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HUMANLY POSSIBLE

Immunization for all

World Immunization Week 2024

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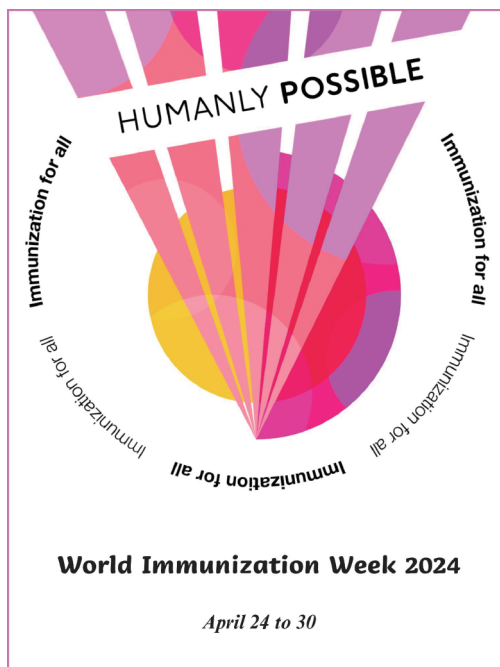
VACCINE ISSUE

Preplanned Studies

China CDC Weekly

Cover Image: adapted from the World Health Organization, https://www.who.int/campaigns/world-immunization-week/2024.
This week's issue was organized by Guest Editor Jingxin Li.

Estimated Human Papillomavirus Vaccine Coverage Among Females 9–45 Years of Age — China, 2017–2022

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Summary

What is already known on this topic?

There is a lack of comprehensive data on the coverage of the human papillomavirus (HPV) vaccine in China. The limited published literature hampers our ability to accurately assess the current situation.

What is added by this report?

This study aimed to determine the rates of HPV vaccine coverage based on data from the electronic vaccination registry reported to the China Immunization Information System between 2017 and 2022. While there was an increase in HPV vaccine coverage each year, the overall coverage remained below the optimal level.

What are the implications for public health practice?

This study presents evidence of low HPV vaccine coverage when administered outside of a national immunization program. Therefore, it is recommended that the HPV vaccine be included in the National Immunization Program in order to meet the 2030 WHO target of achieving 90% vaccination coverage for girls by the age of 15.

Cervical cancer ranks fourth in both incidence and cancer-related deaths among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 (*1*). In China, there were approximately 111,820 new cases and 61,579 deaths due to cervical cancer in 2022 (*2*). The high incidence and mortality rates of cervical cancer not only impose a health burden on individuals but also create a significant economic burden on families. To address this issue, the World Health Organization (WHO) set a global target in 2020, aiming for 90% of girls to receive full human papillomavirus (HPV) vaccination by the age of 15, as a step towards eliminating cervical cancer as a public health problem by 2030 (*3*). In alignment with these goals, China established a national target for 2030 to improve HPV vaccine coverage among young

adolescent females, as part of their efforts to accelerate cervical cancer elimination (*4*). Although the first HPV vaccine was licensed in China in 2016, it has not yet been included in the National Immunization Program (NIP).

Assessing the current HPV vaccination coverage is essential for the development of effective HPV vaccination strategies for young adolescent females in China. However, the existing published literature is insufficient to provide an accurate representation of the national situation. In this study, we aimed to estimate the provincial-level HPV coverage among females aged 9–45 years old in China from 2017 to 2022. Additionally, we estimated the coverage among Chinese females by age group specifically for the year 2022.

Using data from the China Immunization Information System (CIIS) electronic vaccination registries, we analyzed the number of females aged 9–45 years who received the recommended doses of HPV vaccine from 2017 to 2022. Additionally, we recorded the number of vaccinations administered to each age group for the three types of HPV vaccine currently used in China. Detailed information about these HPV vaccines and their recommended schedules can be found in the provided reference (Table 1). The data on number of females aged 9–45 years was obtained from the China Disease Control and Prevention Information System (DCPIS) for the years 2017 to 2020.

We calculated two coverage rates: (1) the estimated cumulative coverage for first-dose and third-dose HPV vaccination among females aged 9–45 years. This was calculated by dividing the total number of females aged 9–45 years in a given study year who received one or three doses of the vaccine from 2017 to the study year, by the total number of females aged 9–45 years in the given study year. (2) The estimated cumulative coverage for first-dose, second-dose, or third-dose HPV vaccination among females by age group by 2022. This was calculated by dividing the number of

females in each age group in 2022 who received one or two doses or three doses of the vaccine, by the corresponding number of females in the population. First-dose coverage refers to having received at least one dose of the HPV vaccine, while third-dose coverage refers to having received all three doses of the vaccine.

Data were compiled and analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) to estimate the four coverage rates mentioned above, based on provincial-level administrative division (PLAD) and age group.

From 2017 to 2022, a total of 85,790,000 doses of the HPV vaccine were administered. The number of doses given each year was as follows: 44,000 in 2017, 1,454,000 in 2018, 4,519,000 in 2019, 10,769,000 in 2020, 21,738,000 in 2021, and 47,266,000 in 2022.

Table 2 presents the cumulative coverage levels by PLAD and year. From 2017 to 2022, the first-dose cumulative coverage increased from 0.01% to 10.15%, while the third-dose cumulative coverage increased from 0% to 6.21%. These findings indicate a consistent annual increase in coverage across all PLADs. The PLADs in the eastern region (Beijing, Shanghai, Guangdong) exhibited the highest coverage, while the PLADs in the western region (Xinjiang, Qinghai, Gansu) had the lowest coverage.

Table 3 presents the coverage levels for different age groups and types of HPV vaccines. In 2022, the highest first-dose coverage was observed among individuals aged 20–24 (14.02%), while the lowest

first-dose coverage was found among those aged 9–14 (4.00%). First-dose coverage above 10% was only observed in the age group of 20–39. The age group with the highest third-dose coverage was 25–29 (9.39%), while the lowest third-dose coverage was observed among individuals aged 9–14 (0.31%). Bivalent HPV vaccine had the highest coverage among the three types, but it remained below 7% for all age groups.

DISCUSSION

We conducted a search in the CIIS electronic vaccination registries, encompassing all immunization clinics across China, to examine HPV vaccination rates. Our findings demonstrate a consistent increase in the number of administered doses and vaccination coverage in each of the six years since the introduction of HPV vaccine in China. However, despite this upward trend, the first-dose coverage was only 10.15%, and the third-dose coverage was only 6.21% by 2022. These rates notably lag behind the global coverage rates of 20% for the first dose and 15% for the full series among females in 2019 (5). A meta-analysis indicates that substantial indirect (herd) protection against HPV occurs when vaccine coverage exceeds 50% (6). Therefore, the current HPV vaccine coverage in China is far below the threshold required for achieving herd immunity.

The study revealed low vaccination coverage for HPV among females under 20 years old. In the 9–14-

TABLE 1. HPV vaccines available in China as of the end of 2022.

Item	2-valent HPV vaccine			4-valent HPV vaccine	9-valent HPV vaccine
Manufacturer	GlaxoSmithKline Biologicals S.A.	Xiamen Innovax Bio-Tech Co., Ltd.	Yuxi Walvax Bio-Tech Co., Ltd.	Merck Sharp & Dohme Corp.	
Licensing year	2016	2019	2022	2017	2018
Approved age range	9 to 45 years*	9 to 45 years	9 to 30 years	9 to 45 years[†]	9 to 45 years[§]
Number of doses in recommended schedule	3 doses; 2 doses also for 9 to 14 years			3 doses	
Recommended schedule	3-dose series, the second dose should be given 1 month after the first dose, and the third dose should be given 6 months after the first dose. 2-dose series is also available for female 9 to 14 years of age, the second dose should be given 6 months after the first dose.	3-dose series, the second dose should be given 2 months after the first dose, and the third dose should be given 6 months after the first dose. 2-dose series is also available for females 9 to 14 years of age, the second dose should be given 6 months after the first dose.		3-dose series, the second dose should be given 2 months after the first dose, and the third dose should be given 6 months after the first dose.	

Abbreviation: HPV=human papillomavirus.
* 2-valent HPV vaccine for females aged 9 to 25 years in 2016–2018. The age range was extended to 9–45 years in July 2018. 2-dose was also available for female aged 9 to 14 years in May 2022.
[†] 4-valent HPV vaccine for females aged 20 to 40 years in 2017–2019. The age range was extended to 9–45 years in December 2020.
[§] 9-valent HPV vaccine for female aged 16 years to 26 years in 2018–2021. The age range was extended to 9–45 years in August 2022.

TABLE 2. HPV vaccination coverage among females aged 9–45 years in China, 2017–2022 (%).

PLAD	2017		2018		2019		2020		2021		2022	
	First dose	Third dose	First dose	Third dose	First dose	Third dose	First dose	Third dose	First dose	Third dose	First dose	Third dose
Beijing	0.02	0	1.50	0.38	4.75	2.86	10.28	5.90	17.64	12.25	25.40	20.29
Tianjin	0	0	0.50	0.15	1.49	0.93	3.65	2.20	7.34	4.39	13.67	9.50
Hebei	0	0	0.09	0	0.67	0.18	2.02	0.79	4.55	1.91	8.95	5.13
Shanxi	0	0	0.09	0.04	0.42	0.18	1.01	0.61	2.76	1.18	6.27	3.85
Inner Mongolia	0	0	0	0	0.10	0.03	0.90	0.19	3.11	1.17	6.60	4.22
Liaoning	0	0	0.05	0.02	0.33	0.16	0.76	0.48	2.90	1.14	7.12	4.28
Jilin	0	0	0.18	0.03	0.85	0.33	2.44	1.17	4.75	2.67	7.99	5.24
Heilongjiang	0	0	0.01	0	0.05	0.02	0.15	0.07	1.06	0.24	3.97	2.17
Shanghai	0.03	0	1.77	0.31	4.13	2.82	8.23	5.30	13.43	9.46	20.99	14.49
Jiangsu	0	0	0.15	0.02	1.43	0.52	3.26	1.96	6.71	3.60	13.05	8.44
Zhejiang	0.03	0	0.62	0.19	1.81	1.18	4.32	2.71	8.17	5.35	14.30	9.76
Anhui	0.01	0	0.08	0.01	0.45	0.18	1.19	0.58	3.71	1.40	8.65	5.33
Fujian	0.01	0	0.09	0.03	0.51	0.22	2.22	1.00	5.28	2.54	13.75	6.56
Jiangxi	0	0	0	0	0.01	0	0.11	0.02	1.72	0.69	4.99	3.16
Shandong	0.01	0	0.36	0.16	1.19	0.60	2.85	1.65	6.14	3.29	11.70	7.40
Henan	0	0	0.04	0.01	0.40	0.09	1.71	0.59	4.37	1.79	8.98	5.12
Hubei	0	0	0.02	0	0.19	0.06	1.44	0.29	4.96	1.61	10.14	5.84
Hunan	0.01	0	0.14	0.04	0.45	0.20	1.16	0.59	2.95	1.31	6.92	3.94
Guangdong	0.01	0	0.42	0.12	1.07	0.60	2.94	1.50	6.75	3.42	15.65	8.63
Guangxi	0.01	0	0.15	0.04	0.66	0.20	1.76	0.77	4.40	1.77	9.37	5.54
Hainan	0	0	0.04	0.01	0.39	0.24	2.24	0.95	6.02	2.96	14.04	7.15
Chongqing	0.07	0	0.47	0.14	1.42	0.67	3.37	1.77	6.96	3.75	12.16	8.29
Sichuan	0.03	0	0.20	0.06	0.62	0.32	1.75	0.99	5.54	2.65	11.36	7.61
Guizhou	0	0	0.03	0.01	0.29	0.09	0.84	0.43	2.04	0.95	4.74	2.74
Yunnan	0	0	0.04	0	0.28	0.08	0.92	0.41	2.66	1.03	6.31	3.66
Xizang	0	0	0	0	0	0	0.01	0	0.48	0.06	3.51	0.88
Shaanxi	0	0	0.07	0.01	0.48	0.14	1.99	0.77	5.78	2.39	11.67	7.12
Gansu	0	0	0.05	0	0.26	0.11	0.65	0.40	1.56	0.83	3.41	2.16
Qinhai	0	0	0	0	0	0	0.05	0	1.10	0.44	2.95	1.78
Ningxia	0	0	0	0	0.01	0	0.53	0.08	3.29	0.87	7.03	4.50
Xinjiang	0	0	0.01	0	0.04	0.01	0.33	0.05	1.17	0.31	2.55	1.27
Total	0.01	0	0.22	0.06	0.78	0.38	2.11	1.09	4.95	2.47	10.15	6.21

Abbreviation: HPV=human papillomavirus; PLAD=provincial-level administrative division.

year-old group, first-dose coverage was 4.00%, and third-dose coverage was 0.31%. In the 15–19-year-old group, first-dose coverage was 4.66% and third-dose coverage was 2.21%. These findings indicate that HPV vaccine coverage is significantly below the WHO's 2030 target of achieving 90% full vaccination among girls by the age of 15.

The low coverage observed in China may be attributed to the limited availability of vaccines during the study period and the exclusion of the HPV vaccine from China's National Immunization Program. Instead, the HPV vaccine is available on a non-program basis, requiring families to pay for it. However, the introduction of domestically produced bivalent HPV vaccines in 2019 and 2022 has helped mitigate vaccine supply challenges.

TABLE 3. HPV vaccination cumulative coverage by age group among females aged 9 to 45 years through the end of 2022.

Age group (years)	2-valent HPV vaccine			4-valent HPV vaccine			9-valent HPV vaccine			Cumulative		
	First dose	Second dose	Third dose	First dose	Second dose	Third dose	First dose	Second dose	Third dose	First dose	Second dose	Third dose
9–14	3.82	1.35	0.22	0.15	0.14	0.08	0.02	0	0	4.00	1.50	0.31
15–19	1.31	1.11	0.67	0.08	0.03	0.04	3.27	2.71	1.49	4.66	3.85	2.21
20–24	1.41	1.26	0.83	0.31	0.22	0.15	12.30	10.98	7.35	14.02	12.46	8.34
25–29	3.26	2.97	1.98	3.21	2.60	1.85	6.76	6.23	5.55	13.24	11.80	9.39
30–34	6.18	5.70	3.84	6.16	5.09	3.82	0.13	0.03	0.02	12.48	10.83	7.68
35–39	6.63	6.15	4.22	5.78	4.80	3.65	0.09	0.01	0.01	12.49	10.96	7.88
40–45	4.53	4.24	3.09	3.29	2.82	2.28	0.04	0.01	0	7.86	7.06	5.37
Total	4.14	3.54	2.35	3.07	2.55	1.93	2.93	2.60	1.94	10.15	8.69	6.21

Abbreviation: HPV=human papillomavirus.

A register-based observational study conducted in England has shown a significant decrease in cervical cancer cases among young women following the implementation of an HPV vaccination program (7). This reduction was particularly notable among those who received the vaccine between the ages of 12 and 18. This finding aligns with a nationwide cohort study in Denmark, which also found a high effectiveness of the HPV vaccine in preventing cervical cancer among girls vaccinated before the age of 20 (8). Collectively, these studies indicate that achieving high HPV vaccine coverage is crucial for ensuring its effectiveness in preventing cervical cancer at the population level.

In 2017, the WHO revised its guidance to suggest that countries should consider vaccinating multi-age cohorts (MAC) instead of a single birth cohort when introducing the vaccine, in order to enhance the impact and efficiency of the program (9). In 2022, the WHO further recommended a vaccination schedule for girls aged 9–14 years, consisting of either two doses or a single dose (10). This recommendation has the potential to expedite China's efforts to achieve the necessary high vaccine coverage for cervical cancer elimination.

In our study, we observed a significant difference in the vaccination coverage between the first and second doses in the 9–14-year-old age group. There are two main contributing factors to this discrepancy. First, the 2-valent HPV vaccine guidelines allow girls in this age group to choose between receiving either 3 doses or 2 doses to complete the full vaccination series. Second, in 2022, certain regions implemented a policy providing free HPV vaccines consisting of 2 doses for middle school girls (11). As a result, some girls have received the first dose but have not yet reached the recommended time for receiving the second dose.

There are significant disparities in HPV vaccine coverage between the eastern and western regions. Cervical cancer has a higher impact on women residing in economically underdeveloped western regions, mainly due to the natural environment and relatively weaker healthcare conditions. As a result, it is crucial to urgently introduce HPV vaccination in these lagging regions to mitigate vaccine-related inequalities (12).

Our study has several limitations. First, the CIIS makes efforts to collect vaccination records from immunization clinics to ensure compliance with the requirements of the vaccine management law for complete traceability. However, there may be cases where certain records are missing due to unsuccessful uploads or data discrepancies. Nonetheless, it is worth noting that the number of missing records is minimal and has minimal impact. Second, we lacked data on the size of the female population in 2021–2022, so we utilized 2020 female population data, which may have had a slight impact on our estimates. Lastly, we did not take into account deaths when calculating HPV vaccine coverage, which may have had a minor effect on our estimates.

In conclusion, our study identified both progress and gaps in the utilization and coverage of the HPV vaccine among females aged 9–45 years in China. However, it is concerning that the rates of HPV vaccination were significantly lower than the global average, particularly among females under 20 years of age, and well below the WHO 2030 target. To address these issues, we recommend incorporating the HPV vaccine into China's National Immunization Program. This should involve implementing routine vaccination across multiple age cohorts to rapidly increase coverage among a wide range of ages, reduce regional disparities, and ensure equitable access to this important vaccine.

The introduction of the HPV vaccine into the National Immunization Program should be supported by evidence of disease burden, immunization strategies to achieve high coverage, assessments of cost-effectiveness, proof of sufficient vaccine supply, and assurance of adequate vaccination service capacity.

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Preplanned Studies

Coverage of the Combined DTaP-IPV/Hib Vaccine Among Children Aged 2–18 Months — 9 PLADs, China, 2019–2021

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Summary

What is already known on this topic?

In China, there is limited data available on the use and coverage of the non-program, combined diphtheria, tetanus toxoid, acellular pertussis adsorbed, inactivated poliovirus and haemophilus influenzae type b (DTaP-IPV/Hib) pentavalent vaccine, and its role as a substitute for the separately administered standalone program vaccines.

What is added by this report?

We evaluated the use and coverage of the pentavalent vaccine in nine provincial-level administrative divisions (PLADs) spanning eastern, central, and western China from 2019 to 2021. Initial use and coverage were low, but demonstrated annual growth albeit with regional and urban-rural discrepancies. The pentavalent vaccine was increasingly substituted for standalone vaccines over the course of this period.

What are the implications for public health practice?

Parents in China are increasingly opting to replace the standard program vaccines with voluntarily purchased combination vaccines, particularly the pentavalent vaccine. The development of combination vaccines should thus be promoted in China, as it could enhance utilization and coverage rates, and decrease the economic burden.

Childhood vaccination plays a crucial role in shielding children from severe and potentially fatal infectious diseases. The main hurdles to childhood immunization encompass an increasing number of vital vaccines advised for young children, the discomfort tied to multiple injections, parental worries about the frequency of vaccination appointments and injection-associated pain, and the need to maintain high vaccination coverage. Combination vaccines present a solution, as they protect against multiple diseases via fewer injections, making the vaccination process more convenient for both parents and healthcare providers.

This also enhances adherence to the vaccination schedule, a factor that is paramount in sustaining high levels of population immunity (*1*).

Vaccines featuring a combination of diphtheria, tetanus, and pertussis (DTP) are extensively utilized globally. In 2022, around 110 million infants, constituting approximately 84% of the worldwide birth cohort, were administered three doses of a DTP-inclusive vaccine (*2*). These DTP-inclusive vaccines comprise DTaP, DTP-Hib (DTP integrated with a *Haemophilus influenzae* type b component), and the pentavalent DTP-inclusive vaccines, such as DTP, IPV, and Hib or hepatitis B components. The only existing pentavalent vaccine in China is Sanofi's DTaP-IPV/Hib vaccine, Pentaxim, which was licensed in the country in 2010 (*3*).

The DTaP-IPV/Hib vaccine serves as a suitable replacement for the DTP and IPV vaccines in the National Immunization Program (NIP) and further expands the spectrum of the NIP vaccines with the addition of the non-NIP Hib vaccine. This leads to a substantial reduction in the number of injections and visits needed for complete vaccination of children within the first two years of life. So far, studies on the pentavalent vaccine within the domestic context have been primarily concentrated on its immunogenicity and safety, with little emphasis on coverage and the ratio of its usage relative to other DTP-containing vaccines — a concept known as the substitution rate. This data are crucial for precise vaccine procurement. Thus, this paper aims to analyze usage, coverage, and the market penetration of the pentavalent vaccine in China.

The study was conducted across 9 provincial-level administrative divisions (PLADs) in China, as classified in the China Statistical Yearbook 2021. These include Jiangsu, Zhejiang, and Shandong provinces in the East; Anhui, Hubei, and Hunan provinces in the Central region; and Sichuan, Guizhou, and Gansu provinces in the West. The suggested schedule for the DTaP-

IPV/Hib vaccine involves a primary series of three doses given either at 2, 3, and 4 months of age, or at 3, 4, and 5 months of age. This regimen is then followed by a booster dose at 18 months.

We sourced the annual birth cohort sizes between 2017 and 2021, along with vaccination histories during 2019–2021, from the provincial Immunization Information Systems (IISs). Please refer to Supplementary Material (available at https://weekly.chinacdc.cn/) for detailed information. Utilizing the vaccination records from the IIS, we were able to establish the annual administration of doses for the pentavalent vaccine and other DTP-containing vaccines. Moreover, we quantified the number of children who had received at least one dose of the pentavalent vaccine, those who completed a primary series of the pentavalent vaccine, and those who were administered a booster dose of the pentavalent vaccine.

The percentage of age-appropriate children who received one or more doses of the pentavalent vaccine was calculated by dividing the number of children receiving at least one dose by the total number of children born over a twelve-month period, spanning from the final two months of the preceding year to the first ten months of the study year. Similarly, the percentage completion of the full primary series among age-appropriate children was derived by dividing the number of children who finished the primary series by the number of children born over a period of twelve months, spanning from the last four months of the preceding year to the first eight months of the study year. The booster administration rate among 18-

month-old children was calculated by taking the ratio of the number of children who received a booster dose to the total number of children born during a eighteen-month period from the last six months of the year before the preceding year to the first six months of the preceding year. The annual usage rate of pentavalent vaccine doses per 100 newborns was established by dividing the quantity of pentavalent vaccine doses administered in a particular study year by the count of newborns in that same study year. We also determined the percentages of the pentavalent vaccine among all DTP-containing vaccines administered in the years 2019, 2020, and 2021.

The data were scrutinized utilizing Microsoft Excel 2021 (Microsoft Corporation, Redmond, WA, USA) to discern patterns of utilisation and coverage on an annual basis and by geographical divisions such as province, region, and urban/rural classifications.

Over the span of 2019 to 2021, a total of 6.79 million doses of the pentavalent vaccine were administered. Table 1 illustrates the dosage rates per 100 newborns, categorized by PLAD, region, and year. Zhejiang commanded the highest vaccine utilization each year, with Guizhou pulling up the rear in 2019 and 2020, and Gansu being the most deficient in 2021. Notably, every PLADs demonstrated an annual growth in the use of the pentavalent vaccine. The use of the pentavalent vaccine per 100 newborns notably surged by 54.66% from 2019 to 2020, and by 24.13% from 2020 to 2021. Anhui observed the most significant advancement, whereas Gansu's growth remained sluggish. In terms of regional comparisons,

TABLE 1. Use of pentavalent vaccine in nine PLADs of China, 2019–2021 (expressed as doses per 100 newborns).

PLADs	2019	2020	2021	Year-on-year growth rate in 2020 (%)	Year-on-year growth rate in 2021 (%)
Eastern Region	37.42	61.23	78.41	63.63	28.05
Jiangsu	33.04	57.24	76.82	73.25	34.21
Zhejiang	64.57	98.12	122.41	51.98	24.75
Shandong	21.71	36.32	45.79	67.33	26.06
Central Region	23.07	34.48	43.81	49.50	27.06
Anhui	14.17	25.54	40.19	80.27	57.35
Hubei	31.30	45.70	61.38	46.00	34.31
Hunan	16.00	25.06	32.99	56.62	31.62
Western Region	19.73	28.47	35.48	44.29	24.63
Sichuan	33.78	49.28	63.06	45.88	27.97
Guizhou	6.03	10.08	12.66	67.16	25.59
Gansu	7.86	10.62	12.21	35.15	15.02
Total	28.81	44.56	55.32	54.66	24.13

Abbreviation: PLADs=provincial-level administrative divisions.

the eastern region consistently reported the highest dosage rates, approximately double that of its western counterpart.

Table 2 presents the annual coverage of the pentavalent vaccine by PLAD and region. An incremental yearly increase was observed in every PLADs and region for ≥1-dose, full primary series, and booster shots. The provincial-specific increase, however, varied. In 2019, the coverage for ≥1 dose was 11.25%, increasing to 18.74% in 2021. The full primary series covered 7.75% in 2019 and extended to 13.42% in 2021. Booster coverage grew from 1.37% in 2019 to 10.13% in 2021. Jiangsu consistently recorded the highest coverage for ≥1 dose every year. The lowest coverage rates for the same were seen in Guizhou in 2019 and 2020, and Gansu in 2021. The highest coverage for ≥1-dose, full primary series, and booster shots were invariably found in the eastern region. In 2021, the eastern region's coverage of ≥1-dose was 1.77 times higher than the central region (27.84% *vs.* 15.77%), and 2.97 times higher than the western region (9.38%).

Figure 1 shows progressively increasing coverage year-by-year, consistently demonstrating higher coverage in urban areas in comparison to rural zones. In 2019, the coverage in urban locales stood at 16.33%, while in 2021 this figure rose to 26.22%. Correspondingly, in rural areas the coverage was considerably lesser at 4.91% in 2019, increasing

marginally to 9.45% in 2021. The PLAD registering the pre-eminent coverage in both urban and rural regions was Jiangsu, whilst Gansu observed the least coverage. The graphs incorporate a 45-degree line, symbolizing parity between urban and rural coverage — with areas experiencing higher urban coverage plotted above the line. The plotted trajectories approach lines indicative of equivalence, signaling a progression towards urban-rural equilibrium.

Table 3 displays a progressive increase in pentavalent vaccine administration from 1.83 million doses in 2019, 2.35 million in 2020 to 2.61 million doses in 2021, reflecting an average annual growth rate of 19.32%. The majority of these doses were utilized in the eastern region, with the western region utilizing the least amount. Additionally, the table provides a proportion (%) of DTP-containing doses that were substituted with pentavalent doses, identified as the "pentavalent substitution rate", by PLAD, region, and year. The substitution rate markedly increased from 7.61% in 2019 to 13.83% in 2021. While the eastern region reported the highest substitution rate in 2019, and the central region the lowest, the western region consistently reported the lowest rates in 2020 and 2021. Notably, an exception to the increasing trend was observed in Gansu, with a drop in substitution rates from 2.52% in 2019 to 1.82% in 2020, followed by a subsequent increase to 2.89% in 2021.

TABLE 2. Percentage of pentavalent vaccine coverage among children aged 2–18 months in nine PLADs of China, 2019–2021.

PLADs	2019			2020			2021		
	At least one dose	Full primary series	Booster dose	At least one dose	Full primary series	Booster dose	At least one dose	Full primary series	Booster dose
Eastern Region	16.02	10.82	1.75	22.30	15.72	8.47	27.84	18.73	14.33
Jiangsu	25.13	9.00	1.09	37.82	14.88	7.33	48.54	18.50	12.79
Zhejiang	21.30	18.88	3.53	25.93	25.32	14.42	30.43	29.25	23.72
Shandong	6.05	6.60	1.09	8.36	9.32	5.22	10.65	10.88	8.68
Central Region	7.81	5.33	1.16	11.55	8.04	4.25	15.77	10.62	6.93
Anhui	5.31	3.88	0.49	7.59	6.78	2.86	11.30	9.93	6.99
Hubei	10.37	8.14	2.00	12.67	11.32	6.03	16.33	14.66	9.30
Hunan	8.09	4.37	1.12	14.52	6.52	4.10	19.72	7.95	4.87
Western Region	7.70	5.70	0.99	8.52	8.26	4.33	9.38	9.02	7.43
Sichuan	13.34	9.92	1.78	14.61	14.42	7.60	16.45	15.93	13.00
Guizhou	2.22	1.71	0.24	3.09	2.70	1.26	3.44	3.22	2.36
Gansu	2.99	1.98	0.36	3.15	2.77	1.52	3.41	3.00	2.35
Total	11.25	7.75	1.37	15.04	11.25	6.05	18.74	13.42	10.13

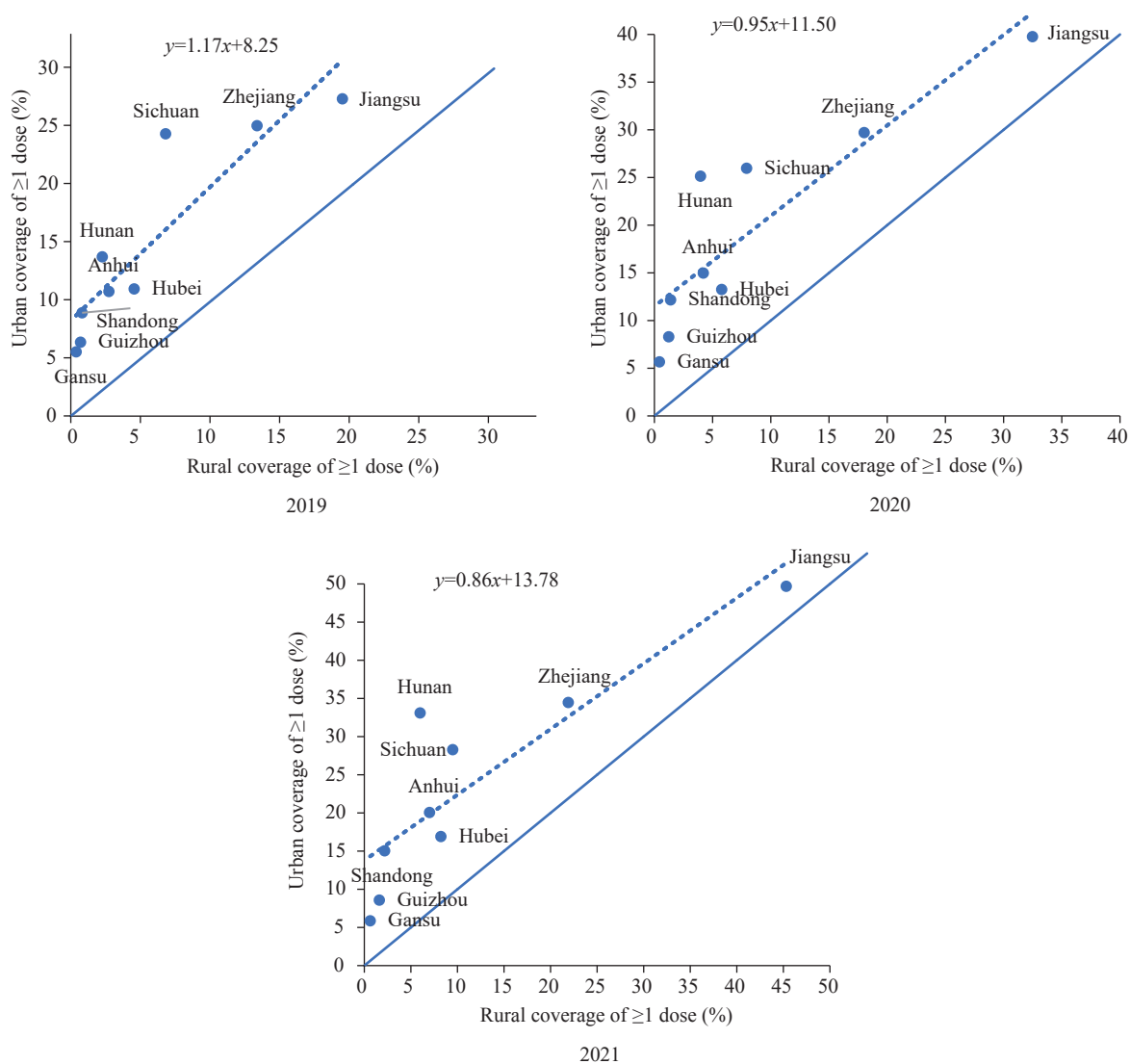Abbreviation: PLADs=provincial-level administrative divisions.

FIGURE 1. Pentavalent vaccine coverage among children aged 2–18 months in urban and rural areas in nine PLADs of China, 2019–2021.

DISCUSSION

Our analysis of real-world data reveal that between 2019 and 2021, the use and coverage of the pentavalent vaccine increased annually across nine PLADs in China. The number of pentavalent vaccine doses used per 100 newborns and the corresponding coverage levels were highest in the eastern region, followed by the central and western regions, although substantial variations were observed at the provincial level. While the pentavalent coverage was consistently higher in urban areas compared to rural areas, we noted a decreasing disparity between the two. Over the years, a growing trend towards the substitution of pentavalent vaccine in place of separately administered standalone vaccines was detected.

Our findings align with previous research. A study conducted in Anhui (4) demonstrated that the coverage for pentavalent vaccination escalated from 2015 to 2020, recording a coverage of 6.11% for 2–3 year olds and 8.51% for 1–2 year olds. These percentages are parallel to our Anhui records in 2019 and 2020, which were 5.31% and 7.59%, respectively. Furthermore, a cross-sectional survey carried out in Hainan (5) during December 2022 and January 2023 reported DTaP-IPV/Hib vaccination rates of 24.4% for at least one dose, 18.5% for the primary series, and 16.0% for the booster dose. Our findings for the eastern region in 2021 showcased similar rates, with at least one dose at 27.84%, the primary series at 18.73%, and the booster at 14.33%.

The inclusion of DTP-containing pentavalent

TABLE 3. Usage and substitution rates (%) of pentavalent vaccine in nine PLADs of China, 2019–2021.

PLADs	2019		2020		2021		Annual growth rate of doses (%)
	Number of Pentavalent (×10,000 dose)	Substitution rate (%)	Number of Pentavalent (×10,000 dose)	Substitution rate (%)	Number of Pentavalent (×10,000 dose)	Substitution rate (%)	
Eastern Region	105.99	9.97	136.01	14.71	149.40	19.26	18.73
Jiangsu	27.36	10.04	37.43	13.63	42.99	18.60	25.35
Zhejiang	52.92	20.03	66.14	28.96	71.55	34.69	16.28
Shandong	25.71	4.88	32.44	7.69	34.86	10.30	16.44
Central Region	40.68	5.48	53.10	8.05	61.22	11.04	22.68
Anhui	10.00	3.90	15.16	6.67	19.74	10.26	40.50
Hubei	19.22	8.70	22.95	11.80	25.05	15.41	14.16
Hunan	11.46	4.33	14.99	6.31	16.43	8.24	19.74
Western Region	36.36	6.07	45.88	6.87	49.96	9.02	17.22
Sichuan	30.14	9.55	37.09	12.64	40.35	15.43	15.70
Guizhou	4.13	2.06	6.10	2.70	6.67	3.51	27.08
Gansu	2.09	2.52	2.69	1.82	2.94	2.89	18.60
Total	183.03	7.61	234.99	10.43	260.58	13.83	19.32

Abbreviation: PLADs=provincial-level administrative divisions.

vaccines in immunization schedules has been a long-standing practice in countries such as the United States and the United Kingdom (6–7). In several low and lower-middle-income countries, this vaccine has been incorporated into their immunization programs, facilitated by Gavi support. In Kenya, the success of the immunization program is often gauged by the coverage percentage for the third dose of the pentavalent vaccine (8). For instance, in Afghanistan in 2018, first-dose and third-dose coverages for 12–23-month-old children were reported at 94.0% and 82.3% respectively (9). However, in China, the pentavalent vaccine is not included in the NIP and is, hence, not subsidized by the government. Parents who wish for their children to receive this vaccine must bear the cost themselves. The out-of-pocket expenses associated with non-program vaccines often contribute to their lower uptake (10).

Our study identified distinct geographical and urban-rural variations over the years. In 2021, for instance, the eastern region administered 2.21 times the number of pentavalent vaccine doses for every 100 newborns compared to the western region (78.41 *vs.* 35.48), and Zhejiang province utilized 10.03 times the doses for every 100 newborns relative to Gansu province (122.41 *vs.* 12.21). These discrepancies illuminate disparities between more and less-developed regions, as well as wealthier and poorer regions in China. In every province, we noted consistently higher vaccine coverage among urban children compared to

their rural counterparts, although the disparities have been progressively diminishing over time. A multitude of factors influenced parental preference for non-NIP vaccines, with vaccine cost and family income proving being major determinants of acceptance (11). Given the high cost of the pentavalent vaccine in China — a four-dose series being priced at 2,488 Chinese Yuan in Hainan, families in less developed, remote, and rural areas may encounter notable limitations (5). However, children in such areas have an elevated demand for combination vaccines to augment vaccination rates and to decrease the number of necessary clinic visits, thus saving the time parents spend taking their children to vaccination clinics.

The Pentavalent vaccine, an alternative to independent vaccines for DTaP, IPV, and oral polio, is part of China's NIP. It additionally includes the non-program Hib vaccine. From 2019 to 2021, usage of the pentavalent doses surged in the PLADs under study, and the substitution of the pentavalent vaccine for standalone vaccines saw an annual increase of approximately 3%. Furthermore, the preference for pentavalent vaccines among parents has been on an upward trend, despite a recent downturn in birth numbers. As the demand for combination vaccines may persistently rise, fostering research and innovation in their development within China is crucial (12).

This study is subject to some limitations. The count of administered pentavalent vaccines hinged on provincial IIS data, which may be slightly deficient due

to unsuccessful data uploads or discrepancies. Nonetheless, China's vaccine management law mandates comprehensive traceability of vaccines, resulting in a minuscule proportion of incomplete records. To mitigate the deficiencies of IIS data, we utilized estimated birth population numbers as denominators for the computation of coverage. We have confidence in the reliability of our findings, given their alignment with prior research, as mentioned above.

Our study poses queries which warrant further investigation. It is crucial to identify the contributing factors behind regional and urban-rural disparity in pentavalent vaccine coverage via observational studies. Experimental studies may be essential to test viable measures to minimize these disparities. Additionally, research focused on maintaining high coverage and analyzing the cost-effectiveness of combined vaccines could justify their inclusion in the NIP.

In conclusion, we observed a progressive increase in the use, coverage, and replacement of the pentavalent vaccine among children aged 2 to 18 months. The pentavalent vaccine's market share has been consistently growing. However, the overall coverage of the pentavalent vaccine remains modest, with variations seen across different regions, provinces, and city size. Parental preference for the pentavalent vaccine is made evident by their willingness to purchase it out-of-pocket over standalone vaccines.

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SUPPLEMENTARY MATERIAL

Immunization Information Systems (IISs) are secure, computerized, population-based systems that gather and control vaccination data (*1*). In China, each provincial-level administrative division (PLAD) operates its own Provincial Immunization Information System (PIIS). As depicted in Supplementary Figure S1, a PIIS consolidates data from various sources to carry out tasks such as management of vaccination records, vaccine handling, cold chain equipment and temperature observing information management, tracking of adverse events post-immunization, delivering public services, and overseeing user authentication along with permission management (*2*). The PIIS ensures the gathering, control, data interchange, sharing, and utilization of immunization-related information within the PLAD.
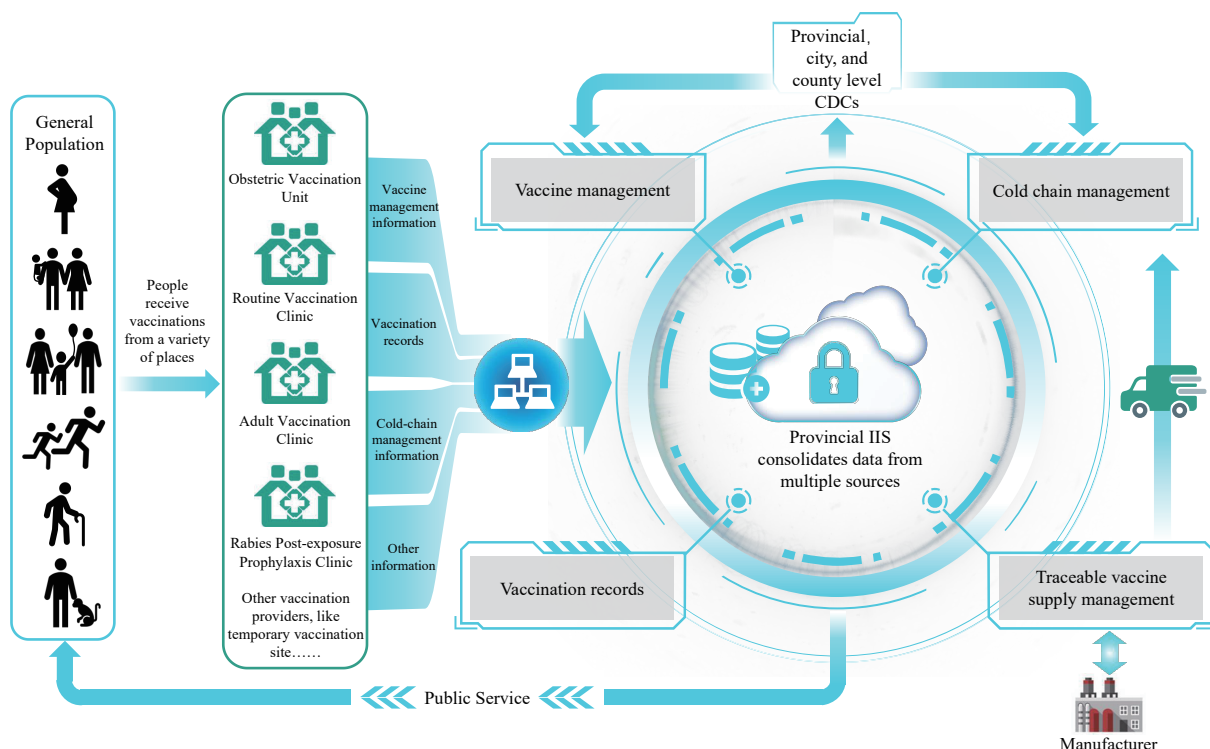
SUPPLEMENTARY FIGURE S1. Overview of the provincial immunization information system used for data collection and management of vaccination records in China.
Abbreviation: IIS=immunization information system.

Data for the Pentavalent vaccine and other DTP-containing vaccines utilized in our study were sourced from the immunization records of qualifying children across the IISs in the nine PLADs under study. Initially, a consensus on computation rules was reached via collaboration with provincial immunization experts. Subsequently, all PIISs uniformly applied these rules to ascertain both the number of individuals and the overall doses of each vaccine administered between 2019 to 2021. As a measure to ensure the validity of the calculation outcomes, these findings were reviewed and verified by the provincial experts.

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Preplanned Studies

Comparison of 1 Versus 2 Doses of Quadrivalent Influenza Vaccine in 3–8-Year-Old Children with Different Immunological States — Jiangsu Province, China, 2021

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Summary

What is already known about this topic?

The quadrivalent influenza vaccine (QIV) provides protection against a broader range of influenza strains by including strains of influenza A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.

What is added by this report?

This study aimed to assess the immunogenicity and safety of administering a single dose compared to two doses of QIV in children, taking into consideration their previous influenza vaccination history.

What are the implications for public health practice?

This study provides evidence supporting the use of a single dose of the QIV in children aged 3–8 years who have previously received two or more doses of influenza vaccine. However, children who have not been previously vaccinated with influenza vaccine should still adhere to the recommended schedule of receiving two doses.

Influenza, a highly contagious respiratory illness, is responsible for a substantial number of severe cases and respiratory-related deaths worldwide (*1*). The annual incidence of influenza in adults is estimated to be between 5% and 10%, while in children, it can be even higher, ranging from 20% to 30% (*2*). Infected children, who typically have a prolonged high viral load lasting up to two weeks, play a significant role in spreading the virus and leading to a greater number of secondary infections. This places a considerable socioeconomic and clinical burden on society (*3*).

Annual influenza vaccination is recommended by many countries to address antigenic drift and declining serum antibody levels over time (*4*). Research has indicated that, for children under 9 years with no prior vaccination, two doses of trivalent influenza vaccine offer higher protective efficacy compared to a single

dose (*5–7*). The quadrivalent influenza vaccine (QIV) contains strains of influenza A/H1N1, A/H3N2, B/Yamagata, and B/Victoria. Studies have demonstrated that QIV exhibits comparable immunogenicity to trivalent influenza vaccine, but outperforms non-trivalent influenza B lineage (*8*). This study aims to assess the immunogenicity and safety of QIV with one or two doses in children aged 3 to 8 years in China while considering their influenza vaccination history.

In this open-label, self-paired clinical trial conducted in Donghai County, Jiangsu Province, China (ClinicalTrials.gov number: NCT05313893), we enrolled healthy children aged 3–8 years. The children were categorized into two groups based on their previous influenza vaccine history: Group A (received two or more doses) and Group B (never received). Please refer to Supplementary Material (available at https://weekly.chinacdc.cn) for detailed inclusion and exclusion criteria. Each group received a two-dose regimen of the QIV on days 0 and 28. The QIV vaccine, manufactured by Changchun Institute of Biological Products Co., Ltd., is meant for seasonal influenza immunization in individuals aged 3 years or older. Each 0.5 mL dose contained 15 µg hemagglutinin for A/Victoria/2570/2019 (H1N1) pdm09, A/Cambodia/e0826360/2020 (H3N2), B/Washington/02/2019 (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage). The trial was reviewed and approved by the Ethics Committee of the Jiangsu CDC, conducted following Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Blood samples were collected at three time points: baseline (referred to as day 0), day 28, and day 56, to quantify antibody titers. The quantification was performed at the China National Institutes for Food and Drug Control using a hemagglutination inhibition

(HI) assay. The strains used for HI testing corresponded to the prevalent influenza strains for the season, which were also included in the vaccine composition. Following vaccination, participants were monitored for 30 minutes to identify any immediate reactions. Solicited local and systemic adverse events within 7 days, unsolicited adverse events within 28 days, and serious adverse events within 6 months after vaccination were also recorded. The severity of adverse events was assessed according to the "Guidelines for Grading Adverse Reactions in Clinical Trials of Preventive Vaccines." The causal relationships between vaccination and adverse events were evaluated by an expert committee organized by Jiangsu CDC.

The primary endpoint for assessing immunogenicity included the measurement of geometric mean titers (GMT) of HI antibodies on day 0, day 28, and day 56, as well as the geometric mean fold increase (GMFI), seroprotection rate (SPR), and seroconversion rate

(SCR) at 28 days post-vaccine dose. The SCR was defined as the percentage of participants meeting either of the following criteria: having a pre-vaccination HI titer <1∶10 and a post-vaccination HI titer ≥1∶40, or having a pre-vaccination HI titer ≥1∶10 and a minimum fourfold increase in post-vaccination HI titer. The primary safety endpoint was the occurrence of adverse reactions within 28 days following each vaccination. A post-hoc analysis was conducted to evaluate the combined effects of dose, sex, age, and baseline serostatus (seronegative if >1∶10, seropositive if ≤1∶10) on the antibody response providing protection.

The sample size calculation was performed to determine the number of participants needed in this study. It was based on the difference in SCR, with a non-inferiority margin set at 0.1 for the lower bound of the one-sided 97.5% confidence interval. Based on the results from a phase III clinical trial, the minimum
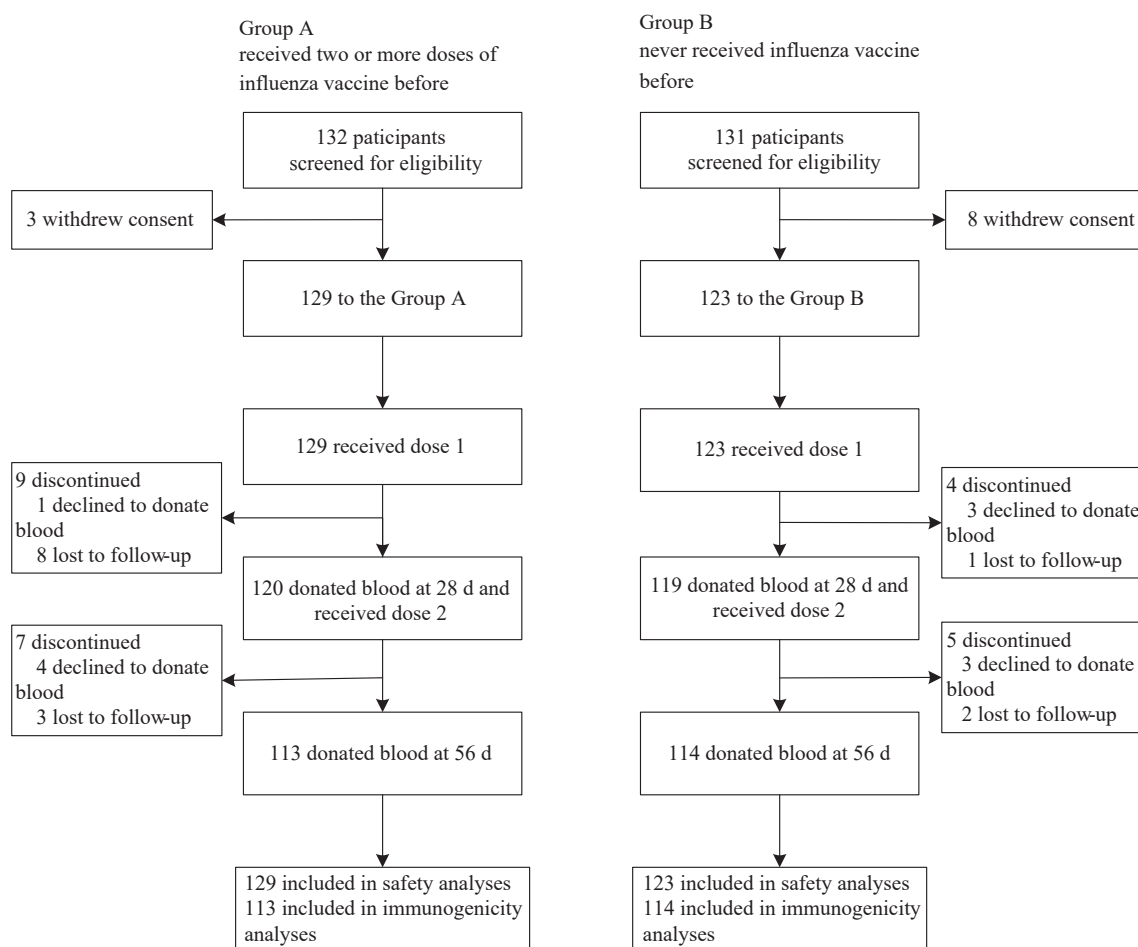

FIGURE 1. Inclusion and follow-up in analyses of immunogenicity and safety in two groups.
Note: Group A is classified as individuals who received two or more doses of influenza vaccine before the current season, while Group B is classified as individuals who have never received influenza vaccine in the past. Additionally, 25 participants dropped out after vaccination.

observed SCR was 64.67%, which was rounded to 60% for conservative estimation. In order to achieve a testing power of 80% (1-β) and account for a dropout rate of 15%, a final determination was made to include approximately 120 participants per group for observation. Further details on additional statistical analysis plans can be found in Supplementary Material. The statistical analysis was conducted using SAS (version 9.4; SAS Institute, Cary, NC).

A total of 252 participants were included in the study, with 129 in Group A and 123 in Group B, enrolled from November 12 to December 30, 2021 (Figure 1). Among them, 16 participants were lost to follow-up, and 9 participants refused to provide blood samples. All 252 children who received at least one dose were included in the final safety analysis. Additionally, 227 children who completed two doses of vaccination and had two blood samples available were included in the immunogenicity analysis. The mean age of children in Group A was 6.00±1.00 years, while in Group B it was 5.00±2.00 years. The proportion of males was 48.06% (62/129) in Group A and 51.22% (63/129) in Group B (Supplementary Table S1, available at https://weekly.chinacdc.cn/).

Antibody responses were examined in Group A. Following the first dose, there was a significant increase in GMTs for all four strains: a fold increase of 8.51 for H1N1 (from GMTs: 672.19 to 79.02), 4.84 for H3N2 (from GMTs: 368.49 to 76.17), 8.15 for BY (from GMTs: 138.10 to 16.95), and 8.40 for BV (from GMTs: 132.29 to 15.74). However, after the second dose, Group A showed a slight decrease in H1N1 and BV strains, with a reduction of 0.92-fold [95% confidence interval (CI): 0.85, 0.99] and 0.86-fold (95% CI: 0.80, 0.93), respectively, compared to the response after the first dose. There were no notable differences in SCR and SPR between the first and second doses, except for a slight increase in SCR for BY strains after the second dose (P=0.039) (Table 1).

Antibody responses were observed in Group B. The GMTs increased significantly after the first dose for H1N1 (533.29 to 26.13, fold change=20.41), H3N2 (283.36 to 34.57, fold change=8.20), BY (70.84 to 10.00, fold change=7.08), and BV (62.35 to 10.25, fold change=6.09). After the second dose, Group B showed slight increases in H1N1, BY, and BV strains with fold changes of 1.48 (95% CI: 1.04, 1.31), 2.15 (95% CI: 1.74, 2.66), and 1.57 (95% CI: 1.33, 1.84) compared to the first dose, respectively. For H3N2, BY, and BV strains, both SCR and SPR consistently increased after the second dose compared to the first

dose (P<0.001) (Table 1).

In a multivariate analysis adjusting for age, sex, number of doses, and baseline serostatus, we found that baseline serostatus significantly impacts antibody titers against four influenza virus strains. Regardless of the dosage, individuals who were seropositive at baseline consistently exhibited higher antibody titers compared to those who were seronegative. Specifically, children who were seropositive at baseline had significantly higher HI GMTs after the first dose compared to children who were seronegative at baseline after the second dose. Therefore, a stratified analysis based on baseline serostatus was conducted in both groups to examine GMTs, SCR, and SPR indicators. Among seronegative individuals before vaccination in Group B, the second dose showed higher GMT, SCR, and SPR compared to the first dose (P<0.001). However, no statistically significant differences were observed in seropositive individuals (Supplementary Tables S2–S3, available at https://weekly.chinacdc.cn/).

Both groups demonstrated good tolerability to QIV after each dose. In the 28-day period following administration of two doses, the overall incidence of adverse reactions in Group A and Group B was 38.8% (50/129) and 22.5% (29/123) respectively. Within 7 days after the first dose, the overall incidence of solicited adverse reactions in Group A and Group B was 31.8% (41/129) and 16.3% (20/123) respectively. Within 7 days after the second dose, the incidence of solicited adverse reactions in Group A and Group B was 16.7% (20/120) and 10.9% (13/119) respectively. It was observed that the incidence of solicited adverse reactions at 28 days after the second dose in Group A was lower than that observed at 28 days after the first dose (P<0.05). Adverse reactions were mainly grade 1 and grade 2, with pain at the injection site as the main local adverse reaction and cough as the main systemic adverse reaction (Figure 2). The incidence of Grade 3 adverse reactions was fever, 0.8% (1/129) in Group A and 1.6% (2/123) in Group B. No serious adverse events were reported during the trial.

DISCUSSION

Our study demonstrated that Group A, comprising individuals who received two or more doses of influenza vaccines prior to the study, exhibited robust immune responses after the first dose, with GMFIs ranging from 4.84 to 8.51. However, there was a slight decrease in antibody titers against H1N1 and BV

TABLE 1. Geometric mean titers, geometric mean fold increase, seroconversion rate, seroprotection rate, and 95% confidence intervals before and after vaccination in two groups.

Statistic	GMT T (95% CI)			GMFI (95% CI)		SCR (95% CI)			SPR (95% CI)		
	Pre-vaccination	28-day post-dose 1	28-day post-dose 2	28-day post-dose 1 *	28-day post-dose 2 †	28-day post-dose 1	28-day post-dose 2 *	P value	28-day post-dose 1	28-day post-dose 2 *	P value
Group A											
A(H1N1)	79.02 (62.10, 100.57)	672.19 (581.95, 776.42)	616.87 (540.36, 704.22)	8.51 (6.69, 10.82)	0.92 (0.85, 0.99)	82.30 (74.00, 88.84)	77.88 (69.10, 85.14)	0.063	100 (96.79, 100)	100 (96.79, 100)	1
A(H3N2)	76.17 (63.26, 91.71)	368.49 (291.52, 465.77)	323.95 (267.92, 391.7)	4.84 (3.79, 6.18)	0.88 (0.75, 1.03)	57.52 (47.87, 66.77)	55.75 (46.11, 65.09)	0.824	97.35 (92.44, 99.45)	99.12 (95.17, 99.98)	0.500
BY	16.95 (14.24, 20.16)	138.10 (113.99, 167.30)	138.95 (119.75, 161.22)	8.15 (6.69, 9.93)	1.01 (0.91, 1.11)	76.99 (68.13, 84.39)	84.07 (76.00, 90.28)	0.039	91.15 (84.33, 95.67)	96.46 (91.18, 99.03)	0.070
BV	15.74 (13.36, 18.56)	132.29 (111.01, 157.66)	114.18 (97.10, 134.27)	8.40 (6.92, 10.20)	0.86 (0.80, 0.93)	84.07 (76.00, 90.28)	79.65 (71.04, 86.64)	0.125	96.46 (91.18, 99.03)	93.81 (87.65, 97.47)	0.250
Group B											
A(H1N1)	26.13 (20.93, 32.63)	533.29 (387.90, 733.16)	791.77 (679.33, 922.83)	20.41 (15.93, 26.13)	1.48 (1.04, 1.31)	88.60 (81.29, 93.79)	94.74 (88.90, 98.04)	0.039	96.49 (91.26, 99.04)	100 (96.82, 100)	0.125
A(H3N2)	34.57 (29.17, 40.97)	283.36 (202.79, 395.94)	321.95 (260.09, 398.53)	8.20 (6.26, 10.73)	1.14 (0.94, 1.38)	72.81 (63.67, 80.72)	91.23 (84.46, 95.71)	<0.001	79.82 (71.28, 86.76)	98.25 (93.81, 99.79)	<0.001
BY	10.00 (8.55, 11.70)	70.84 (54.58, 91.94)	152.40 (132.52, 175.26)	7.08 (5.8, 8.66)	2.15 (1.74, 2.66)	68.42 (59.05, 76.81)	94.74 (88.90, 98.04)	<0.001	71.05 (61.81, 79.16)	99.12 (95.21, 99.98)	<0.001
BV	10.25 (8.70, 12.07)	62.35 (45.29, 85.84)	97.78 (78.45, 121.87)	6.09 (4.89, 7.58)	1.57 (1.33, 1.84)	54.39 (44.79, 63.74)	85.96 (78.21, 91.76)	<0.001	57.02 (47.41, 66.25)	88.60 (81.29, 93.79)	<0.001

Note: Group A refers to individuals who have received two or more doses of influenza vaccine prior to the current season, while Group B refers to individuals who have never received influenza vaccine in the past.

Abbreviation: GMT=geometric mean titer; GMFI=geometric mean fold increase based on a reference; SCR=seroconversion rate; SPR=seroprotection rate; CI=confidence interval.

* Reference is made to pre-vaccination antibody levels.
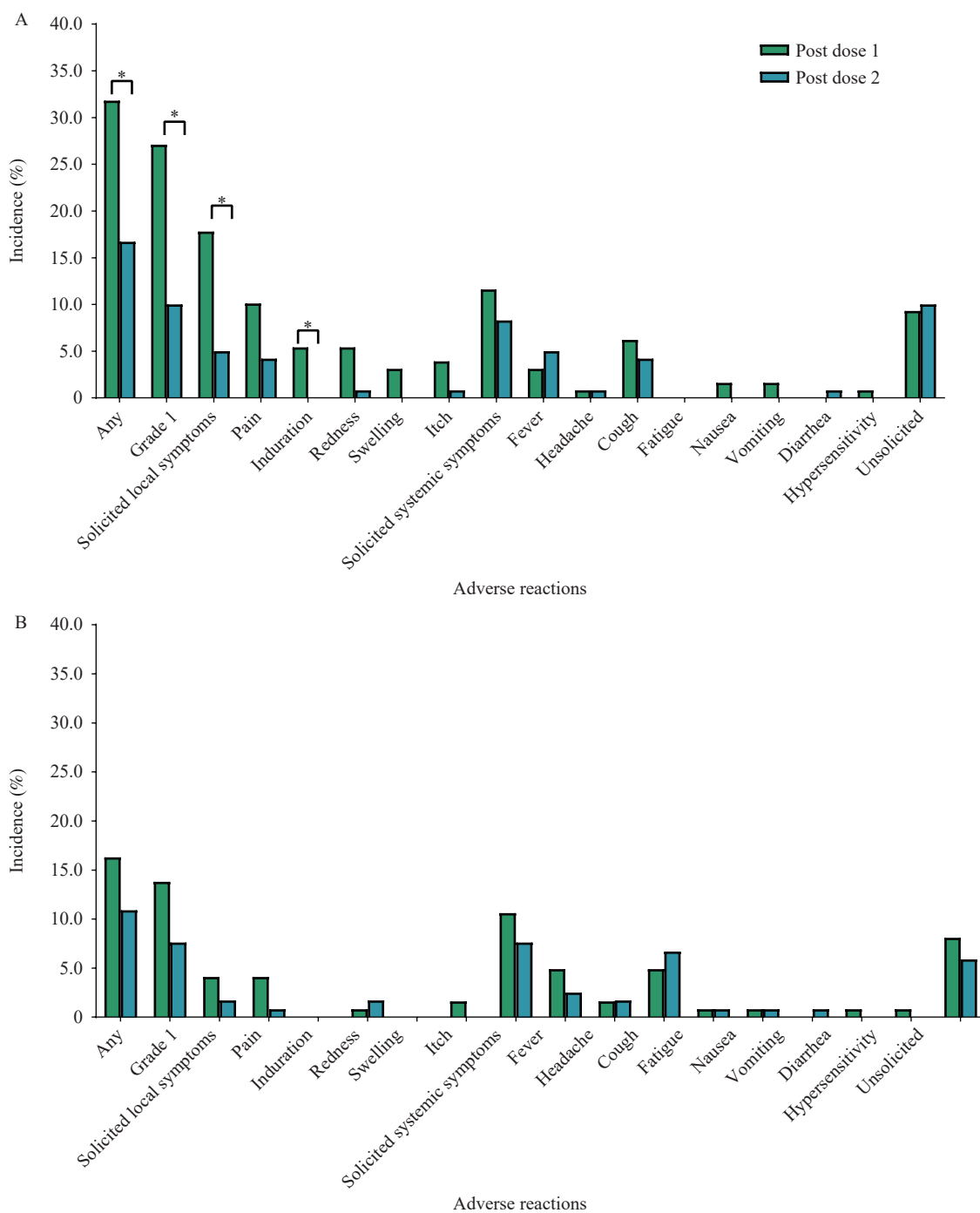† Reference is made to post-dose 1 antibody levels.

FIGURE 2. Incidence of adverse reactions within 28 days after each vaccine in two groups. (A) Incidence of adverse reactions within 28 days after each vaccine in Group A; (B) Incidence of adverse reactions within 28 days after each vaccine in Group B.

Note: Adverse reactions in this context refer to any adverse events associated with the vaccination. The x-axis represents the different types of adverse reactions, while the y-axis represents the incidence of these reactions. The *P* value for comparing the incidence of adverse reactions between different doses is statistically significant (*P*<0.05). Group A refers to individuals who have received two or more doses of influenza vaccine in previous seasons, while Group B refers to individuals who have never received the influenza vaccine before.

following the second dose, while there was no significant change in antibody titers against H3N2 and BY. The second dose did not confer any additional benefits in terms of SCR and SPR for all four viral strains, as the SPR after the first dose was already at least 93.81%.

In contrast, Group B, which consisted of individuals without a vaccination history, also exhibited high antibody titers after the first dose, with GMFIs ranging from 6.09 to 20.41. Following the second dose, antibody titers against H1N1, BY, and BV further increased, with GMFIs ranging from 1.48 to 2.15 compared to post-dose 1 titers. The SPR and SPR against H3N2, BY, and BV were higher after the second dose compared to the first dose. The SPR against BV consistently remained the lowest after each dose, but it did increase from 55.02% to 88.50%.

Additional analysis based on the initial serostatus revealed that the disparities between the two dosage levels were primarily observed in individuals who tested negative for B-type strains before vaccination. Particularly, among seronegative individuals with pre-vaccination serum antibody titers less than 1∶10, administering two doses of the QIV led to a significant elevation in antibody titers against all four viral strains. Our findings endorse the recommendation of administering two doses of QIV to unvaccinated children who have never received an influenza vaccine and are seronegative for maximum protection against B-type influenza viruses.

Differences in immune responses between two doses mainly stem from seronegative individuals in vaccine-naive children. It is hypothesized that these individuals may not have the prior exposure to the antigens that naturally or artificially induce immune memory. Previous studies have indicated that an individual's history of influenza infection can greatly influence the formation of immune memory and the effectiveness of vaccination (9). This suggests that immune system imprinting is involved in conferring protection against specific viral strains. As a result, individuals may display diverse immune responses when exposed to either influenza infection or vaccination.

One limitation of this study is the failure to investigate the durability of immune responses following vaccination. Although we examined immune responses at day 28 after each vaccination, we did not evaluate their persistence over time. For a more comprehensive understanding of how immune responses evolve over time, in relation to the seasonal prevalence of influenza viruses, it would have been ideal to randomly assign participants to two groups: one receiving one dose and the other receiving two doses of the QIV. This approach would have allowed for a comparison not only of immediate immune responses but also their long-term durability. The other limitation is that we did not assess vaccine efficacy.

While previous research has established a correlation between antibody titers and influenza protection, further validation through real-world studies is necessary.

In conclusion, for children aged 3 to 8 years who have previously received two or more doses of the influenza vaccine, a single dose of the seasonal influenza vaccine each year may be sufficient for protection. However, it is recommended that children who have never been vaccinated complete a two-dose immunization regimen, particularly for influenza B.

Conflicts of interest: The quadrivalent influenza vaccine used in the trial was supplied by Changchun Institute of Biological Products Co., Ltd. W.J., X.G., XH.W., and SX.Z. are employees of Changchun Institute of Biological Products Co. No other conflicts of interest.

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SUPPLEMENTARY MATERIAL

Inclusion and Exclusion Criteria

Inclusion criteria:

● Aged 3–8 years old.

● Healthy subjects, as determined by medical history and clinical examination.

● Subjects or their guardians who are able to understand and sign the informed consent

● Subjects or their guardians can and will comply with the requirements of the protocol.

● Subjects had received at least two doses of trivalent or quadrivalent influenza vaccine prior to enrollment. The doses were not necessarily administered during the same or consecutive seasons. Subjects had not received the influenza vaccine before enrollment.

● Subjects with a temperature of 37.0 ℃ or lower on the axillary setting

Exclusion criteria:

● Any prior administration of other research medicine/vaccine within the last 30 days.

● Any prior administration of influenza vaccine in the last 6 months

● Any prior administration of immunosuppressant or corticosteroids in the last 3 months.

● Any previous administration of blood products within the last 3 months.

● Any prior administration of any attenuated live vaccine in the last 14 days.

● Any prior administration of subunit or inactivated vaccines within the last 7 days.

● Subjects who developed Guillain-Barre syndrome post-influenza vaccination.

● Subjects who are allergic to any ingredient of the vaccine.

● Subjects with acute febrile illness or infectious disease

● Thrombocytopenia, blood coagulation disorder, or bleeding difficulties with intramuscular injection.

● Subjects with damaged or compromised immune function, which has already been established

● Subjects with congenital heart disease or other birth defects deemed unsuitable for vaccination.

● The study includes individuals with respiratory diseases (such as pneumonia, tuberculosis, and severe asthma), as well as those with heart, liver, and kidney diseases, mental disorders, or chronic infections.

● Any medical, psychological, social, or other condition that, in the judgment of the investigator, may hinder the subject's compliance with the protocol.

Statistical Analysis

Safety outcomes were reported as a percentage (%) and immunogenicity endpoints, indicated by antibody titers, were expressed as geometric mean titers (GMT) along with corresponding 95% confidence intervals (CIs). The antibody titers were log-transformed for statistical analysis. The two-sided 95% CIs for seroconversion rate (SCR)

SUPPLEMENTARY TABLE S1. Baseline demographic characteristics of participants who received at least one dose of quadrivalent influenza vaccine in two groups.

Characteristic	Group A (N=129)	Group B (N=123)
Age (years), Mean±SD	6.00±1.00	5.00±2.00
Male, n (%)	62 (48.06)	63 (51.22)
Female, n (%)	67 (51.94)	60 (48.78)
BMI (kg/m^2), Median (IQR)	15.75 (14.75–17.19)	15.42 (14.58–16.73)
Vaccine status		
Dose 1, n (%)	129 (100)	123 (100)
Dose 2, n (%)	120 (93.02)	119 (96.75)

Note: The data were presented as Mean±SD for continuous variables, median (IQR, interquartile range) for non-normally distributed variables, and number (percentage) for categorical variables. Group A consisted of individuals who had received two or more doses of influenza vaccine prior to the current season, while Group B consisted of individuals who had never received influenza vaccine in the past. A total of 25 participants dropped out after vaccination.

Abbreviation: BMI=body mass index; SD=standard deviation.

SUPPLEMENTARY TABLE S2. Geometric mean titers, seroconversion rate, seroprotection rate, and 95% confidence interval stratified by Baseline serostatus in Group A.

Statistic Antigen, Baseline serostatus	n	GMT (95% CI)			SCR (95% CI)			SPR (95% CI)		
		Post-dose 1	Post-dose 2	P value	Post-dose 1	Post-dose 2	P value	Post-dose 1	Post-dose 2	P value
H1N1										
All	113									
Seronegative	3	507.97 (187.97, 1372.71)	320.00 (57.19, 1790.4)	0.184	100 (29.24, 100)	100 (29.24, 100)	–	100 (29.24, 100)	100 (29.24, 100)	–
Seropositive	110	677.35 (584.44, 785.02)	628.01 (549.63, 717.58)	0.045	81.82 (73.33, 88.53)	77.27 (68.3, 84.72)	0.063	100 (96.70, 100)	100 (96.70, 100)	–
H3N2										
All	113									
Seronegative	–	–	–	–	–	–	–			–
Seropositive	113	368.49 (291.52, 465.77)	323.95 (267.92, 391.70)	0.113	57.52 (47.87, 66.77)	55.75 (46.11, 65.09)	0.824	97.35 (92.44, 99.45)	99.12 (95.17, 99.98)	0.500
BY										
All	113									
Seronegative	26	45.70 (28.05, 74.47)	64.63 (45.86, 91.09)	0.009	61.54 (40.57, 79.77)	84.62 (65.13, 95.64)	0.070	61.54 (40.57, 79.77)	84.62 (65.13, 95.64)	0.070
Seropositive	87	192.18 (165.94, 222.57)	211.68 (169.26, 264.75)	0.039	81.61 (71.86, 89.11)	83.91 (74.48, 90.91)	0.625	100 (95.85, 100)	100 (95.85, 100)	–
BV										
All	113									
Seronegative	27	82.08 (55.09, 122.29)	63.50 (44.81, 89.97)	0.015	88.89 (70.84, 97.65)	77.78 (57.74, 91.38)	0.250	88.89 (70.84, 97.65)	77.78 (57.74, 91.38)	0.250
Seropositive	86	153.68 (127.46, 185.3)	137.28 (116.04, 162.42)	0.007	82.56 (72.87, 89.90)	80.23 (70.25, 88.04)	0.625	98.84 (93.69, 99.97)	98.84 (93.69, 99.97)	–

Note: SCR and SPR were assessed using pre-vaccination antibody levels. Group A was comprised of individuals who had received two or more doses of influenza vaccine prior to the current season.
"–" means inapplicable, the sample size is insufficient to permit a meaningful comparison.
Abbreviation: GMT=geometric mean titer; SCR=seroconversion rate based on pre-vaccination antibody levels; SPR=seroprotection rate based on pre-vaccination antibody levels; CI=confidence interval.

and seroprotection rate (SPR) were calculated using the Clopper-Pearson method. Comparisons of GMTs, geometric mean fold increase (GMFI), SCR, SPR, and the incidence rate of adverse reactions between dose 1 and dose 2 were analyzed using a paired t-test and McNemar's test, respectively. For the safety analysis, the safety set (SS) included all participants who received at least one dose, while for the immunogenicity analysis, the per-protocol set (PPS) included participants who completed the full two vaccinations and three blood draws. Statistical analysis was performed using SAS (version 9.4; SAS Institute, Cary, NC). Hypothesis testing was two-sided, and a significance level of $P<0.05$ was considered statistically significant.

SUPPLEMENTARY TABLE S3. Geometric mean titers, seroconversion rate, seroprotection rate and 95% confidence interval stratified by Baseline serostatus in Group B.

Statistic Antigen, Baseline serostatus	n	GMT (95% CI)			SCR (95% CI)			SPR (95% CI)		
		Post-dose 1	Post-dose 2	P value	Post-dose 1	Post-dose 2	P value	Post-dose 1	Post-dose 2	P value
H1N1										
All	114									
Seronegative	26	77.90 (53.07, 114.33)	440.64 (342.05, 567.66)	<0.001	88.46 (69.85, 97.55)	100 (86.77, 100)	–	88.46 (69.85, 97.55)	100 (86.77, 100)	0.250
Seropositive	88	941.45 (691.03, 1282.62)	941.45 (794.77, 1115.21)	–	88.64 (80.09, 94.41)	93.18 (85.75, 97.46)	0.219	98.86 (93.83, 99.97)	100 (95.89, 100)	–
H3N2										
All	114									
Seronegative	5	45.95 (4.56, 462.61)	80.00 (18.02, 355.22)	0.242	40.00 (5.27, 85.34)	100 (47.82, 100)	–	21.91 (5.27, 85.34)	100 (47.82, 100)	0.250
Seropositive	109	308.02 (220.35, 430.58)	343.19 (277.88, 423.84)	0.283	74.31 (65.06, 82.2)	90.83 (83.77, 95.51)	<0.001	81.65 (73.09, 88.42)	98.17 (93.53,99.78)	<0.001
BY										
All	114									
Seronegative	62	28.28 (21.32, 37.53)	125.11 (102.51, 152.71)	<0.001	48.39 (35.50, 61.44)	98.39 (91.34, 99.96)	<0.001	48.39 (35.50, 61.44)	98.39 (91.34, 99.96)	<0.001
Seropositive	52	211.68 (169.26, 264.75)	211.68 (169.26, 264.75)	0.266	92.31 (81.46, 97.86)	90.38 (78.97, 96.80)	–	98.08 (89.74, 99.95)	100 (93.15, 100)	–
BV										
All	114									
Seronegative	59	17.78 (13.83, 22.86)	49.42 (40.05, 60.98)	<0.001	25.42 (14.98, 38.44)	83.05 (71.03, 91.56)	<0.001	25.42 (14.98, 38.44)	83.05 (71.03, 91.56)	<0.001
Seropositive	55	239.48 (169.23, 338.88)	203.29 (151.25, 273.22)	0.027	85.45 (73.34, 93.5)	89.09 (77.75, 95.89)	0.687	90.91 (80.05, 96.98)	94.55 (84.88, 98.86)	0.625

Note: SCR and SPR were determined using pre-vaccination antibody levels. Group B consisted of individuals who had never received the influenza vaccine before.

"–" means inapplicable, the sample size is insufficient to permit a meaningful comparison.

Abbreviation: GMT=geometric mean titer; SCR=seroconversion rate based on pre-vaccination antibody levels; SPR=seroprotection rate based on pre-vaccination antibody levels; CI=confidence interval.

Preplanned Studies

Occurrence and Reduction of Hepatitis B Vaccine Hesitancy Among Medical University Students — Shanxi Province, China, 2020

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Summary

What is already known about this topic?

Previous research has primarily examined the issue of hepatitis B vaccine hesitancy in migrant workers and other adult populations. However, there is a lack of studies that have specifically investigated the prevalence of hepatitis B vaccine hesitancy among university students.

What is added by this report?

In this study, 19.84% of students expressed hesitancy towards receiving the hepatitis B immunization. A negative correlation was observed between hepatitis B vaccine hesitancy and knowledge, attitudes, and practices related to hepatitis B. Conversely, a positive relationship was identified between hepatitis B-related knowledge and attitudes and practices.

What are the implications for public health practice?

This study examines the factors contributing to vaccine hesitancy towards hepatitis B at a medical university in China. The results have significant implications for developing strategies to improve hepatitis B vaccination rates.

Hepatitis B virus (HBV) infection is a significant global public health concern (*1*). According to the World Health Organization (WHO), in 2019, an estimated 296 million individuals worldwide had chronic hepatitis B, with 1.5 million new cases reported annually and approximately 820,000 deaths (*2*). In China, universal hepatitis B vaccination for newborns was introduced in 1992, resulting in a high vaccination rate among university students. However, the antibody response to HBsAg (anti-HBs) decreases over time after vaccination (*3*). Additionally, university students are at a higher risk of HBV infection due to various factors such as tattoos, unprotected sexual contact, pierced ears, and accidental blood exposure to

medical students. The WHO recommends booster vaccination for high-risk populations (*4*). However, there is a growing reluctance among individuals to receive recommended vaccinations (*5*). Despite this, there have been limited efforts to evaluate hepatitis B vaccine hesitancy among medical university students. This study was conducted among the class of 2017 at a medical university from April to June 2020, with a total of 1,003 students from different professions completing a questionnaire. The results illustrated that hepatitis B-related knowledge, attitudes, and practices had a negative impact on hepatitis B vaccine hesitancy. The findings from this study provide insights for developing a health education-based hepatitis B vaccination strategy.

A cross-sectional study was conducted in the class of 2017. Out of the 27 professions, nine were randomly selected for recruitment, and all students in those nine professions were included in the study. Prior to enrollment, written informed consent was obtained from all participants. A self-designed questionnaire, consisting of 15 questions on HBV knowledge, 15 questions on HBV attitudes, and 10 questions on practices (Supplementary Table S1, available athttps://weekly.chinacdc.cn/), was distributed through the Wenjuanxing platform. The questionnaire was administered on-site by trained investigators. Students were asked to independently complete the questionnaire. The internal consistency of the questionnaire, measured by Cronbach's α, was determined to be 0.855, indicating good reliability.

Hepatitis B knowledge was categorized into four dimensions based on their relevance to infectious disease epidemics among humans: etiological knowledge (EK), transmission route knowledge (TRK), prevention measures knowledge (PMK), and epidemic status knowledge (ESK). Each correct answer was scored 1 point, while incorrect or unclear answers received 0 points. Hepatitis B attitudes were assessed

using a 5-point Likert scale, ranging from "very consistent" to "very inconsistent," with scores of 5 to 1, respectively, indicating personal inclination. Questions 3, 4, 5, 12, 13, and 14 were reverse-scored. Hepatitis B practices were divided into two dimensions based on behavioral characteristics: health-seeking practices (HSP) and high-risk practices (HRP). A score of 1 point was given for "yes" responses to hepatitis B practice items, while "no" or "unknown" responses received 0 points. Knowledge, attitudes, and practices related to hepatitis B were classified into two groups based on the mean score.

In our study, "vaccine hesitancy" (VH) was defined as the participants' response of "unsure", "basically inconsistent", or "very inconsistent" when asked about their willingness to be vaccinated against hepatitis B in the absence of detectable anti-HBs. This term was used to describe the hesitation towards receiving the hepatitis B vaccine.

The database was established using Microsoft Excel (version 2016; Microsoft Corp, Redmond, USA), and analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC, USA). The chi-square test was used to assess the difference between the groups with vaccine hesitancy and those without. Logistic regression analysis was employed to examine the associations between the independent variables and hepatitis B vaccine hesitancy. Independent variables with $P<0.05$ in the univariate analysis were included in the logistic regression model. Structural equation modeling (SEM) was performed using Amos software (web version 24.0; IBM, New York, USA) to elucidate the interrelationships between latent variables. The model parameters were estimated using maximum likelihood estimation.

A total of 1,012 students were contacted, and 1,003 students responded, resulting in a response rate of 99%. The respondents were predominantly female (75.37%), with a sex ratio of 0.33∶1. Among the respondents, the majority (n=961) were of Han ethnicity. The participants consisted of 747 medical professionals (74.48%) and 256 nonmedical professionals (25.52%) (Table 1).

The Kaiser-Meyer-Olkin coefficient was found to be 0.785, indicating satisfactory sampling adequacy. Additionally, Bartlett's test showed statistical significance ($P<0.001$), supporting the factor analysis. Based on eigenvalues, a total of four factors were extracted, explaining 69.54% of the cumulative variance. These factors were identified as attitude toward the source of infection (ASI), self-protection attitude (SPA), life contact attitude (LCA), and vaccine effect attitude (VEA).

A total of 199 respondents expressed hesitancy towards the hepatitis B vaccine, resulting in a vaccine hesitation rate of 19.84% (199/1,003). In the univariate analysis, significant associations were observed between vaccine hesitancy and factors such as knowledge, attitudes, and health-seeking practices ($P<0.05$) (Table 1).

The logistic regression model revealed that university students with lower TRK and PMK scores had a higher likelihood of hesitating to receive the hepatitis B vaccine (OR=1.947, 95% CI: 1.309, 2.897; OR=2.501, 95% CI: 1.682, 3.719). Participants who held stigmatizing attitudes toward the source of infection were 1.854 times more likely to hesitate in getting the hepatitis B vaccine compared to those with more inclusive attitudes (95% CI: 1.280, 2.684). Vaccine hesitancy was also associated with concerns about vaccine efficacy (OR=6.529, 95% CI: 4.417, 9.650). Furthermore, individuals who adopted fewer health-seeking behaviors were more likely to hesitate to receive the vaccine and had a 2.119-fold increased likelihood of adopting such behaviors (95% CI: 1.357, 3.308) (Table 2).

SEM was developed using the knowledge, attitude, and practice theory model as a basis. The initial model included knowledge-related latent variables as independent variables, attitude and behavior-related latent variables as mediators, and the observed variable VH as the dependent variable. Non-significant paths between latent variables in the hypothetical model ($P>0.05$) were removed and corrected using the correction index. Model fit measurements indicated that the revised model demonstrated a satisfactory fit, and the model was professionally interpreted. The reference standards for the fit indicators, as well as the fit indicators for the final model, are provided in Supplementary Table S2 (available at https://weekly.chinacdc.cn/). A diagram of the standardized model can be seen in Figure 1. The values assigned to each variable in the revised model are presented in Supplementary Table S3 (available at https://weekly.chinacdc.cn/).

Supplementary Table S4 (available at https://weekly.chinacdc.cn/) presents the associations between different factors (TRK, PMK, ASI, HSP, LCA) and vaccine hesitancy for hepatitis B. TRK had an indirect effect on vaccine hesitancy [standard indirect effect (SIE)=−0.301]. PMK, on the other hand, influenced vaccine hesitancy through both direct and indirect

TABLE 1. Characteristics of university students with hepatitis B vaccine hesitancy [n (%)].

Variables	N	Hepatitis B vaccine hesitancy		Univariate analysis	
		Yes (*n*=199)	No (*n*=804)	χ^2	*P* value
Gender				10.935	0.001
Male	247 (24.63)	67 (27.13)	180 (72.87)		
Female	756 (75.37)	132 (17.46)	624 (82.54)		
Locality				< 0.001	0.998
Urban	368 (36.69)	73 (19.84)	295 (80.16)		
Rural	635 (63.31)	126 (19.84)	509 (80.16)		
Ethnicity				0.851	0.356
Han ethnicity	961 (95.81)	193 (20.08)	768 (79.92)		
Other	42 (4.19)	6 (14.29)	36 (85.71)		
Medical Professional				9.766	0.002
Yes	747 (74.48)	131 (17.54)	616 (82.46)		
No	256 (25.52)	68 (26.56)	188 (73.44)		
Etiological knowledge				62.620	<0.001
Good mastery (≥1.82)	662 (66.00)	84 (12.69)	578 (87.31)		
Poor mastery (<1.82)	341 (34.00)	115 (33.72)	226 (66.28)		
Prevention measures knowledge				68.217	<0.001
Good mastery (≥1.44)	605 (60.32)	69 (11.40)	536 (88.60)		
Poor mastery (<1.44)	398 (39.68)	130 (32.66)	268 (67.34)		
Transmission routes knowledge				51.415	<0.001
Good mastery (≥5.12)	686 (68.39)	94 (13.70)	592 (86.30)		
Poor mastery (<5.12)	317 (31.61)	105 (33.12)	212 (66.88)		
Epidemic status knowledge				31.464	<0.001
Good mastery (≥0.57)	570 (56.83)	78 (13.68)	492 (86.32)		
Poor mastery (<0.57)	433 (43.17)	121 (27.94)	312 (72.06)		
Attitude toward the source of infection				45.103	<0.001
Inclusion (≥8.94)	630 (62.81)	84 (13.33)	546 (86.67)		
Stigmatization (<8.94)	373 (37.19)	115 (30.83)	258 (69.17)		
Life contact attitude				32.020	<0.001
Inclusion (≥18.12)	398 (39.68)	44 (11.06)	354 (88.94)		
Stigmatization (<18.12)	605 (60.32)	155 (25.62)	450 (74.38)		
Self-protection attitude				20.715	<0.001
Inclusion (≥8.04)	436 (43.47)	115 (26.38)	321 (73.62)		
Stigmatization (<8.04)	567 (56.53)	84 (14.81)	483 (85.19)		
Vaccine effect attitude				104.763	<0.001
Inclusion (≥9.99)	551 (54.94)	45 (8.17)	506 (91.83)		
Stigmatization (<9.99)	452 (45.06)	154 (34.07)	298 (65.93)		
Health-seeking practices				18.168	<0.001
More practices (≥1.06)	295 (29.41)	34 (11.53)	261 (88.47)		
Fewer practices (<1.06)	708 (70.59)	165 (23.31)	543 (76.69)		
High-risk practices				0.069	0.794
More practices (≥1.25)	376 (37.49)	73 (19.41)	303 (80.59)		
Fewer practices (<1.25)	627 (62.51)	126 (20.10)	501 (79.90)		

TABLE 2. Multivariate analysis of hesitancy towards hepatitis B vaccine among university students.

Variables	β	S $\bar{x}$	Wald χ²	OR (95% CI)*	P value
Transmission routes knowledge					
Good mastery				1	
Poor mastery	0.666	0.203	10.801	1.947 (1.309, 2.897)	0.001
Prevention measures knowledge					
Good mastery				1	
Poor mastery	0.917	0.203	20.492	2.501 (1.682, 3.719)	<0.001
Attitude toward the source of infection					
Inclusion				1	
Stigmatization	0.617	0.189	10.686	1.854 (1.280, 2.684)	0.001
Life contact attitude					
Inclusion				1	
Stigmatization	0.663	0.210	10.002	1.940 (1.287, 2.925)	0.002
Vaccine effect attitude					
Inclusion				1	
Calculation	1.876	0.199	88.573	6.529 (4.417, 9.650)	<0.001
Health-seeking practices					
More behaviors				1	
Fewer behaviors	0.751	0.227	10.913	2.119 (1.357, 3.308)	0.001

Abbreviation: OR=odds ratio; CI=confidence interval.
* Adjusted by Gender, Medical Professional, epidemic status knowledge, and self-protection attitude.
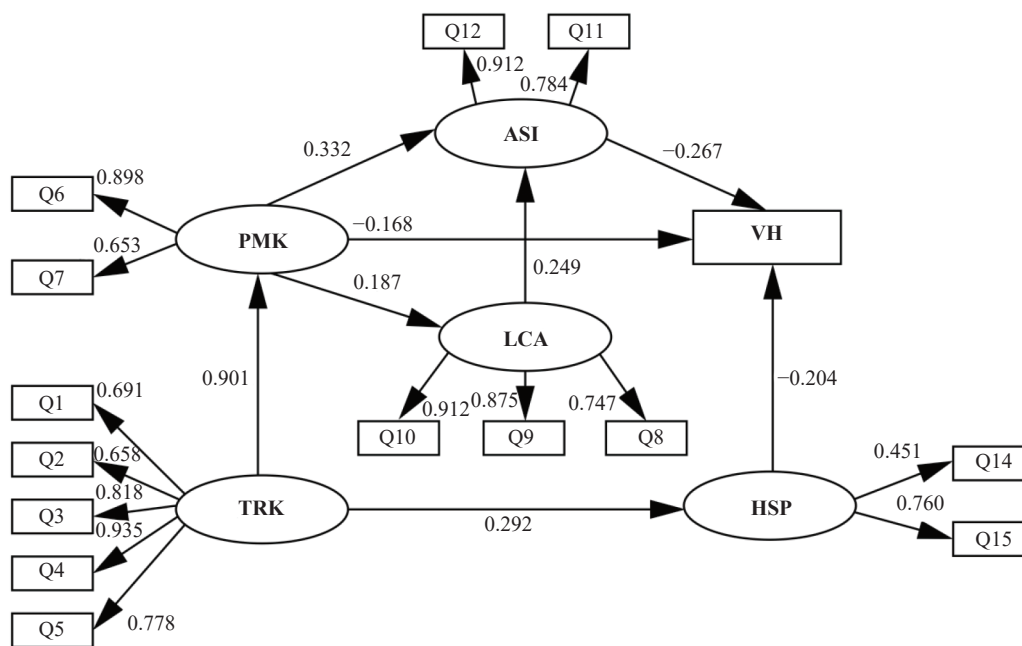
FIGURE 1. Revised model (SEM).
Note: The ellipse and arrow in the structural model represent the effects of factors. One-way straight arrows in the structural model depict the paths of each factor with standardized regression weights, and one-way straight arrows in the measurement model show the measurement loadings of each item in the scale.
Abbreviation: PMK=prevention measures knowledge; ASI=attitude toward the source of infection; PMK=prevention measures knowledge; VH=vaccine hesitancy; LCA=life contact attitude; TRK=transmission route knowledge; HSP=health-seeking practices.

effects (standard direct effect (SDE)=−0.168, SIE=−0.101). ASI (SDE=−0.267) and HSP (SDE= −0.204) only had direct effects on hepatitis B vaccine hesitancy. Additionally, LCA had an indirect effect on vaccine hesitancy (SIE=−0.066), and this relationship was partially mediated by ASI. The analysis also revealed a negative correlation between hepatitis B-related knowledge, attitudes, and practices, and vaccine hesitancy. Further details regarding the structural model parameters can be found in Supplementary Table S5 (available at https://weekly.chinacdc.cn/). These findings indicate the importance of health education that focuses on enhancing knowledge, attitudes, and practices related to hepatitis B, as part of an effective hepatitis B vaccination strategy.

DISCUSSION

The survey results revealed that the rate of vaccine hesitancy for hepatitis B among university students was 19.84%, which was lower compared to other migrant workers (6). This difference may be attributed to the medical students' curriculum, specifically their education on infectious diseases, which contributes to a more accurate comprehension of hepatitis B-related knowledge.

Previous research has indicated that being aware of vaccine-preventable diseases can encourage vaccination (7). Our study found that students who were hesitant about vaccines had significantly less knowledge about hepatitis B compared to students who were accepting of vaccines. SEM also showed that knowledge had an indirect impact on vaccine hesitancy. These results are consistent with previous studies, highlighting the importance of increasing awareness of hepatitis B-related knowledge among university students. This can be achieved through initiatives like campus-wide events and interdisciplinary curricula, which can help mitigate vaccine hesitancy.

Stigma presents a significant obstacle to the effective implementation of preventive measures against HBV infection (8). Our study found that students who expressed stigmatizing attitudes towards hepatitis B patients and carriers were more likely to hesitate in getting vaccinated against hepatitis B. These findings highlight the need for universities and government organizations to provide early and positive guidance to enhance student education and promote understanding of the transmission routes of HBV and other viruses, in order to reduce counterproductive stigmatization among university students.

A survey conducted by the WHO and UNICEF from 2014 to 2016 revealed that doubts regarding vaccine safety and concerns about potential side effects were significant factors contributing to vaccine hesitancy (9). Our study, consistent with previous research on vaccine hesitancy in other contexts (10), identified concerns about the effectiveness and safety of vaccines as crucial determinants for refusing vaccination or lacking the intention to receive it (OR=6.529). We observed that university students who exhibited worry towards the hepatitis B vaccine were more likely to demonstrate vaccine hesitancy, which can have a negative impact on vaccine confidence and communication with both their families and future patients. Thus, our findings underscore the importance of educating university students about the safety and effectiveness of vaccines, as well as raising awareness about the critical role vaccines play in disease prevention. These ongoing issues persistently contribute to confusion and uncertainty surrounding vaccines.

Risk factors associated with hepatitis B vaccine hesitancy among university students include inadequate knowledge, stigmatization of attitudes towards the source of hepatitis B infection, and lacking health-seeking behaviors. Poor understanding, unfavorable attitudes, and inadequate practices related to hepatitis B are associated with increased vaccine hesitancy. Therefore, prioritizing knowledge dissemination is crucial for the development of effective hepatitis B vaccination strategies. Implementing educational programs at universities plays a vital role in raising awareness about prevention and enhancing vaccine coverage among students.

Previous research has primarily examined hepatitis B vaccine hesitancy in migrant workers, with limited attention given to medical university students. However, understanding the factors influencing vaccine hesitancy among medical students and developing effective health education strategies is crucial. This study aimed to address this gap by evaluating hepatitis B vaccine hesitancy in a medical university setting.

This study was subject to some limitations. First, the study utilized closed-ended questions, which limited the students' ability to provide nuanced insights into their knowledge, attitudes, and practices regarding hepatitis B. Second, this study was conducted in a single medical university, and therefore may not fully capture the current status and determinants of hepatitis B vaccine hesitancy among Chinese university

students. Future surveys should include a more diverse range of universities to ensure a representative sample.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Knowledge, attitudes, and practices regarding Hepatitis B among university students.

Latent variables	Items
Etiological knowledge	1. Positive hepatitis B surface antigen (HBsAg) indicates HBV infection.
	2. Hepatitis B surface antibody (anti-HBs) is a protective antibody.
	3. Hepatitis B virus carriers are the source of hepatitis B infection.
Transmission routes knowledge	4. HBV can be transmitted through broken skin or mucous membranes.
	5. HBV can be transmitted by blood-sucking insects.
	6. HBV can be transmitted through pedicures, tattoos, and earrings.
	7. HBV can be transmitted by sharing syringes, razors, and dental tools.
	8. HBV can be transmitted through blood or blood products.
	9. HBV can be transmitted by droplets and dust.
	10. HBV can be transmitted through sexual intercourse.
	11. HBV can be transmitted from mother to child.
	12. HBV can be transmitted through daily study, work, or life contact.
Prevention measures knowledge	13. Hepatitis B vaccination is the primary method of preventing hepatitis B virus infection.
	14. Hepatitis B vaccination is recommended when Hepatitis B Antibody is negative.
Epidemic status knowledge	15. China is now a medium endemic country for hepatitis B virus infection.
Attitude toward the source of infection	1. Hepatitis B patients' privacy should be protected.
	2. Hepatitis B patients should not be discriminated against.
Self-protection attitude	3. Fear that you may be infected with the hepatitis B virus at any time.
	4. Fear of others knowing you are a hepatitis B carrier or patient.
	5. Living in the same dormitory with hepatitis B patients can be psychologically stressful.
Life contact attitude	6. Willing to be friends with chronic asymptomatic HBV carriers.
	7. Willingness to share meals with chronic asymptomatic HBV carriers.
	8. Willingness to live with chronic asymptomatic HBV carriers.
	9. Willingness to have close contact with the hepatitis B virus carriers.
	10. Willingness to marry hepatitis B virus carriers.
	11. Willingness to treat people with hepatitis B as others.
Vaccine effect attitude	12. Fear of side effects of hepatitis B vaccine.
	13. Fear that the hepatitis B vaccine does not provide enough protection against the hepatitis B virus.
	14. Worried that my knowledge of the hepatitis B vaccine is not very comprehensive.
Health-seeking practices	1. Hepatitis B vaccination other than birth.
	2. Tested for HBV serological markers and/or hepatitis B virus DNA in the last three years.
	3. Will take the initiative to pay attention to the knowledge about hepatitis B.
High-risk practices	4. Pedicure.
	5. Tattoo, eyebrow tattoo.
	6. Manicure.
	7. Pierced ears.
	8. Shared eyebrow trimmer, shaver.
	9.Shared toothbrush.
	10. Having sexual intercourse.

SUPPLEMENTARY TABLE S2. Goodness of fit indices of structural equation model.

Indicators	GFI	AGFI	NFI	IFI	CFI	RMR	RMSEA
Reference standards	>0.90	>0.90	>0.90	>0.90	>0.90	<0.05	<0.05
Model results	0.972	0.960	0.971	0.982	0.982	0.024	0.040

Abbreviation: GFI=goodness fit index; AGFI=adjusted goodness of fit index; NFI=normed fit index; IFI=incremental fit index; CFI=comparative fit index; RMR=root mean square residual; RMSEA=root mean square error of approximation.

SUPPLEMENTARY TABLE S3. Revised model (SEM) variables related to hepatitis B vaccine hesitancy among university students.

Latent variables	Items	Assignment
TRK	Q1 HBV can be transmitted through broken skin or mucous membranes	1=correct, 2=wrong, 3=unclear
	Q2 HBV can be transmitted by blood-sucking insects	1=correct, 2=wrong, 3=unclear
	Q3 HBV can be transmitted through pedicures, tattoos, and earrings	1=correct, 2=wrong, 3=unclear
	Q4 HBV can be transmitted through blood or blood products	1=correct, 2=wrong, 3=unclear
	Q5 HBV can be transmitted through sexual intercourse	1=correct, 2=wrong, 3=unclear
PMK	Q6 Hepatitis B vaccination is the primary method of preventing hepatitis B virus infection	1=correct, 2=wrong, 3=unclear
	Q7 Hepatitis B vaccination is recommended when Hepatitis B antibody is negative	1=correct, 2=wrong, 3=unclear
LCA	Q8 Willing to be friends with chronic asymptomatic HBV carriers	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
	Q9 Willingness to share meals with chronic asymptomatic HBV carriers	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
	Q10 Willingness to live with chronic asymptomatic HBV carriers	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
ASI	Q11 Hepatitis B patients' privacy should be protected.	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
	Q12 Hepatitis B patients should not be discriminated against	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
VH	Q13 Detected no hepatitis B antibody and willing to receive hepatitis B vaccination	1=Fully conform, 2=Basically conform, 3=Uncertain, 4=Basically not conform, 5=Not at all conform
HSP	Q14 Hepatitis B vaccination other than birth	1=Yes, 2=No, 3= Unknown
	Q15 Tested for HBV serological markers and/or hepatitis B virus DNA in the last three years	1=Yes, 2=No, 3=Unknown

Abbreviation: TRK=transmission route knowledge; PMK=prevention measures knowledge; LCA=life contact attitude; ASI=attitude toward the source of infection; VH=vaccine hesitancy; HSP=health-seeking practices.

SUPPLEMENTARY TABLE S4. Effect analysis between the latent variable and hepatitis B vaccine hesitancy status.

Latent variable	Hepatitis B vaccine hesitancy		
	Direct effect	Indirect effect	Total effect
Transmission routes knowledge	−	−0.301	−0.301
Preventive measures Knowledge	−0.168	−0.101	−0.296
Attitude toward the source of infection	−0.267	−	−0.267
Life contact attitude	−	−0.066	−0.066
health-seeking practices	−0.204	−	−0.204

Note: "−" means no corresponding effect.

SUPPLEMENTARY TABLE S5. Parameters of the structural model in the university.

Path	Unstandardized coefficients	Standardized coefficients	CR	P value
Hepatitis B vaccine hesitancy – prevention measures knowledge	−0.180	−0.168	−4.531	***
Hepatitis B vaccine hesitancy – attitude towards the source of infection	−0.291	−0.267	−7.696	***
Hepatitis B vaccine hesitancy – health-seeking practices	−0.370	−0.204	−4.843	***
Life contact attitude – prevention measures knowledge	0.174	0.187	5.301	***
Attitude to the source of infection – prevention measures knowledge	0.327	0.332	8.889	***
Attitude towards the source of infection – life contact attitude	0.264	0.249	6.940	***
Prevention measures knowledge – transmission routes knowledge	0.928	0.901	27.857	***
Health-seeking practices – transmission routes knowledge	0.178	0.292	4.634	***

*** $P<0.001$.

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