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REVIEW

Landscape Analysis of Human Papillomavirus (HPV) Prophylactic Vaccine Clinical Trials in China Based on the NMPA Database

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Purpose: Human papillomavirus (HPV) vaccination is key to preventing cervical cancer, and increasing its coverage in China faces complex challenges. Comprehensive literature providing an overview of the current status of HPV vaccine clinical trials in China remains lacking. To address this gap, our study was the first to systematically analyze and summarize the characteristics of HPV prophylactic vaccines clinical trials in China over a decade, providing a reference for HPV vaccine research and development.

Methods: We analyzed HPV prophylactic vaccine clinical trials registered on the Chinese National Medical Products Administration (NMPA) Registration and Information Disclosure Platform (http://www.chinadrugtrials.org.cn) from January 1, 2013, to December 31, 2024.

Results: Eighty registered trials were evaluated, of which 51 trials (63.75%) were ongoing, 27 were completed (33.75%) and 2 were terminated (2.50%). The top three vaccine types by proportion were nonavalent vaccines (38.75%, n=31), followed by bivalent (35.00%, n=28) and quadrivalent (12.50%, n=10) vaccines. Domestic enterprises sponsored most trials (81.25%, n=65). The leading research sites were located mainly in the eastern and western China. Only 31.25% (n=25) of the trials had a data monitoring safety committee, and 43.75% (n=35) had clinical trial insurance. Most trials were in Phase III, with a randomized, double-blind, parallel-group design, and most (82.5%, n=66) enrolled female participants. Domestic vs overseas enterprises differed significantly in terms of phase ($p = 0.010$), intervention ($p = 0.000$), allocation ($p = 0.016$), masking ($p = 0.002$), leading research site region ($p = 0.016$)/type ($p = 0.002$), and insurance ($p = 0.019$).

Conclusion: HPV vaccine clinical trials in China have made significant progress, with most at a crucial stage, featuring diverse vaccine types and high-quality designs. However, more efforts are needed to promote the development and approval of the HPV vaccine by increasing tertiary hospitals' qualifications for conducting clinical trials, establishing a government-led non-profit third-party quality control platform and increasing research and development investment to ensure insurance coverage.

Keywords: HPV prophylactic vaccine, HPV vaccination, clinical trials, NMPA registration and information disclosure platform, pharmaceutical company

Introduction

Human papillomavirus (HPV) is a nonencapsulated deoxyribonucleic acid virus that belongs to the family Papillomaviridae.[1] More than 200 HPV genotypes have been characterized,[2] among which alpha-genus HPV genotypes are the causes of many anogenital cancers in humans and primates, such as cervical, anal, oropharyngeal cancers.[3,4] Persistent infections with high-risk HPVs (HR-HPVs) is a dominant cause of dysplasia and an increased risk of cervical cancer, and HR-HPVs are associated with nearly 75% of cervical cancers worldwide.[5]

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In light of updated estimates from the International Agency for Research on Cancer (IARC), cervical cancer is the fourth most common cancer with respect to both incidence and mortality in women,[6] with nearly 660,000 new cases and 350,000 deaths worldwide in 2022. Reported trends from 1988 to 2017 showed that incidence rates in Oceania (New Zealand), North America (Canada and the United States) and Western Europe continued to decline until the mid-2000s and gradually leveled off thereafter.[7] Moreover, it has been reported that cervical cancer was the most common gynecologic cancer from 1990 to 2019 in China,[8] with 150,659 new cases and 55,694 deaths, accounting for 22.8% of new cases and 16.0% of deaths globally, respectively, as estimated by the IARC.[6]

HPV-associated neoplasia accounts for nearly one-third of all infection-attributable cancer cases.[9,10] Although prevention efforts in the 20th century were largely based on cytology-based screening, current and future HPV-related cancer prevention is primarily focused on HPV vaccination and molecular screening tests.[11] Consequently, prevention of persistent HR-HPV infections reduces the incidence of cervical cancer, and vaccination is the most economical and effective method of prevention.[12]

Some developed countries have achieved relatively high rates of HPV vaccination through the inclusion of the vaccine in national vaccination programs. To date, 148 out of 194 countries have included the HPV vaccine in their national immunization schedules.[13] However, the use of HPV vaccination has been suboptimal in many developed countries.[14] According to the latest research data of the first-dose HPV vaccination coverage for girls in the target age, 132 of the 148 countries reported the coverage data, with 15 countries (Bhutan, Cambodia, Cook Islands, Denmark, Iceland, Niue, Norway, etc) achieving 90% coverage. It was estimated to be highest in upper-middle income countries at 71.7% and lowest in lower-middle income countries at 46.4%.[13] Benefiting from a series of health policies, China has prioritized cancer control, including "the Action Plan for Accelerating the Elimination of Cervical Cancer (2023–2030)" as part of "the Healthy China 2030" outline. Although the incidence of cervical cancer has been increasing in China, the upward trend has slowed significantly since 2008, which is attributed to tertiary prevention measures such as HPV vaccination for young women, cervical cancer screening among women of appropriate age, and timely treatment of cervical cancer and precancerous lesions. This decline is especially notable among younger generations, indicating the efficacy of recent cervical cancer prevention and control strategies in China.

HPV vaccination is not only an effective measure to prevent cervical cancer but also an important complementary strategy to strengthen health equity in low-resource settings.[15] Recently, a summative analysis of infection in Chinese women reported that provinces including Guangxi and Yunnan (which belong to the western region presented in this paper) have relatively high HPV infection rates.[16] Furthermore, research indicates that since the acceleration of Centers for Disease Control and Prevention (CDCs) construction within China's public health system in 2009, unlike the more developed hospitals or pharmaceutical companies in the eastern region, the density of CDCs and disease control personnel has shown a gradual decrease from west to east. The density of CDCs in the western region is significantly greater compared with those in the central and eastern regions.[17] Following the approval of the first HPV vaccine in 2016 by the Chinese National Medical Products Administration (NMPA), clinical trials for more prophylactic HPV vaccines are also in full swing. In summary, because of the burden of cancer in China and the influence of national policies, accelerating the development of HPV vaccines remains an urgent priority. Starting on November 10, 2025, the HPV vaccine will be included in the Chinese National Immunization Program. Two doses of the bivalent HPV vaccine will be administered free of charge to 13-year-old girls born after November 10, 2011, across all regions.[18] This marks a critical step for China in establishing a policy framework for cervical cancer prevention.

Clinical trials are the gold standard and key step for evaluating the efficacy of a particular drug.[19,20] Recently, Edison et al described a cross-sectional analysis of HPV vaccine clinical trials registries globally and demonstrated that as of 2022, most of the HPV vaccine clinical trials were conducted in Europe (26.0%), followed by Asia (25.0%), and North America (20.0%).[21] To promote drug clinical trial transparency, the NMPA established the Registration and Information Disclosure Platform (http://www.chinadrugtrials.org.cn)[22,23] in 2012. This platform includes planned, ongoing and completed clinical trials for the purpose of filing drug registration and contains information regarding study design, administration, investigator and other relevant trial information. One of the most important steps in laying the groundwork for future clinical practice is to conduct statistical and data analyses of the registered clinical trials.

Using data from the above platform, we have innovatively conducted the first comprehensive analysis and summarized the status and characteristics of prophylactic HPV vaccine clinical trials in China over nearly a decade to provide valuable insights into the current clinical development trend and landscape of the HPV vaccine. Moreover, we further analyzed the differences between domestic and overseas sponsors and uniquely focused on key factors as Data Monitoring Committees (DMCs) and insurance to provide perspectives into trial design quality indicators. The results can assist sponsors and researchers as a reference to improve the quality of related research. This systematic analysis of prophylactic HPV vaccine trials in China summarizes recent progress and reflects the accelerated implementation of the "Healthy China 2030" initiative.

Materials and Methods

Data Collection and Selection Criteria

We conducted a systematic analysis of trials on the NMPA Registration and Information Disclosure Platform for HPV vaccine clinical studies that were registered on the platform between January 1, 2013, and December 31, 2024. The search terms "human papillomavirus vaccine" and "HPV" were used as keywords to search for all HPV-related clinical trials registered on the NMPA Registration and Information Disclosure Platform for Drug Clinical Studies as of March 24, 2025. All identified records were downloaded, and the following information was collected: basic information for clinical trials, such as registered number, trial status, study type, study design, sponsor, study site, location, and primary purpose, and information related to study design, such as indications, study title, drug name, study phase, participant characteristics (sex, type and age), design type, intervention model, allocation and masking strategy, etc. Two researchers (HGL and HYM) independently searched the NMPA Registration and Information Disclosure Platform using the same search terms and screened the data from the records to identify eligible trials. All registered HPV vaccine clinical trials in China were initially included in the analysis. A standard Microsoft Excel database was created for further analysis.

Trials were initially included if they met the following criteria: (1) registered on the NMPA platform; (2) focused on prophylactic HPV vaccines; (3) registered between January 1, 2013, and December 31, 2024. Trials were excluded if they: (1) were registered after January 1, 2025; (2) were observational studies (non-interventional); (3) studies not focusing on prophylactic HPV vaccines. All trials were further subclassified according to the study type. Given that the data used in this study were publicly accessible, ethical approval was not needed.

Data Analysis

Descriptive statistical analyses were performed to summarize the characteristics of included trials. Categorical variables were categorized as follows: the types of leading research sites were classified as centers for CDCs, hospitals, CDCs in collaboration with hospitals, or others; Research sponsors were classified as domestic enterprises or overseas enterprises; Geographical areas in China were divided into the eastern, central, western and northeastern regions, as defined by the National Bureau of Statistics of China (NBSC) in 2011.[24] If different leading research sites were present in the same geographical region, we combined the corresponding data into a cumulative calculation for that region. The statistical procedures were performed using the IBM SPSS Statistics 22.0 software. We used descriptive statistics to characterize the trial categories. Frequencies(n) and percentages (%) were calculated for categorical data. Differences in categorical variables between sponsor types (domestic vs overseas enterprises) were assessed using the chi-square test. Correlations were analyzed using Spearman correlation analysis. P values < 0.05 were considered statistically significant.

Results

Screening and Included Trials

During the initial search, a total of 99 clinical trials were identified on the NMPA Registration and Information Disclosure Platform up to March 24, 2025. After excluding data from 2025 and duplicates, 96 trials remained. Following a meticulous review of all available information, 16 trials involving therapeutic drugs focused on cervical

cancer (n=5), cervical HPV infection (n=9) and skin warts (n=2) due to HPV infection were further excluded. As a result, 80 registered trials were ultimately selected for evaluation, as illustrated in Figure 1.

General Characteristics of the Included Trials

Time Trends and Trial Status

The dataset included clinical trials registered between 2013 and 2024, and the general characteristics of the trials are illustrated in Table 1. The years 2013 and 2014 each had 4 trials (5%), whereas in 2015 and 2016, there were 2 trials (2.5%). Since 2017, the number of trials has increased, indicating a general trend of increasing trial numbers over the years, with a notable peak in 2021 (20%, n=16). We also analyzed the correlation between the number of trials and year for the 80 included trials. As depicted in Figure 2, there was a significant correlation between the number of trials and the registration year (r = 0.846, p=0.001). 51 trials (63.75%) were ongoing, followed by those completed (33.75%, n=27), and terminated (2.50%, n=2).

Valence Categories and Sponsors

As shown in Table 1, the majority of the trials utilized nonavalent vaccines (38.75%, n=31), followed by bivalent (35.00%, n=28) and quadrivalent (12.50%, n=10) vaccines. Notably, trials involving trivalent (2.50%, n=2), undecavalent (3.75%, n=3), tetradecavalent (3.75%, n=3), and pentadecavalent (3.75%, n=3) vaccines were less prevalent. The majority of the trials were sponsored by domestic enterprises (81.25%, n=65), with a smaller proportion supported by overseas enterprises (18.75%, n=15) (Table 1).

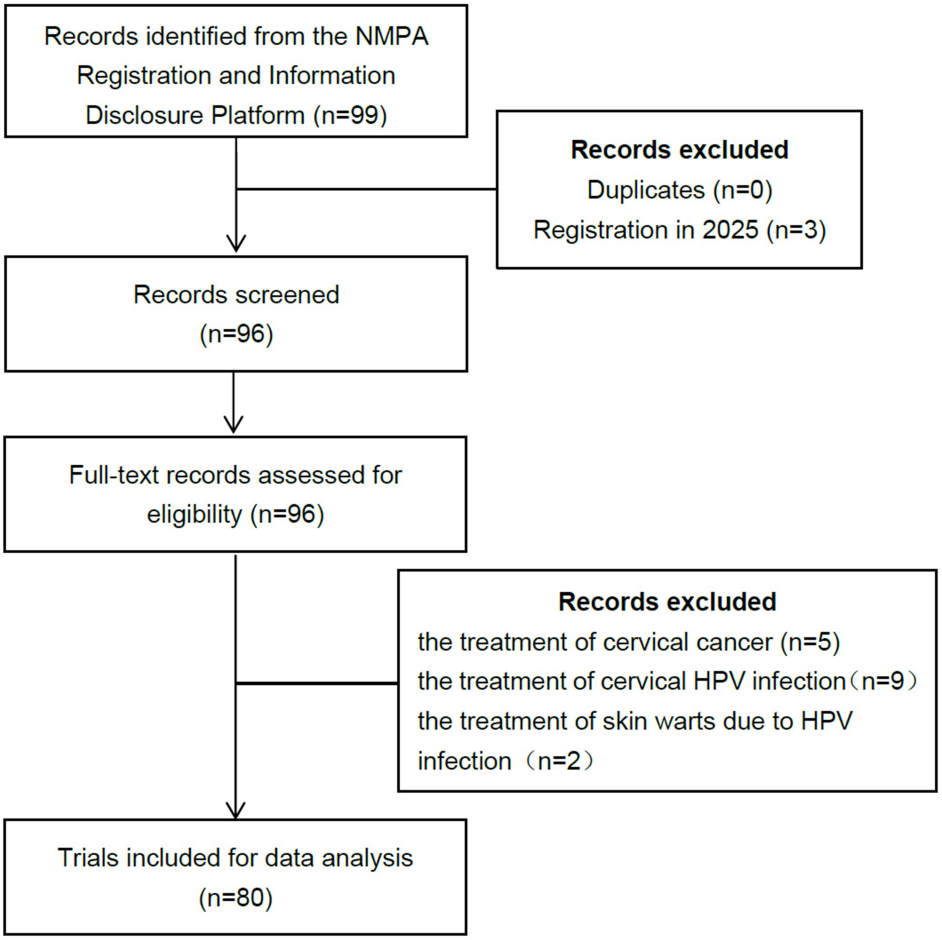

Figure 1 Flowchart of selection trials.

Table 1 Characteristics of All Included Trials (n=80)

Category	Subgroup	N	%
Year	2013	4	5.00
	2014	4	5.00
	2015	2	2.50
	2016	2	2.50
	2017	6	7.50
	2018	6	7.50
	2019	7	8.75
	2020	7	8.75
	2021	16	20.00
	2022	9	11.25
	2023	10	12.50
	2024	7	8.75
Status	Ongoing	51	63.75
	Completed	27	33.75
	Teminated	2	2.50
Valence categories	Bivalent	28	35.00
	Trivalent	2	2.50
	Quadrivalent	10	12.50
	Nonavalent	31	38.75
	Undecavalent	3	3.75
	Tetradecavalent	3	3.75
	Pentadecavalent	3	3.75
Type of Sponsors	Domestic Enterprise	65	81.25
	Overseas Enterprise	15	18.75
Geographical division of the leading site	Eastern region	38	47.50
	Central region	11	13.75
	Western region	31	38.75
	Northeastern region	0	0.00
Type of the leading research site	CDCs	69	86.25
	Hospital	3	3.75
	CDC in collaboration with Hospital	1	1.25
	Others	7	8.75
Data Monitoring Safety Committee	Have	25	31.25
	None	55	68.75
Clinical Trial Insurance	Have	35	43.75
	None	45	56.25

Abbreviation: CDC, Center for Disease Control and Prevention.

Geographic Locations and Types of Leading Research Sites

Geographically, the leading research sites were predominantly located in the eastern region (47.50%, n=38), followed by the western region (38.75%, n=31) and central region (13.75%, n=11), with none in the northeastern region (Table 1). The detailed distribution of leading research sites by province within each region is presented in Figure 3. Furthermore, the results revealed that CDCs (86.25%, n=69) were the most common type of leading research site, followed by hospitals (3.75%, n=3) and others (8.75%, n=7). The combination of CDCs in collaboration with hospitals was the least common, with only 1 associated trial (1.25%) (Table 1).

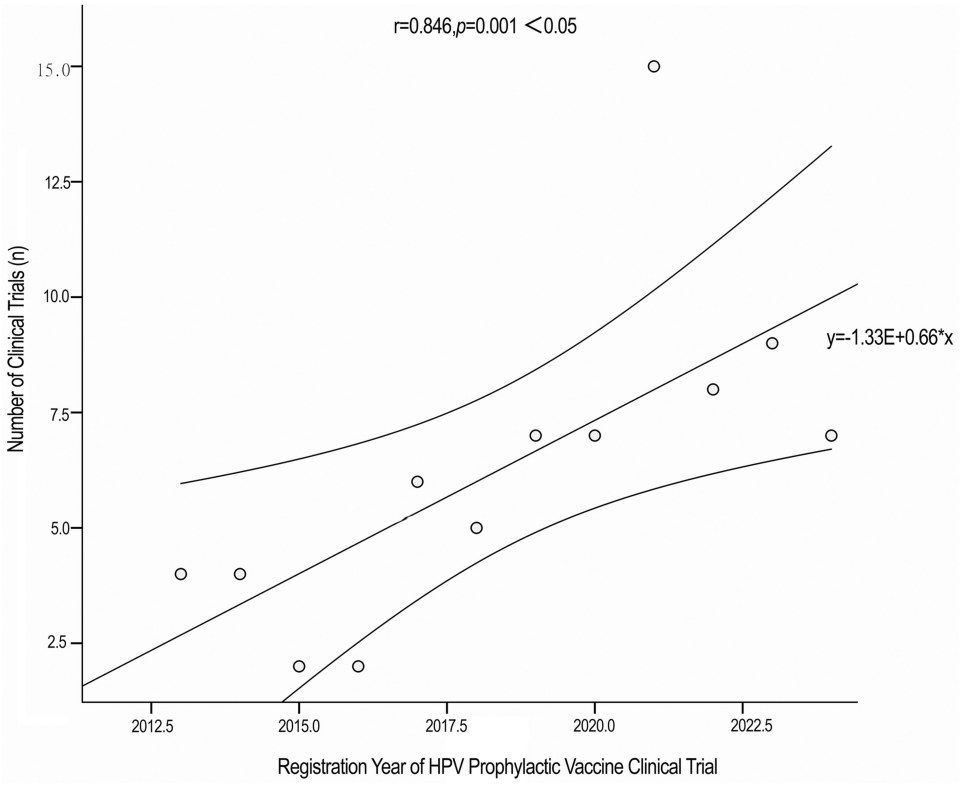

Figure 2 Correlation between the number of trials and the registration year in the 80 included trials.

Data Monitoring Safety Committee and Clinical Trial Insurance

With respect to data safety, 55 trials (68.75%) lacked a data monitoring safety committee, whereas 25 trials (31.25%) had one. Additionally, more than half of the trials (56.25%, n=45) did not include clinical trial insurance, whereas 35 trials (43.75%) did (Table 1).

Study Designs of the Included Trials

The trials were distributed across various phases of clinical development as follows: Phase 1 (21.25%, n=17), Phase 2 (13.75%, n=11), Phase 3 (45.0%, n=36), Phase 4 (17.5%, n=14), and unknown phase (2.5%, n=2). A parallel group design (82.5%, n=66) was the most prevalent, followed by single-arm designs (13.75%, n=11) and factorial analysis (3.75%, n=3). Randomized allocation (67.5%, n=54) was the predominant method, and 26 (32.5%) trials were nonrandomized. More than half of the trials involved masking, including 47 with double masking (58.75%) and 1 with single masking (1.25%), whereas 40% (n=32) of the trials involved no masking. All trials were domestic trials and involved healthy participants. The majority of trials (82.5%, n=66) exclusively enrolled female participants, while 7.5% (n=6) included male participants and 10% (n=8) included both sexes. The proportion of enrolled participants in the 16–45 years age group (31.25%, n = 25) was the highest. The other age groups included 9–45 years (27.50%, n=22), 9–30 years (21.25%, n=17), 18–30 years (11.25%, n=9), 18–55 years (3.75%, n=3), 25–55 years (2.5%, n=2), and 17-unknown (2.50%, n=2). The details of the data are shown in Table 2.

Trial Characteristics and Study Designs Difference Between Domestic and Overseas Sponsors

We further explored the characteristics and design elements of trials sponsored by domestic versus overseas enterprises via a cross-tabulation chi-square test to evaluate differences in various trial features. As shown in Table 3, the distribution of trial status and valence categories between domestic (n=65) and overseas (n=15) enterprises both were not significantly different (p = 0.424 and p = 0.669, respectively). However, we observed significant differences between the two groups with respect to phase, intervention, allocation, masking, geographical division of leading research sites, type of

Province	Number of leading research sites（n=80)
Eastem region **（47.5%）**	**38**
Jiangsu	19
Beijing	9
Zhejiang	4
Guangdong	3
Fujian	1
Shanghai	2
Western region **（38.75%）**	31
Guangxi	23
Sichuan	6
Yunnan	2
Central region **（13.75%）**	11
Henan	6
Hunan	3
Hubei	1
Shanxi	1

Figure 3 Geographic distribution of leading research sites by province within each region.

leading research site and clinical trial insurance (p = 0.010, p =0.000, p = 0.016, p = 0.002, p = 0.016, p = 0.002 and p = 0.019, respectively). Furthermore, no significant differences were observed for the sex distributions of the participants, participant ages or data safety monitoring committees (p = 0.256, p = 0.103 and p = 1.000, respectively).

Discussion

This analysis of clinical trial registries provides substantial information regarding the landscape of prophylactic HPV vaccine clinical trials in China. The increasing trend in the number of initiated trials in China illustrates the progress made from 2013 to 2024. The fact that the majority of the trials are categorized as Phase 3 indicates that the prophylactic HPV vaccine clinical trials in China are at a critical stage of efficacy confirmation. The majority of the trials employed a randomized, blinded, and parallel design. This reflects the principle that high-quality data originate from robust trial designs. Diversified vaccine options contributed to the implementation of China's Action Plan for Accelerating the Elimination of Cervical Cancer (2023–2030). Importantly, the common lack of a data monitoring committee (DMC) and inadequate insurance coverage provide potential targets for policy makers and sponsors to improve data quality and reduce implementation risks.

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Table 2 Study Design Elements of All Included Trials (n=80)

Category	Subgroup	N	%
Phases	Phase 1	17	21.25
	Phase 2	11	13.75
	Phase 3	36	45.00
	Phase 4	14	17.50
	Unknown	2	2.50
Intervention model	Parallel group	66	82.50
	Single-arm design	11	13.75
	Factorial analysis	3	3.75
Allocation	Randomized	54	67.50
	Non-randomized	26	32.50
Masking	Single	1	1.25
	Double	47	58.75
	None (Open label)	32	40.00
Scope	Domestic trials	80	100.00
	International trials	0	0.00
Sex of participants	Female	66	82.50
	Male	6	7.50
	Male and Female	8	10.00
Type of participants	Healthy	80	100.00
	Unhealthy	0	0.00
Age of participants	9–30	17	21.25
	18–30	9	11.25
	9–45	22	27.50
	16–45	25	31.25
	18–55	3	3.75
	25–55	2	2.50
	17-Unknown	2	2.50
Situation of combined medication	None	46	57.50
	Unknown	34	42.50

We analyzed the correlation between the number of trials and the registration year among the 80 included trials. The number of trials was significantly correlated with the registration year. Furthermore, two important inflection points occurred in 2017 and 2021. In 2017, the number of registrations was three times greater than that in 2016 since the China National Medical Products Administration officially approved the first prophylactic HPV vaccine, Cervarix, for marketing on July 18, 2016. Consequently, the first recognition by the regulatory authorities has opened the door for the development of prophylactic HPV vaccines. In 2021, the number of registrations was twice that in 2020; this finding reflects China's enterprises positive response to the Global Strategy to Accelerate the Elimination of Cervical Cancer in 2020 launched by the World Health Organization (WHO). Generally, the increase in HPV vaccine pipeline research is the result of considering market demand and global public health needs.

HPV types are categorized into HR-HPV and LR-HPV types on the basis of their oncogenic potential. HR-HPV mainly includes 14 types, namely, HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68. Of these, HPV 16 and 18 are a dominant cause of an increased risk of cervical cancer, and are associated with approximately 75% of cervical cancers worldwide.[5] LR-HPV is mainly composed of HPV 6/11.[25] We observed that except for three trials focusing exclusively on LR-HPV 6 and 11, the others all included HPV16 and 18. Increasing the valency of a vaccine leads to enhanced coverage of HR-HPV types but also comes with increased Research and Development (R&D) expenditures. Among HPV

Table 3 Trial Characteristics and Study Design According to the Domestic Pharmaceutical Sponsors and Overseas Sponsors

Category	Subgroup	Type of Sponsors		X^2	*p* value
		Domestic Enterprise (n=65)	Overseas Enterprise (n=15)		
Status	Ongoing	39 (76.47)	12 (23.53)	2.260	0.424
	Completed	24 (88.89)	3 (11.11)		
	Teminated	2 (100)	0 (0)		
Valence categories	Bivalent	21 (75)	7 (25)	4.058	0.669
	Trivalent	2 (100)	0 (0)		
	Quadrivalent	9 (90)	1 (10)		
	Nonavalent	24 (77.42)	7 (22.58)		
	Undecavalent	3 (100)	0 (0)		
	Tetradecavalent	3 (100)	0 (0)		
	Pentadecavalent	3 (100)	0 (0)		
Phases	Phase 1	17 (100)	0 (0)	13.187	0.010
	Phase 2	11 (100)	0 (0)		
	Phase 3	27 (75)	9 (25)		
	Phase 4	8 (57.14)	6 (42.86)		
	Unknown	2 (100)	0 (0)		
Intervention model	Parallel group	59 (89.39)	7 (10.61)	16.646	0.000
	Single-arm design	5 (45.45)	6 (54.55)		
	Factorial analysis	1 (33.33)	2 (66.67)		
Allocation	Randomized	48 (88.89)	6 (11.11)	6.364	0.016
	Non-randomized	17 (65.38)	9 (34.62)		
Masking	Single	1 (100)	0 (0)	12.334	0.002
	Double	44 (93.62)	3 (6.38)		
	None (Open label)	20 (62.5)	12 (37.5)		
Sex of participants	Female	53 (80.3)	13 (19.7)	2.723	0.256
	Male	4 (66.67)	2 (33.33)		
	Male and Female	8 (100)	0 (0)		
Age of participants	9–30	13 (76.47)	4 (23.53)	10.549	0.103
	18–30	8 (88.89)	1 (11.11)		
	9–45	18 (81.82)	4 (18.18)		
	16–45	21 (84)	4 (16)		
	18–55	3 (100)	0 (0)		
	25–55	2 (100)	0 (0)		
	17 -Unknown	0 (0)	2 (100)		
Geographical division of the leading site	Eastern region	26 (68.42)	12 (31.58)	8.319	0.016
	Central region	11 (100)	0 (0)		
	Western region	28 (90.32)	3 (9.68)		
	Northeastern region	0 (0)	0 (0)		
Type of the leading research site	CDCs	59 (85.51)	10 (14.49)	14.495	0.002
	Hospital	3 (100)	0 (0)		
	CDC in collaboration with Hospital	1 (100)	0 (0)		
	Others	2 (28.57)	5 (71.43)		

(*Continued*)

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Table 3 (Continued).

Category	Subgroup	Type of Sponsors		X^2	*p* value
		Domestic Enterprise (n=65)	Overseas Enterprise (n=15)		
Data Monitoring Safety Committee	Have None	20 (80) 45 (81.82)	5 (20) 10 (18.18)	0.037	1.000
Clinical Trial Insurance	Have None	24 (68.57) 41 (91.11)	11 (31.43) 4 (8.89)	6.565	0.019

Abbreviations: CDC, Center for Disease Control and Prevention.

vaccine trials, nonavalent vaccines have the highest prevalence, which may be attributed to their potentially higher protective efficacy and relatively lower R&D expenditures. The bivalent vaccine trials followed closely behind; in China, a bivalent vaccine was the first to be incorporated into the national planned immunization program in November 2025.[26] The cost-free rollout of this vaccine represents a landmark achievement in the global campaign to eliminate cervical cancer in China and worldwide.

We found that 69 (86.25%) of the 80 leading research sites were provincial CDCs rather than hospitals. In China, both tertiary hospitals and provincial CDCs certified by the administrative authority (with vaccination and clinical trial qualifications) are allowed to conduct vaccines clinical trials. However, routine vaccination is primarily implemented by CDCs and few tertiary hospitals hold vaccination qualifications. This feature restricts the implementation of vaccine clinical trials in tertiary hospitals. When developing innovative vaccines or obtaining specialized examinations, the capacity of CDCs may be inferior to that of tertiary hospitals to manage risks and perform such procedures. Therefore, it is crucial for vaccine development to appropriately expand vaccination eligibility to encompass a broader range of tertiary hospitals.

Our study revealed a markedly uneven geographical distribution of leading research sites across China, which is consistent with the findings of a previous report.[23] Nearly half of the leading research sites were geographically located in the eastern region of China, followed by the western region. The eastern region is characterized by a more advanced economy and a higher level of public acceptance of HPV vaccination. Consequently, individuals in this region demonstrate a greater willingness to participate in relevant trials than do those in other regions. Certain CDCs in the western regions demonstrate high efficiency in participant recruitment. One example is the Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention that includes numerous trial sites to enroll the target number of participants rapidly.

A DMC plays a crucial role in monitoring and evaluating the safety, efficacy and quality of clinical trials.[27] However, only approximately one-third of prophylactic HPV vaccine clinical trials were monitored by a DMC, and this value is lower than the numbers of respiratory syncytial virus (RSV) and influenza virus trials (56.7%).[28] Although the NMPA has established technical principles for prophylactic HPV vaccine clinical trials, such as recommendations for the establishment of DMCs,[29] the actual implementation of these recommendations has been relatively ineffective in practice. As the most frequently reported adverse events following immunization with prophylactic HPV vaccines are non-serious,[30] and given that these vaccines are administered to healthy populations, sponsors may not always deem it necessary to allocate resources to establish a DMC for safety review. In light of this situation, a not-for-profit, third-party quality control platform led by government regulatory agencies may be established to provid quality improvement recommendations.

Our findings indicate that fewer than half of clinical trials were covered by insurance. Notably, the insurance coverage of overseas enterprises is twice as common as that of domestic enterprises. It is plausible that the lower insurance coverage rate of domestic enterprises is associated with lower R&D investment compared to that of overseas enterprises. For example, relevant reports indicated that one overseas company's R&D investment in nonavalent HPV vaccine development is approximately six times that of a major domestic enterprise.[31,32] A robust clinical trial insurance system

can effectively prevent disputes and ensure that insured parties (including participants, investigators, research sites, etc) can make quick and successful claims. Additionally, sponsors can transfer part of the implementation risk by purchasing insurance to reduce the burden of the development of new vaccines. Thus, domestic companies should appropriately increase their R&D investment to ensure insurance coverage.

A comparison with the cross-sectional analysis data of HPV vaccine clinical trials registries from global populations indicates that China has a higher proportion of prophylactic HPV vaccines in both Phase 1 and 3 trials,[21] suggesting a later entry into the field and implying significant potential for market expansion through further investment in such trials. Domestic pharmaceutical enterprises have conducted trials across Phase 1 to 4, with a primary focus on phase III, whereas overseas enterprises sponsored only Phase 3 and Phase 4 trials. This is a direct result of the focus of most global R&D strategies, as overseas companies often complete small-sample exploratory studies in Europe and America before entering China to conduct large-sample confirmatory studies. In terms of the trial design elements for bias control, most trials adopted a randomized, double-blind, parallel-group design. Further comparative studies (Table 3) revealed that the majority of trials initiated by overseas enterprises utilized open-label, nonrandomized designs, which may be attributed to the relatively high proportion of trials in Phase 4 compared to those in this phase in China (6/15 vs 8/65). The prophylactic HPV vaccine clinical trials sponsored by both domestic and overseas enterprises were predominantly in the ongoing phase. Overall, HPV vaccine clinical trials have become more mature during the current period of efficacy confirmation. A high-quality methodological design can yield a robust evidence-based foundation for vaccine licensure and market authorization.

All trials enrolled healthy participants. The majority of trials enrolled only female participants, whereas 17.5% of the trials included males. The strong correlation between cervical cancer and high-risk HPV infection may be because most trials are conducted primarily among healthy women. Interestingly, despite the relatively low proportion, 14 trials involving men were conducted. HPV infection is considered the most common sexually transmitted disease among both males and females.[33] The prevalence of genital HPV infection in men is as high as 45.2%,[34] and most infected individuals are asymptomatic. Furthermore, owing to the lack of self-awareness, asymptomatic men may carry the virus for a long time and transmit it to female partners through sexual contact. Moreover, studies have demonstrated a significant correlation between HPV infection and the risk of urogenital tumors in males.[35,36] Therefore, developing a prophylactic HPV vaccine designed for the male population underscores the strategy of sex-inclusive prevention and is highly important for the elimination of HPV-related diseases.

Despite these valuable findings, our study has several limitations. Although trial registration on the NMPA Registration and Information Disclosure Platform is mandated by the NMPA, HPV vaccine trials conducted before 2013 might have been omitted. Additionally, the platform only includes clinical trials for drug registration purposes, excluding investigator-initiated trials. However, we also searched the Chinese Clinical Trial Registry (ChiCTR) website (https://www.chictr.org.cn) for investigator-initiated trials, and three trials were identified. One study was a duplicate trial. Another study enrolled patients with cervical intraepithelial neoplasia who have a history of HPV infection. The third study provided a comparison of the safety and efficacy of two licensed vaccines. Given that this analysis focuses on the characteristics of prophylactic HPV vaccine clinical trials designed for regulatory approval, these three studies were subsequently excluded as they did not align with this primary objective.

Conclusions

Prophylactic HPV vaccine trials in China have made progress in recent years. Approximately half of the HPV vaccine clinical trials in China are at the crucial stage of confirming the efficacy of the vaccine. Appropriately expanding vaccination eligibility to encompass a broader range of tertiary hospitals; establishing a not-for-profit, third-party quality control platform led by government regulatory agencies; and increasing R&D investment to ensure insurance coverage may accelerate the advancement of HPV vaccine clinical trials. A vaccine selection based on cost-effectiveness considerations, a recruitment-efficient clinical trial network of CDCs, and effective scientific trial design, enabled the landmark inclusion of the HPV 16/18 bivalent vaccine in China's National Immunization Program. Its current inclusion will substantially contribute to the implementation of the Global Strategy to Accelerate the Elimination of Cervical Cancer launched by the WHO.

Abbreviations

HPV, Human papillomavirus; LR-HPV, low-risk human papillomavirus; HR-HPV, high-risk human papillomavirus; NMPA, the Chinese National Medical Products Administration; CDC, Center for Disease Control and Prevention; IARC, the International Agency for Research on Cancer; NBSC, the National Bureau of Statistics of China; DMC, data monitoring committee; WHO, World Health Organization; RSV, respiratory syncytial virus; R&D, Research and Development.

Data Sharing Statement

Clinical trial data can be obtained from the NMPA Registration and Information Disclosure Platform (http://www.chinadrugtrials.org.cn). All authors have read and reviewed the manuscript.

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Disclosure

We declare no competing interests in this work.

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