Original Article

Seroprevalence of *Helicobacter pylori* and Hepatitis A Virus among Children in Rural Central Taiwan

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SUMMARY: *Helicobacter pylori* and hepatitis A virus (HAV) are thought to have similar routes of transmission and epidemiology. This study investigated the seroprevalence of these 2 pathogens among children in rural, central Taiwan. Serum samples were collected from 856 children between 2010 and 2012 and levels of anti-HAV and anti-*H. pylori* antibodies were measured by ELISA. Questionnaires were used to investigate possible risk factors. The overall *H. pylori* and HAV infection rates were 6% and 0.8%, respectively. There was a significant difference in *H. pylori* infection rates (P value = 0.008), but not HAV infection rates, between different age groups. *H. pylori* infection rates were significantly higher in children whose mothers had lower education levels. In contrast, HAV infection rates were significantly higher in children whose fathers had lower education levels. The risk of HAV infection was also 14.20-fold higher in children whose family members had traveled to China or Southeast Asia. No significant correlation was found between *H. pylori* and HAV seropositivity. The seroprevalences of *H. pylori* and HAV were low in rural central Taiwan. Universal HAV vaccination is highly recommended to prevent outbreak due to low seroprevalence.

INTRODUCTION

The hepatitis A virus (HAV) is a non-enveloped, single-stranded RNA virus which causes the most common form of viral hepatitis worldwide, with approximately 1.4 million new cases annually (1). HAV infection, spread by fecal-oral contact, is considered a marker of fecal exposure; its prevalence is related to poor hygiene practices and low socioeconomic status (2,3). Diagnosis of HAV is based on detection of anti-HAV antibodies, which are also used as a marker to monitor viral transmission (4). Although the prevalence of anti-HAV antibodies varies widely worldwide, it is reportedly very high in most of Southeast Asia (5). However, recent global estimates of anti-HAV seroprevalence suggest an epidemiological transition in many countries, including Taiwan (5–8), which is now classified as a region with intermediate HAV endemicity. It is thought that the significant decrease in anti-HAV seroprevalence in Taiwan over the past decade could lead to an increased risk of sudden HAV outbreaks (9–11).

Helicobacter pylori was first identified as a causal factor of peptic ulcer disease (12), and is reportedly associated with gastric ulcers, but not gastric adenocarcinoma, in Taiwanese patients (13). *H. pylori* has also been associated with gastritis and gastric neoplasms

(14–16), and has been classified by the WHO as a class I carcinogen (17). *H. pylori* infection is primarily acquired in childhood or adolescence, and most children in developing countries are infected by 10 years of age, in contrast to children in developed countries, where the prevalence of infection is low (18,19). Studies from China and Korea showed that low socioeconomic status and rural residence were among the primary risk factors for increased prevalence (20,21). *H. pylori* seroprevalence in children has been reported to increase with age in Northern and Southern Taiwan (22). *H. pylori*, like HAV, is thought to be transmitted via the fecal-oral route (23). However, unlike anti-HAV seroprevalence, which has significantly decreased in recent years, *H. pylori* seroprevalence has remained stable over the past decade, suggesting a different transmission route from the fecal-oral route of HAV transmission (24). Although the developing Taiwanese economy has resulted in increased living standards and consequent decrease in the incidence of HAV and *H. pylori* infections, the low seroprevalence of anti-HAV antibodies and increased frequency of travel to highly endemic areas like Southeast Asia could lead to increased risk of infection.

H. pylori and HAV are thought to have a similar epidemiology, but there are conflicting data on whether there is an overlap in their age-specific seroprevalence (24–28). There is currently limited information on the prevalence of *H. pylori* among children in the Changhua district and Changhua coastal area of Taiwan (20). Additionally, there is no national survey of HAV vaccination rates in Taiwan, and most of the data on anti-HAV seroprevalence are from the Taipei region. There are few reports describing age-specific prevalence in other parts of Taiwan (29,30). This study, therefore, aimed to investigate the (i) age-specific prevalence of anti-HAV and anti-*H. pylori* antibodies; (ii) current in-

Received July 22, 2014. Accepted January 21, 2015.
J-STAGE Advance Publication April 10, 2015.
DOI: 10.7883/yoken.JJID.2014.321

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fection status, the HAV vaccination rates; and (iii) major risk factors of HAV and *H. pylori* infection in a pediatric population from the Changhua District/Changhua coastal area, a rural area of central Taiwan. We also performed a systematic review of previous studies investigating the prevalence and risk factors of HAV and *H. pylori* infections among pediatric populations in Taiwan.

METHODS

This study recruited a total of 856 children between 0 and 15 years of age who required venipuncture at the Chang-Bing Show Chwan Memorial Hospital in Changhua, Taiwan, between December 2010 and October 2012. The hospital is located in a rural, coastal area of central Taiwan. Children who had received blood or immunoglobulin (Ig) during the previous year, and immunocompromised patients were excluded. Questionnaires were administered to their parents or guardians to investigate possible risk factors. This study was approved by the Institutional Review Board of the Show Chwan Memorial Hospital (SCMH IRB No: 991005), and informed consent was obtained from the parents and guardians of all study participants.

Questionnaire: The questionnaire was designed to obtain demographic characteristics and personal and family history, and to assess the association between HAV and *H. pylori* infections. The information collected included age; source of water supply; parent educational levels (either senior high school graduate or higher or junior high school graduate or lower); ethnicity of the mother, number of children/people in the household; family history of *H. pylori* infection, peptic ulcer, or gastritis; history of travel by children/family members to China or Southeast Asia within the past 5 years; and whether children (>3 years) had complained of recurrent abdominal pain. Family history of *H. pylori* infection was considered positive if the study subject had positive findings by gastroscopy, *Campylobacter*-like organism test, pathology, stool antigen test, or serologic test. Questionnaires were completed by the parents or guardians of the enrolled children.

Laboratory examination: Levels of *H. pylori*-specific IgG antibodies were measured using enzyme-linked immunosorbent assays (NovaTec Immundiagnostica GmbH, Germany) according to the manufacturer's instructions. *H. pylori* seropositivity infection was defined as IgG titers >20 unit/ml; HAV seropositivity was also determined using commercially available ELISA kits (Diagnostic Automation, Inc., Calabasas, CA, USA) using cut-off values established by the manufacturer.

Statistical analysis: All variables were categorical and are presented as counts and percentages. Differences were compared using Chi-square or Fisher's exact tests with Yate's correction for cell numbers <5 or close to zero. Age trends of patients infected with *H. pylori* or HAV were analyzed using the Cochran-Armitage test. Logistic regression analyses were used to evaluate the correlation between patient variables and *H. pylori* and HAV infection. HAV-positive, and *H. pylori*-positive subjects were grouped by age in order to more easily compare their data with other studies (1–2.9, 3–5.9,

6–8.9, 9–11.9, and 12–14.9 years for *H. pylori* and 1–2.9, 3–4.9, 5–6.9, 7–8.9, 9–10.9, 11–12.9, and 13–14.9 years for HAV). All statistical assessments were 2-sided and *P* values < 0.05 were considered statistically significant. The Cochran-Armitage test was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), and all other statistical analyses were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Systematic review: We performed a systematic review of all available reports describing the prevalence and risk factors of HAV and *H. pylori* infections in pediatric Taiwanese populations. The methods used in this review adhered to the current best practices for conducting systematic reviews of literature, and also to the PRISMA guidelines (31). The Medline, Cochrane, EMBASE, and Google Scholar databases were searched (until Nov 30, 2013). Reference lists of relevant studies were manually searched using the following keywords: hepatitis A, *H. pylori*, Taiwan, prevalence, epidemiology, and seroprevalence.

Studies were considered for inclusion in the review if they described the prevalence of HAV or *H. pylori* in Taiwan. Studies were excluded from the review if they included non-Taiwanese subjects; if they were published in the form of letters, comments, editorials, or case reports; or if they were non-English or non-Chinese publications.

Data were extracted by 2 independent reviewers and disagreements were resolved by consensus. The following data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, participants' demographic information, location and year of screening, overall prevalence and prevalence by age group, and risk factors.

RESULTS

Of 856 children recruited to this study, 110 were <1 year old. Of these 110 infants, 5 who were *H. pylori*-positive (4.5%) and 22 who were HAV-positive (20%) were excluded due to transplacental transfer of antibody from the mother. Of the remaining 746 study subjects, 31 seropositive children whose vaccination records confirmed that they had received HAV vaccination (3 children aged 1–2.9 years, 8 children aged 3–4.9 years, 13 children aged 5–6.9 years, 6 children aged 7–8.9 years, and 1 child aged 9–10.9 years) were also excluded. Based on these data, the total vaccination rate was $31/746 \times 100\% = 4.16\%$.

The overall *H. pylori* infection rate was 6% (43/715 subjects). Among children less than 12 years of age, there was a significant increase in *H. pylori* seroprevalence with age (4.3% for children aged 1–2.9 years, 3.6% for children aged 3–5.9 years, 5.0% for children aged 6–8.9 years, 14.7% for children aged 9–11.9 years, and 7.1% for children aged 12–14.9 years; *P* value = 0.008). *H. pylori* seroprevalence was also significantly higher in children whose mothers had lower educational levels compared to children whose mothers had senior high school or higher educational levels (5.0% for senior high school or higher and 10.6% for junior high school or lower; *P* value = 0.014) (Table 1).

The overall HAV infection rate was 0.8% (6/715 subjects). The infection rates among children aged 1–2.9 years were 0.6%, 0.6% for children aged 3–4.9 years, 0% for children aged 5–6.9 years, 2.4% for children aged 7–8.9 years, 1.4% for children aged 9–10.9 years,

Table 1. Summary for demographic factors of *Helicobacter pylori* infection

	Total ¹ (n = 715)	Negative ² (n = 672)	Positive ² (n = 43)	P value
Gender ⁵				0.903
Female	339 (47.4)	319 (94.1)	20 (5.9)	
Male	376 (52.6)	353 (93.9)	23 (6.1)	
Age (yr) ⁶				0.008 ⁴
1–2.9	164 (22.9)	157 (95.7)	7 (4.3)	
3–5.9	225 (31.5)	217 (96.4)	8 (3.6)	
6–8.9	139 (19.4)	132 (95.0)	7 (5.0)	
9–11.9	102 (14.3)	87 (85.3)	15 (14.7)	
12–14.9	85 (11.9)	79 (92.9)	6 (7.1)	
Source of drinking water ⁵				0.201
Tap water	374 (52.3)	350 (93.6)	24 (6.4)	
Underground water	21 (2.9)	18 (85.7)	3 (7.0)	
Bottle water	77 (10.8)	71 (92.2)	6 (7.8)	
Water station	243 (34.0)	233 (95.9)	10 (4.1)	
Mother's educational level ⁵				0.014 ⁴
Senior high school or higher	583 (81.5)	554 (95.0)	29 (5.0)	
Junior high school or lower	132 (18.5)	118 (89.4)	14 (10.6)	
Father's educational level ⁵				0.251
Senior high school or higher	550 (76.9)	520 (94.5)	30 (5.5)	
Junior high school or lower	165 (23.1)	152 (92.1)	13 (7.9)	
Ethnicity of mother ⁵				0.612
Taiwanese	637 (89.1)	597 (93.7)	40 (6.3)	
Foreign nationality	78 (10.9)	75 (96.2)	3 (3.8)	
Number of persons in household ⁵				0.222
<6	302 (42.2)	280 (92.7)	22 (7.3)	
≥6	413 (57.8)	392 (94.9)	21 (5.1)	
Number of children in household ⁵				0.343
<3	399 (55.8)	378 (94.7)	21 (5.3)	
≥3	316 (44.2)	294 (93.0)	22 (7.0)	
Family history of peptic ulcer or gastritis ⁵				0.632
No	492 (68.8)	461 (93.7)	31 (6.3)	
Yes	223 (31.2)	211 (94.6)	12 (5.4)	
Family history of <i>H. pylori</i> infection ⁵				0.363
No	661 (92.4)	623 (94.3)	38 (5.7)	
Yes	54 (7.6)	49 (90.7)	5 (9.3)	
Children's complaint of RAP ^{3,5}				0.379
No	412 (74.4)	383 (93.0)	29 (7.0)	
Yes	142 (25.6)	135 (95.1)	7 (4.9)	
Family history of RAP ⁵				0.114
No	506 (70.8)	471 (93.1)	35 (6.9)	
Yes	209 (29.2)	201 (96.2)	8 (3.8)	
Hepatitis A virus infection ⁵				0.312
Negative	709 (99.2)	667 (94.1)	42 (5.9)	
Positive	6 (0.8)	5 (83.3)	1 (16.7)	

¹: data were presented as counts (column percentage).

²: data were presented as counts (row percentage).

³: there were 161 missing values.

⁴: a significant difference between the 2 groups

P values were obtained using ⁵: chi-square/Fisher's exact test;

⁶: Cochran-Armitage trend test.

RAP, recurrent abdominal pain.

0% for children 11–12.9 years, and 2.1% for children aged 13–14.9 years. None of the investigated demographic factors significantly affected HAV seropositivity (all P values > 0.05) (Table 2).

We used logistic regression analysis to investigate the association between demographic factors and *H. pylori* infection. We found no significant association between any of the patient variables and *H. pylori* seropositivity (Table 3).

We also used logistic regression analysis to investigate the association between demographic factors and HAV seropositivity. The risk of HAV seropositivity in this study was 13.52-fold (95% confidence interval [CI]:

Table 2. Summary of demographic factors in patients with Hepatitis A virus infection

	Total ¹ (n = 715)	Negative ² (n = 709)	Positive ² (n = 6)	P value
Gender ⁵				0.221
Female	339 (47.4)	338 (99.7)	1 (0.3)	
Male	376 (52.6)	371 (98.7)	5 (1.3)	
Age (yr) ⁶				0.392
1–2.9	164 (22.9)	163 (99.4)	1 (0.6)	
3–4.9	160 (22.4)	159 (99.4)	1 (0.6)	
5–6.9	122 (17.1)	122 (100)	0 (0.0)	
7–8.9	82 (11.5)	80 (97.6)	2 (2.4)	
9–10.9	74 (10.3)	73 (98.6)	1 (1.4)	
11–12.9	65 (9.1)	65 (100)	0 (0.0)	
13–14.9	48 (6.7)	47 (97.9)	1 (2.1)	
Source of drinking water ⁵				0.369
Tap water	374 (52.3)	372 (99.5)	2 (0.5)	
Underground water	21 (2.9)	21 (100)	0 (0.0)	
Bottle water	77 (10.8)	77 (100)	0 (0.0)	
Water station	243 (34.0)	239 (98.4)	4 (1.6)	
Mother's educational level ⁵				0.599
Senior high school or higher	583 (81.5)	577 (99.0)	6 (1.0)	
Junior high school or lower	132 (18.5)	132 (100)	0 (0.0)	
Father's educational level ⁵				0.139
Senior high school or higher	550 (76.9)	547 (99.5)	3 (0.5)	
Junior high school or lower	165 (23.1)	162 (98.2)	3 (1.8)	
Ethnicity of mother ⁵				0.501
Taiwanese	637 (89.1)	632 (99.2)	5 (0.8)	
Foreign nationality	78 (10.9)	77 (98.7)	1 (1.3)	
Number of persons in household ⁵				1.000
<6	302 (42.2)	300 (99.3)	2 (0.7)	
≥6	413 (57.8)	409 (99.0)	4 (1.0)	
Number of children in household ⁵				0.093
<3	399 (55.8)	398 (99.7)	1 (0.3)	
≥3	316 (44.2)	311 (98.4)	5 (1.6)	
Children travel to China or Southeast Asia ⁵				0.452
No	647 (90.5)	642 (99.2)	5 (0.8)	
Yes	68 (9.5)	67 (98.5)	1 (1.5)	
Family members travel to China or Southeast Asia ⁵				0.191
No	464 (64.9)	462 (99.6)	2 (0.4)	
Yes	251 (35.1)	247 (98.4)	4 (1.6)	
<i>Helicobacter pylori</i> infection ⁵				0.312
Negative	672 (94.0)	667 (99.3)	5 (0.7)	
Positive	43 (6.0)	42 (97.7)	1 (2.3)	

See Table 1, footnote.

Table 3. Association between demographic factors and *Helicobacter pylori* infection¹

	OR	P value
Gender		
Female	Reference	
Male	0.95 (0.49, 1.82)	0.948
Age (yr)		
1–2.9	Reference	
3–5.9	0.85 (0.29, 2.48)	0.771
6–8.9	1.09 (0.35, 3.37)	0.881
9–11.9	2.83 (0.99, 8.11)	0.053
12–14.9	1.42 (0.42, 4.83)	0.576
Source of drinking water		
Tap water	Reference	
Underground water	3.93 (0.99, 15.68)	0.052
Bottle water	1.28 (0.48, 3.38)	0.625
Water station	0.74 (0.33, 1.64)	0.461
Mother's educational level		
Senior high school or higher	Reference	
Junior high school or lower	2.17 (0.96, 4.90)	0.063
Father's educational level		
Senior high school or higher	Reference	
Junior high school or lower	1.15 (0.54, 2.45)	0.716
Ethnicity of mother		
Taiwanese	Reference	
Foreign nationality	0.35 (0.09, 1.31)	0.117
Number of persons in household		
<6	Reference	
≥6	0.68 (0.34, 1.40)	0.296
Number of children in household		
<3	Reference	
≥3	1.20 (0.59, 2.46)	0.613
Family history of peptic ulcer or gastritis		
No	Reference	
Yes	0.85 (0.34, 2.12)	0.731
Family history of <i>H. pylori</i> infection		
No	Reference	
Yes	1.81 (0.56, 5.93)	0.324
Family history of RAP		
No	Reference	
Yes	0.62 (0.24, 1.55)	0.304
Hepatitis A virus infection		
Negative	Reference	
Positive	3.69 (0.35, 39.15)	0.279

¹: Children's complaint of RAP not included because there were 161 missing values.
RAP, recurrent abdominal pain.

Table 4. Association between demographic factors and Hepatitis A virus infection

	OR	P value
Gender		
Female	Reference	
Male	3.96 (0.37, 42.91)	0.257
Age (yr)		
1–2.9	Reference	
3–4.9	2.09 (0.07, 60.68)	0.668
5–6.9	NA	NS
7–8.9	14.33 (0.66, 311.62)	0.090
9–10.9	4.28 (0.09, 213.77)	0.467
11–12.9	NA	NS
13–14.9	4.73 (0.20, 113.01)	0.337
Source of drinking water		
Tap water	Reference	
Underground water	NA	NS
Bottle water	NA	NS
Water station	3.01 (0.39, 23.28)	0.292
Mother's educational level		
Senior high school or higher	Reference	
Junior high school or lower	NA	NS
Father's educational level		
Senior high school or higher	Reference	
Junior high school or lower	13.52 (1.40, 130.51)	0.024*
Ethnicity of mother		
Taiwanese	Reference	
Foreign nationality	2.68 (0.03, 275.182)	0.676
Number of persons in household		
<6	Reference	
≥6	0.98 (0.08, 11.45)	0.986
Number of children in household		
<3	Reference	
≥3	14.07 (0.69, 286.22)	0.085
Children travel to China or Southeast Asia		
No	Reference	
Yes	0.52 (0.01, 44.53)	0.771
Family members travel to China or Southeast Asia		
No	Reference	
Yes	14.20 (1.11, 182.23)	0.042*
<i>Helicobacter pylori</i> infection		
Negative	Reference	
Positive	5.04 (0.22, 114.93)	0.311

* : a significant difference between the 2 groups.
NA, not available; NS, not significant.

1.40, 130.51) higher in children whose fathers had junior high school or lower education levels compared to children whose fathers had senior high school or higher education levels (Table 4). The risk of HAV infection was also 14.20-fold (95% CI: 1.11, 182.23) higher in children whose family members had traveled to highly endemic regions in China and Southeast Asia, compared to children whose family members had not traveled to these regions.

We performed a systematic review of all publications describing the prevalence and risk factors of HAV and *H. pylori* infections in Taiwanese populations. A total of 275 studies were identified using the relevant keywords; among these, 255 non-relevant studies were

excluded. Of the 20 relevant studies, 1 study was excluded because it lacked numerical data (Fig. 1).

A list of the included studies and their characteristics is shown in Table 5. Nine studies each described the prevalence and seroepidemiology of *H. pylori* and HAV. One study described the association between anti-HAV seropositivity and anti-*H. pylori* antibodies. The number of subjects ranged from 106 to 2,551. The overall prevalence of anti-HAV antibodies ranged from 0.6% to 98.1%. The overall anti-*H. pylori* IgG prevalence ranged from 7.6% to 54.7%.

We analyzed the prevalence of anti-*H. pylori* IgG and anti-HAV antibodies by age group; the data are presented in Tables 6 and 7, respectively.

We analyzed studies that performed multivariate analysis to identify risk factors of *H. pylori* or HAV in-

Fig. 1. Flow chart for study selection.

fection (Table 8). *H. pylori* seropositivity was not associated with the number of siblings, parent educational levels, or family income (32); with gender, ethnicity, socioeconomic level, or source of drinking water (33); with family history of peptic ulcer or gastritis, or family member travel to other countries (28); or with region (34). HAV seropositivity was not associated with gender, ethnicity, parental education (35); with source of water supply, family member travel to other countries, or family history of alcohol or smoking (28); or with region and urbanization level (10,36).

DISCUSSION

In this study, we investigated the seroprevalence of HAV and *H. pylori* among children from different age groups in a rural, coastal area of central Taiwan. We found no significant differences in HAV seropositivity between children in different age groups. The total HAV vaccination rate was low. HAV seropositivity was significantly higher in (i) children whose fathers had a lower educational level compared to children whose fathers had a high school or higher level of education and (ii) children whose family members had traveled to China or Southeast Asia. However, *H. pylori* infection rates in children varied significantly with age. *H. pylori* seropositivity was also significantly associated with the educational level of the mother.

Our present study showed low anti-HAV seroprevalence rates among children in rural central Taiwan. The prevalence of anti-HAV antibodies (0.96%; 2/209 patients) in patients born between 1984 and 1985 was shown to be due to natural HAV infection, while the 0.6% (1/168 patients) prevalence in patients born between 1993 and 1994 was due to HAV vaccination (37). Additionally, children aged 7–15 years had a signifi-

cantly lower prevalence of anti-HAV antibodies compared to teachers in central Taiwan, and anti-HAV seroprevalence was higher among children living in rural and aboriginal areas compared to that among those living in urban areas (35). These study findings were consistent with other reports that HAV seropositivity in Taiwan has significantly declined following improvement of socioeconomic status (29,38,39). Since the HAV vaccine was available in central Taiwan only after 2000, the prevalence of anti-HAV antibodies in children older than 7 years of age in the study by Tsai et al. was a reflection of true infection and not vaccination. A recent report on HAV seropositivity among elementary school children in New Taipei City in 2012–2013 showed an overall seropositivity rate of 8.33% in urban areas of Taiwan, whereas seropositivity rates were as low as 0.5% in rural areas (40). The low seropositivity was significantly associated with vaccination status. These data were consistent with the low seroprevalence rates seen in our present study, which was conducted in the Changhua District/Changhua coastal area, a rural area of central Taiwan. It is important to note that the anti-HAV seroprevalence rates in our study were significantly lower than those reported in the USA (41) and South Korea (42,43), where children aged 1–10 years had seroprevalence rates of more than 50%. Based on guidelines issued by the Advisory Committee on Immunization Practices, all children in the USA are vaccinated against HAV between 12 and 23 months of age. This was in contrast to our data, where the vaccination rate was 4.2% and only 31 children were seropositive due to HAV vaccination. The low vaccination rates in Taiwan could be due to the fact that, although the HAV vaccine is available to anyone over 1 year of age, it is not covered under the National Health Insurance program and remains unaffordable, especially in rural

Table 5. Summary of characteristics of included studies

1st author	Publication year	Journal	Screening tool	Screening area	Screening year	Nnum-ber of subjects	Age (yr), mean $\pm$ sd	F/M	Overall prevalence (%)
<i>H. pylori</i>									
Chi	2009	J Formos Med Assoc.	¹³ C urea breath test (UBT)	Lanyu Island	2008	106	14.3 $\pm$ 1.4	51/55	54.7
Lin	2007	Helicobacter.	<i>H. pylori</i> IgG antibodies (ELISA)	Central Taiwan: Taichung County and Taichung City, Changhua County, and Yunlin County	NA	2,203	NA	1,157/1,046	15.1
Lin	2005	J Microbiol Immunol Infect.	<i>H. pylori</i> IgG antibodies (ELISA)	Danshuei Township	2003	289	Range 7–12	141/148	21.4
Lee	2004	Pediatr Int.	<i>H. pylori</i> IgG antibodies (ELISA)	Taipei City	1999	1,800	Range birth-20	835/965	14.8
Yang	2003	J Formos Med Assoc.	<i>H. pylori</i> IgG antibodies (ELISA)	Tainan City and County	1998	924	Range 0.3–40	451/473	23.7
Chen	2003	Helicobacter.	<i>H. pylori</i> IgG antibodies (ELISA)	Green Island and Lanyu Island	1996	229	14.05 $\pm$ 0.74	113/116	75
Lin	2000	Am J Trop Med Hyg.	<i>H. pylori</i> IgG antibodies (ELISA)	Central Taiwan: Taichung County, Taichung City, Miaoli County, Changhua County, and Nantou County	NA	2,151	NA	1,048/1,103	7.6
Lin	1999	Am J Trop Med Hyg.	<i>H. pylori</i> IgG antibodies (ELISA and latex agglutination)	Central Taiwan: Taichung County and Taichung City, Miaoli County, Changhua County, and Nantou County	NA	2,551	Range 3–6	1,193/1,358	8.1
Tsai	1995	Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.	<i>H. pylori</i> IgG antibodies (ELISA)	Taipei City	1989	428	Range 0–12	157/271	8.4
Lin	1993	Scand J Gastroenterol.	<i>H. pylori</i> IgG antibodies (ELISA)	Chu-Tung, Po-Tzu, Pei-Nan, and Ta-An Townships	NA	823	NA	413/410	54.4
HAV									
Tsai	2011	J Med Virol.	anti-HAV IgG (microparticle enzyme immunoassay)	Central Taiwan: Taichung County, Taichung City, Changhua County, and Yunlin County	2004–2006	2,208	NA	1,160/1,048	8
Chen	2010	Chang Gung Med J.	anti-HAV IgG	Taihsi Township	2006	168	NA	NA	0.6
Lin	2005	J Microbiol Immunol Infect.	anti-HAV IgG (qualitative enzyme immunoassay)	Danshuei Township	2003	289	Range 7–12	141/148	1.4
Yang	2003	J Formos Med Assoc.	anti-HAV IgG (radioimmunoassay)	Tainan City and County	1998	500	Range 0.3–40	NA	13
Chen	2003	Helicobacter.	anti-HAV IgG (radioimmunoassay)	Green Island and Lanyu Island	1996	229	14.05 $\pm$ 0.74	113/116	58.5
Wang	2001	J Med Virol.	anti-HAV IgG (radioimmunoassay)	Tainan	1998	948	NA	471/477	15.5
Tseng	2001	J Formos Med Assoc.	anti-HAV IgG (qualitative enzyme immunoassay)	Taipei City: Peitou and Shihlin Districts	1999	1,017	NA	525/492	25.2
Lin	2000	Infection.	anti-HAV IgG (enzyme immunoassay)	Hualien: Fushiu, Sholin, Futien, and Fonbin	1998	1,293	NA	725/568	98.1
Lin	2000	Am J Trop Med Hyg.	anti-HAV IgG (qualitative enzyme immunoassay)	Central Taiwan: Taichung County, Taichung City, Miaoli County, Changhua County, and Nantou County	NA	2,151	NA	1,048/1,103	4.2
Liu	1994	Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.	anti-HAV IgG (radioimmunoassay)	Tainan City and County	1992	738	NA	NA	25.6
Wang	1993	J Med Virol.	anti-HAV IgG (enzyme immunoassay)	Taiwan: 20 townships by stratified random sampling	1991	875	14.3 $\pm$ 1.0	NA	31.5
Hsu	1985	J Med Virol.	anti-HAV IgG (radioimmunoassay)	Taipei City	1984	1,200	NA	553/647	6.1
Hwang	1983	Intervirol.	anti-HAV IgG (radioimmunoassay)	Taipei City	1976	823	NA	355/418	22.1

Table 6. Seroprevalence of *H. pylori* by age group

1st author	Publication year	Journal	Age (yr)	Prevalence (%)
Chi	2009	J Formos Med Assoc.	< 13	47.6
			13-14	50
			14-15	53.8
			> 15	72.2
Lin	2007	Helicobacter.	9-12	11
			13-15	13.5
			≥25	45.1
Lin	2005	J Microbiol Immunol Infect.	7	14.5
			8	16.9
			9	30.4
			10	14.8
			11	35
			12	24.2
Lee	2004	Pediatr Int.	0-1	12.1
			1-3	2.8
			3-6	7.7
			6-9	9.1
			9-12	14
			12-15	19.5
			15-18	21.5
			18-20	16.2
Yang	2003	J Formos Med Assoc.	< 1	10
			1-4	9.6
			5-8	15.4
			9-12	13.9
			13-15	26.1
			16-19	30.7
			20-24	46
			25-29	50
			30-39	42
			13	70
Chen	2003	Helicobacter.	14	68.8
			15	88.7
			children teacher	6.4
Lin	2000	Am J Trop Med Hyg.	30.3	
Lin	1999	Am J Trop Med Hyg.	3	4.5
			4	4.4
			5	9.4
			6	11.7
Tsai	1995	Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.	< 1	10
			1-3	0.9
			3-6	3.7
			6-9	13.2
			9-12	19.4
Lin	1993	Scand J Gastroenterol.	< 10	27.1
			10-19	40.9
			20-29	51.4
			30-39	63.6
			40-49	66.3
			50-59	78.1
			60-69	72.4
			≥70	75.6

Table 7. Seroprevalence of HAV by age group

1st author	Publication year	Journal	Age (yr)	Prevalence (%)
Tsai	2011	J Med Virol.	7-12	2.5
			13-15	1.2
			≥20	52
Lin	2005	J Microbiol Immunol Infect.	7	1.8
			8	0
			9	0
			10	3.7
			11	0
Yang	2003	J Formos Med Assoc.	12	3
			< 1	17.1
			1-4	0
			5-8	0
			9-12	0
			13-15	2
			16-19	1.9
			20-24	12.8
			25-29	38.1
			30-39	72.3
Chen	2003	Helicobacter.	13	35
			14	69.8
			15	57.5
Tseng	2001	J Formos Med Assoc.	< 1	23.3
			1-4	2
			4-20	5
			21-30	40.7
			31-50	80
			≥50	97.8
			< 1	20.7
			1-2	0
			3-4	0
			5-6	1.1
Wang	2001	J Med Virol.	7-8	0.8
			9-10	1.4
			11-12	0
			13-15	2
			16-19	4.9
			20-24	12.1
			25-29	36.4
			30-39	65.9
			40-49	89.1
			≥50	94.1
Lin	2000	Am J Trop Med Hyg.	children teacher	0.4
Liu	1994	Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.	< 1	64.6
			1-2	3.6
			3-4	2.9
			5-6	2.3
			7-8	3.7
			9-10	3.3
			11-12	4.1
			13-15	22.9
			16-19	60.7
			20-29	66.7
Hsu	1985	J Med Virol.	30-39	92
			40-49	100
			≥50	100
			< 1	27
			1-2	1.2
			3-4	1.1
			5-6	0.9
			7-8	5.8
			9-10	4.1
			11-12	10.7
Hwang	1983	Entervirology.	13-14	13.6
			Cord blood	96.7
			1-11 mo	35.9
			12-23	1.6
			24-35	1.7
			36-47	3.1
			48-59	11.8
			60-71	14.7
			72-83	15.6
			7-8 yr	17.9
			9-10	25.9
			11-12	50
			13-14	86
			15-19	92

areas. Although selective vaccination based on serostatus is more cost-effective than universal vaccination in areas with high anti-HAV seroprevalence, universal vaccination may be the best strategy in regions where anti-HAV seroprevalence is <45% (44). The low anti-HAV seroprevalence rates among children from rural central Taiwan in our present study suggest a lack of protection against HAV in this population. Based on our data, childhood vaccination may aid in preventing and

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Table 8. Risk factors of infection

1st author	Publication year	Journal	Risk factor	Not risk factor
<i>H. pylori</i>				
Chi	2009	J Formos Med Assoc.	• No	<ul style="list-style-type: none"> • Number of sibship • Number of siblings • Number of person sharing bed • Paternal educational level • Maternal educational level • Family annual income
Lin	2007	Helicobacter.	• No	<ul style="list-style-type: none"> • Gender • Ethnicity • Resident areas • Socioeconomic level • Source of drinking water • No. of family members • Number of siblings • Parental education
Lin	2005	J Microbiol Immunol Infect.	• Family members' knowledge of <i>H. pylori</i> (yes vs no)	<ul style="list-style-type: none"> • Gender • Blood type • Source of water supply • Father's educational status • Mother's educational status • Family history of <i>H. pylori</i> infection • Family members' knowledge of relationship between <i>H. pylori</i> and gastritis • Family history of peptic ulcer or gastritis • Family members' smoking • Family members' use of alcohol • Family members' betel nut habit • Family members' travel to China • Student's travel to China • Students' complaint of recurrent abdominal pain
Lin	1999	Am J Trop Med Hyg.	• Study areas (aboriginal townships vs metropolitan precincts)	<ul style="list-style-type: none"> • Gender • Number of Siblings • Study areas (urban townships vs metropolitan precincts)
HAV				
Tsai	2011	J Med Virol.	• Sources of drinking water (river, lake, ground water, and well water vs Tap-water)	<ul style="list-style-type: none"> • Gender • Ethnicity • Resident areas • Parental education • No. of household
Lin	2005	J Microbiol Immunol Infect.	<ul style="list-style-type: none"> • Family members' knowledge of HAV (yes vs no) • Family history of HAV (yes vs no) 	<ul style="list-style-type: none"> • Gender • Blood type • Source of water supply • Father's educational status • Mother's educational status • Family members' knowledge about HAV vaccination • Family members' smoking • Family members' use of alcohol • Family members' betel nut habit • Family members' travel to China • Student's travel to China
Tseng	2001	J Formos Med Assoc.	• Traveling to regions with a higher anti-HAV endemicity than Taipei (yes vs no)	• no
Wang	1993	J Med Virol.	<ul style="list-style-type: none"> • Geographical Location (south vs north, central vs north) • Urbanizational Level (aboriginal township vs metropolitan precinct) 	<ul style="list-style-type: none"> • Urbanizational Level (rural township vs metropolitan precinct, urban township vs metropolitan precinct)

eradicating acute hepatitis A in high-risk Taiwanese children, such as those whose family members frequently travel to endemic areas in China and Southeast Asia.

A high proportion of HAV infections are reportedly imported by second-generation migrants to low endemic countries like the Netherlands (7). In the present study,

we showed a significant association between HAV infection rates and travel by a family member to areas like China and Southeast Asia. We also showed a significant association between the education level of fathers and HAV infection rates. Based on our data, we speculate that the necessity for fathers with low educational qualifications to travel frequently to regions in China or Southeast Asia to look for employment may contribute to increased infection rates. Our findings also agree with previous studies showing that anti-HAV seroprevalence was not associated with ethnicity (45).

The overall prevalence of *H. pylori* was previously reported to be as high as 54.7% among high school children, significantly higher than the HAV prevalence among children 13–15 years of age (82.4% vs. 5.5%) in Lanyu Island and Green Island, Taiwan (32,46). Recent studies also showed significantly higher prevalence of anti-*H. pylori* antibodies among teachers compared to children 9–15 years of age (33,47), possibly due to improved socioeconomic and environmental conditions in Taiwan between the 1980s and recent years.

H. pylori prevalence rates have been shown to increase with age (22,48). Our results were consistent with these data, showing the highest and lowest *H. pylori* infection rates in children aged 9–12 and 3–6 years, respectively. Our data agreed with a feco-prevalence study conducted in Changhua (20), which strongly suggests that children aged 9–12 years who have symptoms of peptic ulcer in this geographical area should be evaluated for *H. pylori*. The relatively small sample size in the 12–15 year age group may have contributed to the low *H. pylori* seropositivity in this group.

Previous reports showed a significant relationship between low maternal education and *H. pylori* seropositivity in children (20,23,49). It is not clear if this association is due to the education level, or other related factors such as parent income levels, environment, or lack of awareness of good sanitation practices among these women. We are currently unable to conclusively address this issue based on data collected from this study. It will be interesting to investigate the association between maternal educational levels and *H. pylori* seropositivity among children in future studies. Our data were also consistent with a previous study that reported no significant association between *H. pylori* infection and family history of peptic ulcers or gastritis (20). The association between *H. pylori* infection and recurrent abdominal pain in children remains unclear (20,50,51); in this study, we found no significant association between these factors. Additionally, the findings of the present study were in contrast to a previous study from the USA, which reported a significant association between *H. pylori* seropositivity rates and ethnicity (52).

Although some sero-epidemiologic studies reported a common mode of transmission for HAV and *H. pylori* (46,53,54), another study showed no significant association between *H. pylori* and HAV seropositivity (28). Because HAV is a sensitive marker of fecal exposure, correlation between HAV and *H. pylori* seropositivity rates would indicate similar modes of transmission for these 2 pathogens. However, although there was a significant association between the prevalence of anti-*H. pylori* antibodies and anti-HAV antibodies among teachers born before 1980, this was not true among children born

after 1990, suggesting independent *H. pylori* and HAV transmission routes after 1990 (47). In fact, using the kappa statistic to measure seropositivity differences between *H. pylori* and HAV in 500 study subjects, 1 study reported that that was no evidence for a fecal-oral route of transmission for *H. pylori* (55). In the present study, our data agreed with a number of other studies disputing the theory that HAV and *H. pylori* share a common mode of transmission (45,56,57). There is still an intense focus on the transmission route of *H. pylori*. In addition to fecal-oral and oral-oral routes, iatrogenic route, defined as the transmission through food and water or dental plaque, saliva, and periodontal disease, may be another potential route of transmission (58). Elucidation of transmission mechanisms is a crucial goal for management of *H. pylori* infection.

Our study has a number of limitations. The study was not nation-wide and identified a local trend among children in rural central Taiwan. Certain age groups in this hospital-based study had a relatively small sample size. Lastly, although serologic tests are a simple and relatively sensitive way to evaluate *H. pylori* prevalence, the ELISA assay might not be as sensitive in children and the true prevalence may therefore be underestimated.

In conclusion, *H. pylori* and HAV seroprevalence rates were low among children in rural central Taiwan. HAV vaccination is highly recommended for high-risk populations such as children whose family members frequently travel to endemic areas such as China and Southeast Asia.

Conflict of interest None to declare.

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