CSIRO PUBLISHING
Sexual Health
https://doi.org/10.1071/SH19029

Factors associated with hepatitis A virus infection among HIV-positive patients before and after implementation of a hepatitis A virus vaccination program at a medical centre in central Taiwan

Jia-Juen Lin[A,B], *Yuan-Ti Lee*[B,C] *and Hao-Jan Yang*[A,D,E]

[A]Department of Public Health, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan.
[B]Department of Infection Diseases, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan.
[C]School of Medicine, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan.
[D]Department of Family and Community Medicine, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan.
[E]Corresponding author. Email: hjyang@csmu.edu.tw

Abstract. ***Background*:** Taiwan government has promoted the administration of a hepatitis A vaccine at public expense for high-risk groups as a preventive measure after the outbreak of hepatitis A virus (HAV) infections in 2015. The aim of this study was to evaluate the efficacy of such vaccination policy in patients with human immunodeficiency virus (HIV). ***Methods*:** From January 2016 to July 2017, we enrolled 658 HIV-positive male participants. Participants were stratified into anti-HAV-positive (n = 165) and anti-HAV-negative (n = 493) groups. A total of 364 anti-HAV-negative patients received vaccination against HAV and were followed up for 1.5 years. A Cox regression model was used to estimate the effects of factors predicting positive anti-HAV detection after vaccination. ***Results*:** Patients with HIV had an anti-HAV-positive prevalence of 25.1% before vaccination. Of the 364 patients inoculated with the first dose of vaccine, 58.0% received the second dose. Seroresponse rates were 50.0% and 80.6%, respectively. Antibody production was 30.0% lower in patients with a CD4 T-cell count <200 cells/μL (adjusted relative risk (ARR) = 0.7; 95% confidence interval (CI) = 0.5–0.9) compared with those with 500 cells/μL. Hepatitis C co-infection reduced the production of antibodies by 50.0% (ARR = 0.5; 95% CI = 0.2–0.8). ***Conclusion*:** This study suggests that vaccination against hepatitis A be administered when the immunity of an HIV-positive patient is strong. The promotion of the current vaccination policy against hepatitis A in Taiwan has improved the vaccination rate; the response rate for receiving one dose of the vaccine doubled.

Additional keywords: hepatitis C co-infection, immunity, prevalence, seroresponse rates.

Received 26 February 2019, accepted 4 February 2020, published online 23 June 2020

Introduction

Hepatitis A virus (HAV) is primarily transmitted through the faecal–oral route.[1] In previous decades, poor hygienic conditions were a primary factor associated with an extremely high risk of hepatitis A infection in Taiwan. Before 1980, ~85% of the population in Taiwan became infected with HAV between birth and the age of 15 years.[2] Similar poor hygienic conditions contributed to a hepatitis A outbreak in Qingdao, China, between 1986 and 1988.[3] At present, adults aged <40 years in developed countries normally do not have anti-HAV antibodies; the rate of transmission through non-sexual pathways is now reduced owing to improvements in quality of life as well as personal and environmental hygiene.[4,5] As a result, there is currently a larger susceptible population and a higher likelihood of an outbreak.

Between 1992 and 2017, several outbreaks of hepatitis A occurred worldwide.[6–10]

Men who have sex with men (MSM)[11–15] and injecting drug users (IDUs)[16,17] are at higher risk of acquiring hepatitis A.

Taiwan also experienced an outbreak of acute hepatitis A infection between June 2015 and August 2016. Cases in this

outbreak shared similar risk factors with cases reported overseas. During this period, a total of 730 local Taiwanese people were diagnosed with acute hepatitis A infection. Approximately 55.0% of these were co-infected with human immunodeficiency virus (HIV) or other sexually transmissible diseases, such as gonorrhoea and syphilis. Moreover, findings based on the 730 subjects showed that the majority of the cases were MSM.[18]

Hepatitis A infection does not result in chronic hepatitis, and most patients recover naturally and gain lifelong immunity. However, the risk of hepatitis A infection is reportedly increased 2.6-fold in HIV-positive patients compared with HIV-negative individuals.[19] In addition, a greater risk of death following the development of fulminant hepatitis has been reported in patients co-infected with chronic hepatitis B or C.[19–21] Studies have also shown that the virus was present for an extended period of time in the serum of HIV-positive patients with hepatitis A infection; this led to a prolonged period of transmission risk,[22,23] triggering public hygiene problems. Vaccination is a safe and effective preventive measure against hepatitis A. It has been recommended that inoculation programs be targeted to those exhibiting risky behaviour and to HIV-positive patients with specific chronic diseases.[19,21] Vaccination against hepatitis A was previously implemented at personal expense, but since 1 October 2016, Taiwan has been providing HIV-positive patients with one dose of the vaccine at public expense. The HAV vaccine used was VAQTA, 50 units (Merck and Co., Inc., West Point, PA, USA); if administered in two doses, these were given 6–12 months apart.

More than 90.0% of adults produce protective antibodies after the second dose of vaccination,[21,24,25] and the acquired immunity may last for >10 years if the two doses of the vaccine are administered according to the recommended time schedule.[26,27] However, other studies have shown that this vaccine provokes a weaker immune reaction in HIV-positive patients than in HIV-negative individuals. The seroconversion rates of the hepatitis A vaccine in HIV-positive patients were 37.0–49.6% after the first dose,[28,29] 68.0–88.2% after the second dose[21,24] and 91.7% after the third dose.[21] The seroconversion reaction in test subjects injected with three doses of the vaccine was also longer-lasting than that observed in subjects who received two doses.[21] In view of the current situation of the national policy, the aims of this study were to: (1) investigate the prevalence and factors affecting the production of anti-HAV antibodies in HIV-positive patients at a medical centre in central Taiwan before the adoption of the free vaccination policy; and (2) track the seroconversion rate after vaccination against hepatitis A and determine the factors affecting the production of anti-HAV antibodies after the adoption of the free vaccination policy. The results of this study are expected to be useful as feedback for this policy.

Methods

Study design

From January 2016 to July 2017, we selected all (n = 699) HIV-positive patients from a medical centre in central Taiwan. All of these patients were tested for anti-HAV antibodies and assessed for history of receiving the HAV vaccine before the implementation of the free vaccination policy against hepatitis A. We excluded all female patients (n = 23) to prevent gender bias and maintain the homogeneity of the study sample. In addition, patients with incomplete medical records (n = 18) were excluded. The recruitment process and selection criteria are shown in detail in Figure 1.

Data collection

The data collection included assessment of the risk of HIV infection, routine checks of hepatitis A/B/C status, vaccination against hepatitis A, baseline CD4 T-cell count, HIV RNA load, CD4 T-cell count when anti-HAV(+) after vaccination, HIV RNA load when anti-HAV(+) after vaccination, rapid plasma reagin test (RPR titre), amoebiasis history, and use of antiretroviral therapy. Acute hepatitis A infection is defined as meeting the clinical criteria together with the presence of immunoglobulin M (IgM) antibodies against HAV (IgM anti-HAV) in the serum. According to *Morbidity and Mortality Weekly Reports: Recommendations and Reports*, 2004,[30] 'serum IgM antibodies are detectable at the time of symptom onset, peak during the acute or early convalescent phase of the disease, and remain detectable for approximately three to six months'. Patients exhibiting IgM antibodies against HAV were therefore considered to have had acute hepatitis A. These data were obtained after consultation with a physician at the clinic. The patients provided consent for their data to be used for research purposes.

Laboratory investigations

Anti-HAV antibodies were detected using a qualitative test (Architect HAVAb-IgG and IgM assay; Abbott, Wiesbaden, Germany). Hepatitis B surface antigen (HBsAg), anti-HBs antibodies, and anti-hepatitis C virus (anti-HCV) titres were determined by using enzyme immunoassays (Architect HBsAg; anti-HBs; anti-HCV; Abbott). The IHA test (Cellognost Amoebiasis; Siemens Health Care Diagnostics, Marburg, Germany) detects antibodies specific to *Entamoeba histolytica*. Plasma HIV RNA loads were quantified by using reverse transcription-polymerase chain reaction (Roche AmpLi-Cor, version 2.0; Roche, Branchburg, NJ, USA) with a lower detection limit of 20 (log10-transformed: 1.30) copies/mL, and CD4 counts were determined using flow cytometry (BD FACS Calibur; Becton Dickinson, San Jose, CA, USA). Diagnosis of syphilis was made on the basis of a titre of RPR $\geq$1:4 (RPR Card Test; Becton Dickinson).

Statistical analysis

All statistical analyses were performed using SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY, USA). Uni- and multivariable logistic models were used to estimate the prevalence of anti-HAV antibodies before the implementation of the government-sponsored vaccination program against hepatitis A. The anti-HAV-negative patients received vaccination against HAV and were followed up for 1.5 years. A Cox regression model was used to estimate the effects of factors predicting positive anti-HAV detection after

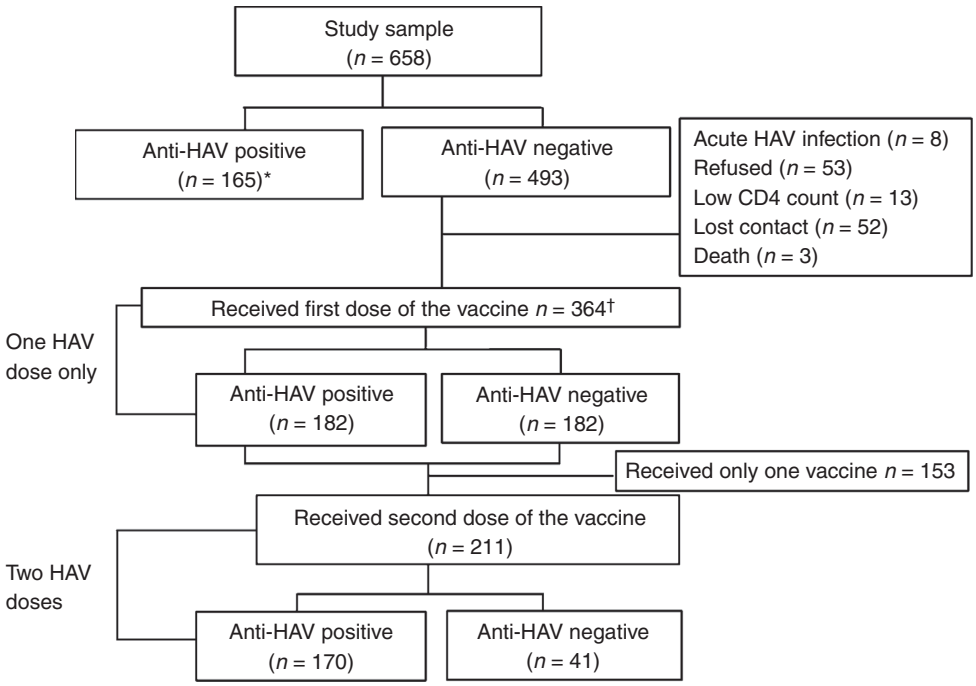

Fig. 1. Study flow diagram. Anti-HAV, Anti-hepatitis A virus. *149 patients were anti-HAV immunoglobulin G (IgG) reactive and 16 patients had acute HAV infection (anti-HAV IgM reactive). †100 patients received self-paid vaccination before the implementation of the policy, whereas 264 patients received government-sponsored vaccination after the implementation of the policy, and 211 patients received two vaccinations and 153 patients received only one vaccination.

vaccination. In this model, the variable 'Age' was merged into two groups, rather than four, as there was only one subject aged >50 years among the 364 anti-HAV negative patients who received vaccinations. In addition, the 'Both Hepatitis B and Hepatitis C co-infection' variable was not included in the Cox regression model because only four out of 364 subjects had co-infection with hepatitis B and hepatitis C and all of them were anti-HAV negative. Due to these modifications, different relative risks (RRs) are available. Differences with $P < 0.05$ were considered statistically significant.

Ethics approval and consent to participate

All the participants in the study gave written informed consent, and the Chung Shan Medical University Hospital Institutional Review Board approved the study (CS16127).

Results

A total of 658 male HIV-positive patients were included in the analysis of this study. Prior to the introduction of the free vaccination policy against hepatitis A, 25.1% (n = 165) of patients tested positive for anti-HAV antibodies, with an acute hepatitis A infection rate of 9.7% (n = 16). After implementation of the policy, the HIV-positive patients received vaccination against HAV and were followed up for 1.5 years. The reasons for missing the vaccination included: refusal of the booster vaccine (n = 53), acute HAV infection (n = 8), low CD4 count (n = 13), loss to follow up (n = 52) and death (n = 3). The rate of acute hepatitis A diagnosis decreased to 1.6% (n = 8) among patients who tested negative for anti-HAV antibodies (n = 493).

According to medical records, of the 364 patients who received vaccination against HAV, 100 patients received self-paid vaccination before the implementation of the policy, while 264 patients received government-sponsored vaccination after the implementation of the policy. Vaccination against HAV can be performed in one or two doses, depending on the ability to pay and intention to receive the booster secondary dose vaccination. Additionally, the rates of vaccination against HAV increased from 20.3% (100/493) to 73.8% (364/493) as a result of the policy rollout.

During the study, as many as 74.9% of the patients (n = 364) showing negative anti-HAV antibody status were inoculated with the first dose of the vaccine; of these, 58.0% (n = 211) received the second dose. The seroresponse rates in these groups were 50.0% (182/364 patients) and 80.6% (170/211 patients), respectively. Accordingly, the overall response rate to the vaccine was 62.9% (229/364 patients) (Fig. 1).

There were 658 male HIV-positive patients (average age: 35.7 years; standard deviation (s.d.): 9.9 years; 95% CI: 34.9–36.4), 72.6% of whom were aged <40 years. The characteristics of subjects at baseline are summarised in Table 1. Briefly, in terms of other comorbid conditions, 13.4% (95% CI: 10.9–16.2) were co-infected with hepatitis C and 28.1% (95% CI: 24.7–31.7) showed a RPR titre ≥4. Twelve percent (95% CI: 9.9–15.1) did not receive the therapy because their CD4 T-cell counts were mostly >200 cells/μL

Table 1. Characteristics of HIV-positive patients at the time of anti-HAV testing (n = 658)

HIV, human immunodeficiency virus; HAV, hepatitis A virus; CI, confidence interval; Non-MSM, including heterosexual and injecting drug users; MSM, men who have sex with men; s.d., standard deviation; IDU, injecting drug users; RPR, rapid plasma reagin test

Variable		*n*	%	95% CI
Age (years)	>50	66	10.0	7.8–12.6
	40–49	114	17.3	14.5–20.4
	30–39	277	42.1	38.3–46.0
	20–29	201	30.5	27.5–34.7
Mean age (mean, s.d.)		35.7	9.9	34.9–36.4
MSM		33.1	7.4	32.6–33.7
Non-MSM		49.3	10.6	48.5–50.1
Risk factors for HIV infection	Heterosexual	61	9.3	7.2–11.7
	MSM	555	84.3	81.3–87.0
	IDU	42	6.4	4.6–8.5
Hepatitis B co-infection	Yes	61	9.3	7.2–11.7
	No	597	90.7	88.3–92.8
Hepatitis C co-infection	Yes	88	13.4	10.9–16.2
	No	570	86.6	83.8–89.1
Both hepatitis B and hepatitis C co-infection	Yes	12	1.8	0.9–3.2
	No	646	98.2	96.8–99.1
Syphilis history	Yes	273	41.5	37.7–45.4
	No	385	58.5	54.6–62.3
RPR titre	<4	473	71.9	68.3–75.3
	≥4	185	28.1	24.7–31.7
Amoebiasis history	Yes	24	3.6	2.4–5.4
	No	634	96.4	94.6–97.6
Antiretroviral therapy	Yes	577	87.7	84.9–90.1
	No	81	12.3	9.9–15.1
CD4 T-cells (cells/μL) (mean, s.d.)		559.5	276.2	538.4–580.7
HIV RNA load, $\log_{10}$ copies/mL (mean, s.d.)		2.1	1.3	2.0–2.2

during the research period and the patients refused treatment at that time. The mean CD4 T-cell count was 559.5 cells/μL (s.d.: 276.2; 95% CI: 538.4–580.7).

We performed uni- and multivariable analyses of factors associated with the detection of positive anti-HAV status in HIV-infected patients before the implementation of the vaccination program. The odds of having anti-HAV antibodies detected was 140.3-fold higher in men aged >50 years (odds ratio (OR): 140.3; 95% CI: 46.2–426.3) and 6.3-fold higher in men aged 40–49 years (OR: 6.3; 95% CI: 3.5–11.5). In MSM at risk of HIV infection, the positive rates of anti-HAV antibodies were reduced by 90.0% (OR: 0.1; 95% CI: 0.1–0.2) compared with non-MSM. IDUs were 4.5-fold more likely to test positive for anti-HAV antibodies (OR: 4.5; 95% CI: 2.4–8.5). In terms of comorbid conditions, patients co-infected with hepatitis B or C were also 2.1-fold (OR: 2.1; 95% CI: 1.2–3.6) and 2.5-fold (OR: 2.5; 95% CI: 1.6–4.0) more likely to test positive for anti-HAV antibodies, respectively.

Multivariable analysis indicated that the factors associated with anti-HAV antibody positivity were age, having sex with men and an RPR titre ≥4. The odds of detecting anti-HAV antibodies increased by 86.6-fold (adjusted OR (AOR): 86.6; 95% CI: 26.1–287.8) in patients aged >50 years and 5.2-fold higher in men aged 40–49 years (AOR: 5.2; 95% CI: 2.7–10.1), respectively. Compared with non-MSM, the positive rate of anti-HAV antibodies in MSM was reduced by 70.0% (AOR: 0.3; 95% CI: 0.1–0.6). Patients with an RPR titre ≥4 showed a 1.7-fold higher positive rate for the presence of anti-HAV antibodies (AOR: 1.7; 95% CI: 1.0–2.8) (Table 2).

We further analysed the factors affecting the production of anti-HAV antibodies in 364 patients who had received the vaccination (Table 3). According to the results of the Cox regression model, antibody production in patients with a CD4 T-cell count <200 cells/μL was decreased by 40.0% (RR: 0.6; 95% CI: 0.5–0.9) compared with those having CD4 T-cell counts ≥500 cells/μL; furthermore, hepatitis C co-infection reduced the antibody production by 60.0% (RR: 0.4; 95% CI: 0.2–0.8). CD4 T-cell count and hepatitis C co-infection continued to be associated factors. Antibody production in patients with a CD4 T-cell count <200 cells/μL was decreased by 30.0% (adjusted RR: 0.7; 95% CI: 0.5–0.9) versus those with a CD4 T-cell count ≥500 cells/μL; similarly, hepatitis C co-infection reduced antibody production by 50.0% (adjusted RR: 0.5; 95% CI: 0.2–0.8).

Discussion

Factors associated with positive anti-HAV detection in HIV-infected patients before the implementation of the vaccination program

Our results show that the prevalence of anti-HAV antibody positivity in patients before the implementation of the free vaccine policy against hepatitis A was 25.1%. This rate was lower than the rates reported in a study conducted by the National Taiwan University Hospital in 2007 (60.9%),[19] in Greece between 2007 and 2011 (35.7%)[4] and the United States between 2009 and 2012 (64.0%).[31] One factor affecting these results may be age. The average age of patients included in this study was 35.7 years, whereas the median ages in the studies conducted by the National Taiwan University Hospital and in Greece were 39.0 and 41.3 years, respectively. Our study found that the positive anti-HAV detection was affected by age, and a greater positive rate of anti-HAV antibodies was observed in older individuals. This result is consistent with research findings from Taiwan and abroad, which have suggested that age is correlated with an increase in the prevalence of hepatitis A infection.[19,32] In the present study, the patients in the MSM group were younger than those in the non-MSM group. After controlling for these two variables, age and MSM, through multivariable analysis, our results still showed that MSM had lower HAV-seropositive rates. Therefore, the lower HAV-seropositive rate found in the MSM participant group in our study could be a result of their relatively younger age. Thus, they were less likely to have produced anti-HAV antibodies through environmental exposure, resulting in a low prevalence of positive detection of anti-HAV antibodies before the implementation of the free vaccination program.

In the multivariable analysis, it was found that syphilis infection was associated with the production of anti-HAV

Table 2. Uni- and multivariable analysis for factors associated with positive anti-HAV detection in HIV-positive patients before the vaccination program (n = 658)

Bold values represent statistical significance. HAV, hepatitis A virus; CI, confidence interval; RPR, rapid plasma reagin test

Variables	Anti-HAV Negative (n = 493) n (%)	Positive (n = 165) n (%)	Odds ratio (95% CI)	Adjust odds ratio (95% CI)
Age (years)				
>50	4 (6.1)	62 (93.9)	**140.3 (46.2–426.3)**	**86.6 (26.1–287.8)**
40–49	67 (58.8)	47 (41.2)	**6.3 (3.5–11.5)**	**5.2 (2.7–10.1)**
30–39	241 (87.0)	36 (13.0)	1.4 (0.8–2.4)	1.3 (0.7–2.3)
20–29	181 (90.0)	20 (10.0)	1.0	1.0
Sexual behaviour/orientation				
MSM	461 (83.1)	94 (16.9)	**0.1 (0.1–0.2)**	**0.3 (0.1–0.6)**
Non-MSM	32 (31.1)	71 (68.9)	1.0	1.0
Injection drug use				
Yes	18 (42.9)	24 (57.1)	**4.5 (2.4–8.5)**	0.4 (0.1–1.4)
No	475 (77.1)	141 (22.9)	1.0	1.0
Hepatitis B co-infection				
Yes	37 (60.7)	24 (39.3)	**2.1 (1.2–3.6)**	1.6 (0.8–3.5)
No	456 (76.4)	141 (23.6)	1.0	1.0
Hepatitis C co-infection				
Yes	51 (58.0)	37 (42.0)	**2.5 (1.6–4.0)**	1.7 (0.8–3.7)
No	442 (77.5)	128 (22.5)	1.0	1.0
Both hepatitis B and hepatitis C co-infection				
Yes	6 (50.0)	6 (50.0)	3.1 (0.9–9.6)	0.4 (0.1–2.7)
No	479 (74.1)	167 (25.9)	1.0	1.0
RPR titre				
≥4	139 (75.1)	46 (24.9)	1.0 (0.7–1.5)	**1.7 (1.0–2.8)**
<4	354 (74.8)	119 (25.2)	1.0	1.0
Amoebiasis history				
Yes	15 (62.5)	9 (37.5)	1.8 (0.8–4.3)	2.3 (0.8–6.2)
No	478 (75.4)	156 (24.6)	1.0	1.0
Antiretroviral therapy				
Yes	433 (75.0)	144 (25.0)	1.0 (0.6–1.6)	0.6 (0.3–1.1)
No	60 (74.1)	21 (25.9)	1.0	1.0

antibodies. Thus, far few studies have investigated the effect of syphilis on the positive rate of anti-HAV antibodies. Notably, the study performed in Greece between 2007 and 2011 did not show an association between sexually transmissible infections and positivity of anti-HAV antibodies.[4] We suggest that syphilis infection implies the participation in unprotected sexual activity, which increases the risk of exposure to hepatitis A through sex.

Effectiveness of the vaccination after implementation of the vaccination program

The HAV seroconversion rate after the first dose of the vaccine against hepatitis A was 50.0%; this rate was at the high end of rates reported in previous studies (37.0–49.6%).[28,29] The seroconversion rate increased to 80.6% after the second dose, similar to previous study results (37.0–88.2%).[21,24,28,29]

Factors associated with successful vaccination included immune conditions and HCV co-infection. A previous study observed a poor response rate to the vaccine against hepatitis A in patients with a CD4 T-cell count <200 cells/μL.[23] However, other research findings regarding the relationship between CD4 T-cell count and response rate to the vaccine were contradictory, with some showing a positive correlation[21,24,25,33] and others not detecting a correlation.[28] In our study, the association between the presence of anti-HAV and CD4 count was statistically significant based on the Cox regression model. Despite the lack of consistent findings from other studies, our study suggests that better immune conditions improved the effectiveness of the vaccine against hepatitis A.

Previous studies suggested that HCV co-infection may affect the vaccination reaction due to immune mechanisms.[34] Similarly, our results showed that HIV/HCV

Table 3. Effects of factors predicting positive anti-HAV detection after vaccination (n = 364)

Bold values represent statistical significance. Note 1: The variable 'Age' was merged into two groups, rather than four, as there was only one subject aged >50 years among the 364 anti-HAV-negative patients who received vaccinations. Note 2: The 'Both hepatitis B and hepatitis C co-infection' variable was not included in the Cox regression model because only 4 out of 364 subjects had co-infection with hepatitis B and hepatitis C and all of them were anti-HAV negative. HAV, hepatitis A virus; CI, confidence interval; RPR, rapid plasma reagin test; s.d., standard deviation; HIV, human immunodeficiency virus

Variables	Anti-HAV			
	Negative (n = 135) n (%)	Positive (n = 229) n (%)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Age (years)				
>40	14 (43.8)	17 (56.3)	0.7 (0.4–1.2)	0.7 (0.4–1.1)
≤ 40	121 (36.4)	212 (63.6)	1.0	1.0
Hepatitis B co-infection				
Yes	9 (36.0)	16 (64.0)	0.9 (0. 6–1.6)	1.1 (0.6–1.8)
No	126 (37.2)	213 (62.8)	1.0	1.0
Hepatitis C co-infection				
Yes	22 (66.7)	11 (33.3)	**0.4 (0.2–0.8)**	**0.5 (0.2–0.8)**
No	113 (34.1)	218 (65.9)	1.0	1.0
RPR titre				
≥4	36 (38.7)	57 (61.3)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
<4	99 (36.5)	172 (63.5)	1.0	1.0
Antiretroviral therapy				
Yes	132 (36.9)	226 (63.1)	1.2 (0.4–3.9)	0.8 (0.2–3.4)
No	3 (50.0)	3 (50.0)	1.0	1.0
CD4 T-cells count when Anti-HAV(+) after vaccination				
<200 cells/μL	6 (85.7)	1 (14.3)	**0.6 (0.5–0.9)**	**0.7 (0.5–0.9)**
200–499 cells/μL	50 (52.1)	46 (47.9)	0.2 (0.0–1.4)	0.3 (0.0–2.3)
≥500 cells/μL	79 (30.3)	182 (69.7)	1.0	1.0
HIV RNA load when Anti-HAV(+) after vaccination, $\log_{10}$ copies/mL (mean, s.d.)	1.6 (1.0)	1.4 (0.5)	0.8 (0.6–1.0)	0.9 (0.6–1.2)

co-infection led to a poor reaction to vaccination against hepatitis A. Individuals with HCV co-infection belong to a high-risk group, among whom vaccinations induce the production of antibodies less easily; consequently, the risk of hepatitis A infection in such patients is higher. Thus, it is important to encourage vaccination and monitor antibody reactions in these individuals.

Vaccination against HAV is the best approach to prevent outbreaks of hepatitis A in high-risk groups. Several recent model papers have estimated that the critical vaccination threshold for preventing outbreaks of hepatitis is >70.0%.[35] In Taiwan, the incidence rate of acute hepatitis A declined when ~65.0% of the patients were immunised or tested positive for HAV.[36] According to a previous study, high-risk individuals were willing to receive the vaccine against hepatitis A, but they were unwilling to pay the vaccination fee.[7] This finding raised the question of whether the inoculation rate could be increased by promoting a national vaccination policy against hepatitis A. The present study showed an increase in the inoculation rate for hepatitis A from 20.3% to 73.8% after the implementation of the free vaccination policy. This represents a substantial improvement compared with the data shown in a previous study, in which the inoculation rates in the MSM and IDU groups were 15.0–21.0% and 5.0–10.3%, respectively.[19] Additionally, the rate of acute hepatitis A infection in our patients decreased from 9.7% to 1.6%. Furthermore, the positive detection of anti-HAV antibodies increased from 25.1% before vaccination to 50.0% after the first dose of the vaccine and 80.6% after the second dose of the vaccine.

Limitations

This study was subject to several limitations. First, this was a single-centre study, and extrapolations based on these data must therefore remain limited. Second, the anti-HAV negative patients were followed up for only 1.5 years, and approximately half of the patients did not receive the secondary dose; the estimate of immunity may thus have been low. Finally, some potential confounding factors, such as recreational drug use or risky sexual behaviours, were not examined. Although this study is thus not fully representative, the data allow us to rethink the current practices in the vaccination policy. We believe that administration of the first dose of the vaccine against hepatitis A to high-risk populations at public expense should not be delayed.

Conclusions

Owing to improvements in quality of life and personal and environmental hygiene, the incidence of hepatitis A infection caused by environmental factors is decreasing. However, intermittent clustered infections in high-risk populations continue to demand attention. Vaccination is one of the best approaches for the prevention of hepatitis A. It is

recommended that the vaccine is administered when HIV-positive patients show strong immune function to achieve the best vaccine performance. Promotion of the vaccination policy in Taiwan has helped to improve the inoculation rate. Our research findings further demonstrate that the vaccine response rate doubled (from 25.1% to 50.0%) after the first dose of the vaccine, and that the second dose further increased effectiveness to 80.6%. In conclusion, our findings support the interpretation that the national policy of providing the first dose of the vaccine against hepatitis A at public expense is reasonable.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

The authors wish to acknowledge all the participating patients of the study and the technical support from laboratory members of Chung Shan Medical University Hospital. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1 Binns C, Low WY. Hepatitis requires public health action. *Asia Pac J Public Health* 2017; 29(5): 348–50. doi:10.1177/1010539517720311

2 Wu JS, Lu CF, Wu LZ, Wong CK, Wu YC, Lee TC, *et al*. Changing seroepidemiology of hepatitis A virus infection between two regions in Taiwan differing in socioeconomic status. *J Formos Med Assoc* 1993; 92(9): 812–5.

3 Chu QS, Xiu YZ, Suen SY, Xie ZB, Yu P. A study of hepatitis outbreaks in between 1986 and 1988. *Asia Pac J Public Health* 1995; 8(1): 3–7. doi:10.1177/101053959500800101

4 Kourkounti S, Paparizos V, Leuow K, Kyriakis K, Antoniou C. Prevalence and titre of antibodies against hepatitis A virus in HIV-infected men having sex with men in Greece. *Infez Med* 2014; 22(3): 206–12.

5 Goh KT, Wong LY, Oon CJ, Kumarapathy S. The prevalence of antibody to hepatitis A virus in Singapore. *Asia Pac J Public Health* 1987; 1(2): 9–11. doi:10.1177/101053958700100203

6 Leentvaar-Kuijpers A, Kool JL, Veugelers PJ, Coutinho RA, van Griensven GJ. An outbreak of hepatitis A among homosexual men in Amsterdam, 1991–1993. *Int J Epidemiol* 1995; 24(1): 218–22. doi:10.1093/ije/24.1.218

7 Mazick A, Howitz M, Rex S, Jensen IP, Weis N, Katzenstein TL, *et al*. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill* 2005; 10(5): 536. doi:10.2807/esm.10.05.00536-en

8 Stokes ML, Ferson MJ, Young LC. Outbreak of hepatitis A among homosexual men in Sydney. *Am J Public Health* 1997; 87(12): 2039–41. doi:10.2105/AJPH.87.12.2039

9 Tortajada C, de Olalla PG, Pinto RM, Bosch A, Caylà J. Outbreak of hepatitis A among who have sex with men in Barcelona, Spain, September 2008-March 2009. *Euro Surveill* 2009; 14(15): 19175.

10 Uhlmann S, Buxton JA. A provincial and territorial review of hepatitis A in men who have sex with men. *Can Commun Dis Rep* 2007; 33(11): 1–11.

11 Friesema IH, Sonder GJ, Petrignani MW, Meiberg AE, van Rijckevorsel GG, Ruijs WL, *et al*. Spillover of a hepatitis A outbreak among men who have sex with men (MSM) to the general population, the Netherlands, 2017. *Euro Surveill* 2018; 23(23): 1800265. doi:10.2807/1560-7917.ES.2018.23.23.1800265

12 Ndumbi P, Freidl GS, Williams CJ, Mårdh O, Varela C, Avellón A, *et al*. Hepatitis A outbreak disproportionately affecting men who have sex with men (MSM) in the European Union and European Economic Area, June 2016 to May 2017. *Euro Surveill* 2018; 23(33): 1700641. doi:10.2807/1560-7917.ES.2018.23.33.1700641

13 Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, *et al*. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. *Euro Surveill* 2017; 22(5): 30454. doi:10.2807/1560-7917.ES.2017.22.5.30454

14 Dabrowska MM, Nazzal K, Wiercinska-Drapalo A. Hepatitis A and hepatitis A virus/HIV coinfection in men who have sex with men, Warsaw, Poland, September 2008 to September 2009. *Euro Surveill* 2011; 16(34): 19950.

15 Tortajada C, de Olalla PG, Diez E, Pinto RM, Bosch A, Perez U, *et al*. Hepatitis A among men who have sex with men in Barcelona, 1989–2010: insufficient control and need for new approaches. *BMC Infect Dis* 2012; 12: 11. doi:10.1186/1471-2334-12-11

16 Perevoscikovs J, Lucenko I, Magone S, Brila A, Curikova J, Vennema H. Community-wide outbreak of hepatitis A in Latvia in 2008 – an update. *Euro Surveill* 2009; 14(3): 19092.

17 Lugoboni F, Pajusco B, Albiero A, Quaglio G. Hepatitis A virus among drug users and the role of vaccination: a review. *Front Psychiatry* 2012; 2: 79. doi:10.3389/fpsyt.2011.00079

18 Centers for Disease Control (Taiwan). Free hepatitis A vaccination pilot program. Taipei: Taiwan Centers for Disease Control; 2017. Available online at: https://www.cdc.gov.tw/professional/info.aspx?treeid=F6A75B7E8EBD8AC2&nowtreeid=58C9F68989623F48&tid=F83ED7AEC6BC7618 [verified 18 September 2018].

19 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(5): e199–205. doi:10.1016/j.ijid.2008.12.009

20 Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, Chen PJ, *et al*. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. *J Infect Dis* 1990; 162(4): 817–22. doi:10.1093/infdis/162.4.817

21 Tseng YT, Chang SY, Liu WC, Sun HY, Wu CH, Wu PY, *et al*. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. *Hepatology* 2013; 57: 1734–41. doi:10.1002/hep.26210

22 Ida S, Tachikawa N, Nakajima A, Daikoku M, Yano M, Kikuchi Y, *et al*. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. *Clin Infect Dis* 2002; 34(3): 379–85. doi:10.1086/338152

23 Mena G, Garcia-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: a review. *Hum Vaccin Immunother* 2015; 11(11): 2582–98. doi:10.1080/21645515.2015.1055424

24 Kemper CA, Haubrich R, Frank I, Dubin G, Buscarino C, McCutchan JA, *et al*. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis* 2003; 187(8): 1327–31. doi:10.1086/374562

25 Neilsen GA, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. *J Infect Dis* 1997; 176(4): 1064–7. doi:10.1086/516512

26 World Health Organization (WHO). WHO position paper on hepatitis A vaccines – June 2012. *Wkly Epidemiol Rec* 2012; 87(28/29): 261–76.

27 Hens N, Habteab Ghebretinsae A, Hardt K, Van Damme P, Van Herck K. Model based estimates of long-term persistence of inactivated hepatitis A vaccine-induced antibodies in adults. *Vaccine* 2014; 32(13): 1507–13. doi:10.1016/j.vaccine.2013.10.088

28 Overton ET, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. *J Viral Hepat* 2007; 14(3): 189–93. doi:10.1111/j.1365-2893.2006.00822.x

29 Quaglio G, Pajusco B, Civitelli P, Migliozzi S, Des Jarlais DC, Romanò L, *et al*. Immunogenicity, reactogenicity and adherence with hepatitis A vaccination among drug users. *Drug Alcohol Depend* 2004; 74(1): 85–8. doi:10.1016/j.drugalcdep.2003.12.001

30 Foodborne Illness Primer Work Group. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR Recomm Rep* 2004; 53(RR-4): 1–33.

31 DeGroote NP, Mattson CL, Tie Y, Brooks JT, Garg S, Weiser J. Hepatitis A virus immunity and vaccination among at-risk persons receiving HIV medical care. *Prev Med Rep* 2018; 11: 139–44. doi:10.1016/j.pmedr.2018.06.006

32 Jabłonowska E, Kuydowics J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: a 5-year observation. *Int J STD AIDS* 2014; 25(10): 745–50. doi:10.1177/0956462413518902

33 Wallace MR, Brandt CJ, Earhart KC, Kuter BJ, Grosso AD, Lakkis H, *et al*. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis* 2004; 39(8): 1207–13. doi:10.1086/424666

34 Huang SH, Huang CH, Wang NC, Chen TC, Lee YT, Lin SP, *et al*. Early seroreversion after 2 doses of hepatitis A vaccination in human immunodeficiency virus-positive patients: incidence and associated factors. *Hepatology* 2019; 70(2): 465–75. doi:10.1002/hep.30495

35 Regan DG, Wood JG, Benevent C, Ali H, Smith LW, Robertson PW, *et al*. Estimating the critical immunity threshold for preventing hepatitis A outbreaks in men who have sex with men. *Epidemiol Infect* 2016; 144(7): 1528–37. doi:10.1017/S0950268815002605

36 Chen GJ, Lin KY, Sun HY, Sheng WH, Hsieh SM, Huang YC, *et al*. Incidence of acute hepatitis A among HIV-positive patients during an outbreak among MSM in Taiwan: impact of HAV vaccination. *Liver Int* 2018; 38(4): 594–601. doi:10.1111/liv.13468