



# Elimination of Cervical Cancer: Challenges Promoting the HPV Vaccine in China

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## Abstract

**Objective** Cervical cancers present major threats to women's health in China. Eliminating cervical cancer in China is a huge challenge, with application of the HPV vaccine, which is an important part.

**Methods** There are currently four HPV vaccines available in China: *E-coli* bv-HPV (Wantai, China), bv-HPV, qv-HPV (GSK, UK), and 9v-HPV (MSD, USA). To observe the immunogenicity, efficacy, and safety of these four vaccines in China, we formed the “Chinese Expert Consensus on the Clinical Application of HPV Vaccine.”

**Results** At 7 months after vaccination, all vaccinated subjects had the same immunogenic response to either HPV16 or HPV18, ranging from 96 to 100%, and antibody production in girls aged 9–14 years was 2–3 times higher than that in adult women. Efficacy of the four vaccines against CIN2 + ranged from 87.3% to 100%, with prevention of HPV-associated infection reaching 96% ~ 97% at 12 months. Clinical trials showed bv-HPV and qv-HPV vaccine were also safe in women aged 18–45 years. Clinical trials of the 9v-HPV vaccine are underway. HPV vaccination is currently voluntary and self-paid in China. The “Chinese Expert Consensus on the Clinical Application of HPV Vaccine” will work to promote the application of HPV vaccine in China.

**Conclusions** In clinical studies, the available HPV vaccines showed excellent efficacy, safety, and immunogenicity in Chinese women. We will continue strengthening screening and encouraging HPV vaccination.

**Keywords** HPV vaccine · Efficacy · Safety · Expert consensus

## Introduction

Cervical cancer is the most common malignant tumor in women and poses a significant threat to the health of Chinese women [1, 2]. The “Global strategy to accelerate the elimination of cervical cancer as a public health problem” was released at the WHO in November 2020 [3]. Elimination of cervical cancer by promoting the use of HPV vaccine is an important step.

HPV vaccines have been used globally for more than 10 years, and the efficacy of these vaccines, particularly in

adolescent women, has been shown to be effective in reducing the incidence of HPV infection and CIN2 +, according to international data [4]. Promoting the use of the HPV vaccine is a health challenge for China.

## Characteristics of HPV Infection in Chinese Women

Among Chinese adult women, the rate of HR-HPV infection is 19.4% by opportunistic screening in hospitals [5], and is 15.0% by general population [6]; HR-HPV infection rate of women aged 15–19 years (who have had sexual experience) has reached 31% [7]. Among HR-HPV positive cases, 72% were infected with single HPV type, < 20% were infected with two HPV types, and < 8% were infected with three or more HPV types [8]. Age-specific

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HPV prevalence peaked at two age groups in Chinese women (17–24 y and 40–44 y) [9]. These data show that HPV vaccination in China is a necessary prevention method for adolescents and can also be effective for adult women.

## Clinical Trial Results for HPV Vaccines in China

From 2016, four kinds of HPV vaccines have been approved in China [10–12] (Table 1).

### Immunogenicity of HPV Vaccines

In clinical trials in China, at 7 months after vaccination immunogenicity (96% to 100%) was observed after vaccinating women (ages 9–45y), regardless of which vaccine was used. After vaccination, antibody titers produced were 2 to 3 times higher in the younger age group than in older age group [10–12]. With the *E-coli* bv-HPV vaccine, immune response (IgG) was achieved after 2 or 3 doses in women aged 9–14y, but required 3 doses in women 18–26y. In women 9–14y, the neutralizing antibody level was higher after 2 doses than in women 18–26y after receiving 3 doses [13].

### Efficacy of HPV Vaccines

Efficacy of the four vaccines against CIN2 + was 87.3–100%. Prevention of HPV-associated infection reached 96–97% at 12 months in clinical trials of the *E-coli*-bv-HPV, bv-HPV, and qv-HPV vaccines [10–12]. Clinical trials of the 9v-HPV vaccine are underway in China.

## Safety of HPV Vaccines

Adverse events such as inoculation site side effects or systemic reactions may occur after vaccination from four types of HPV vaccine showed similar safety in clinical trials (Table 2). All four vaccines caused primarily local reactions, mostly presenting as transient mild reaction (> 10%) and moderate symptoms (1–10%). The most common local reactions were pain, erythema, and swelling. Systemic reactions included fever, headache, dizziness, muscle pain, arthralgia, and gastrointestinal symptoms (nausea, vomiting, or abdominal pain). No suspension of vaccination was required due to serious adverse events related to the vaccine; the rates of serious adverse events were comparable between the vaccine and placebo groups.

## Challenges to HPV vaccination in China

Currently in China, vaccination is administered by the CDC, and the effects are observed by clinicians. The principle of voluntary and self-paid inoculation is used. The main reason is the high price of HPV vaccine in China, with the supply of vaccine insufficient, and the vaccine is not listed in the national immunization program. More education, research and development of HPV vaccines, expanded production, and promotion of the application of HPV vaccines in China are required.

## Chinese Experts Consensus on the Clinical Application of HPV Vaccines

The Vaccine and Immunization Branch of Chinese Preventive Medical Association organized Chinese experts to discuss the etiology and related diseases of HPV and the

**Table 1** Four types HPV vaccines approved in China

Project	<i>E-coli</i> -bv-HPV vaccine	bv-HPV vaccine	qv-HPV vaccine	9v-HPV vaccine
Production enterprise	INNOVAXi, China	GSK, UK	MSD, USA	MSD, USA
Approved time	–	2007	2006	2014
Approved time in China	2019.12	2016.7	2017.5	2018.4
Prevention of HPV types	HPV 16/18	HPV 16/18	HPV 6/11/16/18	HPV 6/11/16/18/31/33/45/52/58
Prevent HPV infection-related diseases (approval by China)	Cervical cancer, CIN1,CIN2/3,AIS, HPV16/18 persistent infection	Cervical cancer, CIN1, CIN2/3,AIS	Cervical cancer, CIN1, CIN2/3,AIS	Cervical cancer, CIN1, CIN2/3,AIS,9 HPV-associated subtypes of infection
Age of women vaccinated in China	9–45 y	9–45 y	9–45 y	16–26 y
Expression system	<i>E-coli</i>	Baculovirus	Saccharomyces cerevisiae	Saccharomyces cerevisiae
Vaccination schedule	0 M,1 M, 6 M (9–14 y: 0 M, 6 M)	0 M,1 M, 6 M	0 M, 2 M, 6 M	0 M, 2 M, 6 M

**Table 2** Adverse effects from four types of HPV vaccine

vaccine	Very common $\geq 10\%$		Common 1%-10%		Accidental 0.1%-1%	
	Local	Body	Local	Body	Local	Body
<i>E-coli</i> -bv-HPV	Pain	Fever	Induration redness, itching	Fatigue, headache, cough, myalgia, diarrhea, nausea, hypersensitivity, reactions	Rash	Vomiting
bv-HPV	Pain, redness, swelling	Fatigue, myalgia, headache, fever ( $\geq 37\text{ }^{\circ}\text{C}$ )	Induration and itching	Joint pain, gastrointestinal symptoms (including nausea, vomiting, diarrhea, and abdominal pain), hives and rashes	Rash	
qv-HPV	Pain, redness, swelling		Induration and itching	Diarrhea, hypersensitivity reactions, cough, nausea, Vomiting	Rash	
9v-HPV	Pain, redness, swelling		Induration and itching	Diarrhea, hypersensitivity reactions, cough, nausea, Vomiting	Rash	Allergic reaction

**Table 3** Recommended levels of HPV vaccination for general and special populations

Crowd characteristics	Recommended level
General population	
9–26 y female	Priority recommended
27–45 y female	Recommended
Special population	
HPV infection/cytological abnormal	Recommended
Pregnancy woman	Not recommended
Lactation woman	Caution recommended
People with genetic susceptible population and high-risk population of cervical cancer	Priority recommended
People with immunodeficiency:	
HIV infection	Recommended
Autoimmune diseases:	Recommended
Systemic lupus erythematosus,	
Rheumatoid arthritis,	
Connective tissue disease,	
Sicca syndrome	
Sjogren’s syndrome,	
Hashimoto’s thyroiditis	
Diabetes (types I and II)	Recommended
Patients with renal failure and Hemodialysis	Discuss with your clinician
Patients taking long-term immunosuppressive drugs after organ/bone marrow transplantation	Discuss with your clinician

application of HPV vaccines and reached a consensus and wrote the “Expert consensus on immunological prevention of Human Papillomavirus-related diseases” [14] in 2017.

To aid Chinese clinicians in understanding and guiding the use of HPV vaccine in Chinese women, especially in special populations, we have written the “Chinese experts consensus on the clinical application of HPV vaccine” [15]. In the consensus, recommended principles and precautions for vaccination of different populations are outlined, and challenges are addressed.

Recommendations for HPV vaccination are divided into five levels in China (Table 3):

**Recommendations of Vaccination**

- (1) Recommended priority vaccination: for young women, because they potentially benefit the most, a preferred HPV vaccination strategy is promoted.
- (2) Recommended priority vaccination: preferential recommendation should also be taken for susceptible populations and those with a high-

risk of cervical cancer. (3) Recommended vaccination: recommended for adult women. (4) Recommended vaccination: women with immunodeficiency. (5) Vaccination not recommended: the vaccine is not recommended for pregnant women, who should be vaccinated 3 months after delivery. If pregnancy is discovered after initial vaccination dose, unfinished doses should be completed postpartum. (6) Caution is recommended: although the WHO proposed that vaccination can be done during lactation, it should be done cautiously, and vaccination should be delayed until after lactation.

## Conclusion

In clinical studies, the HPV vaccine has shown efficacy, safety, and immunogenicity in Chinese women. We will continue to strengthen screening and push for HPV vaccination in the population. Much work is still required in the fight against cervical cancer. Through ongoing efforts, we can surely achieve the strategic goal of eliminating cervical cancer in China.

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## Declaration

**Conflict of interest** The authors declared no potential conflicts of interest.

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