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Real-world data of China: Analysis of HPV vaccine coverage and post-vaccination adverse reaction monitoring in Western Chinese provinces from 2018 to 2021

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ABSTRACT

To investigate the HPV vaccine coverage and post-vaccination adverse reactions in Gansu Province, Western China, from 2018 to 2021. Data on suspected adverse reactions to HPV vaccines were collected from the Chinese Vaccine Adverse Event Following Immunization (AEFI). Estimate the incidence rates of Common Adverse Reaction and Rare Adverse Reaction. HPV vaccine coverage among females in different age groups was calculated using data from the Gansu Provincial Immunization Information Platform. The first-dose HPV vaccine coverage rate among females aged 9 to 45 was 2.02%, with the lowest rate of less than 1% observed in females aged 9 to 14. From 2018 to 2021, the incidence rates of Common Adverse Reaction and Rare Adverse Reaction reported in females after HPV vaccination were 11.82 and 0.39 per 100,000 doses, respectively. Common Adverse Reaction included fever (5.52 per 100,000 doses), local redness and swelling (3.33 per 100,000 doses), fatigue (3.15 per 100,000 doses), headache (2.76 per 100,000 doses), as well as local induration and nausea/vomiting (1.97 per 100,000 doses). Adverse reactions mainly occurred within 1 day after vaccination, followed by 1 to 3 days after vaccination. The HPV vaccine coverage rate among females aged 9 to 14 in Gansu Province is remarkably low, and there is an urgent need to enhance vaccine coverage. From 2018 to 2021, the incidence of Adverse reaction Following Immunization HPV vaccination fell within the expected range, indicating the vaccine's safety profile.

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Introduction

Cervical cancer is the fourth most common malignant tumor among women globally,[1] poses a significant threat to women's health and is a critical public health issue. Globally, there are approximately 570,000 new cases of cervical cancer and 270,000 deaths annually.[2] A staggering 85% of new cases occur in low and middle-income countries, with nearly one-fourth of cases originating in China.[3] Cervical cancer is now the second most common malignant tumor among Chinese women aged 15–44, second only to breast cancer.[4] Despite a global trend of declining cervical cancer incidence rates, China has witnessed an annual increase in cases,[5,6] with a growing number of young women affected.[7] Compared to global and national statistics, Gansu Province has a higher standardized incidence rate for cervical cancer, with incidence and mortality rates 1.34 and 1.62 times higher than the national average.[8] Respectively, highlighting the disproportionate impact of cervical cancer on women's lives and health in the province. 99.7% of cervical cancer cases are linked to high-risk HPV infections. Sexual transmission is the primary mode of HPV infection, and mucous membrane contact during sexual activity, whether heterosexual or homosexual, can lead to infection.[9] Between 80% to 90% of women experience at least one HPV infection after the onset of sexual activity. Around 90% of women who acquire HPV infections can naturally clear them, while a minority may experience persistent infections, eventually leading to cervical precancerous lesions and cancer development.[10] The prevalence of HPV infection varies depending on the age group and sexual behavior of the population. Among sexually active young women, the HPV infection rate can be as high as 20% to 40%, with the peak incidence occurring between the ages of 16 to 20.[11]

Vaccination against HPV is one of the effective measures for preventing cervical cancer. Various guidelines, including those by the World Health Organization (WHO), recommend girls aged 9–14 as the primary or routine vaccination target group.[12] Where feasible, the vaccination scope can be extended to include adolescent girls and young women. However, as of 2016, only 12% of adolescent girls globally received the HPV vaccine.[13] In 2019, developed countries like the United States, the United Kingdom, and Australia achieved vaccination rates of 60%-80%, while some countries and regions, including Bhutan, Rwanda, and Panama, exceeded 90%. In Europe, the vaccination rate stood at 31.1%.[14] The HPV vaccine was introduced to the mainland of China in 2016. Currently, the HPV vaccine has not been included in the national immunization program. Only a few provinces offer free vaccination for females aged 9–14, while the majority of provinces, including Gansu, require payment for HPV vaccination. The nationwide

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HPV vaccination rate for females aged 9–45 is less than 0.05%, with a particularly low uptake among girls aged 9–14, accounting for less than 5%.[15] Economically developed provinces and cities in China, such as Beijing and Shanghai, have achieved vaccination rates of only 7%, and Zhejiang Province reported a rate of 4.68%.[16] However, there has been no relevant research on the status of HPV vaccination among eligible females in Gansu Province, a western region of China.

This study analyzes real-world vaccination cases to understand the current status of HPV vaccination among females of different age groups in Gansu Province. It also evaluates the safety of HPV vaccines post-market release. The findings aim to provide a basis for future efforts to increase HPV vaccine coverage and work toward the elimination of cervical cancer.

Materials and methods

Data sources

Data on HPV vaccine administration cases in Gansu Province from 2018 to 2021 were obtained from the Gansu Provincial Immunization Information System. This dataset included information such as birthdates, vaccination dates, vaccine names, vaccine manufacturers, doses administered, and vaccination units. Reports of HPV vaccine-related AEFI in Gansu Province from 2018 to 2021 were collected from the National AEFI Information Management System. AEFI case information included birthdates, vaccination dates, vaccine names, vaccine manufacturers, doses administered, reaction occurrence dates, clinical manifestations, and reaction classifications. Population data for different age groups were sourced from the 2020 National Census, and the female population in each age group was estimated based on the gender ratio from the 2020 Census.

HPV vaccines

A 2-valent HPV vaccine (adsorbed) produced by GlaxoSmithKline (GSK) was introduced in China in 2016; A 4-valent HPV vaccine (S. cerevisiae) and a 9-valent HPV vaccine (S. cerevisiae) produced by Merck & Co., Inc. (Merck) were introduced in China in 2017 and 2018, respectively.[17] All three of these vaccines were imported. Xiamen Wantai's 2-valent HPV vaccine (E. coli) was launched on December 31, 2019, as a domestically-produced HPV vaccine. The imported HPV vaccine and domestically produced HPV vaccine in Gansu Province were launched in 2018 and 2020, respectively.

AEFI classification and definitions

AEFI cases were classified according to the criteria outlined in the "National Program for Monitoring Adverse Events Following Immunization,"[18] AEFI cases were categorized into five types: adverse reactions (including Common Adverse Reaction and Rare Adverse Reaction), vaccine quality incidents, vaccination accidents, coincidental events, and psychogenic reactions.

AEFI refer to reactions or events suspected to be related to preventive vaccination. Adverse reactions are harmful responses occurring after the proper administration of a qualified vaccine, unrelated to the intended preventive purpose or unexpected. Common Adverse Reaction are responses occurring after preventive vaccination, primarily induced by the inherent characteristics of the vaccine, causing transient physiological dysfunction in the body. Mainly, they include symptoms such as fever and local redness, possibly accompanied by systemic discomfort, fatigue, loss of appetite, and other comprehensive symptoms. Rare Adverse Reaction involve damage to the tissues or organs of the vaccinated organism during or after the proper vaccination process, and adverse drug reactions occur without fault from any involved party, given that the vaccine is qualified and administered correctly.

Statistical analysis

Age at vaccination was calculated based on birthdates and the interval between birthdates and vaccination dates. The first-dose HPV vaccination rate among females within an age group is calculated as the number of females receiving the first dose of HPV vaccine in that age group divided by the total female population in that age group, multiplied by 100%. This calculation is performed sequentially for females aged 9–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–45, and 9–45 years to determine the first-dose vaccination rates for each specified age group. The AEFI reporting rate for HPV vaccines (per 100,000) is calculated as the number of cases with AEFI after receiving the HPV vaccine divided by the total number of HPV vaccine doses administered, multiplied by 100,000 doses. The incidence rate of HPV vaccine for different age groups of females is determined by dividing the number of AEFI cases reported after HPV vaccination in specific age groups by the total number of HPV vaccine doses administered to females in those age groups. Access databases and R software version 4.0.5 were used for data organization and statistical analysis. AEFI, Common Adverse Reaction, and Rare Adverse Reaction reporting rates were calculated, as well as Relative Risk (RR) values with 95% Confidence Intervals (*CI*).

Results

HPV vaccine administration

From 2018 to 2021, a total of 253,759 doses of HPV vaccine were administered in Gansu Province. This included 57,284 doses of 2-valent HPV vaccine (adsorbed), 26035 doses of 2-valent HPV vaccine (E. coli-derived), 108,322 doses of 4-valent HPV (S. cerevisiae), and 62,118 doses of 9-valent HPV vaccine (S. cerevisiae). The first, second, and third doses were administered to 107,925, 87397, and 58,437 individuals, respectively (Table 1).

Among the various cities and regions in Gansu Province, a total of 107,925 individuals received the first dose of the HPV vaccine. Notably, among females aged 9–45, JiaYuGuan City exhibited the highest first-dose vaccination rate at 6.4%, followed by Lanzhou City at 4.9% (Figure 1).The first-dose vaccination rate among females aged 9 to 45 in the entire province is 2.02%. The highest

Table 1. HPV vaccination doses of different types in Gansu Province from 2018 to 2021.

Type	1st Dose	2nd Dose	3rd Dose	Total[1]
2-valent HPV (Adsorbed Vaccine)	31,609	21,422	4,253	57,284
2-valent HPV (E. coli)	9,699	9,165	7,171	26,035
4-valent HPV (S. cerevisiae)	41,920	36,101	30,301	108,322
9-valent HPV (S. cerevisiae)	24,697	20,709	16,712	62,118
Total[2]	107,925	87,397	58,437	253,759

Total[1]: Total doses administered for the same vaccine type.
Total[2]: Total doses administered for different vaccine types per dose.

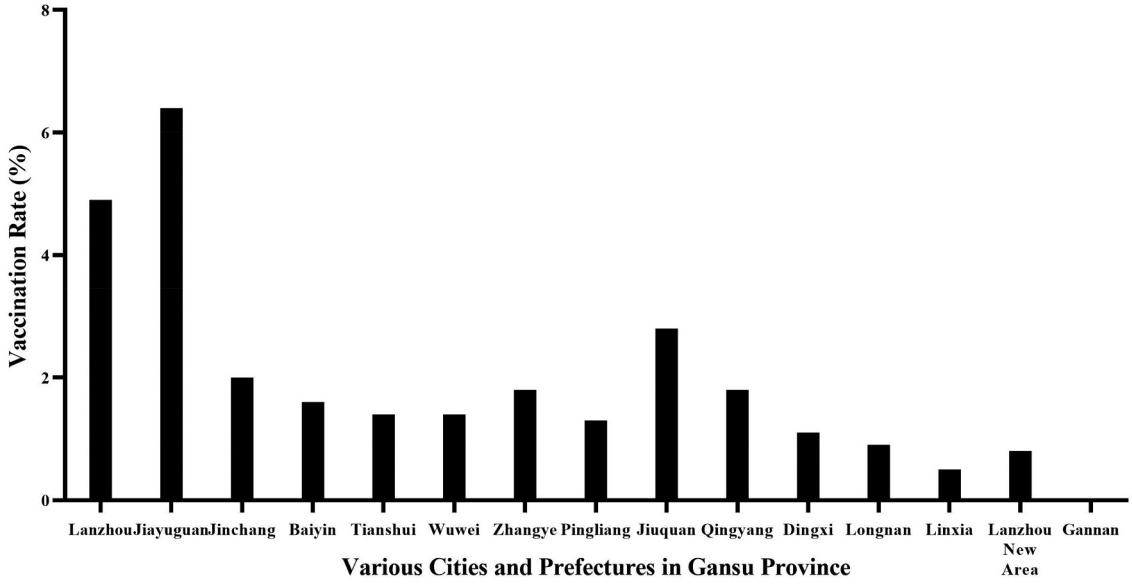

Figure 1. HPV vaccine first dose coverage (%) among 9–45 year-old females in different regions of Gansu Province, 2018–2021.

first-dose vaccination rate was observed in the 35–39 age group at 3.25%, followed by the 25–29 age group at 3.07% and the 30–34 age group at 2.73%. The lowest first-dose vaccination rate was among females aged 9 to 14 (Figure 2).

Among those who received the first dose 63,557 individuals reported their occupation. Among these, healthcare professionals accounted for 16.08%, followed by administrative staff at 15.97%, individuals in the education sector at 11.93%, and agricultural workers at 9.79%.

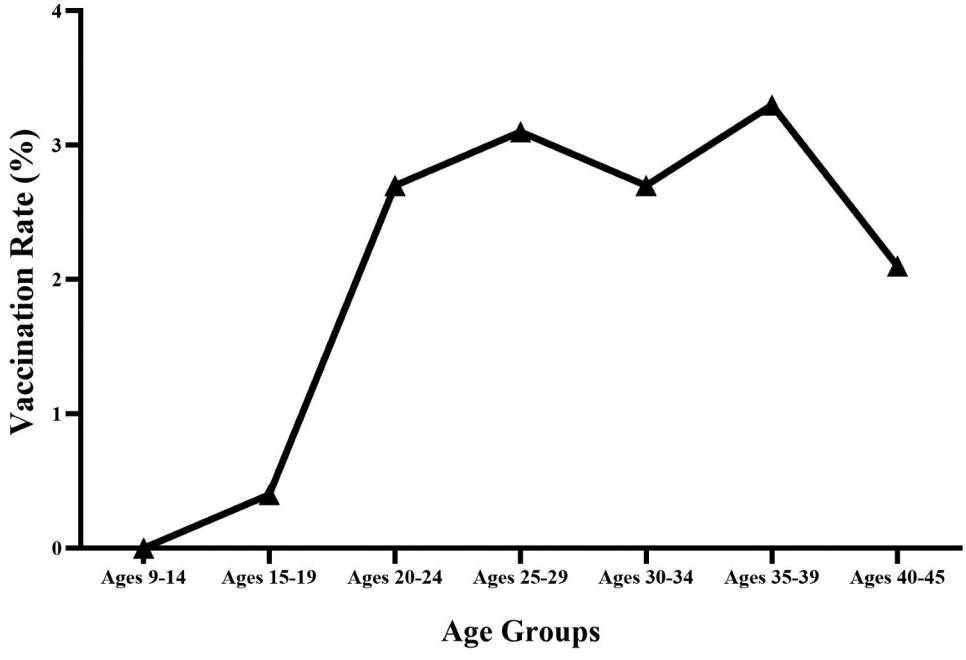

Figure 2. Gansu province first dose HPV vaccine coverage rates (%) in Different Age Groups, 2018–2021.

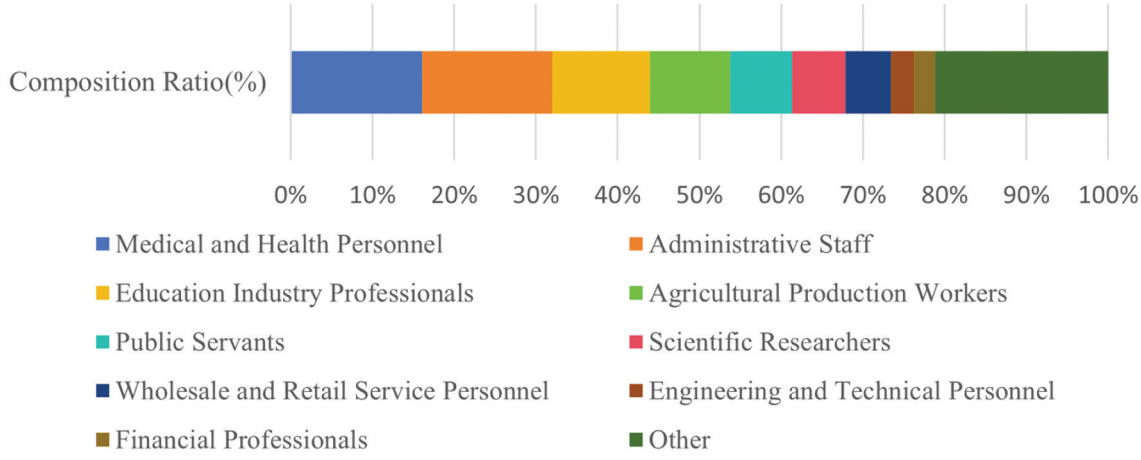

Figure 3. Composition of first dose HPV vaccination numbers among women in different occupations in Gansu Province from 2018 to 2021.

These four occupational groups comprised over 50% of the first-dose recipients in the reported occupational data (Figure 3).

HPV vaccine-related AEFI reports and classification

A total of 33 AEFI cases related to HPV vaccines were reported, resulting in a reporting rate of 13.00 per 100,000 doses. These cases were categorized based on the cause of occurrence, with 32 cases classified as adverse reactions, leading to a reporting rate of 12.22 per 100,000 doses. Among the adverse reactions, 31 cases were Common Adverse Reaction, with a reporting rate of 11.82 per 100,000 doses, and 1 case was classified as a Rare Adverse Reaction, with a reporting rate of 0.39 per 100,000 doses. Common Adverse Reaction accounted for 96.77% of adverse reactions (Table 2). There was 1 case classified as coincidental events, with a clinical diagnosis of renal hydronephrosis with renal ureteral calculi, and 1 case classified as a psychogenic reaction with a clinical diagnosis of syncope.

HPV vaccine-related AEFI reports and classification

The general reaction reporting rates for the age groups 9–18 years and 19–45 years were 77.72/100,000 and 11.66/100,000, respectively. Only one case of abnormal reaction was reported in the 19–45 age group, with a reporting rate of 0.40/100,000 (Table 2). According to statistical analysis, the general reaction reporting rate for the 9–18 age group was significantly higher than that for the 19–45 age group ($p = .007$, RR = 6.66, 95% CI (1.81–17.07)).

Adverse reaction incidence following vaccination with different types of HPV vaccines

Among individuals who received the 9-valent HPV vaccine (S. cerevisiae), the highest reported incidence of Common Adverse Reaction was 20.93 per 100,000 doses, followed by the 4-valent HPV vaccine (S. cerevisiae) at 9.23 per 100,000 doses (Table 3). There was no statistically significant difference in the incidence of Common Adverse Reaction between different types of HPV vaccines ($p > .05$).

Table 2. Adverse reaction reports of HPV vaccination in different age groups in Gansu Province from 2018 to 2021 (reported rate: per 100,000).

		AEFI		Common Adverse Reaction		Rare Adverse Reaction	
Age	Vaccine doses administered	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)
Age 9–18*	5,147	4	77.72	4	77.72	–	–
Age 19–45	248,612	29	11.66	26	10.46	1	0.40
Total	253,759	33	13.00	30	11.82	1	0.39

*Ages 9–14 received only 3 doses, combined and grouped together with ages 15–18 for statistical purposes.

Table 3. Adverse reaction reporting for different types of HPV vaccines in Gansu Province from 2018 to 2021 (reporting rate: per 100,000).

		AEFI		Common Adverse Reaction		Rare Adverse Reaction	
Type	Number of Different Types of Vaccines Administered	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)
HPV2 (Adsorbed Vaccine)	57,284	5	8.73	5	8.73	–	–
HPV2 (E. coli)	26,035	2	7.68	2	7.68	–	–
HPV4 (S. cerevisiae)	108,322	13	12.00	10	9.23	1	0.92
HPV9 (S. cerevisiae)	62,118	13	20.93	13	20.93	–	–
Total	253,759	33	13.00	30	11.82	1	0.39

Table 4. Adverse reaction reports of different doses of HPV vaccination in Gansu Province from 2018 to 2021 (reported incidence rate: per 100,000).

	Common Adverse Reaction						Rare Adverse Reaction
	1st Dose		2nd Dose		3rd Dose		
Type	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)	1st Dose
HPV2 (Adsorbed Vaccine)	4	12.65	–	–	1	23.51	–
HPV2 (E. coli)	1	10.31	1	10.91	–	–	–
HPV4 (S. cerevisiae)	8	19.08	2	5.54	–	–	1
HPV9 (S. cerevisiae)	6	24.29	–	–	7	41.89	–
Total	19	17.60	3	3.43	8	13.69	1

Adverse reaction incidence following HPV vaccination at different doses

The incidence of Common Adverse Reaction following the first, second, and third doses of HPV vaccine were 17.60 per 100,000 doses, 3.43 per 100,000 doses, and 13.69 per 100,000 doses, respectively. (Table 4). Among individuals who received the first dose of the 9-valent HPV vaccine (S. cerevisiae), the highest reported incidence of Common Adverse Reaction was 24.29 per 100,000 doses, followed by the 4-valent HPV vaccine (S. cerevisiae) at 19.08 per 100,000 doses. There was no statistically significant difference in the incidence of Common Adverse Reaction following the first dose between different types of HPV vaccines ($p > .05$). There was also no statistically significant difference in the incidence of Common Adverse Reaction following the second dose between the 2-valent HPV vaccine (E. coli-derived) and the 4-valent HPV vaccine (S. cerevisiae) ($p > .05$). Similarly, there was no statistically significant difference in the incidence of Common Adverse Reaction following the third dose between the 2-valent HPV vaccine (adsorbed) and the 9-valent HPV vaccine (S. cerevisiae) ($p > .05$).

HPV vaccine adverse reactions

The incidence rates of adverse reactions following HPV vaccine administration were as follows: fever (5.52 per 100,000 doses), local redness and swelling (3.33 per 100,000 doses), fatigue (3.15 per 100,000 doses), headache (2.76 per 100,000 doses), and local induration as well as nausea and vomiting (both 1.97 per 100,000 doses), among others (Table 5). Following vaccination with the 9-valent HPV vaccine (S. cerevisiae), the reporting rates for fever and body temperature ≥ 38.6°C were higher than those for the 4-valent HPV vaccine (S. cerevisiae) ($p = .012$, $RR = 6.975$, 95% CI [1.392–67.426]; $p = .009$, $RR = 1.221$, 95% CI [1.568–550.143], respectively). There were no statistically significant differences in the reporting rates of other adverse reactions between different types of HPV vaccines.

Time interval for adverse reactions following HPV vaccine administration

Adverse reactions following HPV vaccine administration primarily occurred within less than 1 day, accounting for 67.74% of cases. The next most common timeframe for adverse reactions was between 1 and 3 days, accounting for 25.81% of cases. Adverse reactions that occurred beyond 3 days were very rare (Table 6).

Discussion

Epidemiological studies in China have found that the median age of first sexual activity among women aged 13–24 is 17 years.[4]

Table 5. The occurrence of adverse reactions after receiving different types of HPV vaccines (reported incidence: 1 per 100,000).

	HPV2 (Adsorbed Vaccine)		HPV2 (E. coli)		HPV4 (S. cerevisiae)		HPV9 (S. cerevisiae)		Total	
Adverse Reactions	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)	Case	Reporting Rate (%)
Common Adverse Reaction										
Fever (Axillary °C)	4	6.98	–	–	2	1.85	8	12.88	14	5.52
37.1~	2	3.49	–	–	–	–	–	–	2	0.79
37.6~	2	3.49	–	–	1	0.92	1	1.61	4	1.58
≥38.6	–	–	–	–	1	0.92	7	11.27	8	3.15
Swelling (Diameter cm)	–	–	1	3.84	3	2.77	5	8.05	9	3.55
≤2.5	–	–	–	–	2	1.85	–	–	2	0.79
2.6~	–	–	–	–	–	–	4	6.44	4	1.58
>5.0	–	–	1	3.84	1	0.92	1	1.61	3	1.18
Lump (Diameter cm)	–	–	1	3.84	–	–	4	6.44	5	1.97
≤2.5	–	–	1	3.84	–	–	–	–	1	0.39
2.6~	–	–	–	–	–	–	3	4.83	3	1.18
>5.0	–	–	–	–	–	–	1	1.61	1	0.39
Headache	2	3.49	–	–	2	1.85	3	4.83	7	2.76
N/V	1	1.75	1	3.84	3	2.77	1	1.61	5	1.97
Muscle Pain	1	1.75	–	–	2	1.85	1	1.61	4	1.58
Fatigue	2	3.49	–	–	4	3.69	2	3.22	8	3.15
Skin Rash	–	–	–	–	1	0.92	1	1.61	2	0.79
Vaginal Bleeding	1	1.75	–	–	–	–	–	–	1	0.39
Rare Adverse Reaction										
Non-Cardiogenic Chest Pain	–	–	–	–	1	0.92	–	–	1	0.39

N/V: Nausea/Vomiting.

Table 6. Adverse reactions at different time intervals after vaccination with different types of HPV vaccines (reported incidence: 1 per 100,000).

	HPV2 (Adsorbed Vaccine)		HPV2 (E. coli)		HPV4 (S. cerevisiae)		HPV9 (S. cerevisiae)		Total	
Time Interval	Case	Composition (%)	Case	Composition (%)	Case	Composition (%)	Case	Composition (%)	Case	Composition (%)
<1 day	3	60.00	2	100.00	7	63.64	9	69.23	21	67.74
1 day ~	2	40.00	–	–	4	36.36	2	15.38	8	25.81
3 days ~	–	–	–	–	–	–	1	7.69	1	3.23
7 days ~	–	–	–	–	–	–	1	7.69	1	3.23
Total	5	100.00	2	100.00	11	100.00	13	100.00	31	100.00

Vaccination against HPV is one of the effective measures to prevent cervical cancer. Australia was the world's first country to provide free quadrivalent HPV vaccination. The results showed that prior to the introduction of the HPV vaccine, the infection rate of HPV types 16/18/6/11 among women aged 18–24 in Australia was 22.7%. After the introduction of the vaccine, this rate decreased to 1.5%. HPV vaccination can significantly reduce the prevalence of HPV infections in the population. Cost-effectiveness studies of HPV vaccine implementation in high-income countries like Europe and the United States have consistently demonstrated its cost-effectiveness, even at different vaccination coverage rates ranging from 33% to 100%. Various guidelines, including those from the WHO, recommend vaccination for girls aged 9 to 14 as the primary or routine target group.[12] Where feasible, vaccination can be expanded to include adolescent girls and young women. However, the results of this study reveal that in Gansu Province, the first-dose HPV vaccination rate among women aged 9 to 45 is only 2.02%, much lower than in more developed coastal cities in China, such as Shanghai (7%) and Zhejiang Province (4.68%), and similar to rates in Africa and Asia (1.1–1.2%), but significantly lower than in developed countries like the United States, the United Kingdom, Australia, and Europe.

Currently, there are three main reasons contributing to the low HPV vaccination rate in Gansu Province. Firstly, it is closely related to insufficient vaccine supply.[16] Between 2018 and 2020, a total of 32.977 million doses of HPV vaccine were issued nationwide.[19,20] However, Gansu Province received less than 1% of this supply, and more than 80% of the HPV vaccines were administered to women aged 25 and above. Secondly, it is influenced by parental willingness and the recommendations from vaccination clinics. As of June 2020, HPV vaccines had been included in the national immunization programs of 107 countries (55%) according to the WHO.[13] In many Chinese provinces, HPV vaccines are not provided free of charge, and due to the large population, the cost of including them in the immunization program is high, which requires parents or their guardians to bear the expensive vaccine costs. Moreover, since the target population is minors, their decision to get vaccinated heavily relies on parental consent. Reports[4,21]indicate that approximately 40% of parents of girls aged 9 to 14 are willing to have their daughters vaccinated against HPV. Factors affecting this willingness include parental education, occupation, awareness level, and the age of the daughters (with some parents believing that younger children are not at high risk for HPV infection). Parents often fail to recognize that girls in the 11 to 13 age group may engage in sexual activity, missing the optimal window for prevention. The willingness of healthcare professionals in vaccination clinics to recommend HPV vaccines also impacts vaccination rates and timeliness.[22,23] Surprisingly, even in countries that have incorporated HPV vaccines into their immunization programs,[24] such as Chengdu and Xiamen in China,[25,26] vaccination delays and resistance still occur, often attributed to parental vaccine hesitancy and concerns about vaccination risks.[23,27] Thirdly, the low vaccination rate among girls aged 9 to 14 may be due to the fact that 4-valent and 9-valent HPV vaccines were not previously available for this age group, leading to hesitancy among the public, who were more familiar with the 2-valent vaccine.[28] This study found that economically independent individuals with stable incomes and higher levels of awareness, such as healthcare workers, administrative staff, and teachers, were more willing to get vaccinated against HPV, sometimes even at their own expense. Therefore, to uphold the principles of fairness and accessibility, HPV vaccines should also be included in immunization programs and provided free of charge to girls aged 9 to 14.

HPV vaccines showed their safety in pre-market clinical trials, with adverse reactions primarily consisting of local responses (including pain, redness, and swelling) and systemic reactions (such as fever, headache, dizziness, muscle pain, joint pain, and gastrointestinal symptoms).[29–32] These reactions were mostly transient and of mild to moderate intensity, with a very low rate of severe adverse reactions, the majority of which were unrelated to vaccine administration. However, since the pre-market vaccination population was relatively small, it was challenging to detect rare adverse reactions. Hence, post-market safety monitoring is essential. While HPV vaccines have been on the market in foreign countries for many years with AEFI surveillance in place, they were introduced to the market in China more recently, making it necessary to conduct AEFI monitoring. An analysis of suspected adverse reactions related to HPV vaccination in Gansu Province revealed an AEFI reporting rate of 13.00 per 100,000 population in our province. Specifically, the reporting rate for AEFI related to the 4-valent vaccine was 12.00 per 100,000, which is lower than rates reported in the United States through the Vaccine Adverse Event Reporting System (VAERS)[33–35] and in the European Union.[36] This difference may be attributed, in part, to variances in AEFI definitions between our monitoring system and the WHO adverse event definitions. Additionally, in our AEFI monitoring system, minor Common Adverse Reaction, such as fever below 38.5 degrees Celsius and local redness and swelling with a diameter less than 2.5 cm, are not required to be reported. In Gansu Province, the rates of Common Adverse Reaction and Rare Adverse Reaction to

HPV vaccines were 11.82 per 100,000 and 0.39 per 100,000, respectively. Compared to Shanghai, China,[37] both Common Adverse Reaction and Rare Adverse Reaction reporting rates were lower in Gansu Province. However, when compared to Fujian Province,[38] the Common Adverse Reaction reporting rate was higher while the Rare Adverse Reaction reporting rate was lower.

The analytical findings of this study indicate that, following the introduction of HPV vaccines in Gansu Province, the Common Adverse Reaction reported among females aged 9–45 years primarily included fever (5.52 per 100,000), local redness (3.33 per 100,000), fatigue (3.15 per 100,000), headache (2.76 per 100,000), local swelling, and nausea/vomiting. These clinical symptoms align with those re-ported in Shanghai[37]and Fujian Province.[38] Notably, this study reported a Rare Adverse Reaction of non-cardiac chest pain, which has not been documented in similar studies and warrants further investigation. Our safety monitoring data in Gansu Province have not identified any reports of rare severe adverse reactions such as neurological or autoimmune-related conditions resulting from HPV vaccination. The results of this study also indicate that the safety profile of HPV vaccines remains within expected parameters in a large population. Authoritative organizations like Global Advisory Committee on Vaccine Safety (GACVS) have assessed HPV vaccines as having an excellent safety profile.[12] Literature reports indicate that common reactions to HPV vaccination include not only Common Adverse Reaction but also psychogenic reactions such as needle phobia and fainting. This is primarily because the literature reports vaccination of adolescents aged 9–14, who may experience nervousness or fasting-related factors during vaccination. Therefore, it is recommended to administer the vaccine while the individual is seated and to avoid vaccinating on an empty stomach. Following vaccination, individuals should be observed for 30 minutes. Adverse reactions occurring after HPV vaccination are mainly concentrated within less than 1 day, followed by 1–3 days, with a very low proportion of adverse reactions occurring after more than 3 days. This pattern is similar to that observed with other vaccines. All reported AEFI cases have fully recovered.

This study found that the rate of Common Adverse Reaction was higher in the 9–18 age group compared to other age groups ($p < .05$). This could be attributed to increased awareness among individuals or their guardians in this age group, leading to more reporting of adverse reactions. Due to limited data related to adverse reactions associated with different vaccine doses, there is no clear trend indicating an increase in adverse reactions with increasing vaccine doses. However, some reports suggest that as the number of vaccine doses increases, the rate of local reactions also increases. Nevertheless, there is no significant increase in reported cases of fever with increasing vaccine doses. No significant difference has been found in the overall incidence of Common Adverse Reaction among different types of HPV vaccines ($p > .05$). However, the reported rates of fever and body temperature ≥ 38.6°C after vaccination with the 9-valent HPV (yeast) vaccine are both higher than those with the 4-valent HPV (yeast) vaccine ($p < .05$). Further research is needed to confirm these results. This study did not find a higher rate of local adverse reactions after vaccination with the 9-valent HPV vaccine compared to the 4-valent HPV vaccine.[39]

Additionally, this study has limitations. As an early adopter of AEFI monitoring since 2005 and one of the seven provinces to do so nationwide, Gansu Province has demonstrated a commendable commitment to post-vaccination safety, reflected in a reporting rate that exceeds the national average. However, the AEFI data collected for HPV vaccines in this study is relatively limited. This limitation arises from non-mandatory reporting within China's AEFI monitoring framework, and less reporting diligence among the adult vaccination cohort, leading to potential underreporting. In order to obtain a more accurate evaluation of the post-licensure safety profile for HPV vaccines, it is imperative to conduct targeted active surveillance.

Conclusion

The HPV vaccine coverage among females aged 9–14 in Gansu Province is extremely low and needs improvement. From 2018 to 2021, the incidence of Adverse reaction Following Immunization adverse reactions following HPV vaccination fell within the expected range, indicating the vaccine's safety profile. It is recommended that the government should intensify HPV vaccine promotion, conduct health education for parents or their guardians, actively coordinate vaccine supply, and include the HPV vaccine in the national immunization program to enhance HPV vaccine coverage among females aged 9–14.

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Disclosure statement

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Ethical approval

The study protocol and informed consent form were approved by the Medical Ethics Committee of the Gansu Provincial Center for Disease Control and Prevention (Approval notice: 2023019). Written informed consent was obtained from all study participants.

Abbreviations

HPV: Human papillomavirus; WHO: World Health Organization; AEFI: Adverse Events Following Immunization; GSK: GlaxoSmithKline; S. cerevisiae: Saccharomyces cerevisiae; Merck: Merck & Co., Inc.; RR: Relative Risk; CI: Confidence Intervals; N/V: Nausea/Vomiting; VAERS: Vaccine Adverse Event Reporting System; GACVS: Global Advisory Committee on Vaccine Safety.

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