vaccination status. Because of the low HAV vaccination rate and low seropositive rate for the HAV, an effective hepatitis A vaccine is a useful tool to prevent HAV infection. It is worthy

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to discuss whether to include the HAV vaccine as part of a routine vaccination program in Taiwan.

Introduction

Acute hepatitis A virus (HAV) infection is the most common form of acute viral hepatitis throughout the world. It is more common in regions of the world with poor sanitation and insufficient safe water. In the developing world, approximately 90% of children have been infected by the age of 10 years and thus are immune by adulthood.[1] Acute hepatitis A virus often occurs in outbreaks in moderately developed countries.[2,3] In young children, acute HAV infection is often asymptomatic. In older children and adults, the infection is usually symptomatic with jaundice occurring in >70% of patients.[4] Fulminant hepatitis occurs in approximately 8% of patients.[5]

Hepatitis A vaccine effectively prevents HAV infection.[6,7] In general, approximately 95—100% of children older than 2 years who receive one dose of HAV vaccine will produce protective antibodies.[8] The hepatitis A vaccine used in Taiwan is an inactivated virus vaccine. The hepatitis A vaccine is freely provided by the government for children living in aboriginal townships and neighboring townships (in total, 30 townships) The HAV vaccine is self-paid and mostly administered in private sectors. The recommended vaccination schedule is one dose at the age of at least 1 year and a second dose 6—12 months later (in total, 2 doses).

In the early 1970s, > 90% of Taiwanese adults had anti-HAV antibodies, and most of them had contracted HAV infection during childhood.[8,9] During 1975—1976, the seropositive rate of anti-HAV immunoglobulin G (IgG) was 15.2% for children under 6 years of age, 15—25% for children 6—10 years of age, and up to 50—86% for adolescents 11—15 years of age.[10] With economic growth, people in Taiwan have made progress in sanitation and thus reduce the pollution of drinking water and food. The improvements in social and personal sanitation reduce the transmission of infectious agents via the fecal—oral route and reduces the opportunities for HAV infection. In 1984, one study conducted in Taipei showed that the seroprevalence of hepatitis A infection was only approximately 1% for children under 6 years of age, approximately 5% for children aged 6—10 years, and 10—13% for children aged 10—15 years.[11] Few people had experienced HAV infections in childhood, and HAV infection caused more severe symptoms when the infection occurred in adulthood. With the accumulation of nonimmune people, a large-scale of HAV outbreak can happen such as the 1988 epidemic of hepatitis A in Shanghai that involved 30,000 cases.[12]

Hepatitis A vaccine has been used in Taiwan for years, primarily in the private sectors, and may be included in an expanded program of immunization. However, for at least 10 years, there have been no seroepidemiologic data for the targeted population. Therefore, we conducted this study, which was supported by the Centers for Diseases Control of Taiwan (CDC Taiwan), to evaluate the seroprevalence of HAV among Taiwanese school children aged 7—12 years.

Materials and methods

Ethics statement

In 2012, the Institutional Review Board of the Chang Gung Memorial Hospital, Taoyuan, Taiwan reviewed and approved the study proposal. Written informed consent was obtained from all participants or their guardians.

Study populations and selection of patients

From September 2012 to June 2013, a cross-sectional survey of HAV-specific IgG antibody in a population of elementary school children (age, 7—12 years) was conducted in New Taipei City. New Taipei City comprises 29 administrative districts and is the second largest special municipality in northern Taiwan. The elementary students residing in this city accounted for 16.5% of the whole population of primary school children in Taiwan in 2012. A multistage stratified systematic sampling design was employed to obtain samples.[13] The 29 administrative districts of New Taipei City were arbitrarily classified into five strata, based on 14 variables that included four demographic variables [i.e., the population density (persons/km^2); the proportion of the population older than 65 years; the proportion of population younger than 15 years; the proportion of the population younger than 6 years]; four socioeducational variables (i.e., the number of low-income households per 10,000 people; the number of near-poor households per 10,000 people; the proportion of agricultural population; and the proportion of population with college degree or above); and six medical facility variables (i.e., the number of physicians per 10,000 people; the number of nursing staffs per 10,000 people; the number of nursing staffs in health centers per 10,000 people; the number of medical personnel in health centers per 10,000 people; the number of staff in health centers per 10,000 people and the number of health care settings per 10,000 people). Elementary schools in each stratum were selected with selection probability proportional to their size (PPS).[13] One class was drawn from each grade in a sampled school (i.e., in total, 6 classes were drawn from each sampled school). In each selected school, the number of students in each class was also selected with PPS. In each class, students were finally selected randomly. Students (n = 558) were accordingly selected from six schools in Stratum 1; 130 students, from two schools in Stratum 2; 66 students, from two schools in Stratum 3; 140 students, from

two schools in Stratum 4; and seven students, from two schools in Stratum 5. In total, at least 901 students were obtained. We subsequently planned to recruit 936 students from the selected schools, as shown in Fig. 1. All study participants were manifestly healthy without acute illness at blood drawing. Past medical history was obtained by questionnaire from each participant and the information of vaccination status was reliably obtained by vaccination records.

Each student included in this study had 5–10 mL of blood drawn for HAV antibodies examination by the qualitative Liaison Anti-HAV IgG chemiluminescence assay (Diasorin, Saluggia, Italy). The antibody test procedure followed the original company's recommendation. The test was repeated if the first operation had indeterminate results, and was recorded as "negative" if the second results remained indeterminate.

Statistical analysis

A comparison of the seropositive rate or vaccination rate between different groups was tested by the Chi-square test. A multivariate logistic regression model was used to evaluate the factors of seropositive HAV. Data analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

This study recruited 936 school children from 14 schools. Among the 936 students, anti-HAV IgG was positive for 78 children, which gives a seropositive rate of 8.33%. For each stratum, the difference in the seropositive rate ranged from 0% (the lowest, Stratum 5) to 10.24% (the highest, Stratum 1), but there was no statistical significance between the strata ($p = 0.059$). There was no statistical difference of vaccination rate between the strata ($p = 0.1$) (Table 1). For each participant school, the seropositive rate for anti-HAV IgG ranged 0–18.75%. The seropositive rate was statistically significantly different between the schools in Stratum 1 ($p = 0.033$), ranging from 6.25% for San-Zhong school and Zhong-Gang school to 18.75% for Ju-Guang school; however, there was no statistically significant differences between the schools in the second to fifth strata. There were also no statistically significant differences in the seropositive rate between the grades, and it ranged from 5.13% (the lowest, Grade 5) to 10.26 (the highest, Grade 2; $p = 0.57$; Table 2).

The seroprevalence of anti-HAV IgG was significantly higher in females than in males ($p = 0.02$; Table 3). However, the vaccination rates between males and females, based on questionnaire data and vaccination records of the CDC Taiwan, were not significantly different [7.5% (male) vs. 9.5% (female); $p = 0.3$; data not shown]. The HAV seropositive rate in the participants was significantly associated with the vaccination rate ($p < 0.001$; Table 3). Thirty-nine (95.12%) of 41 people who received two doses of the HAV vaccine were seropositive for HAV. Sixteen (41.03%) of 39 people who received one dose of the HAV vaccine were positive for anti-HAV IgG, whereas only 23 (2.69%) of 856 people who had never received the HAV vaccine had a positive result. Multiple logistic regression analysis showed that the independent factors for anti-HAV seropositivity

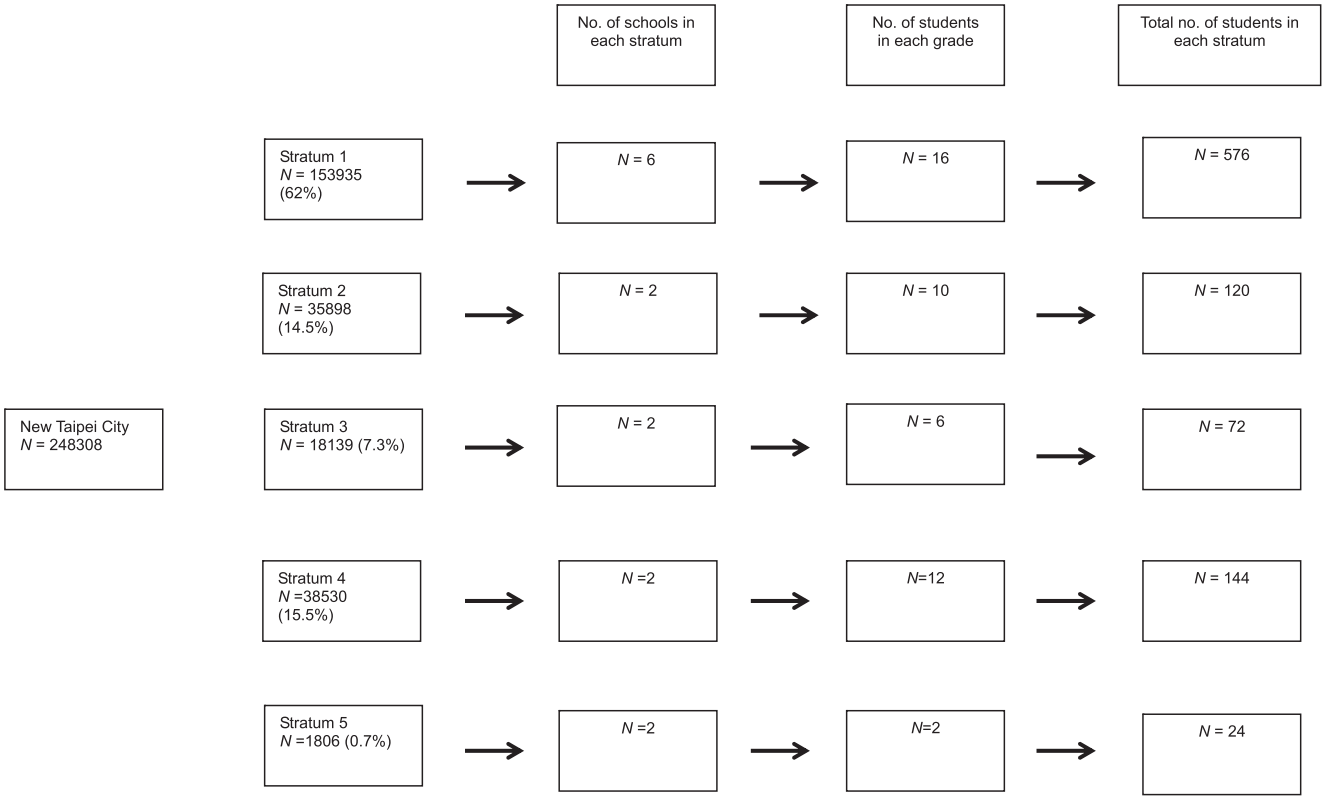

Figure 1. Study flow diagram of the sampling. N = number.

Table 1 Results of seropositivity and vaccination against hepatitis A virus for school children in New Taipei City, stratified by administrative area strata

School (administrative district)	No. of students	M:F ratio	Seropositive, *N* (%)	Vaccination, *N* (%)
1st stratum	576	0.97	59 (10.24)	61 (10.59)
Zhong-Shan (Ban-Qiao)	96	0.81	11 (11.46)	11 (11.46)
San-Zhong (San-Zhong)	96	0.92	6 (6.25)	10 (10.42)
Zhong-Gang (Xin-Zhuang)	96	0.85	6 (6.25)	7 (7.29)
Lu-Zhou (Lu-Zhou)	96	1.09	7 (7.29)	3 (3.13)
Ji-Mei (San-Zhong)	96	1.29	11 (11.46)	9 (9.36)
Ju-Guang (Ban-Qiao)	96	0.96	18 (18.75)	21 (21.86)
2nd stratum	120	0.82	8 (6.67)	6 (5.00)
Cheng-Fu (San-Xia)	60	0.62	2 (3.33)	2 (3.33)
Xin-Xing (Dan-Shui)	60	1.07	6 (10)	4 (6.67)
3rd stratum	72	0.64	2 (2.78)	3 (4.17)
Jin-Mei (Jin-Shan)	36	0.71	1 (2.78)	0 (0)
Jin-Long (Xi-Zhi)	36	0.57	1 (2.78)	3 (8.33)
4th stratum	144	0.95	9 (6.25)	10 (6.94)
Gan-Yuan (Shu-Lin)	72	1.00	4 (5.56)	4 (5.56)
Wu-Gu (Wu-Gu)	72	0.89	5 (6.94)	6 (8.33)
5th stratum	24	2.00	0 (0)	0 (0)
Shi-Ding (Shi-Ding)	12	5.00	0 (0)	0 (0)
Shuang-Xi (Shuang-Xi)	12	1.00	0 (0)	0 (0)
Total	936	0.93	78 (8.33)	80 (8.54)

were female sex [odds ratio (OR) = 2.0; 95% confidence interval (CI) = 1.04—03.8; $p = 0.04$] and vaccination against HAV (OR = 82.3; 95% CI = 43.3—156.4; $p < 0.001$).

Discussion

This study showed that the HAV seropositive rate was 8.33% in elementary school children in New Taipei City. The seropositive rate for school children was not significantly different with regard to administrative area, school, and class grade. In the first stratum, the seropositive rate for the children in Ju-Guang school was highest and so was its vaccination rate (21.86%), whereas the children in San-Zhong school and Zhong-Gang school with the lowest seropositive rate had the two lowest vaccination rates at 1.2% and 0.5%, respectively. The seropositive rate was in parallel with the HAV vaccination rate. Parental awareness and physician's suggestion are associated with a higher vaccination rate. Ju-Guang school is situated in the Ban-Qiao area, the urban area of New Taipei City, and thus parents of these school children may have a higher awareness of the vaccine and a greater willingness to vaccinate their children.

We further analyzed vaccination and seropositivity. We found that the presence of anti-HAV antibody was significantly associated with the vaccination status, and the seropositive rate was higher in children with a history of two doses of the vaccination, compared to children with one dose. This finding was compatible with previous studies showing that individuals vaccinated with two or more doses of hepatitis A vaccine had a seroprotective level of

Table 2 Distribution of the seropositive rate of hepatitis A virus for elementary school children in New Taipei City, stratified by class grades

Grade	Number of people	Positive results (*N*)	Positive rate (%)	*p*
1	156	13	8.33	0.570
2	156	16	10.26	
3	156	15	9.62	
4	156	15	9.62	
5	156	8	5.13	
6	156	11	7.05	
Total	936	78	8.33	

Table 3 Factors associated with positive anti-hepatitis A virus antibody in 936 school children

Factor	Patients with positive anti-HAV antibody, *n* (%) *N* = 78	Patients without anti-HAV antibody, *n* (%) *N* = 858	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Female sex	50 (64.1)	434 (50.6)	1.7 (1.1—2.8)	0.02	2.0 (1.04—3.8)	0.04
Unvaccinated	23 (29.5)	833 (97.1)	79.7 (42.5—149.4)	<0.001	82.3 (43.3—156.4)	<0.001
1 dose	16 (20.5)	23 (2.7)				
2 doses	39 (50)	2 (0.2)				

CI = confidence interval; HAV = hepatitis A virus; OR = odds ratio.

antibodies for at least 14 years after vaccination.[14] Kinetic models of antibody decay indicate that the duration of protection is likely to be at least 20 years and possibly lifelong.[15,16] This study revealed that the seropositive rate for children receiving one dose of HAV vaccine was only 41.03%, whereas the rate was increased to 95.12% for children receiving two doses. A previous study shows that the seropositive rate was increased to 100% for vaccinees 21—137 days after one dose of HAV vaccination[15]; however, there were no studies to evaluate the duration that the seroprotection level of antibodies remained after one dose of HAV vaccine. This study indicated that the antibody waned 5—12 years after one dose of HAV vaccine.

In the present study, there were 23 students who had a positive result for anti-HAV antibody but no history of HAV vaccination. We could only presume that these 23 students may have obtained their anti-HAV antibody from a natural infection. Because most children with HAV infection are asymptomatic and a tour to China or Southeast countries is common for the children in Taiwan, the issue of when and where these children contracted the HAV infection could not be identified and remained unknown from the questionnaire.

The seropositive rate of anti-HAV IgG for elementary school children (age, 7—12 years) in the present study was higher than that in previous studies from Taiwan in which the seropositive rate ranged from $<$0.5% to 1.4%.[17—19] The higher seroprevalence of anti-HAV IgG in this study may be because of the higher vaccination rate of HAV in the present study population. This study also identified female sex as significantly associated with the seropositive rate among school children in New Taipei City in Taiwan. The sex difference in human immunity has been recognized in many vaccines against a variety of diseases, including the HAV vaccine.[20—23]

Because of the large population of school-aged children susceptible to HAV infection, we believe an issue is whether HAV vaccine should be included in the routine vaccination program in Taiwan to achieve a better herd immunity against HAV. However, this study was only a pilot study supported by the CDC-Taiwan to preliminarily understand the seroepidemiology of this population group. A nationwide survey for the seroprevalence of children and adolescents should be conducted to understand better the seroepidemiology of this vulnerable population. In addition, the cost-effectiveness of HAV in mass vaccination also should be evaluated before including HAV in a routine vaccine program in Taiwan.

Conflicts of interest

All authors have no conflicts of interest to declare in association with the materials discussed in the article.

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