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Prevention of human papillomavirus (HPV) infection and cervical cancer in China: How does HPV vaccination bring about benefits to Chinese women?

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Summary **Cervical cancer is the second leading cause of cancer deaths among women in the world and more than 85% of cervical cancer cases occur in women living in developing countries. Human papillomavirus (HPV) infection is the major cause of cervical cancer. Since 2006, two prophylactic vaccines against the high-risk strains of HPV have been developed and approved in more than 100 countries around the world. However, in China, HPV vaccines are still under clinical trials for government approval. In this paper feasibility and justification of HPV vaccine introduction into China is examined by reviewing experiences in both developed and developing countries where the vaccination program has been implemented. The vaccination program has showed significant cost-effectiveness and great health and economic impacts on cervical cancer prevention and control in both high-income and middle- and low-income countries. On the other hand, based on the lessons from both developed and developing countries, secondary prevention alone cannot fully play a role to reduce the incidence and the disease burden, and neither does the vaccination program. The epidemiological characteristics in China suggest an urgent need to introduce the vaccines and the geographically diversified prevalence of oncogenic HPV types as well as socioeconomic status also highlight the importance of region-driven approaches for cervical cancer prevention and control by integration of a screening and vaccination program.**

Keywords: Human papillomavirus (HPV), cervical cancer, vaccination, screening, China

1. Introduction

Cervical cancer is the second leading cause of cancer death among women in the world and more than 85% of cervical cancer cases occur in women living in developing countries, where approximately 529,000 new cases and 275,000 deaths occur every year (*1*). Human papillomavirus (HPV) infection acquired from sexual activities is the most common viral infection of the reproductive tract and the causal relationship between HPV infection and the cervix and cervical cancer was built by zur Hausen, the Nobelist in Physiology and Medicine in 2008 for his epoch-making findings. The infection can be detected in more than 95% of carcinoma issues (*2*). So far, more than 100 different HPV genotypes have been detected, and among them type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are a high-risk for cervical carcinoma. The most common genotypes among infected women are 16, 18, 31, 58, and 52, accounting for approximately half of HPV infections (*3*).

Recently, there has been a milestone which prevents HPV infection and development of cervical cancer: two prophylactic vaccines against the high-risk strains of HPV, a quadrivalent vaccine *Gardasil* developed by *Merck* and a bivalent vaccine *Cervarix* by *GlaxoSmithKline* have been developed and approved in more than 100 countries around the world. The prophylactic vaccines mainly target HPV-16 and -18 types, which are the most prevalent genotypes globally

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and responsible for about 70% of cervical cancer worldwide (*1*). To fully play a role for the prevention of cervical cancer and diseases related to HPV infection, they need to be widely implemented in the appropriate target population, as both are only effective for those not infected with HPV, preferably prior to sexual debut. When girls begin having sex, the risk of HPV infection increases dramatically, weakening the effectiveness of the vaccination strategy. Table 1 summarizes basic information of the two vaccines (*4,5*). Both vaccines have shown excellent efficacy with minimal toxicity; on the other hand, numerous questions remain, such as delivery strategies, accessibility to vaccination for underserved populations, social acceptance, monitoring of safety and effectiveness post-licensure, and integration of current existing HPV screening in both developed and developing countries. Monitoring and evaluation of the long-term health and socioeconomic impacts including side effects is necessary not only for each country, but also for the global society.

Having characterized the geographical diversity, epidemiological characteristics of HPV infection in China is quite different by region (*6*). The disease burden of cervical cancer is high, particularly in the rural area. It is estimated that among Chinese women aged 30 to 50 years, the prevalence of infection with high-risk HPV is 15.0~20.8%, and the mortality of cervical cancer increases 4.1% per year (*7*). On the other hand, the two prophylactic vaccines are still under clinical trials among the Chinese population for government approval. Although time is needed for the introduction of the HPV vaccines in China, it is expected to bring benefits to Chinese women with more effective prevention of HPV infection and cervical cancer in the long-term and the feasibility and justification should be examined by reviewing experiences in developed and developing countries where the vaccination program has been launched.

2. Strategies and impacts of HPV vaccination on the prevention of HPV infection and cervical cancer

The World Health Organization (WHO) strongly recommended an introduction and scaling-up of the HPV vaccination program (*1*). So far, there are more than 160 countries which have approved the prophylactic vaccines and have gradually introduced the vaccines into the national routine immunization program. Generally, the program in most countries targets pre-adolescent and adolescent girls whose age ranges from 9 to 13 years old by school-based or healthcare facility-based or mixed approaches with a catch-up group aged up to 26 years old. It provides 3 injections during a 6 month period, as the protective effect by the vaccines has been shown prior to exposure of the risk to HPV infection, *i.e.*, the sexual debut. In

Table 1. Basic information of two types of HPV vaccine

Items	*Gardasil* (*quadrivalent*)[a]	*Cervarix* (*bivalent*)[b]
Pharmaceutical company	Merck, Whitehouse Station, NJ, USA	GlaxoSmithKline, Rixensart, Belgium
HPV types	6, 11, 16, 18	16, 18
Prevention of diseases	Girls and women • Cervical, vulvar, vaginal and anal cancer caused by HPV types 16 and 18 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 • Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18 Boys and men • Anal cancer caused by HPV types 16 and 18 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 • Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18	Girls and women Following diseases caused by HPV types 16 and 18 • cervical cancer • cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and cervical intraepithelial neoplasia (CIN) grade 1
Target population	Females and males aged 9 to 26 years	Females aged 9 to 25 years
Administration	Intramuscular shoulder injection	Intramuscular shoulder injection
Efficacy against precancerous lesions	For females without infection of types 16 and 18: 98% (95% CI: 86-100%) For females with infection of types 16 and 18: 44% (95% CI: 26-58%)	For females without infection of types 16 and 18: 93% (95% CI 80-98%) For females with infection of types 16 and 18: less efficient
Cross-protection effects	Protection against types 31 was 46% (95% CI 15-66) for persistent infection and 57% (29-75) for any CIN or adenocarcinoma in situ	Protection against CIN2 or worse associated with types 31 and 33 in lesions with no co-infection with the vaccine types, and to a lesser extent against types 45 and 51
Safety	0.8% of individuals who received the vaccine and 1.0% of individuals who received the placebo reported a serious systemic adverse reaction	5.3% of individuals who received the vaccine and 5.9% of individuals who received the placebo reported at least one serious adverse event, without regard to causality

[a], Merck & Co. Gardasil (Human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant; [b], GlaxoSmithKline. Cervarix (Human papillomavirus bivalent (types 16 and 18) vaccine, recombinant).

developed countries, during the past several years, the coverage of the vaccines has increased and caused a significant impact on reduction of the incidence of cervical and other HPV-associated cancers, including prevalence of HPV infection, genital warts and cervical lesions (*8*). With evidence that showed high efficacy for prevention of genital warts and anal precancerous lesions in males, *Gardasil* is also licensed and recommended for use in boys in some countries such as the United States since last year (*9*). In middle- and low-income countries, although several challenges such as affordability, infrastructure for delivery, coverage, and communication strategies to boost public acceptability still remain in the national cervical cancer prevention and control strategies (*10*), the vaccination program has been adopted by public financing, out-of-pocket payment or donations. The GAVI Alliance has subsidized low-income countries to increase financial feasibility for the introduction.

As summarized in Table 2 (*11-42*), the vaccination program has showed significant cost-effectiveness and great health and economic impacts on cervical cancer prevention and control in both high-income and middle- and low-income countries, even if the protocol of vaccination and coverage is diversified depending on the specific situation of each country. In middle- and low-income countries, the combination of vaccination and screening showed better cost-effectiveness than that of vaccination or screening alone. On the other hand, uncertainties for the cost-effectiveness of the different options of the prevention and control programs included coverage, price of vaccines, oncogenic and epidemiological characteristics of HPV infection, suggesting the issues should be carefully examined when introducing the vaccination program. Moreover, the vaccination program has also brought significant cross-protection impacts on prevention of HPV-related diseases, such as cervical intraepithelial neoplasia (CIN), adding further value to the preventive potential and clinical benefits of the vaccines (*43*).

3. Cervical cancer control in China: current status and challenges

3.1. *Strategies and limitations of early detection of cervical cancer by the screening program*

Recently in China, without official approval of the vaccines, the most essential strategy for cervical cancer prevention and control is the routine screening program targeting women at reproductive age for early detection and treatment of HPV infection, CIN (from which developing cervical cancer generally needs several years) and cervical cancer at an early stage. Based on previous large-scale studies, a systematic routine screening program can reduce the incidence of cervical cancer by at least 60% and has been recommended by WHO, particularly in developing countries (*44*). The major methodologies of screening include: *i*) Pap smear cytology test; *ii*) liquid-based cytology test; *iii*) HPV DNA test (HC-II); *iv*) visual inspection with acetic acid (VIA); *v*) colposcopy. Table 3 briefly lists advantages and limitations of each methodology (*45*).

The Ministry of Health of China has launched the Guideline for Screening and Early Detection and Treatment of Cervical Cancer. According to the guideline, the target population is women older than 21 years old or with sexual intercourse experience for more than three years. The guideline also defined high-risk women as those with several sexual partners, too early sexual debut, HPV infection, low immunity, poor health knowledge and accessibility to healthcare. Depending on diversified geographical socioeconomic status and levels of exposure to the risks of the population, the guideline has recommended three protocols with a different combination of methodologies based on feasibility and a cost-effectiveness evaluation. The three protocols are: *i*) primary screening by liquid-based cytology test + HPV DNA test, an optimal one with best sensitivity and specificity but relevantly high cost, suitable for a screening program in developed regions and/or women with good economic status; *ii*) primary screening by Pap smear cytology test + HPV DNA test, suitable in moderately developed regions; *iii*) primary screening by VIA, a basic one as an alternative in low-resource settings. High-risk women are prioritized in the guideline, with a recommended more intensive frequency of screening and follow-up. Ideally, with such a strengthened HPV screening program, early detection and treatment of cervical cancer can be realized and incidence as well as disease burden can be reduced.

For women living in rural areas, among whom the incidence and the disease burden of cervical cancer is much higher, since 2009 the nationwide pilot campaign of free screening for cervical cancer and breast cancer has been implemented with a strong political commitment from the annual government report and the 12th Five-Year Plan for Healthcare System Reform. On the other hand, due to huge geographical diversity in socioeconomic development, the current screening program has limitations accomplishing its function. Although the national guideline recognized the huge gap in technical capacity and accessibility in different regions, the current recommended region-driven protocols for screening need to be re-examined, because incidence and disease burden in less developed regions tends to be higher and the difference of the protocol implementation may enlarge the gap. In reality, a relevant amount of high-risk cases from patients living in low resource regions may be missed due to low sensitivity of the screening protocols and bad performance of healthcare facilities at the primary level, in which the technical capacity tends to be poor and human resources are lacking. This remains an

Table 2. Strategy of HPV vaccination in some countries

Country/Region (Year introduced)	Protocol of vaccination	Estimated coverage	Impacts, effectiveness and economic evaluation	References
High-income				
The United States (2006)	3 doses targeting females aged 11-12 and catch-up ages 13-26, delivered at facilities	32%	Vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence.	Kulasingam *et al*, 2003; Markowitz *et al*, 2013
Canada (2007)	3 doses targeting females aged 12 and catch-up ages different by regions, delivered at schools	75% (estimated in the simulation model)	The bivalent vaccine had lower ICER compared to quadrivalent vaccine. It is associated with more reduced cervical cancer morbidity and mortality. Differences in these outcomes depend on the extent of cervical disease prevented by cross-protection and the burden of GW caused by HPV-6/11.	Kohli *et al*, 2012; Anonychuk *et al*, 2009
The United Kingdom (2008)	3 doses targeting females and males aged 12-13 and catch-up ages 13-17, delivered at schools	84%	The quadrivalent HPV vaccination programme that includes a catch-up strategy can reduce the incidence of cervical cancer, CIN and genital warts at a cost per QALY ratio within the range typically regarded as cost-effective. Vaccination with screening, compared to screening alone, was associated with an incremental cost-effectiveness ratio of 21,059 pound per QALY.	Dasbash *et al*, 2008; Kulashingam *et al*, 2008
France (2007)	3 doses targeting females aged 14 and catch-up ages 15-23, delivered at schools or facilities	80% (estimated in the simulation model)	The incremental cost per QALY for the introduction of HPV vaccination alongside the French cervical cancer screening program was €8,408, suggesting that a quadrivalent HPV vaccine in the current screening program in France is cost-effective.	Bergeron *et al,* 2008
Germany (2007)	3 doses targeting females aged 12-17, delivered at schools or facilities	-	The quadrivalent HPV vaccination programme of females ages 12 to 17 in Germany is cost-effective with an ICER of 5,525€/QALY. The current vaccination and cervical cancer screening programmes in Germany will substantially reduce the incidence of cervical cancer, CIN and genital warts.	Damm *et al*, 2009; Schobert *et al*, 2012
Italy (2008)	3 doses targeting females aged 11 and catch-up ages different by regions, delivered at schools or facilities	56%	The bivalent vaccine would prevent an additional reduction of 7976 abnormal pap smears, 601 CIN1, 1826 CIN2/3 and 295 CC cases compared to the quadrivalent vaccine while 25,848 genital wart cases would be prevented by the quadrivalent vaccine. The additional cost averted with the bivalent vaccine was estimated at €2,385,354 per year.	Capri *et al,* 2011; Mennini *et al*, 2009
Netherlands (2010)	3 doses targeting females aged 12 with catch-up ages 13-16, delivered at schools or facilities	50% (estimated in the simulation model)	The bivalent or quadrivalent vaccine reduces the cervical cancer incidence by 221 and 207 /100,000, corresponding to ICERs of €17,600 /QALY and €18,900 /QALY, respectively. The quadrivalent vaccine additionally prevents 4390 cases of genital warts, reducing the ICER to €16,300 /QALY.	Westra *et al*, 2013
Belgium (2007)	3 doses targeting females aged 12-18 with catch-up ages 13-18, delivered at schools or facilities	82%	The vaccine reduces the lifetime risk of cervical cancer from 0.94% to 0.34%, preventing 362 cases of cervical cancer and 131 related deaths in a cohort of 60,000 girls aged 12 years. The vaccination with current screening is at €10,546 /QALY.	Annemans *et al,* 2009
Irelands (2010)	3 doses targeting females aged 12-13, delivered at schools or facilities	-	ICER for quadrivalent vaccine would be 25,349 euros/QALY and 30,460 euros/QALY for the bivalent vaccine. At current prices, the bivalent vaccine would need to be 22% cheaper than the quadrivalent vaccine in order to have equivalent cost effectiveness.	Dee *et al*, 2010
Norway (2009)	3 doses targeting females aged 11-12 with catch-up ages 12-24, delivered at schools	63%	Implementation of a quadrivalent HPV vaccine national program in Norway could reduce the incidence of cervical cancer, cervical intraepithelial neoplasia and genital warts at a cost-effectiveness ratio.	Dasbash *et al*, 2008; Sander *et al*, 2012
Switzerland (2008)	3 doses targeting females aged 10-14 with catch-up ages 14-19, delivered at schools or facilities	80% (estimated in the simulation model)	Compared to screening only, adding a quadrivalent vaccine could prevent over lifetime 62% of cervical cancers and related deaths, 19% of Cervical Intraepithelial Neoplasia (CIN 1), 43% of CIN 2, 45% of CIN 3 and 66% of genital warts per cohort. ICER were estimated to be CHF45,008 /life-year and CHF26,005 / QALY.	Szucs *et al*, 2008
Australia (2007)	3 doses targeting females aged 12-13 with catch-up ages 13-26, delivered at schools	71%	Vaccination with screening compared with screening alone was associated with ICER of $51,103 /life-year and $18,735 /QALY.	Kulasingam *et al*, 2007
Japan (2009)	3 doses targeting females aged 12-16, delivered at schools or facilities	-	Vaccinating a 12-year-old cohort can reduce CC incidence and deaths from CC by 73%, associated with ICER of yen1.8 million per QALY gained.The vaccination program is more cost-effective to increase the coverage of the screening along with the universal administration of HPV vaccine.	Yamamoto *et al*, 2012; Konno *et al*, 2010

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(Table 2. continued)

Country/Region (Year introduced)	Protocol of vaccination	Estimated coverage	Impacts, effectiveness and economic evaluation	References
Singapore (2010)	3 doses targeting females aged 9-26, delivered at facilities	-	Comparing the bivalent to the quadrivalent vaccine, the ICER was $12,488 per life-year saved. The quadrivalent vaccine dominates to the bivalent vaccine due to the additional QALY effect from reduction in genital warts. The overall outcomes were most sensitive to vaccine cost and coverage.	Lee *et al*, 2011
Taiwan (2006)	3 doses targeting females aged 9-26, delivered at facilities	-	An additional 768 QALY and 11.6 million new Taiwan dollars costs saved for the bivalent vaccine versus the quadrivalent vaccine after discounting.	Demarteau *et al*, 2012
Middle- and low- income				
Thailand (2010)	3 doses targeting females aged 9-12, delivered at schools or facilities	80% (estimated in the simulation model)	Pre-adolescent HPV vaccination alone was projected to reduce the lifetime risk of cervical cancer by 55%, which was greater than any strategy of screening alone. Pre-adolescent vaccination and HPV DNA testing five times per lifetime, starting at age 35 years, reduced the lifetime cervical cancer risk by 70%, and had a cost-effectiveness ratio less than Thailand's GDP per capita.	Sharma *et al*, 2012
Malaysia (2010)	3 doses targeting females before age 13 with catch-up ages 13-18, delivered at schools	-	Vaccination increase life expectancy with better QOL of women when cancer can be avoided. Cost effective strategies will include increasing the screening coverage to 70% or higher. Since feasibility and long term screening adherence is doubtful among Malaysian women, vaccination is a more cost effective strategy against cervical cancers.	Ezat *et al*, 2010
India (2011)	3 doses targeting females aged 11-12 with catch-up ages 13-26, delivered at facilities	70% (estimated in the simulation model)	If high coverage of pre-adolescent girls with a low-cost HPV vaccine that provides long-term protection is achievable, vaccination followed by screening three times per lifetime is expected to reduce cancer deaths by half, and be cost-effective.	Diaz *et al*, 2008
Hungary (2010)	3 doses targeting females aged 12 with catch-up ages 12-24, delivered at facilities	-	The ICER of adding bivalent vaccine to the current national cancer screening program was estimated to be 27 588 $/QALY. By quadrivalent vaccine, the ICER of the routine vaccination targeting females aged 12 and the routine vaccination plus the catch-up group were €9,577 and €10,646 per QALY.	Voko *et al*, 2011; Dasbash *et al*, 2010
Mexico (2008)	3 doses targeting females aged 9-12 with catch-up ages 12-24, delivered at schools or facilities	67%	The quadrivalent vaccine could reduce the probability of persistent HPV-16/18 infection by at least 60%, resulting in a near-proportional reduction in HPV-16/18-associated invasive cervical cancer and CIN 3. The most effective strategy therein was vaccination of 12-year-olds, plus a temporary 12-24-year-old catch-up program covering both sexes; whereby HPV 6/11/16/18-related cervical cancer, high-grade cervical pre-cancer and genital wart incidence was reduced by 84-98%.	Reynales-Shigematsu *et al*, 2009; Insinga *et al*, 2007; CDC, 2011
Peru (2011)	3 doses targeting females aged 10-13, delivered at schools	82%	Enhanced screening in adult women combined with preadolescent vaccination had incremental cost-effectiveness ratios lower than Peru's 2005 per capita GDP and considered to be cost-effective.	Goldie *et al*, 2012
Brazil (2006)	3 doses targeting females aged 9-12, delivered at schools or facilities	50% (estimated in the simulation model)	Vaccination in addition to the current screening programme is likely to save years of life and, depending on the cost of vaccination, may even save resources.	Vanni *et al*, 2012

obstacle for implementation and effective coverage of the regular screening program. Accessibility to regular screening is limited for quite a large number of high-risk women due to lack of knowledge and awareness as well, leading to a loss of opportunity for prevention of cancer development. Therefore, the technical capacity at the primary level and in less developed regions urgently needs to be strengthened; moreover, in the long-term, the introduction of the prophylactic vaccines is crucial to supplement the screening program, especially targeting high-risk women.

3.2. *Factors potentially affecting the introduction of HPV vaccination*

Although it showed great health and socioeconomic impacts in numerous countries, the worldwide introduction of the HPV vaccination program still has a short history with various questions remaining. In China, the government has showed a conservative attitude for approval of the current vaccines and has strictly required clinical trials targeting the Chinese population, even though it met with opposition from some scholars and the mass media. Because political commitment plays a core role in the introduction, solid evidence is necessary to persuade the policy makers. Table 4 summarizes factors potentially affecting the introduction based on results of studies having been implemented in China so far, including epidemiological characteristics, efficacy

Table 3. Major advantages and limitations of the screening methodologies for cervical cancer

Methodology	Advantages	Limitations
Pap smear cytology test	Regular screening tool for more than 50 years in settings where the cytology screening system has been established, with relevantly high sensitivity (50-80%) and specificity (85-90%)	The operation requires well trained personnel, maturelaboratory technique, high financial costs, and three or more diagnostic follow-ups and treatment for the positive cases.
Liquid-based cytology test	Similar to Pap smear cytology test, while the operation improved collection efficacy accuracy of samples, with higher sensitivity (85%) and specificity (90%). In settings where the laboratory technical capacity for the cytology screening is weak, samples can be restored and sent to outside.	High financial costs (prolonged screening interval may reduce the costs)
HPV DNA test (HC-II)	It can explore the level of the risks and determine the screening interval with higher sensitivity than liquid-based cytology test for detecting significant precancerous lesions. Moreover, the processing of results can be automated, making the test more objective and requiring less training of personnel. It is especially suitable for large-scale screening in high-risk populations.	High financial costs (prolonged screening interval may reduce the costs)
Visual inspection with acetic acid (VIA)	Simple, less personnel and laboratory requirement, low financial costs, quick result and easy to operate, particularly suitable for low-resource setting with limited technical capacity of the cytology screening	Relatively low sensitivity (50-70%) and specificity (85%)
Colposcopy	As an essential supplementary tool for the early detection of cervical cancer and precancerous lesions, it is conducted for suspicious cases and positive results from the screening test. The combination of colposcopy with HPV DNA test and the cytology tests can further improve sensitivity and specificity.	Facility-based, intensive personnel and technical requirement and not suitable for a large-scale screening

Table 4. Literature review for factors affecting implementation of HPV vaccination program in China

Literature review
Epidemiological characteristics of HPV infection
● In rural Guangdong Province: HPV types 16 and 18 accounted for 28.52% of total infection while types 52 and 58 presented 48.24%. (Chen *et al*, 2012)
● HPV 16 (76.7%) and HPV 18 (7.8%) were the most common, together accounting for 84.5% of squamous cell carcinoma (SCC), followed by HPV 31 (3.2%), HPV 52 (2.2%), and HPV 58 (2.2%). Positive HPV in SCC did not differ notably by region. The potential impact of vaccines against oncogenic HPV types 16 and 18 is estimated to be high (84.5%) against total SCC. (Chen *et al*, 2009)
● In Western China: HPV-16 and -58 were the most prevalent types, with prevalence of 37.8% and 21.8%, respectively; HPV-18 and -45 were uncommon types. (Li *et al*, 2012)
● In Wufeng County: HPV 16, 52, and 58 are common genotypes. (Zhang *et al*, 2012)
● The most prevalent HPV are types 52 and 58 with positive rate of 42.5% in cervical cancer patients, greater than types 16 and 18 in Shanghai, in southern China the HPV 52- and 58-positive rate is greater than that in northern China. (Lo *et al*, 2002)
● The most prevalent types found were HPV16 (2.9 %), HPV52 (1.7 %), HPV58 (1.5 %), HPV33 (1 %), and HPV18 (0.8 %). Patterns of HPV prevalence differed by age, geographic region, and cytology findings. (Wu *et al*, 2013)
Efficacy, safety and immunogenicity
● A double-blinded RCT in China showed the quadrivalent vaccine was generally well tolerated, with no vaccine-related serious adverse events. High antibody levels were observed for each of the four HPV types and sero-conversion was > 96%. (Li *et al*, 2010)
Cost-effectiveness of cervical cancer prevention and control strategies
● Per-dose HPV vaccine cost of approximately < $9-14 would be required for strategies involving vaccination to be cost-effective. Combined screening and vaccination approaches are required to maximize outcomes in rural China. (Canfell *et al*, 2011)
● Assuming a cost per vaccinated girl of I$25, the cost per DALY averted is I$1,360 in China, reflecting the greater number of girls that need to be vaccinated to prevent a death from cervical cancer in China. Vaccine price has an even greater effect on predicted affordability. (Goldie *et al*, 2008)
● Making an HPV16, 18 vaccine accessible to 70% of young adolescent girls in 72 countries including China could prevent the future deaths of more than four million women vaccinated over the next decade. Provided the cost per vaccinated girl is less than $10-$25, adolescent HPV16,18 vaccination would be cost-effective even in relatively poor countries. (Goldie *et al*, 2008)
Knowledge and attitude
● Only 15.0% of women have ever heard of HPV, and this knowledge differs by rural (9.3%) and metropolitan areas (21.6%) and also by education. Most (84.6%) participants were willing to be vaccinated if HPV vaccine became available to them. (Li *et al*, 2009)
● Knowledge of HPV among the general female population was low; only 24% had heard of HPV. Less than 20% of healthcare providers recognized sexually naive women as the most appropriate population for HPV vaccination. There was high acceptance of the HPV vaccine for all categories of respondents. Only 6% of women were willing to pay more than US $300 for the vaccine. (Zhao *et al*, 2012)

and safety of the vaccines, cost-effectiveness of cervical cancer prevention and control strategies Sexual behavior of the population, and knowledge and attitudes towards the vaccines and HPV-related diseases are also important (*46-57*).

In China, the prevalence of HPV 16 and 18, which are prevented by the current vaccines, is generally high, while there is a huge geographic diversity of the prevalence of oncogenic HPV types. Other prevalent genotypes include HPV 52 and 58, as well. Such epidemiological trends suggest introduction of the prophylactic vaccines and development of vaccines targeting other prevalent genotypes have potential clinical and social benefits. The clinical trials for the development are ongoing. Based on the current data, the quadrivalent vaccine showed great efficacy in the Chinese population and no vaccine-related serious adverse events were reported so far. Based on a mathematical simulation model, introduction of the vaccines and integrated vaccination and screening program will potentially be very cost-effective in China. Providing the program universally covers the high-risk and high-burden population and the price is low enough to ensure accessibility for the underserved. Like other developing countries, there is a concern about financial costs and affordability, highlighting the need for lowering vaccine prices, cost-efficient mechanisms for delivery of vaccinations to high-risk and high-burden populations, and creative sources of financing. A strong political commitment by the government is essential, because universal coverage is expected to be achieved by injection of public subsidies and adaptation of medical insurance, rather than out-of-pocket payment, particularly for the poor living in rural areas. An interesting finding shown in the previous studies is that although the overall related knowledge is lacking, people have a good willingness to receive the vaccines when they are available in China. Strengthening of health education on the prevention and control of cervical cancer and HPV-related disease is another important issue to improve potential coverage.

4. Prospects for the future

Although the disease burden of cervical cancer is relatively high in China, the two current prophylactic vaccines are currently not available due to ongoing clinical trials among Chinese women and multivalent vaccines that encompass additional oncogenic HPV strains are under development as well. The major strategy for cervical cancer prevention and control is screening of women at reproductive ages and secondary prevention. Time is still needed to introduce the prophylactic vaccines, currently, early detection and treatment by the universal coverage screening program is the core of a comprehensive strategy with region-driven approaches for cervical cancer prevention and control.

So far, based on lessons from both developed and developing countries, secondary prevention alone cannot fully play a role to reduce the incidence and the disease burden, and neither does the vaccination program. As a preventive tool, both these vaccines prefer girls and women not yet exposed to the risk of infection, *e.g.*, prior to first sexual intercourse, and are not effective for those already infected. Moreover, because immunity to HPV is primarily type specific, protection by the current generation of vaccines with a limited number of HPV types cannot provide complete protection against all oncogenic HPV types. Therefore, the functional screening program is still necessary. Previous economic evaluations indicated that an integrated vaccination and screening program is the most effective tool for great cost-effectiveness and health impact. According to WHO, a HPV vaccination program combined with regular screening in women over age 30 for precancerous lesions followed by adequate treatment are key tools to prevent the 530,000 new cervical cancer cases diagnosed every year (*1*). Therefore, like other countries in the Asia Pacific area and the world, the short-term goal for cervical cancer control is to identify feasible and effective screening measures, and to find the most effective way to combine vaccination with sustainable screening programs (*58,59*).

The high prevalence of HPV 16 and 18 in the overall population in China suggests an urgent need to introduce the current vaccines (*60*). The geographically diversified prevalence of oncogenic HPV types as well as socioeconomic status also highlights the importance of region-driven approaches for cervical cancer prevention and control. With the profound tendency for cervical cancer epidemics and the tremendous task of control, in the long-term the introduction of the vaccines and the development of the new generation vaccines for additional oncogenic HPV types are crucial. Besides the current genotypes protected by the vaccines, cross-reactivity suggests that even better clinical benefits may be achieved by its wide application. Challenges for ensuring the benefits for Chinese women by the HPV vaccines include political commitment of the government, provision of solid evidence for policy making, monitoring of safety and side effects, health education, affordable prices and possible public subsidies for the poor and the vulnerable, and strengthened screening programs particularly for the high-risk population and for primary level healthcare facilities with poor technical capacity.

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References

1. The World Health Organization. Comprehensive cervical cancer prevention and control: A healthier future for girls and women. The World Health Organization, Geneva, Swizerland, 2013.
2. Lowy DR, Solomon D, Hildesheim A, Schiller JT, Schiffman M. Human papillomavirus infection and the primary and secondary prevention of cervical cancer. Cancer. 2008; 113 (Suppl 7):1980-1993.
3. de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, Bosch FX. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: A meta-analysis. Lancet Infect Dis. 2007; 7:453-459.
4. Merck & Co. Gardasil [Human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant]. *http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf* (accessed June 02, 2013).
5. GlaxoSmithKline. Cervarix [Human papillomavirus bivalent (types 16 and 18) vaccine, recombinant]. *http://us.gsk.com/products/assets/us_cervarix.pdf* (accessed June 02, 2013).
6. Zhao FH, Lewkowitz AK, Hu SY, *et al*. Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: A pooled analysis of 17 population-based studies. Int J Cancer. 2012; 131:2929-2938.
7. Li J, Kang LN, Qiao YL. Review of the cervical cancer disease burden in mainland China. Asian Pac J Cancer Prev. 2011; 12:1149-1153.
8. Markowitz LE, Tsu V, Deeks SL, Cubie H, Wang SA, Vicari AS, Brotherton JM. Human papillomavirus vaccine introduction – The first five years. Vaccine. 2012; 30(Suppl.):F139-148.
9. Palefsky JM, Giuliano AR, Goldstone S, *et al*. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Eng J Med. 2011; 365:1576-1585.
10. Kane MA, Serrano B, Sanjose S, Witter S. Implementation of human papillomavirus immunization in the developing world. Vaccine. 2012; 30(Suppl.):F192-200.
11. Westra TA, Stirbu-Wagner I, Dorsman S, Tutuhatunewa ED, de Vrij EL, Nijman HW, Daemen T, Wilschut JC, Postma MJ. Inclusion of the benefits of enhanced cross-protection against cervical cancer and prevention of genital warts in the cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. BMC Infect Dis. 2013; 13:75.
12. Annemans L, Remy V, Oyee J, Largeron N. Cost-effectiveness evaluation of a quadrivalent human papillomavirus vaccine in Belgium. Pharmacoeconomics. 2009; 27:231-245.
13. Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, Roder D, Ross J, Wain G. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health. 2007; 4:165-175.
14. Szucs TD, Largeron N, Dedes KJ, Rafia R, Benard S. Cost-effectiveness analysis of adding a quadrivalent HPV vaccine to the cervical cancer screening program in Switzerland. Curr Med Res Opin. 2008; 24:1473-1483.
15. Lee VJ, Tay SK, Teoh YL, Yok MY. Cost-effectiveness of different human papillomavirus vaccines in Singapore. BMC Public Health. 2011; 11:203.
16. Dee A, Howell F. A cost-utility analysis of adding a bivalent or quadrivalent HPV vaccine to the Irish cervical screening program. Eur J Public Health. 2010; 20:213-219.
17. Kohli M, Lawrence D, Haig, J, Anonychuk A, Demarteau N. Modeling the impact of the difference in cross-protection data between a human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and human papillomavirus (HPV)-6/11/16/18 vaccine in Canada. BMC Public Health. 2012; 12:872.
18. Anonychuk AM, Bauch CT, Merid MF, Van Kriekinge G, Demarteau. A cost-utility analysis of cervical cancer vaccination in preadolescent Canadian females. BMC Public Health. 2009; 9:401.
19. Demarteau N, Tang CH, Chen HC, Chen CJ, Van Kriekinge G. Cost-effectiveness analysis of the bivalent compared with the quadrivalent human papillomavirus vaccines in Taiwan. Value Health. 2012; 15:622-631.
20. Dasbach EJ, Insinga RP, Elbasha EH. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK. BJOG. 2008; 115:947-956.
21. Kulasingam SL, Benard S, Barnabas RV, Largeron N, Myers ER. Adding a quadrivalent human papillomavirus vaccine to the UK cervical cancer screening program: A cost-effectiveness analysis. Cost Eff Resour Alloc. 2008; 6:4.
22. Capri S, Gasparini R, Panatto D, Demarteau N. Cost-consequences evaluation between bivalent and quadrivalent HPV vaccines in Italy: The potential impact of different cross-protection profiles. Gynecol Oncol. 2011; 121:514-521.
23. Mennini FS, Giorgi Rossi P, Palazzo F, Largeron N. Health and economic impact associated with a quadrivalent HPV vaccine in Italy. Gynecol Oncol 2009; 112:370-376.
24. Damm O, Nocon M, Roll S, Vauth C, Willich S, Greiner W. Human papillomavirus (HPV) vaccination for the prevention of HPV 16/18 induced cervical cancer and its precursors. GMS Health Technol Assess. 2009; 5:Doc04.
25. Schobert D, Remy V, Schoeffski O. Cost-effectiveness of vaccination with a quadrivalent HPV vaccine in Germany using a dynamic transmission model. Health Econ Rev. 2012; 2:19.
26. Bergeron C, Largeron N, McAllister R, Mathevet P, Remy V. Cost-effectiveness analysis of the introduction of a quadrivalent human papillomavirus vaccine in France. Int J Technol Assess Health Care. 2008; 24:10-19.
27. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA. 2003; 290:781-789.
28. Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, Unger ER. Reduction in human papillomavirus prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. J Infect Dis 2013; 208:385-393.
29. Dasbash EJ (b), Largeron N, Elbasha EH. Assessment of the cost-effectiveness of a quadrivalent HPV vaccine in Norway using a dynamic transmission model. Expert Rev Pharmacoecon Outcomes Res. 2008; 8:491-500.
30. Sander BB, Rebolj M, Valentiner-Branth P, Lynge E. Introduction of human papillomavirus vaccination in Nordic countries. Vaccine 2012; 30:1425-1433.
31. Yamamoto N, Mori R, Jacklin P, Osuga Y, Kawana K, Shibuya K, Taketani Y. Introducing HPV vaccine and scaling up screening procedures to prevent deaths from cervical cancer in Japan: A cost-effectiveness analysis.

BJOG. 2012; 119:177-186.
32. Konno R, Sasagawa T, Fukuda T, Van Kriekinge G, Demarteau N. Cost-effectiveness analysis of prophylactic cervical cancer vaccination in Japanese women. Int J Gynecol Cancer. 2010; 20:385-392.
33. Voko Z, Nagyjanosi L, Kalo Z. Cost-effectiveness of adding vaccination with AS04-adjuvanted human papillomavirus 16/18 vaccine to cervical cancer screening in Hungary. BMC Public Health. 2011; 12:924.
34. Dasbach EJ, Nagy L, Brandtmüller A, Elbasha EH. The cost effectiveness of a quadrivalent human papillomavirus vaccine (6/11/16/18) in Hungary. J Med Econ. 2010; 13:110-118.
35. Reynales-Shigematru LM, Rodrigues ER, Lazcano-Ponce E. Cost-effectiveness analysis of a quadrivalent human papilloma virus vaccine in Mexico. Arch Med Res. 2009; 40:503-513.
36. Inshiga RP, Dasbash EJ, Elbasha EH, Piug A, Reynales-Shigematsu LM. Cost-effectiveness of quadrivalent human papillomavirus (HPV) vaccination in Mexico: A transmission dynamic model-based evaluation. Vaccine. 2007; 26:128-139.
37. Centers for Disease Control and Prevention (CDC). Progress toward implementation of human papillomavirus vaccination – the Americas, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011; 60:1382-1384.
38. Vanni T, Mendes Luz P, Foss A, Mesa-Frias M, Legood R. Economic modeling assessment of the HPV quadrivalent vaccine in Brazil: A dynamic individual-based approach. Vaccine. 2012; 30:4866-4871.
39. Goldie SJ, Levin C, Mosqueira-Lovón NR, Ortendahl J, Kim J, O'Shea M, Diaz Sanchez M, Mendoza Araujo MA. Health and economic impact of human papillomavirus 16 and 18 vaccination of preadolescent girls and cervical cancer screening of adult women in Peru. Rev Panam Salud Publica. 2012; 32:426-434.
40. Diaz M, Kim JJ, Albero G, de Sanjosé S, Clifford G, Bosch FX, Goldie SJ. Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India. Br J Cancer. 2008; 99:230-238.
41. Sharma M, Ortendahl J, van der Ham E, Sy S, Kim JJ. Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in Thailand. BJOG. 2012; 119:166-176.
42. Ezat WP, Aljunid S. Cost-effectiveness of HPV vaccination in the prevention of cervical cancer in Malaysia. Asian Pac J Cancer Prev. 2010; 11:79-90.
43. De Vincenzo R, Ricci C, Conte C, Scambia G. HPV vaccine cross-protection: Highlights on additional clinical benefit. Gynecol Oncol. 2013. (doi: 10.1016/j.ygyno.2013.05.033)
44. The World Health Organization. Cervical cancer screening in developing countries: Report of a WHO consultation. The World Health Organization, Geneva, 2002.
45. Dong Z. The Guideline for Screening and Early Detection and Treatment of Cancer in China. Peking University Medical Press, Beijing, China, 2005.
46. Chen Q, Xie LX, Qing ZR, *et al*. Epidemiologic characterization of human papillomavirus infection in rural Chaozhou, Eastern Guandong Province of China. PLoS One. 2012; 7:e32149.
47. Chen W, Zhang X, Molijn A, *et al*. Human papillomavirus type-distribution in cervical cancer in China: The importance of HPV 16 and 18. Cancer Causes Control. 2009; 20:1705-1713.
48. Li J, Mei J, Wang X, Hu L, Lin Y, Yang P. Human papillomavirus type-specific prevalence in women with cervical intraepithelial neoplasm in Western China. J Clin Microbiol. 2012; 50:1079-1081.
49. Zhang L, Wang Y, Peng M, She Q, Xiang Q, Chen Q, Liu Z, Zhang W, Tao N, Qiu L, Wu X. Prevalence and type distribution of high-risk human papillomavirus infections among women in Wufeng County, China. Arch Gynecol Obstet. 2012; 286: 695-699.
50. Lo KW, Wong YF, Chan MK, *et al*. Prevalence of human papillomavirus in cervical cancer: A multicenter study in China. Int J Cancer. 2002; 100:327-331.
51. Wu EQ, Liu B, Cui JF, *et al*. Prevalence of type-specific human papillomavirus and pap results in Chinese women: A multi-center, population-based cross-sectional study. Cancer Causes Control. 2013; 24:795-803.
52. Li R, Li Y, Radley D, Liu Y, Huang T, Sings HL, Zhang L, Wang W, Zhong X, Saah AJ. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: A randomized, double-blinded placebo-controlled trials in Chinese males and females. Vaccine. 2010; 30:4284-4291.
53. Canfell K, Shi JF, Lew JB, Walker R, Zhao FH, Simonella L, Chen JF, Legood R, Smith MA, Nickson C, Qiao YL. Prevention of cervical cancer in rural China: Evaluation of HPV vaccination and primary HPV screening strategies. Vaccine. 2011; 29:2487-2494.
54. Goldie SJ, Diaz M, Kim SY, Levin CE, Van Minh H, Kim JJ. Mathematical models of cervical cancer prevention in the Asia Pacific Region. Vaccine. 2008; 26(Suppl 12):M17-M29.
55. Goldie SJ, O'Shea M, Diaz M, Kim SY. Benefits, cost requirements and cost-effectiveness of the HPV 16, 18 vaccines for cervical cancer prevention in developing countries: Policy implications. Reprod Health Matters. 2008; 16:86-96.
56. Li J, Li LK, Ma JF, Wei LH, Niyazi M, Li CQ, Xu AD, Wang JB, Liang H, Belinson J, Qiao YL. Knowledge and attitudes about human papillomavirus and HPV vaccines among women living in metropolitan and rural regions of China. Vaccine. 2009; 27:1210-1215.
57. Zhao FH, Tiggelaar SM, Hu SY, *et al*. A multi-center survey of HPV knowledge and attitudes toward HPV vaccination among women, government officials and medical personnel in China. Asian Pac J Cancer Prev. 2012; 13:2369-2378.
58. Garland SM, Cuzick J, Domingo EJ, Goldie SJ, Kim YT, Konno R, Parkin DM, Qiao YL, Sankaranarayanan R, Stern PL, Tay SK, Bosch FX. Recommendations for cervical cancer prevention in Asia Pacific. Vaccine. 2008; 26(Suppl 12):M89-M98.
59. Hakim AA, Dinh TA. Worldwide impact of the human papillomavirus vaccine. Curr Treat Options Oncol. 2009; 10:44-53.
60. Shi JF, Qiao YL, Smith JS, Dondog B, Bao YP, Dai M, Clifford GM, Franceschi S. Epidemiology and prevention of human papillomavirus and cervical cancer in China and Mongolia. Vaccine. 2008; 26(Suppl 12):M53-M59.

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