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RESEARCH ARTICLE

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# Immunogenicity and safety of a live attenuated varicella vaccine co-administered with inactive hepatitis A vaccine: A phase 4, single-center, randomized, controlled trial

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**ABSTRACT**

Co-administration of vaccines can facilitate the introduction of new vaccines in immunization schedules. This study aimed to evaluate the immunogenicity and safety of co-administration with live attenuated varicella vaccine (VarV) and inactivated hepatitis A vaccine (HepA) among children aged 12 ~ 15 months. In this phase 4 clinical trial, 450 children were randomized with a ratio of 1:1 to receive VarV and Hep A simultaneously (Group A) or separately (Group B). The primary endpoints were the seroconversion rate of anti-varicella-zoster virus (VZV) antibodies 42 days after vaccination of VarV and the seroconversion rate of anti-Hepatitis A virus (HAV) antibodies 30 days after two-dose vaccination of HepA. After full immunization, the seroconversion rates of anti-VZV antibodies were 91.79% in Group A and 92.15% in Group B; the geometric mean titers (GMTs) were 11.80 and 12.19, respectively. The seroconversion rates of anti-HAV antibodies were 99.48% in Group A and 100.0% in Group B; the geometric mean concentrations (GMCs) reached 9499.11 and 9528.36 mIU/ml, respectively. The lower limits of the 95% CI for the seroconversion difference of anti-VZV antibodies and anti-HAV antibodies were −5.86% and −2.90%, which greater than the predefined non-inferiority margin (−10%). The incidence rate of adverse reactions in Group A was lower than Group B (9.33% vs 16.22%), and only one serious adverse event was reported in Group B, which was unrelated to the study vaccine. In conclusion, the co-administration of VarV with HepA has non-inferior immunogenicity and safety profiles were quite comparable with the separate administration of both vaccines.

**Trial registration number**: NCT05526820 (ClinicalTrials.gov).

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## Introduction

Varicella is an acute, highly contagious viral disease caused by the first infection of varicella-zoster virus (VZV). It is an airborne infection that spreads by droplet and direct contact transmission characterized by pruritic varicella rashes and systemic papules.[1–3] Varicella mainly occurs in childhood. More than 80% of infections in China occur in children under 14 years old.[4] In the past few years, the annual average incidence of varicella in China has experienced a 30% increase, and it has become a public health threat and an economic burden.[4–6]

Inoculation of varicella vaccine (VarV) is one of the most effective means to prevent and control varicella. The effectiveness of VarV after a single dose ranged from 76% to 85% and reached 100% after two doses of vaccination, which significantly reduced varicella incidence and hospitalization.[7,8] In China, VarV has not been included in National Immunization Program (NIP) at present.[9] As more vaccines are included in NIP, the more complex the vaccination schedule becomes, which may increase the risk of low vaccination compliance and reduce vaccination coverage rates.[10] Co-administration is an effective measure to solve these problems. World Health Organization (WHO) recommended that VarV could be co-administered with other childhood routine vaccines.[3] The hepatitis A vaccine (HepA) has been included in the NIP as a routine vaccine since 2007 in China, and previous studies proved that co-administration of inactivated HepA with measles-mumps-rubella (MMR) and VarV in children under 2 years old did not impact the immunogenicity of any vaccines and had a good safety profile.[11,12] Another study that evaluated the immunogenicity and safety of co-administration of a VarV with a live attenuated HepA also proved the feasibility of co-administration of these two vaccines.[13]

The VarV developed by Sinovac (Dalian) Vaccine Technology Co., LTD. has good safety, immunogenicity, and efficacy in children aged 1 to 12 years.[14] It was licensed in China in 2019. The inactivated HepA developed by Sinovac Biotech Co., LTD. has shown good safety and immunogenicity for both adults and children, and was licensed in China in

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2002.[15] Currently, the inactivated HepA is widely used in the world, but there were no data on co-administration with VarV alone. In this study, we aimed to evaluate the immunogenicity and safety of the live attenuated VarV co-administered with inactive HepA; this could ensure that children are vaccinated on time against both varicella and hepatitis A, and provide evidence for counties to revise guidelines and optimize immunization programs.

## Materials and methods

### Study design and participants

This study was a phase 4, single-center, open-label, randomized, controlled trial conducted in Feicheng City, Shandong Province, China, conducted from April 2021 to February 2022. Healthy children aged 12 to 15 months were enrolled in this trial. The main exclusion criteria included: 1) previous vaccination with VarV or HepA; 2) history of varicella or hepatitis A infection (self-reported); 3) family history of mental illness or severe neurological disorders (seizures, convulsions); 4) allergy or severe adverse reactions (ARs) to any study vaccine components; 5) receipt of blood products within 3 months before the study; 6) receipt of any live attenuated vaccines within 4 weeks before the study; 7) receipt of any subunit/inactivated vaccines within 7 days before the study.

Participants were randomly assigned to two groups with a ratio of 1:1. In the co-administration group (Group A), participants received the first dose of HepA co-administrated with one dose of VarV on day 0 and the second dose of HepA on day 180. In the single-dose group (Group B), participants received one dose of VarV on day 0, the first dose of HepA on day 42, and the second dose of HepA on day 222. In this study, the HepA was uniformly administered by intramuscular injection into the deltoid region in the left upper arm. The VarV was administered by subcutaneous injection into the lower edge of the lateral deltoid muscle in the right upper arm.

The trial was conducted following Good Clinical Practice and the Declaration of Helsinki, and was reviewed and approved by the Ethics Committee of the Shandong Provincial Center for Disease Prevention and Control (approval number: 2020–12). Written informed consent was obtained from each children's parent or guardian before enrollment. The trial was registered at ClinicalTrials.gov (NCT05526820) and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice Guideline.

### Study vaccines

Live attenuated VarV (lot 202006018) was derived from the Oka strain and was propagated in human diploid cell SV-1 strain, with no less than 3.3 log PFU antigen per dose (0.5 mL). The inactive HepA, Healive® (lot 202004027) was derived from the TZ84 strain of HAV and was propagated in 2BS human diploid cells, containing 250 U antigen per dose (0.5 mL). All vaccines were tested and approved for lot release by the Chinese National Institute for Food and Drug Control.

### Immunogenicity assessment

Blood samples were collected on day 0, 42, and 210 in Group A, and on day 0, 42 and 252 in Group B. Anti-VZV antibodies were measured using the fluorescent antibody to membrane antigen (FAMA) assay, which has been considered the gold standard for measuring immunity to VZV.[16,17] There were no testing kits used in the process. Anti-HAV antibodies were assessed using electrochemiluminescence immunoassays (ECLIA) (Elecsys® Anti-HAV, Roche Diagnostics). The primary endpoints for immunogenicity were the seroconversion rate of anti-VZV antibodies 42 days after vaccination of VarV and the seroconversion rate of anti-HAV antibodies 30 days after two-dose vaccination of HepA. For VarV, the seroconversion rate was defined as the percentage of participants whose anti-VZV antibody titer either 1) <1:4 before vaccination and ≥1:4 after vaccination or 2) ≥1:4 before vaccination and reaching at least a fourfold increase after vaccination. For HepA, the seroconversion rate was defined as the percentage of participants whose anti-HAV antibody concentrations of either 1) < 20 mIU/ml before vaccination and ≥20 mIU/ml after vaccination or 2) ≥ 20 mIU/ml before vaccination and at least a fourfold increase after vaccination. Participants with anti-VZV antibody titers <1:4 and anti-HAV antibody concentrations <20 mIU/ml were defined as the susceptible population for VZV and HAV, respectively. The noninferiority criteria were reached when the lower limit of the 95% confidence interval (CI) of the differences of seroconversion rates in Group A to those in Group B was greater than −10%.

### Safety assessment

The safety endpoints included 1) The incidence of ARs within 42 days after VarV vaccination or co-administration, and the incidence of ARs within 30 days after HepA separate vaccination; 2) The incidence of local and systemic solicited ARs within 14 days after VarV vaccination or co-administration, and the incidence of local and systemic solicited ARs within 7 days after HepA separate vaccination; 3) The incidence of serious adverse events (SAEs) within 42 days after VarV vaccination or co-administration, and the incidence of SAEs within 30 days after HepA separate vaccination. Solicited local adverse events (AEs) included pain, induration, swelling, erythema, rash, and pruritus; solicited systemic AEs included fever (axillary temperature), acute allergic reaction, skin and mucous membrane defects, diarrhea, decreased appetite, vomiting, new convulsions, irritability, and decreased activity. The causality of AEs was assessed by the investigators.

Diary cards were given to the participant's guardians after each dose. On-site observations were conducted for immediate

AEs within 30 minutes after vaccination. Solicited systemic AEs within 14 days; solicited local AEs within 7 days on the HepA-vaccinated arm in Group A and 14 days on the VarV-vaccinated arm in Group B; unsolicited AEs and SAEs occurring within 0–30 days (HepA) or 0–42 days (VarV) after vaccination were recorded on diary cards. On the 30th or 42nd day after vaccination, face-to-face interviews were conducted to confirm the accuracy of AE data.

### Sample size assessment

The sample size for a non-inferiority design was calculated by NCSS-PASS (version 11.0) using the Miettinen & Nurminen method.[18] In this study, only when 1) the seroconversion rate of anti-VZV antibodies 42 days after VarV administration and 2) the seroconversion rate of anti-HAV antibodies 30 days after HepA administration met the non-inferiority criterion was the study considered successful. Therefore, we didn't need to consider Type I error when calculating the sample size. To ensure that the total power of the study reached 80%, we considered the power of 87.5% (calculated as 1-β) for evaluating the seroconversion rate of anti-VZV antibodies. We assumed that the seroconversion rate of anti-VZV antibodies 42 days after administration of VarV alone (Group B) was 90%. A sample size of 190 participants per group was required for a one-sided α of 0.025 with a non-inferiority margin of −10%. With an estimated dropout rate of 15%, a total of 450 participants were finally recruited for this trial.

### Statistical analysis

The immunogenicity analysis was performed for the per-protocol set (PPS) with participants who met the eligibility criteria, complied with the protocol, and had immunogenicity results before and after vaccination. Safety analysis was performed for the safety set (SS) with participants who completed at least one vaccination. The student t-test was used for comparison of continuous variables, and the $\chi^2$ test or the Fisher exact test was used for comparison of categorical variables. The Clopper-Pearson method was used to calculate the 2-sided 95% CI. All analyses were done with SAS (version 9.4).

## Results

### Study subjects

The study flowchart is shown in Figure 1. From April 2021 to February 2022, 450 participants aged between 12 to 15 months were recruited and randomly allocated into two groups in a 1:1 ratio, among which 447 participants received VarV, 419 received the first dose of HepA, and 399 received the second dose of HepA. 398 and 357 participants were included in the per-protocol population for VZV and HAV immunogenicity, respectively. The mean age was 13.16 ± 1.17 months in Group A and 13.33 ± 1.19 months in Group B. The baseline characteristics of the subjects in each group are shown in Table 1. No significant difference was found in age, sex, ethnicity, height, and weight between Group A and Group B in the SS.

### Immunogenicity

#### Total population

For the immunogenicity of anti-VZV antibodies, the seropositive rates in Group A and Group B were 16.43% (95% CI, 11.65–22.19) and 16.23% (95% CI, 11.30–22.24) before vaccination while the geometric mean titers (GMTs) were 2.38 (95% CI, 2.24–2.53) and 2.42 (95% CI, 2.26–2.60), respectively. No significant differences were found between the two groups, with $p = .958$ and 0.421, respectively. After vaccination, the seroconversion rates increased to 91.79% (95% CI, 87.18–95.14) and 92.15% (95% CI, 87.38–95.5) in Group A and Group B ($p = .895$), with a difference of −0.36% (95% CI, −5.86–5.25). The lower limit of the 95% CI was higher than the predefined non-inferiority margin of −10%. Similarly, the GMTs increased to 11.80 (95% CI, 10.47–13.29) and 12.19 (95% CI, 10.75–13.82), respectively, with $p = .920$. (Table 2)

For the immunogenicity of anti-HAV antibodies, the seropositive rates in Group A and Group B were 13.02% (95% CI, 8.61–18.62) and 9.70% (95% CI, 5.64–15.27) before vaccination ($p = .326$)while the geometric mean concentrations (GMCs) were 6.37 mIU/ml (95% CI, 5.38–7.53) and 6.13 mIU/ml (95% CI, 5.25–7.16), respectively. There were no significant differences between the two groups, with $p = .326$ and 0.559, respectively. After vaccination, the seroconversion rates raised to 99.48% (95% CI, 97.13–99.99) and 100% (95% CI, 97.79–100.00), with a difference of −0.52% (95% CI, −2.90–1.77). The lower limit of the 95% CI was, likewise, greater than the predefined non-inferiority margin of −10%. The GMC raised to 9499.11 mIU/ml (95% CI, 8609.53–10480.62) and 9528.36 mIU/ml (95% CI, 8497.09–10684.79), respectively, with $p = .886$.

#### Susceptible population

There were 333 susceptible participants enrolled to enable the assessment of the immunogenicity of VarV. After vaccination, the seroconversion rates in Group A and Group B were 94.22% (95% CI, 89.63–97.19) and 96.25% (95% CI, 92.02–98.61), with GMTs of 9.85 (95% CI, 8.77–11.07) and 10.11 (95% CI, 8.97–11.39), respectively. No significant differences were observed between the two groups in seroconversion rates and GMTs.

There were 316 susceptible participants enrolled to enable the assessment of the immunogenicity of HepA. After vaccination, the seroconversion rates in Group A and Group B all reached 100% while the GMC were 9657.25 mIU/ml (95% CI, 8676.96–10748.30) and 9537.87 mIU/ml (95% CI, 8417.88–10806.86) respectively. There were no significant differences between the two groups.

### Safety

The incidences of solicited and unsolicited ARs in the two groups are shown in Table 3. Overall, ARs occurred in 57 (12.75%) participants, and the incidence of ARs was higher in Group B compared to Group A (16.22% vs 9.22%, $p = .033$).

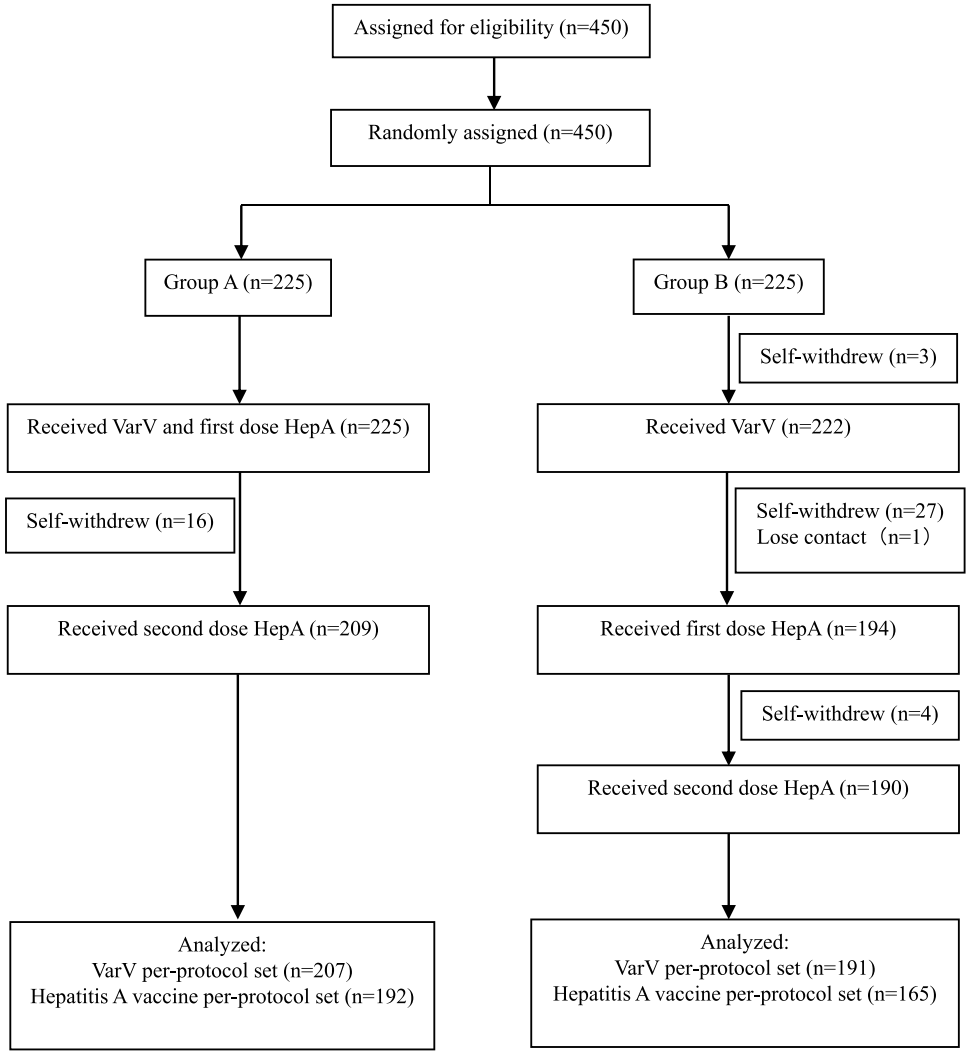


**Figure 1.** Flowchart of study design. Participants inGroup a simultaneously receive VarV and the first dose of HepA on day 0 and the second dose of HepA on day 180. Group B receive VarV on day 0, the first dose of HepA on day 42, and the second dose of HepA on day 210.

**Table 1.** Baseline characteristics of the study participants in the safety set.

| Characteristic | Group A (n- = 225) | Group B (n = 222) | *p* |
|---|---|---|---|
| Male, no. (%) | 116 (51.56) | 118 (53.15) | .735 |
| Ethnic Han, no. (%) | 222 (98.67) | 217 (97.75) | .501 |
| Age, months | 13.16 ± 1.17 | 13.33 ± 1.19 | .107 |
| Height, cm | 78.16 ± 3.21 | 78.61 ± 3.02 | .098 |
| Weight, kg | 10.70 ± 1.40 | 10.94 ± 1.31 | .053 |

Most ARs were grade 1 and 2, with only one grade 3 AR reported in Group B. There were significant differences between two groups in grade ($p = .018$). (Table 4)

The ARs were mainly solicited (9.17%, 41/447), and the incidences in Group A and Group B were 7.11% (16/225) and 11.26% (25/222), respectively, with no significant differences between the two groups ($p = .142$). However, the incidence of unsolicited ARs in Group B was higher than that in Group A ($p = .046$). The incidence of local ARs was low, with each symptom below 1%. The most frequently systemic ARs were fever (5.82%, 26/447) and diarrhea (2.24%, 10/447), and the incidences of other systemic ARs were less than 1%. No significant differences in either local or systemic ARs were found between the two groups, with $p = .214$ and 0.301, respectively. Only one reported SAE, acute upper respiratory tract infection, occurred in Group B, considered unrelated to the study vaccines.

## Discussion

The busy vaccination strategies adopted in childhood make it challenging for newborns, parents, and health professionals to fulfill the vaccination schedule. Co-administration can maximize the likelihood of children receiving age-appropriate

**Table 2.** Antibody responses to VZV, HAV before and after vaccination: per-protocol sets.

| Variable | Group A | Group B | Total | *p* | Difference |
|---|---|---|---|---|---|
| **Varicella** | | | | | |
| **Total immunogenicity cohort** | | | | | |
| Pre-vaccination (day 0) | | | | | |
| Seropositivity ≥1:4 | | | | .958 | |
| Proportion | 34/207 | 31/191 | 65/398 | | |
| Percentage (95% CI) | 16.43 (11.65–22.19) | 16.23 (11.30–22.24) | 16.33 (12.84–20.34) | | |
| GMT (95% CI) | 2.38 (2.24–2.53) | 2.42 (2.26–2.60) | 2.40 (2.29–2.51) | .967 | |
| Post-vaccination (day 42) | | | | | |
| Seropositivity ≥1:4 | | | | .391 | −0.36 |
| Proportion | 197/207 | 185/191 | 382/398 | | −5.86–5.25 |
| Percentage (95% CI) | 95.17 (91.30–97.66) | 96.86 (93.29–98.84) | 95.98 (93.55–97.68) | | |
| Seroconversion ≥1:4 | | | | .895 | |
| Proportion | 190/207 | 176/191 | 366/398 | | |
| Percentage (95% CI) | 91.79 (87.18–95.14) | 92.15 (87.38–95.54) | 91.96 (88.84–94.44) | | |
| GMT (95% CI) | 11.80 (10.47–13.29) | 12.19 (10.75–13.82) | 11.98 (10.99–13.06) | .920 | |
| GMI (95% CI) | 4.96 (4.46–5.51) | 5.03 (4.50–5.62) | 4.99 (4.62–5.39) | .775 | |
| **Susceptible population** | | | | | |
| Post-vaccination (day 42) | | | | | |
| Seroconversion ≥1:4 | | | | .387 | |
| Proportion | 163/173 | 154/160 | 317/333 | | |
| Percentage (95% CI) | 94.22 (89.63–97.19) | 96.25 (92.02–98.61) | 95.20 (92.31–97.23) | | |
| GMT (95% CI) | 9.85 (8.77–11.07) | 10.11 (8.97–11.39) | 9.98 (9.18–10.84) | .956 | |
| GMI (95% CI) | 4.93 (4.39–5.53) | 5.05 (4.49–5.70) | 4.99 (4.59–5.42) | .956 | |
| **HAV** | | | | | |
| **Total immunogenicity cohort** | | | | | |
| Pre-vaccination (day 0) | | | | | |
| Seropositivity ≥20 mIU/ml | | | | .326 | |
| Proportion | 25/192 | 16/165 | 41/357 | | |
| Percentage (95% CI) | 13.02 (8.61–18.62) | 9.70 (5.64–15.27) | 11.48 (8.37–15.26) | | |
| GMC (95% CI) | 6.37 (5.38–7.53) | 6.13 (5.25–7.16) | 6.26 (5.58–7.02) | .559 | |
| Post-vaccination (day 30) | | | | | |
| Seropositivity ≥20 mIU/ml | | | | / | |
| Proportion | 192/192 | 165/165 | 357/357 | | |
| Percentage (95% CI) | 100 (98.10–100.00) | 100.00 (97.79–100.00) | 100.00 (98.97–100.00) | | |
| Seroconversion | | | | 1.000 | −0.52 |
| Proportion | 191/192 | 165/165 | 356/357 | | −2.90–1.77 |
| Percentage (95% CI) | 99.48 (97.13–99.99) | 100.00 (97.79–100.00) | 99.72 (98.45–99.99) | | |
| GMC (95% CI) | 9499.11 (8609.53–10480.62) | 9528.36 (8497.09–10684.79) | 9512.62 (8830.00–10248.01) | .886 | |
| GMI (95% CI) | 1491.66 (1224.16–1817.60) | 1553.97 (1292.93–1867.72) | 1520.14 (1327.55–1740.67) | .801 | |
| **Susceptible population** | | | | | |
| Post-vaccination (day 30) | | | | | |
| Seroconversion ≥20 mIU/ml | | | | / | |
| Proportion | 167/167 | 149/149 | 316/316 | | |
| Percentage (95% CI) | 100.00 (97.82–100.00) | 100.00 (97.55–100.00) | 100.00 (98.84–100.00) | | |
| GMC (95% CI) | 9657.25 (8676.96–10748.30) | 9537.87 (8417.88–10806.86) | 9600.78 (8851.87–10413.04) | .767 | |
| GMI (95% CI) | 2071.80 (1756.16–2444.17) | 1941.18 (1655.15–2276.63) | 2009.15 (1791.48–2253.26) | .731 | |

vaccines in a timely manner, reduces the number of vaccination visits, and allows easier inclusion of new vaccines into the schedule. In this phase 4, single-center, open-label, randomized controlled trial, we evaluated the immunogenicity and safety of VarV co-administrated with HepA. The results showed that co-administration of VarV with HepA had no significant effect on immunogenicity and the safety profile of co-administration is at least as good.

In our study, the seropositive rates, antibody levels against VZV and HAV, and GMTs were low before vaccination, indicating most children were susceptible to VZV and HAV, thus it was very timely for children around 1-year-old to receive the VarV and the HepA.

After vaccination, the seroconversion rates of anti-VZV antibodies increased to 91.79% in Group A and 92.15% in Group B, and the seroconversion rates of anti-HAV antibodies increased to 99.48% in Group A and 100.0% in Group B. The lower limits of the 95% CI for the seroconversion difference of anti-VZV and HAV antibodies were −5.86% and −2.90%, which were both greater than the predefined non-inferiority

**Table 3.** Summary of adverse reactions (ARs) of any dose.

| | Group A (N = 225) | | | Group B (N=222) | | | Total (N = 447) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| AR | Frequency | Number | % | Frequency | Number | % | Frequency | Number | % | *p* |
| **Overall** | 28 | 21 | 9.33 | 47 | 36 | 16.22 | 75 | 57 | 12.75 | .033 |
| **Solicited** | 21 | 16 | 7.11 | 32 | 25 | 11.26 | 53 | 41 | 9.17 | .142 |
| Local | 2 | 1 | 0.44 | 7 | 4 | 1.80 | 9 | 5 | 1.12 | .214 |
| Vaccination site rash | 0 | 0 | 0.00 | 2 | 2 | 0.90 | 2 | 2 | 0.45 | .246 |
| Vaccination site pain | 1 | 1 | 0.44 | 1 | 1 | 0.45 | 2 | 2 | 0.45 | 1.000 |
| Vaccination site pruritus | 0 | 0 | 0.00 | 1 | 1 | 0.45 | 1 | 1 | 0.22 | .497 |
| Vaccination site induration | 1 | 1 | 0.44 | 3 | 3 | 1.35 | 4 | 4 | 0.89 | .370 |
| Systemic | 19 | 15 | 6.67 | 25 | 21 | 9.46 | 44 | 36 | 8.05 | .301 |
| Decreased appetite | 0 | 0 | 0.00 | 2 | 2 | 0.90 | 2 | 2 | 0.45 | .246 |
| Irritability | 1 | 1 | 0.44 | 0 | 0 | 0.00 | 1 | 1 | 0.22 | 1.000 |
| Fever | 12 | 11 | 4.89 | 15 | 15 | 6.76 | 27 | 26 | 5.82 | .426 |
| Diarrhea | 4 | 4 | 1.78 | 6 | 6 | 2.70 | 10 | 10 | 2.24 | .542 |
| Vomiting | 1 | 1 | 0.44 | 1 | 1 | 0.45 | 2 | 2 | 0.45 | 1.000 |
| Enanthema | 1 | 1 | 0.44 | 1 | 1 | 0.45 | 2 | 2 | 0.45 | 1.000 |
| **Unsolicited** | 7 | 6 | 2.67 | 15 | 15 | 6.76 | 22 | 21 | 4.70 | .046 |
| Respiratory, thoracic and mediastinal disorders | 2 | 2 | 0.89 | 3 | 3 | 1.35 | 5 | 5 | 1.12 | .684 |
| Laryngeal pain | 0 | 0 | 0.00 | 1 | 1 | 0.45 | 1 | 1 | 0.22 | .497 |
| Cough | 0 | 0 | 0.00 | 1 | 1 | 0.45 | 1 | 1 | 0.22 | .497 |
| Sneezing | 2 | 2 | 0.89 | 1 | 1 | 0.45 | 3 | 3 | 0.67 | 1.000 |
| Skin and subcutaneous tissue disorders | 0 | 0 | 0.00 | 1 | 1 | 0.45 | 1 | 1 | 0.22 | .497 |
| Rash | 0 | 0 | 0.00 | 1 | 1 | 0.45 | 1 | 1 | 0.22 | .497 |
| General disorders and administration site conditions | 1 | 1 | 0.44 | 3 | 3 | 1.35 | 4 | 4 | 0.89 | .370 |
| Fever | 1 | 1 | 0.44 | 3 | 3 | 1.35 | 4 | 4 | 0.89 | .370 |
| Gastrointestinal disorders | 2 | 1 | 0.44 | 1 | 1 | 0.45 | 3 | 2 | 0.45 | 1.000 |
| Diarrhea | 1 | 1 | 0.44 | 1 | 1 | 0.45 | 2 | 2 | 0.45 | 1.000 |
| Vomiting | 1 | 1 | 0.44 | 0 | 0 | 0.00 | 1 | 1 | 0.22 | 1.000 |
| Infections and infestations | 2 | 2 | 0.89 | 7 | 7 | 3.15 | 9 | 9 | 2.01 | .104 |
| Nasopharyngitis | 2 | 2 | 0.89 | 7 | 7 | 3.15 | 9 | 9 | 2.01 | .104 |

**Table 4.** Grading of ARs.

| | Group A (N = 225) | | | Group B (N = 222) | | | Total (N = 447) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| AR n(%) | Grade 1 | Grade 2 | Grade 3 | Grade 1 | Grade 2 | Grade 3 | Grade 1 | Grade 2 | Grade 3 | *p* |
| **Overall** | 11(4.89) | 10(4.44) | 0(0.00) | 8(3.60) | 27(12.16) | 1(0.45) | 19(4.25) | 37(8.28) | 1(0.22) | .018 |
| **Solicited** | 7(3.11) | 9(4.00) | 0(0.00) | 8(3.60) | 17(7.66) | 0(0.00) | 15(3.36) | 26(5.82) | 0(0.00) | .452 |
| Local | 1(0.44) | 0(0.00) | 0(0.00) | 2(0.90) | 2(0.90) | 0(0.00) | 3(0.67) | 2(0.45) | 0(0.00) | .414 |
| Systemic | 6(2.67) | 9(4.00) | 0(0.00) | 6(2.70) | 15(6.76) | 0(0.00) | 12(2.68) | 24(5.37) | 0(0.00) | .480 |
| **Unsolicited** | 4(1.78) | 2(0.89) | 0(0.00) | 3(1.35) | 11(4.95) | 1(0.45) | 7(1.57) | 13(2.91) | 1(0.22) | .045 |

margin of −10%, suggesting that co-administration has similar immune responses compared to separate administration. In the susceptible population, the seroconversion rates of anti-VZV antibodies in the two groups were 94.22% and 96.25%, and the seroconversion rates of anti-HAV antibodies all reached 100.0%, suggesting that co-administration induces an excellent immune response in this population. The immune responses of HepA and VarV were consistent with previous research, and the results that the co-administration of VarV and HepA was non-inferior to separate administration of each vaccine was consistent with the previous studies.[19,20]

Regarding the safety profiles, the overall incidence of ARs was 12.75%, and the incidence was higher in Group B. The ARs were mainly solicited, and the most common AR was fever. The grades of ARs were mainly 1 and 2, and the incidences of high-grade ARs were higher in Group B. Only one participant reported SAEs in Group B (acute upper respiratory tract infection), which was unrelated to the vaccine, indicating that the vaccination schedules in the two groups were well tolerated. These results demonstrated that co-administration of VarV and HepA is favorable and has no adverse effect on the safety of either vaccine.

This study has certain limitations. First, we could only assess the short-term immunogenicity and safety of the vaccines. Although previous researches have proved the safety and effectiveness of co-administration of VarV with other vaccines, long-term follow-up studies are needed to evaluate the immune persistence of co-administration of VarV and

HepA.[21] Besides, it was an open-label design, which was necessary due to the different vaccination schedules followed by each group. So some bias inevitably occurred. However, AEs would achieve more attention in recipients of concomitant VarV and HepA vaccines, we believe this limitation doesn't substantially affect the findings of this study.

To summarize, co-administration of VarV and HepA did not affect the immunogenicity and had at least as good safety profiles. Further, the susceptible population can achieve excellent immune protection after vaccination. These results suggest that VarV and HepA vaccines can be administered simultaneously to children around 1 year old, based on the vaccination strategy adopted in our study. This strategy can enhance vaccination efficiency, be time-saving and cost-saving for parents and doctors, offer pain reduction to children, and can establish immune protection earlier. Therefore, the strategy can be considered for further promoting the co-administrated vaccination of VarV and HepA in children of 1-year-old.

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## Author contributions

Dianmin Kang, Yongjun Gao, Xueyan Sha, Li Zhang, contributed to the study concept and design. Zhenhua Du contributed to site organization management. Ningning Jia, Qing Xu, Jingjing Lv, Ping Xiong contributed to data acquisition and sorting. Xiaodong Liu, Jianwen Sun, Zhuoqun Sun contributed to data quality control. Dan Yu, Chunfang Luan contributed to the sample collection. Dapeng Sun and Dan Yu contributed to the data analysis and initial drafting of the manuscript. Li Zhang contributed to the critical review and revision of the article. All authors contributed to the interpretation of data and critical revision of the manuscript.

## Disclosure statement

Dan Yu, Ningning Jia, Yongjun Gao are current employees of Sinovac Biotech Co., Ltd. Jianwen Sun and Zhuoqun Sun are current employees of Sinovac Life Sciences Co., Ltd. Chunfang Luan and Xueyan Sha are current employees of Sinovac (Dalian) Vaccine Technology Co., Ltd. All the other authors have no conflicts of interest to declare.

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