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RESEARCH ARTICLE

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Immunogenicity and safety of hepatitis A vaccine at different vaccination intervals among adults aged 18 years and above: Interim results

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ABSTRACT

This study aims to evaluate the immunogenicity and safety of hepatitis A vaccine administered with one or two doses among adults. Participants aged 18 y and above were recruited, with blood samples collected prior to vaccination for anti-HAV antibodies screening. All participants received a single dose of hepatitis A vaccine. Participants who tested negative for anti-HAV antibodies before vaccination were randomly assigned to four groups to receive the second dose at different intervals. Blood samples were collected for antibody testing. Adverse events were reported within 28 d after each vaccination for safety assessment. A total of 1,042 participants were included in study analysis. The seroprevalence of anti-HAV antibodies was 52.56%, with the lowest seroprevalence observed among adults aged 36–40 y. The overall seroconversion rate 1 month after the first dose of hep A vaccine was 67.68%. For participants in group A, the second dose was administered at a 6-month interval, both the seropositivity and seroconversion rates reached 100%, with a GMC of 3602.44 IU/L 1 months after the second vaccination. Difference of GMCs had no statistical significance across age groups. The incidence of adverse reactions (ARs) within 28 d after second vaccination in group A was 3.85%. No serious adverse events (SAEs) related to vaccination were reported. This interim analysis highlights the susceptibility of adults to hepatitis A virus (HAV). One or two doses of hepatitis A vaccine demonstrated good immunogenicity and safety in adults.

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Hepatitis A; seroprevalence; hepatitis A vaccine; safety; immunogenictiy; seroconversion rate; adults

Introduction

Hepatitis A is a preventable disease caused by the hepatitis A virus (HAV). It can spread through numerous outbreaks, especially related to contaminated fruits and vegetables both fresh and frozen.[1] In recent years, hepatitis A outbreaks caused by fresh and frozen fruits, or frozen seafood have been frequently reported in various countries.[2–4] Between 2013 and 2014, a major outbreak in several European countries resulted in 1,589 hepatitis A cases attributed to frozen mix berries.[2,3] In 2022 and 2023, there were multistate outbreaks linked to imported organic strawberries in the United States reported.[4,5] Additionally, reported cases among adults increased in recent years. In 2022, the reported number of hepatitis A cases in the United States was nearly double that of 2015, with 49% of cases occurring among people aged 30–49 y.[6] Similar situations were found in Brazil, South Korea and other countries by cases and incidences according to years and ages.[7–13] Consequently, there was still high possibility that hepatitis A may potentially cause outbreaks in adults by contaminated food.

In China, the introduction of the hepatitis A vaccine into the Expanded Program on Immunization (EPI) in 2008, along with improvements in sanitation and hygiene, has significantly reduced the incidence of Hepatitis A.[14] However, National Serological Surveys indicated a susceptibility gap among individuals born between 1988 and 2004, as they were born before the vaccines were introduced and had limited exposure to HAV.[14] Additionally, lifestyle factors in coastal cities, such as the consumption of raw or undercooked seafood, contribute to the increased risk of Hepatitis A in certain populations. For example, Liaoning Province reported a 138.2% increase in hepatitis A cases in February 2020 compared to the same period in 2019, with most cases occurring among adults aged 20–59 y in Dalian and Dandong.[15]

Above all, data from different countries indicated the susceptibility to HAV of adults, especially those aged 30–49 y old. Given that adults are more likely to experience severe symptoms, including liver failure or, in rare cases, death when compared to children less than 6 y of age,[1,16,17] attention must be paid, and actions are essential to prevent the potential outbreak. Vaccination has been shown to be an effective measure to prevent HAV infection and control related outbreaks. *Expert recommendation on hepatitis A vaccination*, published in 2023 by the China Foundation for Hepatitis Prevention and Control,

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emphasized the necessity of hepatitis A vaccination and gave suggestions.[18]

Despite these recommendations, there is limited data on hepatitis A prevalence and vaccination effect among adults. Evaluating the immunogenicity and safety of hepatitis A vaccination at different interval is critical for guiding real-world vaccination. Therefore, we conduct this study to explore the immunogenicity and safety of hepatitis A vaccine at different vaccination interval among adults, so as to provide more evidence of seroprevalence of anti-HAV antibodies and vaccination effect among adults in China.

The vaccine used in this study was an inactivated hepatitis A vaccine (Healive®) developed by Sinovac Biotech Co., Ltd. This vaccine has been licensed for more than 20 y, and more than 100 million doses have been used globally in about 40 counties. The safety and immunogenicity have been verified via lots of studies and post-marketing surveillance.[19–21]

Method

Study design

This was a single-site, open-label, phase IV clinical trial conducted in Fengcheng, Liaoning province, China. Participants aged 18 y and older were recruited, and blood samples were collected prior to vaccination to screen for anti-HAV antibodies. All participants received one dose of hepatitis A vaccine. Those who tested negative for anti-HAV antibodies (HAV-susceptible individuals) were randomly assigned to four groups to receive the second dose at different intervals. Blood samples were collected 1 month after the first dose, before and 1 month after the second dose to evaluate immunogenicity. Adverse events were reported within 28 d after vaccination for safety assessment.

This study was approved by the Ethics Committee of the Liaoning Provincial Center for Disease Control and Prevention (ref. number 2023–001). Written informed consents were obtained from all participants. All procedures were conducted per the guidelines of the Institutional Ethics Committee and the tenets of the Declaration of Helsinki. This study was registered with ClinicalTrials.Gov (NCT06058416).

Participants who met any of the following exclusion criteria were excluded from this study: (1) individuals with a clear history of hepatitis A infection; (2) individuals who had received inactivated hepatitis A vaccine, live-attenuated hepatitis A vaccine or hepatitis A and B combined vaccine; (3) individuals who experienced severe allergic reactions to the study vaccines or similar vaccines accepted in the past; and other detailed exclusion criteria listed on ClinicalTrials.gov (NCT06058416).

Procedures

This study aimed to recruit 1,000 participants aged 18 y and older. Eligible participants who provided written informed consent and agreed to follow the study procedures were enrolled with a unique subject ID. Demographic information was collected, including gender, ethnicities, and health conditions.

Before vaccination, blood samples were collected from all participants to screen for anti-HAV antibodies. Subsequently, all participants received a single dose of hepatitis A vaccine. Blood samples were tested using an enzyme-linked immunosorbent assay (ELISA) method, which took less time to show results and more convenient for determining HAV-susceptible participants who needed blood samples collected 1 month after the first vaccination.

However, ELISA only gave the qualitative results, thus the quantitative detection using electrochemiluminescence immunoassays (ECLIA) method was needed to re-test the blood samples to give the concentrations of anti-HAV antibody. In cases where discrepancies arose between qualitative (ELISA) and quantitative (ECLIA) results for the same samples, the quantitative results obtained using the ECLIA assay were considered definitive in defining HAV-susceptible participants.

Finally, HAV-susceptible individuals were randomly divided (1:1:1:1) into Groups A to D using random numbers generated by Excel. Participants in these groups received the second dose of vaccine at different intervals: 6 months (Group A), 18 months (Group B), 36 months (Group C), and 60 months (Group D). Blood samples were collected before and 1 month after the second vaccination. All blood samples, together with those collected 1 month after the first vaccination, were tested for concentrations of anti-HAV antibodies using only ECLIA assay (Figure 1).

For safety assessment, all participants were required to report any adverse events (AEs) occurring within 28 d after each vaccination dose using a WeChat mini-program. The data collection system and WeChat mini-program utilized in this study were developed by Beijing Shengyuan Jiaye Biotechnology Co., Ltd., as described in detail elsewhere.[22] To ensure timely reporting of safety data on the mini-program, investigators conducted follow-up phone calls on the seventh and twenty-eighth d after each vaccination.

All reported AEs were assessed and classified in accordance with the guidelines issued by the China's National Medical Products Administration (NMPA).[23] Investigators evaluated the causality between AEs and vaccination. Any AE determined as possibly, probably, or definitely related to vaccination was classified as an adverse reaction (AR). Serious adverse events (SAE) were recorded throughout the study.

Vaccines

Hepatitis A vaccine (Healive®) was developed and produced by Sinovac Biotech Co., Ltd (Beijing, China). Hepatitis A virus strain TZ84 was cultivated in human embryonic lung diploid fibroblast cell line (2BS) by cell factory technology. The virus was harvested, purified by chromatography, inactivated by formalin, and then adsorbed onto aluminum hydroxide. Healive® (for people aged 16 y and above) contains 500 U inactivated hepatitis A virus per dose in 1 mL of aluminum hydroxide solution, without preservative (batch: 202206038).

Outcome

For immunogenicity assessment, the primary immunogenicity outcome was the seroconversion rate 1 month after the second

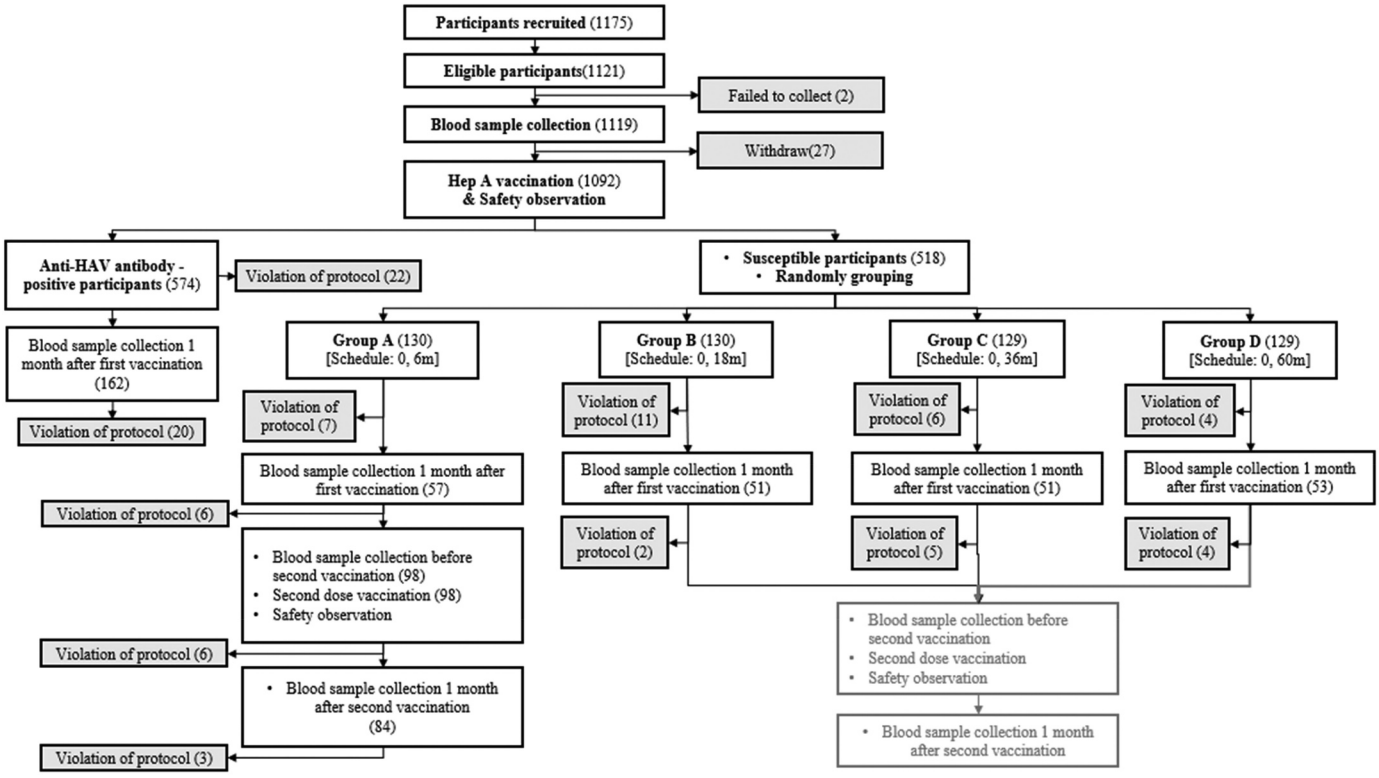

Figure 1. The study procedure.

dose at a 6-month interval. Secondary outcomes included seroprevalence before vaccination; seroconversion rates 1 month after the second dose at different intervals; the seropositivity rates, geometric mean concentrations (GMCs) and geometric mean increases (GMIs) at 1 month after the second vaccination at different intervals in different subgroups of participants.

For safety assessment, the primary outcome was the incidence of ARs within 28 d after the first vaccination. Secondary outcomes included the incidences of ARs within 28 d after the second vaccination in different subgroups of participants.

Participants were divided into subgroups according to health condition or susceptibility against hepatitis A. Those who were negative for anti-HAV antibody before vaccination were considered susceptible to HAV.

Laboratory detection

All anti-HAV antibody testing were performed by Sinovac Biotech Co., Ltd (Beijing, China).

Pre-vaccination screening for anti-HAV antibody was performed using enzyme-linked immunosorbent assay (ELISA) method with commercial kits provided by Beijing Beier Bioengineering Co., Ltd. Qualitative results were issued for randomly grouping.

The Quantitative detection of anti-HAV antibody was carried out using electrochemiluminescence immunoassays (ECLIA) method with commercially available kits from Roche Diagnostics (Elecsys Anti-HAV, ECLIA method). To determine the concentration of each sample, a lyophilized powder standard of human anti-HAV immunoglobulin (49 IU/ampoule) from the National Institute for Biological Standards and Control (NIBSC) with known specific concentration was used.

The standard was serially diluted into six gradients representing high, medium and low levels (raged from 15.31 IU/L to 490 IU/L). These diluted standards were analyzed using ECLIA to obtain the corresponding cutoff index (COI) values. A standard curve was then established by plotting the COI values against the dilution factors. The specific concentration for each sample was calculated by multiplying the concentration derived from the standard curve by an appropriate dilution factor.

In this study, seropositive was defined as an anti-HAV antibody concentration ≥20 IU/L. Consequently, the seropositive rate was defined as the percentage of participants whose anti-HAV antibody were positive; and the seroconversion rate was defined as the percentage of participants whose anti-HAV antibody concentrations of either 1) <20 IU/L before vaccination and ≥20 IU/L after vaccination or 2) ≥20 IU/L before vaccination and at least a fourfold increase after vaccination.

Statistical methods

All participants who received at least one dose of hepatitis A vaccine were included in the seroprevalence and safety analysis set.

The immunogenicity analysis set included all participants who had received at least one dose of the hepatitis A vaccine and provided at least one blood sample according to the protocol, without major protocol violations.

The per-protocol analysis set consisted of all participants who completed the full vaccination schedule and provided blood samples as required by the protocol without violation.

For the analysis of pre-vaccination anti-HAV antibody seroprevalence, participants were sub-grouped by age. Pearson's chi-square test with continuity correction was used for the comparison of seroprevalences among different age groups, and Bonferroni correction was applied to adjust for multiple comparisons when conducting pairwise tests across age groups.

For the immunogenicity analysis of a single dose of hepatitis A vaccine, participants were sub-grouped as anti-HAV antibody-positive (those with detectable antibodies before vaccination) and susceptible (those without detectable antibodies before vaccination).

Geometric mean concentrations (GMCs) of anti-HAV antibodies and their 95% confidence intervals (CIs) were calculated by taking anti-logarithm of the mean of the log-transformed antibody titers. Seropositivity rates and seroconversion rates of anti-HAV antibody were statistically described, and their 95% CIs were calculated using the Clopper-Pearson method. The t-test or ANOVA was used to compare the GMCs between subgroups. Pearson's chi-square test or Fisher's exact test was used for the comparisons of seropositivity and seroconversion rates between subgroups.

The safety assessment included the descriptions and comparisons of adverse reaction (AR) incidences across subgroups. Comparisons were conducted using Pearson's chi-square test or Fisher's exact test.

All statistical analyses were performed using SAS software (version 9.4), with a two-tailed p value less than 0.05 considered statistically significant.

The immunogenicity and safety of the hepatitis A vaccine in this interim analysis reported the results from participants in Group A, who completed the full vaccination schedule and blood sample collection. Results from group B, C, and D will be reported in subsequent articles.

Results

Demographic characteristic and anti-HAV antibody seroprevalence before vaccination

A total of 1,175 participants were recruited and 1,092 of them enrolled in this study (Figure 1), with a mean age of 40.9 ± 6.99 y. Among them, 39.74% (434/1,092) were male, and 75.46% (824/1,092) identified as Man ethnicity.

All participants had blood samples collection before vaccination and received a single dose of the hepatitis A vaccine. ELISA results showed that 407 participants were negative for anti-HAV antibodies, and 374 of them completed blood sample collection 1 month after the first dose. ECLIA results indicated that 518 participants were negative for anti-HAV antibody, and 574 were positive before vaccination. Results obtained using the Roche ECLIA assay were considered definitive and were used in the following analysis.

The overall seroprevalence of anti-HAV antibodies among participants was 52.56% (574/1,092), and the GMC was 247.17 IU/L. Differences of seroprevalence and GMC among the age groups were all statistically significant ($p < .001$ and $p < .001$). Adults aged 36–40 y had the lowest seroprevalence at 39.58% (76/192), followed by those aged 18–25 y. A seroprevalence exceeding 70% was observed in participants aged 46 y and older (Figure 2). When conducting pairwise comparison, the differences in seroprevalence between group aged 46–50 y and other age groups were all statistically significant ($p < .001$ for all comparisons). For GMCs, there were differences of statistical significance between group aged 41–45 y and other age groups ($p < .01$ for all comparisons), and between group aged 46–50 y and other age groups ($p < .01$ for all comparisons). See Supplementary Materials for details.

The seroprevalence of participants aged 18–40 y old was 41.25% (172/417), with a GMC of 74.98 IU/L. The seroprevalence of participants aged 18–45 y old was 44.65% (346/775), with a GMC of 134.72 IU/L.

A total of 1,042 participants were included in the immunogenicity analysis set. The demographic characteristics of

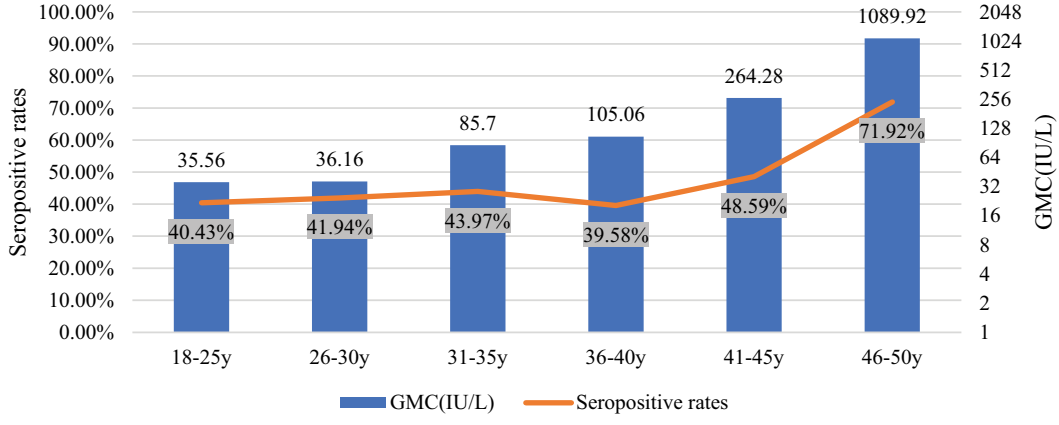

Figure 2. GMCs and seropositive rates of hepatitis A among all participants before vaccination.

Table 1. The demographic information of participants in the immunogenicity set.

	Total ($N = 1042$)	Anti-HAV positive ($N = 552$)	Anti-HAV negative ($N = 490$)	*P* value	Group A ($N = 123$)	Group B ($N = 119$)	Group C ($N = 123$)	Group D ($N = 125$)	*P* value
Age (y)									
Mean (SD)	41.0(6.93)	42.2(6.78)	39.6(6.83)	<0.001[a]	40.0(6.70)	40.0(6.91)	39.2(6.72)	39.1(7.00)	0.569[c]
Min, Max	18, 50	19, 50	18, 50		20,50	20,50	19,50	18,50	
Gender									
Male, n (%)	408(39.16)	204(36.96)	204(41.63)	0.123[b]	49(39.84)	57(47.90)	58(47.15)	40(32.00)	0.038[b]
Female, n (%)	634(60.84)	348(63.04)	286(58.37)		74(60.16)	62(52.10)	65(52.85)	85(68.00)	
BMI									
Mean (SD)	26.2(4.51)	25.9(4.37)	26.5(4.64)	0.022[a]	26.0(3.72)	26.5(4.90)	26.6(4.65)	27.0(5.16)	0.342[a]
Minority									
Han, n (%)	173(16.60)	107(19.38)	66(13.47)	0.032[b]	16(13.01)	10(8.40)	22(17.89)	18(14.40)	0.139[b]
Man, n (%)	788(75.62)	406(73.55)	382(77.96)		93(75.61)	98(82.35)	89(72.36)	102(81.60)	
Others, n (%)	81(7.77)	39(7.07)	42(8.57)		14(11.38)	11(9.24)	12(9.76)	5(4.00)	
UMC*									
Yes, n (%)	143(13.72)	95(17.21)	48(9.80)	<0.001[b]	14(11.38)	10(8.40)	12(9.76)	12(9.60)	0.893[b]
No, n (%)	899(86.28)	457(82.79)	442(90.20)		109(88.62)	109(91.60)	111(90.24)	113(90.40)	

*UMC: underlying medical condition.
[a]Independent-sample t-test; [b]Chi-square test; [c]ANOVA

participants across different anti-HAV antibody levels and groups were presented in Table 1. Ninety-three (8.93%) of these participants had hypertension, and 33 (3.17%) had diabetes. Other underlying medical conditions included coronary heart disease, hepatitis B, and so on.

Additionally, 42 participants in Group A were included in the per-protocol analysis set.

The immunogenicity of a single dose of the hepatitis A vaccine

The seropositivity rate 1 month after a single dose of the hepatitis A vaccine was 98.78% (324/328). The overall seroconversion rate was 67.68% (222/328). Among the susceptible participants, the seroconversion rate was significantly higher at 97.85% (182/186), compared to 28.17% (40/142) for antibody-positive participants. The GMC of anti-HAV antibodies increased significantly from 250.82 IU/L before vaccination to 1,847.85 IU/L 1 month after vaccination. For susceptible participants, the GMC rose from 19.11 IU/L to 579.94 IU/L (Table 2).

The seroconversion rates for those aged 18-40 and 18-45 years old were 83.93%(94/112) and 74.46%(172/231), respectively. And the GMCs were 1,058.85 IU/L and 1,445.90 IU/L, respectively.

Notably, for participants with positive anti-HAV antibodies pre-vaccination, the seroconversion rate for those aged 18–40 y old was 52.94% (18/34), and for those aged

Table 2. The immunogenicity of one dose of hepatitis A vaccination.

Indicators	Total	Anti-HAV antibodies positive	Anti-HAV antibodies negative	*P* value
Immunogenicity set				
Pre-vaccination (Day 0)				
N	1042	552	490	
GMC (IU/L)	250.82	2465.63	19.11	<0.001[a]
95% CI (%)	209.97, 299.61	2049.37, 2966.45	18.46, 19.78	
Post-vaccination (1 month)				
N	328	142	186	
Seropositive rate, n(%)	324(98.78)	142(100.00)	182(97.85)	0.136[b]
95% CI (%)	96.91, 99.67	97.44, 100.00	94.59, 99.41	
GMC (IU/L)	1847.85	8431.30	579.94	<0.001[a]
95% CI (%)	1507.61, 2264.88	6740.95, 10545.51	480.29, 700.28	
Seroconversion rate, n(%)	222(67.68)	40(28.17)	182(97.85)	<0.001[c]
95% CI (%)	62.33, 72.72	20.95, 36.33	94.59, 99.41	
GMI	11.32	3.13	30.23	<0.001[a]
95% CI (%)	9.29, 13.80	2.45, 4.00	24.72, 36.97	
Per-protocol set				
Pre-vaccination (Day 0)				
N	319	142	177	
GMC (IU/L)	172.86	2693.99	19.09	<0.001[a]
95% CI (%)	125.62, 237.85	1857.00, 3908.24	17.95, 20.31	
Post-vaccination (1 month)				
Seropositive rate, n(%)	315(98.75)	142(100.00)	173(97.74)	0.132[b]
95% CI (%)	96.82, 99.66	97.44, 100.00	94.32, 99.38	
GMC (IU/L)	1938.21	8431.30	595.89	<0.001[a]
95% CI (%)	1578.66, 2379.66	6740.95, 10545.51	491.97, 721.76	
Seroconversion rate, n(%)	213(66.77)	40(28.17)	173(97.74)	<0.001[c]
95% CI (%)	61.31, 71.92	20.95, 36.33	94.32, 99.38	
GMI	11.21	3.13	31.21	<0.001[a]
95% CI (%)	9.17, 13.72	2.45, 4.00	25.42, 38.32	

[a]Independent-sample t-test; [b]Fisher exact test; [b]Chi-square test

41–50 y old was 20.37% (22/108) ($p < .001$). And the GMCs for participants aged 18–40 y old and 41–50 y old were 4082.69 IU/L and 11,973 IU/L, respectively ($p = .001$).

The immunogenicity of two doses at a vaccination interval of 6 months (group A)

Following two doses of vaccination, both seropositivity and seroconversion rates reached 100%. The GMCs increased significantly from 18.02 IU/L before vaccination to 523.79 IU/L 1 month after the first dose and further to 3,602.44 IU/L 1 months after the second dose.

In the per-protocol set, similar results were observed, with GMCs increasing from 17.46 IU/L before vaccination to 4,104.16 IU/L 1 month after the second dose (Table 3).

Additionally, analysis was conducted within different age groups. The seropositivity and seroconversion rates after one or two doses of vaccination for people aged 18–30, 31–40 and 41–50 y old were all 100%. GMCs at 7-month after the first vaccination of people aged 18–30, 31–40 and 41–50 y old were 4,219.93, 4,564.49 and 3,177.93 IU/L, respectively ($p = .238$). And the GMIs at 7-month after the first vaccination for three age groups were 206.77, 251.11 and 179.76, respectively ($p = .374$) (Table 3).

Safety

The incidence of adverse reactions (ARs) within 28 days of a single dose of vaccination was 2.75% (30/1,092). There was no statistically significant difference in AR incidences between anti-HAV-positive and -negative participants ($p = .408$) or between the healthy group and those with underlying medical conditions (UMCs) ($p = 1.000$). The most common symptom was pain at the injection sites (0.92%, 10/1,092) and most ARs

Table 3. The immunogenicity among participants of the group A before, 1 month after each dose of hepatitis A vaccination.

		After vaccination			P value		
Indicators	Pre-vaccination	1 month	6 months	7 months	D 0 vs1m	1m vs 6 m	D 6 m vs 7 m
Immunogenicity set							
N	123	51	92	81			
Seropositive rate n(%)	0(0.00)	51(100.00)	92(100.00)	81(100.00)	<0.001[a]	1.000[b]	1.000[b]
95% CI (%)	0.00, 2.95	93.02, 100.00	96.07,100.00	95.55, 100.00			
Seroconversion rate* n(%)	–	51(100.00)	–	81(100.00)	–	–	–
95% CI (%)	–	93.02, 100.00	–	95.55, 100.00	–	–	–
GMC (IU/L)	18.02	523.79	460.41	3602.44	<0.001[c]	0.528[c]	<0.001[c]
95% CI (%)	16.66, 19.49	363.56, 754.64	384.38,551.47	2969.82, 4369.81			
GMI	–	29.01	–	199.11	–	–	–
95% CI (%)	–	19.98, 42.10	–	162.56, 243.88	–	–	–
18–30 y old							
N	13	6	12	9			
Seropositive rate n(%)	0(0.00)	6(100.00)	12(100.00)	9(100.00)	<0.001[b]	1.000[b]	1.000[b]
95% CI (%)	0.00, 24.71	54.07,100.00	73.54,100.00	66.37,100.00			
Seroconversion rate* n(%)	–	6(100.00)	–	9(100.00)	–	–	–
95% CI (%)	–	54.07,100.00	–	66.37,100.00	–	–	–
GMC (IU/L)	21.13	528.99	554.48	4219.93	0.0031[c]	0.943[c]	<0.001[c]
95% CI (%)	19.15,23.31	111.09,2518.85	394.42,779.50	2840.71,6268.80			
GMI	–	24.49	–	206.77	–	–	–
95% CI (%)	–	5.51,108.77	–	139.73,305.99	–	–	–
31–40 y old							
N	41	16	26	21			
Seropositive rate n(%)	0(0.00)	16(100.00)	26(100.00)	21(100.00)	<0.001[b]	1.000[b]	1.000[b]
95% CI (%)	0.00, 8.60	79.41,100.00	86.77,100.00	83.89,100.00			
Seroconversion rate* n(%)	–	16(100.00)		21(100.00)	–	–	–
95% CI (%)	–	79.41,100.00		83.89,100.00	–	–	–
GMC (IU/L)	18.71	640.55	646.70	4564.49	<0.001[c]	0.981[c]	<0.001[c]
95% CI (%)	16.25,21.55	295.46,1388.68	453.89,921.40	3624.55,5748.18			
GMI	–	35.04		251.11	–	–	–
95% CI (%)	–	15.76,77.91		186.58,337.95	–	–	–
41–50 y old							
N	69	29	54	51			
Seropositive rate n(%)	0(0.00)	29(100.00)	54(100.00)	51(100.00)	<0.001[a]	1.000[b]	1.000[b]
95% CI (%)	0.00, 5.21	88.06, 100.00	93.40,100.00	93.02, 100.00			
Seroconversion rate* n(%)	–	29(100.00)	–	51(100.00)	–	–	–
95% CI (%)	–	88.06, 100.00	–	93.02, 100.00	–	–	–
GMC (IU/L)	17.10	467.79	375.10	3177.93	<0.001[c]	0.389[c]	<0.001[c]
95% CI (%)	15.30, 19.11	295.93, 739.45	294.99, 476.97	2388.39, 4228.46			
GMI	–	27.06	–	179.76	–	–	–
95% CI (%)		16.89, 43.36	–	133.83, 241.46			
Per-protocol set ($N = 42$)							
Seropositive rate n(%)	0(0.00)	42(100.00)	42(100.00)	42(100.00)	<0.001[d]	NA	<0.001[d]
95% CI (%)	0.00, 8.41	91.59,100.00	91.59,100.00	91.59, 100.00			
Seroconversion rate* n(%)	–	42(100.00)	–	42(100.00)	–	–	–
95% CI (%)	–	91.59, 100.00	–	91.59, 100.00	–	–	–
GMC (IU/L)	17.46	574.54	405.25	4104.16	<0.001[e]	0.041[e]	<0.001[e]
95% CI (%)	15.09, 20.19	388.78, 849.07	311.36,527.45	3373.45, 4993.14			
GMI	–	32.91	–	235.10	–	–	–
95% CI (%)	–	22.17, 48.86	–	186.84, 295.83	–	–	–

*The seroconversion rates were calculated with GMCs of pre-vaccination.
[a]Chi-square test; [b]Fisher; [c]Independent-sample t-test; [d]McNemar's; [e]Paired-sample t-test

Table 4. The incidences of adverse reactions within 28 days after one dose of hepatitis A vaccination.

Adverse reaction	Total (*N* = 1092)	Anti-HAV positive (*N* = 574)	Anti-HAV negative (*N* = 518)	*P* value	Healthy (*N* = 940)	UMCs* (*N* = 152)	P value
Total	**30(2.75)**	**18(3.14)**	**12(2.32)**	.408	**26(2.77)**	**4(2.63)**	1.000
Severity							
Mild (grade 1)	26(2.38)	16(2.79)	10(1.93)	.693	23(2.45)	3(1.97)	.501
Moderate (grade 2)	4(0.37)	2(0.35)	2(0.39)		3(.32)	1(0.66)	
Symptoms							
Solicited	**27(2.47)**	**16(2.79)**	**11(2.12)**	.481	**24(2.55)**	**3(1.97)**	1.000
Local	17(1.56)	10(1.74)	7(1.35)	.602	15(1.60)	2(1.32)	1.000
Pain	10(0.92)	6(1.05)	4(0.77)	.460	8(0.85)	2(1.32)	.657
Swelling	3(0.27)	2(0.35)	1(0.19)	1.000	3(0.32)	0(0.00)	1.000
Pruritus	2(0.18)	2(0.35)	0(0.00)	.500	2(0.21)	0(0.00)	1.000
Redness	1(0.09)	0(0.00)	1(0.19)	.474	1(0.11)	0(0.00)	1.000
Induration	1(0.09)	0(0.00)	1(0.19)	.474	1(0.11)	0(0.00)	1.000
Systemic	11(1.01)	7(1.22)	4(0.77)	.460	10(1.06)	1(0.66)	1.000
Headache	4(0.37)	2(0.35)	2(0.39)	1.000	4(0.43)	0(0.00)	1.000
Nausea	2(0.18)	1(0.17)	1(0.19)	1.000	2(0.21)	0(0.00)	1.000
Muscle pain	2(0.18)	2(0.35)	0(0.00)	.500	2(0.21)	0(0.00)	1.000
Fever	1(0.09)	0(0.00)	1(0.19)	.474	0(0.00)	1(0.66)	.139
Fatigue	1(0.09)	1(0.17)	0(0.00)	.500	1(0.11)	0(0.00)	1.000
Unsolicited	**5(0.46)**	**3(0.52)**	**2(0.39)**	1.000	**4(0.43)**	**1(0.66)**	.528

*UMCs: underlying medical conditions.

were mild (2.38%, 26/1,092). No serious adverse events (SAEs) related to vaccination were reported (Table 4).

For Group A, the incidence of ARs within 28 days after two doses of vaccination was 3.85% (5/130). All ARs were solicited and mild. Reported symptoms included pain and swelling at the injection sites and headache. No SAEs related to vaccination were reported.

Discussion

With available data from different countries, recent outbreaks of hepatitis A caused by fresh and frozen food were reported, and cases among adults also increased. This highlighted the high risk that hepatitis A may potentially cause outbreaks in adults by contaminated food. Vaccination remains the most effective measure for preventing hepatitis A. The WHO position paper on hepatitis A vaccines identified their excellent safety and immunogenicity for both children and adults.[24]

In China, the introduction of hepatitis A vaccines into the EPI program since 2008 has significantly reduced incidences of cases. However, adults born between 1988 and 2004 remain susceptible as they were born before the introduction of the hepatitis A vaccines and limited exposure to HAV.[14] While China has made recommendations for hepatitis A vaccination in adults, evidence regarding the immunogenicity of one- or two-dose regimens, as well as the impact of different vaccination intervals, remains limited, creating an urgent need for further research to inform catch-up vaccination strategies.

Liaoning Province, with its coastal areas such as Dandong, has been identified as having a significant burden of hepatitis A since people there love raw or undercooked seafood. Consequently, we conducted this study in Fengcheng, Dandong to explore immunogenicity and safety of hepatitis A vaccine in adults, using different vaccination intervals, so that to provide further evidence to support adult vaccination strategies.

In our study, the seroprevalence of anti-HAV antibodies among individuals aged 18 y and older was 52.56%. The lowest seroprevalence was observed in the 36–40 y old group, followed by those aged 18–25 y old. These findings are consistent with the National Serological Surveys,[14] which underscored the need for catch-up of Hepatitis A vaccination in adults. Another study reported a prevalence of 41% in adults aged 18–21 y,[25] which was close to 40.43% that observed in our study for the 18–25 y old group. Additionally, the seroprevalence in 46–50 years old age group (over 70%) in our study was significantly higher than all other age groups. That may suggest that catch-up vaccination for adults could set a target age group at 18–45 y old.

Regarding immunogenicity, our study demonstrated that a single dose of the hepatitis A vaccine resulted in a seroconversion rate of 67.68% and a seropositive rate of 97.85% among all participants, regardless of their anti-HAV antibody status prior to vaccination. Given that real-world vaccination, such as catch-up activities, may not consider pre-vaccination seropositivity, it is particularly significant to evaluate the seroconversion rate in such scenarios. In this study, we calculated the seroconversion rate for participants with anti-HAV antibodies positive or negative to provide more evidence for further analysis or studies. Additionally, we calculated a seroconversion rate of 74.46% in participants aged 18–45 y old, which we suggested as the target age group for catch-up activities. A study showed that the GMC of anti-HAV antibodies in people aged 40 y and older was 329.1 IU/L at 1 month after the first dose, compared to 469.2 IU/L for people aged 20–30 y.[26]

In our study, a two-dose vaccination regimen also showed excellent immunogenicity in HAV-susceptible people, with both the seropositive and seroconversion rates reaching 100%. GMCs of anti-HAV antibodies 1 month after the first and second dose were 523.79 IU/L and 3,602.44 IU/L, respectively, with GMIs being 29.01 and 199.11, respectively. These findings suggested that a two-dose vaccination regimen was optimal for achieving higher antibody levels. Our results aligned with those of previous study[27] of this vaccine.

To explore the difference of immunogenicity in people of different ages, we conducted subgroup analysis. Results showed GMCs and GMIs across different age groups had

no statistically significant difference, that indicated the good immunogenicity of hepatitis A vaccine in people of different age groups. Other studies showed similar results. A study[28] conducted in people aged 18–50 y old showed a GMT of 5048. Another study[29] showed that the mean antibody titers 4 weeks after the second hepatitis A vaccine dose in people aged 18–30 y were 1589 to 4346 mIU/mL.

Additionally, the hepatitis A vaccine demonstrated good safety across all dose regimens and subgroups. The incidence of adverse reactions (ARs) within 28 days after one or two doses of vaccination were 2.75% and 3.85%, respectively. Most ARs were solicited and mild. The most common symptoms were pain at the injection sites and headache. And the difference of incidences between healthy participants and those with UMCs had no statistical significance. This showed that hepatitis A vaccine was safe for people with UMCs. These findings are consistent with those from our previous studies.[30] No SAEs related to vaccination were reported.

There were limitations in this study. As we described in the method, we used qualitative results to decide whose blood samples collected 1 month after the first vaccination, and we used quantitative results to group the participants. This may cause that not all susceptible participants have blood samples collected 1 month after the first vaccination. But considering it did not influence the primary outcomes, which was the seroconversion rate after two doses of vaccination, thus, we thought this limitation acceptable. Another limitation was the limited participants in different age groups when we conducted the subgroup analysis of immunogenicity after two doses of vaccination. This may be related to the population structure of Fengcheng City where young people go outside the city for work, resulting in many local elderly people. Since the subgroup analysis was used for exploration and evidence providing, this limitation may be reconsidered in future studies.

Since this is an interim report of our ongoing study, not all results are available for a comprehensive evaluation. However, our study has confirmed that adults, particularly those under 45 y old, are susceptible to HAV. Identifying immunogenicity in populations, including those already seropositive for anti-HAV antibodies, is crucial for the broader application of vaccines, especially in real-world vaccination campaigns that may not involve pre-screening. The interim results demonstrate that the hepatitis A vaccine offers good immunogenicity and safety, whether administered as a single or two-dose regimen in people of different ages. Further results on the immunogenicity of different vaccination intervals will be presented in future publications. This study aims to explore the immunogenicity of two doses of hepatitis A vaccine at different intervals and provides evidence of the dynamics of antibodies against HAV at 18, 36 and 60 months after one dose of vaccination. And future study may be conducted based on this study to explore the immune persistence.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Zhen Li, Jun Li, Ling Tuo, Xuemei Wu, Yanwei Zhao, and Jing Li are current employees of Sinovac Biotech Ltd. All the other authors have no conflicts of interest to declare.

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