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REVIEW

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Opportunities and challenges for human papillomavirus vaccination in China

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ABSTRACT

Current estimates of the HPV infection rate in China vary by geographic region (9.6–23.6%), with two age peaks in prevalence in women ≤20–25 years of age and 50–60 years of age. HPV-16, 52 and 58 are the most commonly-detected HPV genotypes in the Chinese population. In China, five HPV vaccines are licensed and several others are undergoing clinical trials. Multiple RCTs have shown the efficacy and safety of the bvHPV (Cervarix), *Escherichia coli*-produced bvHPV (Cecolin), *Pichia pastoris*-produced bvHPV (Walrinvax), qvHPV (Gardasil) and 9vHPV (Gardasil-9) vaccines in Chinese populations, including two studies showing long-term efficacy (≥8 years) for the bvHPV and qvHPV vaccines. Real-world data from China are scarce. Although modeling studies in China show HPV vaccination is cost-effective, uptake and population coverage are relatively low. Various policies have been implemented to raise awareness and increase vaccine coverage, with the long-term aim of eliminating cervical cancer in China.

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Introduction

Cervical cancer is the fourth most common cancer in women worldwide and nearly all cases are caused by chronic infection with the human papillomavirus (HPV).[1] In 2018, a global call to action toward the elimination of cervical cancer was announced by the World Health Organization (WHO).[2] This initiative aims to achieve the 90-70-70 targets by 2030, defined as 90% of girls fully vaccinated with the HPV vaccine by 15 years of age, 70% of women screened with a high-performance test two times per life by 35 and 45 years of age, and 90% of women identified with cervical disease receiving treatment and care. However, HPV vaccination population coverage in China is currently relatively low due to multiple factors including low public knowledge of HPV, limited supply, cost and because the vaccine is not currently included in the national immunization program. Therefore, reviewing and understanding the current situation for HPV vaccination in China is highly valuable.

More than 200 types of HPV have been identified to date and, of these, 15 have been associated with the development of cervical cancer [types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82].[1] Vaccination against HPV is a major preventative strategy for cervical cancer[1] and several vaccines are currently licensed for use based on efficacy and safety data from clinical trials.[3] Current HPV vaccines are described as bivalent (bvHPV – targeting HPV-16 and 18), quadrivalent [qHPV – targeting HPV-6, 11, 16 and 18] or 9-valent [9vHPV – targeting HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58].[3]

To date, the U.S. Food and Drug Administration (FDA) has licensed a bvHPV vaccine (AS04-HPV-16/18, Cervarix®, GSK), a qvHPV vaccine (Gardasil®, MSD), and a 9vHPV vaccine (Gardasil® 9, MSD).[4] These three vaccines plus an independently developed bvHPV vaccine (Cecolin, Xiamen Innovax Biotech Co, Ltd) are all included in the WHO List of Prequalified Vaccines[5] and have been approved by the China National Medical Products Administration (NMPA).[6] In addition, a second independently developed bvHPV vaccine (Walrinvax™, Shanghai Zerun Biotechnology Co., Ltd.) has been approved by the NMPA (Table 1).[6] Multiple additional HPV vaccines are currently under development in China, including a qvHPV vaccine, several 9vHPV vaccines, an 11vHPV vaccine, and a 14vHPV vaccine (Table 2).

In this article, we identify and review recent literature on HPV vaccination in China, with a focus on the epidemiology of HPV infection and the performance of HPV vaccines in Chinese populations. Furthermore, studies describing the barriers to HPV vaccination in China are reviewed and policies aimed at overcoming vaccine hesitancy are highlighted.

Literature search methodology

A narrative literature search was performed to identify recently published data on the epidemiology of HPV infection in China, the efficacy, effectiveness and safety of HPV vaccines in Chinese populations and the cost effectiveness of HPV vaccination in China. PubMed and Chinese-language databased were searched on 12 September 2023 and 3 January 2024, respectively, using the following search string: ((human papillomavirus[Title/Abstract] OR HPV[Title/Abstract]) AND (vaccine[Title/Abstract] OR vaccination[Title/Abstract])) AND (China[Title/Abstract] OR Chinese[Title/Abstract]). Articles published between January 2021 and December 2023 were reviewed for inclusion in this article. These dates were selected to avoid overlap with prior

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Table 1. HPV vaccines currently approved in China.

	Cervarix	Gardasil	Gardasil-9	Cecolin	Walrinvax
Manufacturer	GlaxoSmithKline (UK)	Merck, Sharp and Dohme (USA)	Merck, Sharp and Dohme (USA)	Xiamen Innovax Biotech (China)	Yuxi Zerum Biotechnology (China)
Valency	Bivalent	Quadrivalent	9-valent	Bivalent	Bivalent
HPV type targeted	HPV-16/18	HPV-6/11/16/18	HPV-6/11/16/18/31/33/45/52/58	HPV-16/18	HPV-16/18
Launch date in mainland China	2016	2017	2018	2020	2022
Recombinant expression system	Insect Cell-Baculovirus	Saccharomyces cerevisiae	Saccharomyces cerevisiae	Bacillus coli	Pichia pastoris
Indications (mainland China)	• Cervical cancer, CIN2/3, AIS, CIN1 caused by HPV-16/18	• Cervical cancer, CIN2/3, AIS, CIN1 caused by HPV-16/18	• Cervical cancer caused by HPV-16/18/31/33/45/52/58 • CIN2/3, AIS, CIN1, and persistent infections caused by HPV6/11/16/18/31/33/45/52/58	• Cervical cancer, CIN2/3, AIS, CIN1, and persistent infections caused by HPV16/18	• Cervical cancer, CIN2/3, AIS, caused by HPV16/18
Recommended vaccination schedule	• 9–14 years old: 2 doses (0 and 6 months) • 15–45 years old: 3 doses (0, 1 and 6 months)	• 3 doses (0, 2 and 6 months)	• 3 doses (0, 2 and 6 months)	• 9–15 years old: 2 doses (0 and 6 months) • 16–45 years old: 3 doses (0, 1 and 6 months)	• 9–14 years old: 2 doses (0 and 6 months) • 15–30 years old: 3 doses (0, 1 and 6 months)
Eligible age and sex (mainland China)	Females aged 9 – 45 years	Females aged 9 – 45 years	Females aged 9 – 45 years	Females aged 9 – 45 years	Females aged 9 – 30 years

AIS, Adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

reviews of HPV vaccination and focus on the most recent data. The articles identified by literature searching were filtered manually by reviewing the titles and abstracts using the following inclusion criteria: (1) studies reporting data collected in China, (2) studies reporting epidemiology of HPV infection in China, (3) clinical studies reporting the efficacy, effectiveness and safety of HPV vaccines in Chinese populations, (4) real-world studies of HPV vaccination in China, (5) articles on HPV vaccination knowledge, attitudes and practices and (6) cost effectiveness studies. If multiple studies were identified for the same topic, the references were evaluated for scientific robustness and risk of bias and the highest quality evidence was selected (Supplemental Figure 1). Exclusion criteria included: (1) review articles, (2) clinical studies reporting low quality data (small patient numbers, single center studies, single region studies) (3) real-world studies not conducted in China. Additional relevant articles were identified from the bibliographies of the selected articles.

The prevalence of HPV infection and genotype distribution in Chinese women

In China, cervical cancer is the fourth most common cancer among women, with approximately 110,000 new cases and 60,000 associated deaths reported per year.[9] There has been year-on-year growth in the incidence and mortality of this disease, with the National Cancer Center of China reporting an 8.5% annual increase in incidence and a 5.4% increase in mortality between 2000 and 2016.[10] In addition, other cancers such as anal cancer, oropharyngeal cancer, penile cancer, vaginal cancer, laryngeal cancer, oral cancer, and vulvar cancer are also associated with HPV infection.[11]

The HPV infection rate in Chinese women varies across different regions, with estimates ranging from 9.6% to 23.6%.[12–23] In general, these rates are high compared with the global rate of HPV infection.[24] In addition, studies in several regions of China have shown two age peaks in the prevalence of high-risk HPV infection; in younger women (around ≤20–25 years of age) and older women (around 50–60 years of age).[12,17,25]

HPV-16 and −18 are the most commonly detected types of HPV infection in patients with cervical cancer in China, and are detected in as many as 69.1% of patients.[26,27] However, non-HPV -16 or −18 infections are also commonly detected in patients with cervical cancer or cervical abnormalities.[28] Multiple recent studies conducted across China have demonstrated that HPV-16, −52 and −58 are the most prevalent HPV genotypes, both in women with cervical abnormalities and women undergoing routine cervical screening or physical examination.[12–14,16,21–23,27,29–36] Of note, the HPV-52/58 infection rate is higher in China compared with the global rate; for women with low-grade cervical lesions, the incidence of HPV-52/58 infection in China is 28.6% compared with 15.6% worldwide. Similarly, for women with high-grade cervical lesions, the incidence of HPV-52/58 infection is 33.3% versus 19.1% for China versus worldwide. For women with cervical cancer, HPV-52/58 infection is detected in 14.7% of cases in China compared with 7.4% worldwide.[27,37]

Clinical studies of HPV vaccines in China

Pivotal, international, randomized controlled trials (RCTs) have demonstrated the efficacy and safety of the bvHPV[38–40] qvHPV[41,42] and 9vHPV[43] vaccines, including in subgroup analyses of participants from Asia who received the 9vHPV vaccine.[44]

Several RCTs of bvHPV vaccines have been performed in China. In a phase II/III RCT of the bvHPV vaccine (Cervarix) in Chinese participants, 87.3% vaccine efficacy against HPV-16/18-associated cervical intraepithelial neoplasia (CIN)2+ was

Table 2. HPV vaccines under development in China.

Manufacturer	HPV type targeted	Recombinant expression system	ClinicalTrials.gov ID	Phase	Population	Outcomes	Status
qvHPV							
Chongqing Bovax Pharmaceutical Co Ltd	6/11/16/18	Hansenula polymorpha	NCT03085381	Phase 1	Chinese females aged 9–45 years ($n = 90$)	Safety, immunogenicity	Complete
			NCT04425291	Phase 3	Chinese females aged 20–45 years ($n = 560$)	Safety, immunogenicity	Complete[7]
9vHPV							
Shanghai Bovax Biotechnology Co., Ltd	6/11/16/18/31/33/45/52/58	Hansenula polymorpha	NCT04425291	Phase 3	Chinese females aged 20–45 years ($n = 560$)	Safety, immunogenicity	Complete[7]
			NCT04422366	Phase 3	Chinese females aged 20–45 years ($n = 8000$)	Efficacy, safety, immunogenicity	Recruiting
			NCT04895020	Phase 3	Chinese females aged 9–19 years vs 20–45 years ($n = 1200$)	Immunobridging	Recruiting
			NCT05518201	Phase 1	Chinese males aged 9–45 years ($n = 8000$)	Safety, immunogenicity	Recruiting
Xiamen Innovax Biotech Co., Ltd	6/11/16/18/31/33/45/52/58	Escherichia coli	NCT03813940	Phase 1	Chinese females and males aged 18–45 years ($n = 27$)	Safety. Immunogenicity	Complete[8]
			NCT04537156	Phase 3	Chinese females aged 18–45 years ($n = 9237$)	Efficacy, safety, immunogenicity	Active
			NCT05056402	Phase 3	Chinese females aged 9–17 years vs 18–26 years ($n = 1382$)	Immunobridging	Active
Beijing Health Guard Biotechnology, Inc	6/11/16/18/31/33/45/52/58	Escherichia coli	NCT05668572	Phase 3	Chinese females aged 20–45 years ($n = 12,000$)	Efficacy, safety, immunogenicity	Active
			NCT05662020	Phase 3	Chinese females aged 9–26 years ($n = 2750$)	Safety, immunogenicity	Active
Walvax Biotechnology Co., Ltd	6/11/16/18/31/33/45/52/58	Pichia Pastoris	NCT05580341	Phase 3	Chinese females aged 16–26 years ($n = 1200$)	Safety, immunogenicity	Active
Jiangsu Recbio Technology Co., Ltd.	6/11/16/18/31/33/45/52/58	Hansenula polymorpha		Phase 3	n = 16,050	Efficacy, safety, immunogenicity	Active
11vHPV							
National Vaccine and Serum Institute, China	6/11/16/18/31/33/45/52/58/59/68	Hansenula polymorpha	NCT05262010	Phase 3	Chinese females aged 9–45 years ($n = 13500$)	Efficacy, safety, immunogenicity	Recruiting
14vHPV							
Sinocelltech Ltd.	6/11/16/18/31/33/35/39/45/51/52/58/59/68	Insect cells (SCT1000)	NCT04921111	Phase 1	Chinese females aged 18–45 years ($n = 240$)	Safety, immunogenicity	Recruiting
			NCT05060484	Phase 2	Chinese females aged 18–45 years ($n = 1800$)	Safety, immunogenicity	Recruiting

HPV, human papillomavirus.

demonstrated up to Month 72 in the according-to-protocol cohort.[45] Moreover, no fatal events or vaccine-related serious adverse events (SAEs) or congenital abnormalities were reported in the vaccine group. Similarly, in a phase III RCT conducted at five sites in China, the *Escherichia coli*-produced bvHPV vaccine (Cecolin) was shown to be 100% efficacious against HPV-16/18-associated high-grade genital lesions and 97.3% efficacious against persistent HPV infection after 66 months of follow-up. No SAEs related to vaccination were reported in this study.[46] The *Pichia pastoris*-produced bvHPV vaccine (Walrinvax) has also been investigated in clinical trials in Chinese participants. In a phase I RCT in Chinese women aged 9–45 years, immune responses were elicited in 100% of participants and no SAEs were reported.[47] In addition, in a Phase III RCT conducted in China in females aged 18–30 years, efficacy for HPV-16/18-related CIN2+ was 78.6% after 48 months of follow-up.[6,48]

The qvHPV vaccine (Gardasil) has also been studied in clinical trials in Chinese participants. In an RCT conducted in Chinese males (9–15 years) and females (9–45 years), high antibody levels were observed for each of the four HPV types and seroconversion was >96%. The vaccine was well-tolerated, with no vaccine-related SAEs reported.[49] Furthermore, in a phase III RCT that included 3006 Chinese women, the qvHPV vaccine was 100% efficacious against HPV-16/18-related CIN2 or 3 and cervical cancer and 100% efficacious against HPV-6/11/16/18-related CIN1 over a 78-month follow-up. Efficacy against 6-month and 12-month persistent cervical infection was 91.6% and 97.5% at Months 30 and 78, respectively.[50] No vaccine-related SAEs were reported and pregnancy outcomes were similar between the vaccine and placebo groups and within normal ranges.[51] In a prospective open-label study conducted in China, the qvHPV vaccine also reduced the risk of high-grade squamous intraepithelial lesion recurrence after loop electrosurgical excision of CIN2+ disease. In this study, CIN2+ recurrence rates were ~12-fold higher in unvaccinated versus vaccinated women (OR = 12.25, 95% CI 1.919–79.492, $p = .008$).[52]

A phase III open-label study conducted in China demonstrated that antibody responses to the 9vHPV vaccine (Gardasil-9) were non-inferior in participants aged 9–19 years and 27–45 years compared to those aged 20–26 years.[53] In this study, the vaccine was well-tolerated and there were no vaccine-related SAEs, discontinuations due to AEs or deaths. A 9vHPV vaccine produced in *E. coli* is also under development in China (Xiamen Innovax Biotech Co., Ltd). In a phase I clinical trial, this vaccine was shown to be well-tolerated and immunogenic.[8]

In a meta-analysis of 11 RCTs and 4 follow-up studies including Chinese patients, HPV vaccines were shown to reduce the incidence of CIN1+ and CIN2+. The risk of SAEs was comparable between the vaccinated and placebo arms.[54]

Long-term efficacy and safety of HPV vaccines

Multiple studies have shown long-term efficacy (after a follow up of ≥8 years) for HPV vaccines in preventing HPV-related disease, including two studies that were conducted in China (Table 3). For the bvHPV vaccine (Cervarix), two long-term follow-up studies (10–11 years) in patients in Costa Rica and Finland demonstrated high efficacy against HPV-16/18-associated disease[56,57] and no vaccine-related SAEs were reported.[56] Four studies have evaluated the efficacy and safety of the qvHPV vaccine (Gardasil) in participants worldwide. These studies followed the participants for 10 to 14 years and reported 100% efficacy against HPV-associated disease.[57–59,61] Two of these studies reported long-term safety data, with no vaccine-related SAEs[59] or new safety events[61] occurring. Finally, no new cases of HPV-16/18/31/33/45/52/58-related high-grade cervical dysplasia were observed in participants from Denmark, Norway and Sweden during an 8-year follow-up to the pivotal 9vHPV (Gardasil-9) efficacy study.[63]

In China, long-term studies have been conducted for the bvHPV vaccine (Cervarix) and the qvHPV vaccine (Gardasil). In a 10-year follow-up study of Cervarix in 1791 Chinese women, vaccine efficacy was 97.2%, 94.8% and 90.5% against HPV-16/18-associated atypical squamous cells of undetermined significance, CIN1+ and CIN2+, respectively.[55] There were also no vaccine-related SAEs, immune-mediated diseases or adverse pregnancy outcomes reported. In an eight-year follow-up study of Gardasil in 368 Chinese female participants, vaccine efficacy against HPV-16/18-associated CIN, vulval intraepithelial neoplasia or vaginal intraepithelial neoplasia was 100%.[60]

Real-world data for HPV vaccines

Real-world effectiveness

Multiple real-world studies have demonstrated the effectiveness of HPV vaccines. However, there is currently a lack of real-world data on the effectiveness of HPV vaccines in Chinese populations. A comprehensive global meta-analysis that included data from over 60 million people following vaccination with either bv or qvHPV vaccines demonstrated a substantial impact of vaccination on rates of HPV infections and HPV-associated disease. Notably, 51% and 31% reductions in the incidence of CIN2+ among females aged 15–19 years and 20–24 years, respectively, were observed 5–9 years after vaccination.[64] Similarly, a systematic review of global real-world data for qvHPV vaccination revealed a significant reduction in the prevalence of HPV type 6/11/16/18 infection in females aged 14–19 years and a reduction in genital infections and HPV-related disease outcomes following the introduction or expansion of HPV vaccination programs.[65]

Several real-world studies have specifically shown that HPV vaccination programs offer protection against the development of CIN2+ or cervical cancer. For example, vaccination with the bvHPV (Cervarix) vaccine at age 14–17 years resulted in a reduction in the detection of CIN2+ from 6% to 3% during routine cervical screening at age 24–25 years in women in the UK (estimated vaccine effectiveness of 87%).[66] Similarly, in a systematic review of real-world studies conducted in Canada, vaccination with the qvHPV vaccine was associated with an up to 86% reduction in the incidence of CIN2+,[67] and in Denmark, a 73% reduction in the incidence of CIN2/3 was observed in females vaccinated with the qvHPV vaccine compared with non-vaccinated females (1993–1994 birth cohort).[68] In a real-world study conducted in the USA, there was a 72% decrease in the proportion of CIN2+ attributable to HPV16/18 in women who had received a HPV vaccine more than 48 months before their diagnosis of CIN2+.[69] In Sweden, the qvHPV vaccine was

Table 3. Long-term safety and efficacy of HPV vaccines.

Citation	Study	Countries (number of participants*)	Length of follow-up	Efficacy data	Safety data
bvHPV vaccine (Cervarix)					
Zhao 2023[55]	NCT03629886	China ($n = 1791$)	10 years	• 92.7% efficacy vs HPV-16/18 ASC-US+ • 94.8% efficacy vs HPV-16/18- CIN1+ • 90.5% efficacy vs HPV-16/18-CIN2+	No vaccine-related SAEs, immune-mediated diseases or adverse pregnancy outcomes
Porras 2020[56]	Costa Rica Vaccine Trial (NCT00867464)	Costa Rica ($n = 2073$)	11 years	• 90.5% efficacy vs HPV-16/18-CIN2+ • 94.9%% efficacy vs HPV-16/18-CIN3	No vaccine-related SAEs or deaths
bvHPV vaccine (Cervarix) and qvHPV vaccine (Gardasil)					
Lehtinen 2021[57]	PATRICIA (NCT00122681) 012 (NCT00169494) FUTURE II (NCT00092534)	Finland ($n = 3341$)	11 years	• 100% efficacy vs all HPV-positive cancers	Not reported
qvHPV vaccine (Gardasil)					
Kjaer 2020[58]	FUTURE II (NCT00092534)	Denmark, Iceland, Norway, Sweden ($n = 2121$)	14 years	• 100% efficacy vs HPV-16/18-related CIN2	Not reported
Maldonado 2022[59]	FUTURE III (NCT00090220)	Colombia ($n = 529$)	10 years	• 100% efficacy vs HPV-6/11/16/18-related CIN or condyloma reported	No vaccine-related SAEs reported
Zhao 2022[60]	NCT00834106	China ($n = 368$)	8 years	• 100% efficacy vs HPV-16/18-related cases of CIN, VIN, or VaIN in the vaccine group	Not reported
Ferris 2017[61]	V501-018 (NCT00092547)	International ($n = 528$)	10 years	• 100% efficacy vs cases of HPV-6/11/16/18–related diseases were observed	No new safety events reported
9vHPV vaccine (Gardasil 9)					
Kjaer 2021[7]	V503-001 (NCT00543543)	Denmark, Norway, Sweden ($n = 1448$)	8 years	• 100% efficacy vs HPV-16/18/31/33/45/52/58-CIN2+	Not reported
Restrepo 2023[62]	V503-002 (NCT00943722)	International ($n = 1272$)	10 years	• 81.3–97.7% seropositivity to targeted HPV types • No cases of cancers related to the targeted HPV types	No vaccine-related SAEs were reported

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; SAE, serious adverse event; VaIN, vaginal intraepithelial neoplasia; VIN, vulval intraepithelial neoplasia.

associated with an 88% and 53% reduction in the risk of cervical cancer among women who had been vaccinated before the age of 17 years or from 17–30 years, respectively.[70]

Real-world safety

The safety profile of HPV vaccinations observed in the pivotal clinical trials has been confirmed in several real-world studies.[71,72] The HPV vaccines are mainly associated with non-serious AEs, with observational data from the USA showing dizziness and syncope being among the most commonly reported events.[73] In China, the safety of the HPV vaccines was confirmed in a surveillance study, where the rates of vaccine-related reactions were only 4.00 and 3.46 per 100,000 doses following administration of the qvHPV and 9vHPV vaccines, respectively.[74] Similarly, in a post-marketing surveillance study of the 9vHPV vaccine in China, no safety signals were observed and no stillbirths were reported among 41,609 women who received the vaccine between 2019 and 2021.[75]

Current status of HPV vaccine use in China

In China, HPV vaccination is voluntary and self-paid[76] and is administered by the Chinese Center for Disease Control and Prevention. However, HPV vaccination is not included in the national immunization program and supply remains limited and costly.[77] In addition, HPV vaccines are only approved for females, with RCTs in males ongoing. The vaccine is also only approved for the prevention of cervical cancer, precancerous lesions and HPV persistent infection, and not for other HPV-related diseases. As a result of these limitations, population coverage is currently low, with only 3% of females vaccinated three years after HPV vaccine licensure in China.[78] In addition, as of 2022 there was no HPV vaccination program for males, which limits the ability to achieve herd immunity.[79]

Several policies have been implemented in order to increase vaccination rates. These include the China Action Plan for Accelerated Elimination of Cervical Cancer (2023–2030),[80] and free HPV vaccination pilot studies in some provinces.[76,81] For example, driven by the Healthy City innovation pilot policy, multiple cities in China are carrying out government-led HPV vaccination programs based on local requirements and conditions. Cities participating include Ordos City in Inner Mongolia, Xiamen City in Fujian Province, Jinan City in Shandong Province, Wuxi City in Jiangsu Province, and Chengdu City in Sichuan Province.[82–87] The majority of these cities are utilizing a two-dose vaccination schedule for girls in middle school (aged 13–14

years). In addition, it has been reported that six Chinese provinces have decided to provide free vaccinations for eligible women. Recent years have also seen the publication of several technical papers, including "Expert consensus on immunological prevention of human papillomavirus-related diseases,"[88] "Chinese experts consensus on the clinical application of HPV vaccine"[89] and "China Tertiary Prevention for Cervical Cancer (Blue Book)." Multiple Chinese-language treatment guidelines and consensus statements have also been published, all of which emphasize the effectiveness and safety of the HPV vaccine.[90–94] Multiple HPV vaccines are also currently under development in China (Table 2).

HPV vaccination knowledge, attitudes and practices

Since the introduction of the HPV vaccine programs in China, knowledge, attitudes and practices toward HPV vaccination have been studied extensively. Multiple recent studies have indicated that low levels of knowledge of cervical cancer and the HPV vaccine persist among young adults and also among the mothers of daughters who are eligible for the vaccine.[95–100] One Chinese-language systematic review article published in 2022 estimated that the total awareness rate of HPV among the Chinese population is 65.9%, with high variability by geographic region.[101] Another study of 13,914 child-bearing women in China conducted between 2009 and 2016 revealed that only 24.1% had heard of the HPV vaccine and of these 76.1% reported willingness to receive the vaccine; reasons for lack of intention to vaccinate included low knowledge of the risks of HPV infection (52.7%) and concerns around safety (30.3%) and efficacy (31.7%).[102] Levels of knowledge can also vary among healthcare professionals (HCPs), with a study conducted in Shenzhen revealing that HPV and HPV vaccine knowledge varied between different types of medical institutions, with the lowest scores achieved by private hospitals.[103] The authors concluded that private clinics, non-physician HCPs and HCPs with a low annual income were most in need of further education and training. A cross-sectional study in Shanghai, Guangzhou and Shenzhen also reported that only 30% of HCPs were frequently recommending HPV vaccination to patients.[104]

Despite low levels of knowledge around HPV vaccines, a high willingness toward vaccination has been reported among Chinese females, both of themselves (92.8–93.6%) and their daughters (83.3%).[98,99,105] Although, it should be noted that in several online surveys discrepancies between high HPV vaccine intent and low uptake have been observed.[106,107] Lower maternal education, rural residence, inadequate knowledge of HPV or the HPV vaccine, costs of the vaccine, and household income have frequently been identified as barriers to HPV vaccination.[108–111] In contrast, facilitators of vaccination included vaccine information from reliable sources, a vaccination program arranged by schools and the government, and recommendations from HCPs.[109]

The introduction of the 9vHPV vaccine may have increased interest in HPV vaccination amongst the Chinese population. For example, in an online cross-sectional survey of mothers of primary school-aged children in China, over one third (41.4%) expressed a preference for their daughter to be vaccinated with the 9vHPV vaccine.[105] Similarly, in a nationwide, cross-sectional study of 15,967 female healthcare workers, 58.6% preferred to receive the 9vHPV vaccine.[112] Moreover, after the expansion of the indication for the 9vHPV vaccine in China to women aged 9–45 years, vaccine non-coverage decreased from 83.3% to 57.6% in a study conducted in Wuhan.[12] There is also a high willingness to pay for the 9vHPV vaccine in China, as evidenced by a nationwide online survey among 15,969 female healthcare workers in which 66.2% of respondents indicated willingness to pay 800–1200 RMB for HPV vaccination.[113] However, when China's provinces (including autonomous regions and municipalities) provide free HPV vaccination for adolescent girls, they usually include only the bvHPV or qvHPV vaccines, as they have a lower cost compared to the 9vHPV vaccine. In addition, the increased demand and preference for the 9vHPV vaccine among Chinese women is coupled with supply issues. These factors can cause a barrier to vaccination and lead to vaccination delays. However, efforts are being made to improve the supply of the 9vHPV vaccine in China.

Cost-benefit of HPV vaccination

Several studies have indicated that HPV vaccination is likely to be cost-effective in China. However, it should be noted that there is no established cost-effectiveness threshold used in China, and various thresholds are utilized. For example, the cost-effectiveness of HPV vaccination was assessed nationally and in 31 provinces in China in 2019 using the Papillomavirus Rapid Interface for Modeling and Economics (PRIME) model.[114] The results showed that a total of 12,545 cervical cancer cases and 5109 deaths could be averted by use of the bvHPV and qvHPV vaccines. This increased to 28,140 cases and 11,459 deaths averted after use of the 9vHPV vaccine. Overall, inclusion of HPV vaccination in the immunization program was considered to be cost-effective at a national level and in most provinces, with a maximum cost of $18,165 USD per disability-adjusted life-year (DALY) gained which was below the threshold for cost effectiveness of three times GDP per capita ($30,837 US).[114] Furthermore, a systematic review of modeling studies indicated that the HPV vaccine was generally cost-effective in China, across 14 studies using various methodologies and thresholds for cost-effectiveness.[115] When specifically considering women who have previously been treated for HPV-related cervical precancerous lesions, a three-dose qvHPV vaccine was predicted to be highly cost-effective in China, with an Incremental Cost-Effectiveness Ratio (ICER) of $27,785USD per quality-adjusted life year (QALY) gained.[116] In a model-based economic evaluation, the use of an optimal pathway that integrates tailored optimal strategies for different birth cohorts is predicted to eliminate cervical cancer in China by the late 2040s and would result in savings in net economic costs, with a discounted ICER of $-339 (95% CI −687 to −79) per QALY.[117] A Chinese-language systematic review of 15 pharmacoeconomic studies concluded that HPV vaccination plus cervical cancer screening is more cost effective than screening alone, although the study found variability in cost-benefit between the different types of HPV vaccination.[118]

Expert commentary

Cervical cancer is the fourth most common cancer in women. Cervical cancer in China accounts for 18% of new cases and 17% of cervical cancer related deaths globally. In this article we reviewed the epidemiological characteristics of HPV infection in China, summarized the results of randomized controlled trials of HPV vaccines conducted in China, and evaluated available data from real-world research and cost-effectiveness studies. Overall, our review confirms that vaccination with HPV vaccine is the most effective way to prevent cervical cancer in China.

In order to protect and promote women's health, China has responded to the WHO's call to accelerate the elimination of cervical cancer and has taken numerous measures to promote HPV vaccination, including releasing specific plans to eliminate cervical cancer, promulgating relevant guidelines and consensus statement, and waiving or subsidizing the cost of HPV vaccination for teenagers in pilot areas. The WHO's current position paper on HPV vaccination schedule states that a single-dose schedule, referred to as an alternative, off-label single-dose schedule, can provide comparable efficacy and durability of protection to a two-dose regimen.[119] Once the China NMPA approves a single-dose indication for the HPV vaccine, we predict it will promote increased vaccination uptake and increase the vaccination rate. However, more Chinese research data are still required to confirm the long-term effectiveness of single-dose HPV vaccines. At the same time, in addition to the five HPV vaccines already on the market, China is developing multiple novel HPV vaccines, with several candidate vaccines currently entering phase 3 trials. The successful launch of locally developed HPV vaccines may help to solve supply problems and increase the vaccination rate. These measures will bring great opportunities for HPV vaccination in China.

However, despite current efforts and initiatives, HPV vaccination in China still faces many challenges. For example, the HPV vaccination rate in China is still very low, and there is also a problem of insufficient vaccine supply. In addition, HPV vaccines have not yet been included in the national immunization program and are paid for out-of-pocket, representing a significant expense for most Chinese people. Public awareness of HPV-related diseases and HPV vaccines is also insufficient. These specific challenges are superimposed against a large national population with an uneven distribution of economic development. In areas of China with limited health resources, strong government support is required to promote HPV vaccination. In summary, there is a need to continue to vigorously strengthen health education for the Chinese population, expand the production of HPV vaccines, and promote the application of HPV vaccines in China.

In conclusion, in China, a lot of work remains to meet the goal of eliminating cervical cancer. In developing strategic plans to eliminate cervical cancer, the prevalence of HPV infection and cervical cancer should be continuously monitored to assess the effectiveness of preventive measures, including HPV vaccination. Since China has a large population and the cost of the HPV vaccine is relatively high for most Chinese citizens, the government should also consider economic cost-effectiveness when funding HPV vaccination programs and consider the accessibility and equity of HPV vaccination for women of an appropriate age across different geographic regions.

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Author contributions statement

Chao Zhao conducted the literature search and interpreted the findings, wrote sections of the initial draft and provided substantial intellectual contributions to the subsequent drafts. Yun Zhao conducted the literature search, interpreted the findings and provided substantial intellectual contributions during revision of manuscript drafts. Jingran Li, and Mingzhu Li interpreted the findings and provided substantial intellectual contributions during the revision of manuscript drafts. Yujing Shi conceived and planned the review, conducted the literature search, wrote sections of the initial draft and provided substantial intellectual contributions during revision of manuscript drafts. Lihui Wei conceived and planned the review, interpreted the findings and provided substantial intellectual contributions during revision of manuscript drafts. All authors reviewed and approved the final submitted version and agree to be accountable for all aspects of the work after publication.

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Yujing Shi is employee of MSD China. All the other authors have no conflict of interest to declare.

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