

MINI-REVIEW

Cervical Cancer Prevention Through HPV Vaccination in Low- and Middle-Income Countries in Asia

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Abstract

Cervical cancer is ranked the first or second most common cancer in women of low- and middle-income countries (LMICs) in Asia. Cervical cancer is almost exclusively caused by human papillomavirus (HPV), and majority of the cases can be prevented with the use of HPV vaccines. The HPV vaccines have demonstrated high vaccine efficacies against HPV infection and cervical cancer precursors in clinical and post-marketing studies, and are in use in most high-income countries. However, their use in LMICs are limited mainly due to the high costs and logistics in delivering multiple doses of the vaccine. Other issues such as the safety of the vaccines, social and cultural factors, as well as poor knowledge and awareness of the virus have also contributed to the low uptake of the vaccine. This mini-review focuses on the need for HPV vaccine implementation in Asia given the substantial disease burden and underuse of HPV vaccines in LMICs in this region. In addition, the progress towards HPV vaccine introduction, and barriers preventing further rollout of these essential, life-saving vaccines are also discussed in this article.

Keywords: HPV vaccine- low- and middle-income countries- cervical cancer

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Introduction

Globally, approximately 530,000 new cases of cervical cancer (CC) occur each year, with 85% of these cases occurring in low- and middle-income countries (LMICs) (Globocan, 2012). The human papillomavirus vaccines (HPV) currently available include Cervarix® (2vHPV, GlaxoSmithKline), Gardasil® (4vHPV, Merck and Co., Inc.) and the recently licensed Gardasil® 9 (9vHPV, Merck and Co., Inc.) (Table 1), have huge potential in preventing the majority of CC and other HPV-associated diseases, based on the high vaccine efficacy against CC precursors observed in clinical and post-marketing studies (Future II study group, 2007; Paavonen et al., 2009; Joura et al., 2015). A systematic review of the 4vHPV 10 years post-licensure, demonstrated dramatic reductions in vaccine and vaccine-related HPV type infection and short incubation HPV diseases (i.e. genital warts), as well as low- and high-grade cervical dysplasia. In countries with high vaccination coverage. In addition, herd protection has also been found in these populations (Garland et al., 2016). The 9vHPV is approved for use in USA, Canada

and Europe, and while both 4vHPV and 2vHPV are in use in most high-income countries around the world, their use in LMICs is mainly limited to the private sector due to their high cost, low demand and logistical challenges in delivering multiple doses of the vaccine to a school-age population.

Many countries in Asia have not introduced HPV vaccine into their national immunization program. There are also large disparities in CC incidence between countries of Asia, with the highest rates in LMICs due to poor diagnosis and treatment, as well as the lack of access to HPV vaccines due to their high costs and logistical difficulties in vaccine implementation. Furthermore, many LMICs do not have accurate CC burden data to justify the cost-effectiveness and use of HPV vaccines. Social and cultural issues associated with HPV infection have also impeded the use of these important vaccines. It is therefore critical that justification for the use of HPV vaccines be based on accurate and reliable CC burden and cost-effectiveness data, especially for LMICs in Asia. This article highlights the significant burden of cervical cancer in LMICs and the potential impact of HPV vaccines in CC

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Table 1. Characteristics of HPV VLP Vaccines

Manufacturer	Merck™ (Gardasil®, 4vHPV)	GlaxoSmithKline™ (Cervarix®, 2vHPV)	Merck™ (Gardasil® 9, 9vHPV)
L1 VLP types	6, 11, 16 and 18	16 and 18	6, 11, 16, 18, 31, 33, 45, 52, and 58
Dose	20/40/40/20 µg	20/20 µg	30/40/60/40/ 20/20/20/20/20
Producer cells	<i>Saccharomyces cerevisiae</i> (baker's yeast) expressing L1	<i>Trichoplusia ni</i> (Hi 5) insect cell line infected with L1 recombinant baculovirus	<i>Saccharomyces cerevisiae</i> (baker's yeast) expressing L1
Adjuvant	225 µg aluminium hydroxyphosphate sulfate	500 µg aluminium hydroxide, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A	500 µg aluminium hydroxyphosphate sulfate
*Vaccination schedule	0, 2 and 6 months	0, 1 and 6 months	0, 2 and 6 months

HPV, Human papillomavirus; VLP, Virus-like particles; * WHO recommends two-dose schedule for girls <15 years old, provided the second dose is given at least six months apart

prevention. Moreover, the contribution of philanthropic organisations as well as strategies to overcome some of the recognised barriers to HPV vaccine introduction are also discussed.

Burden of cervical cancer in Asia

Cervical cancer remains the second highest cause of morbidity and mortality among women in Asia (Bruni et al., 2015). As in other regions, HPV16 and 18 are the most common types in Asia, and the percentage of CC deaths attributed to these two types ranges from 48%-88% depending on the country (Bruni L et al., 2015), indicating that many of these deaths are vaccine preventable.

Actual CC data based on available cancer

registries in Asia are very limited and are mainly from middle- to high-income countries (summarised in Table 2). Furthermore, a huge disparity in the CC incidence exists between these countries. For LMICs in Asia, data on CC rates are largely derived from Globocan and are mainly estimates based on modelled data from neighbouring countries as cervical cancer registries are limited and cases are under reported (Globocan, 2012). Accurate disease burden data are important to justify the need for HPV vaccination, as well as ultimately measuring vaccine effectiveness. For example, the burden of cervical cancer in Fiji was not known until epidemiological data was collected from both the national cancer registries and laboratory records. Fiji has one of the highest CC rates in

Table 2. Cervical Cancer (CC) Incidence Rate in Asia from 2003-2007 Based on Available Population-Based Cancer Registries from International Agency for Research on Cancer, and Cervical Cancer Prevention Programmes

Country based on WHO regional offices	No. of CC cases	Frequency of CC (%)	Crude rate/ 100,000	ASR/ 100,000	HPV vaccination program	Estimated coverage of cervical cancer screening (%)
Eastern Mediterranean						
Bahrain	44	3.7	3.9	5.7	No	43.1
Kuwait	161	4.1	3	4.6	No	22.3
Islamic Republic of Iran, (Golestan Province)	91	3.8	3.7	5.4	No	49.4
Israel	918	1.6	5.5	5	National	32
Qatar	17	3.6	3.4	5.3	No	39.4
Saudi Arabia	103	1.9	1.1	2	No	No data
Western Pacific						
^China	40-2,080	1.8-27.1	4.2-78.2	2.6-71.8	No	17.2
^Japan	264-2,509	2.2-3.4	10.0-15.0	6.9-10.2	*National	31.5
Republic of Korea	20,234	6.2	16.7	12.5	No	76.2
Singapore	1,013	4.6	11.6	8.9	Private sector	47.9
Philippines (Manila and Rizal)	1,991-2,008	8.9-9.2	12.1-13.4	16.6-17.0	National	7.7
Malaysia (Penang)	342	8.4	12.2	12.5	National	22.2
South-East Asia						
^Thailand	459-3,214	11.1-18.0	14.0-32.0	11.8-26.1	Pilot	60.2
^India	87-4280	8.8-36.4	6.5-24.1	8.9-24.5	Pilot	4.9

Source of data: (Forman D and E, 2014); *suspended in 2013 (<1% coverage); ASR, Age-standardised rate; No., number; ^CC incidence rates based on cancer registry from multiple cities within the country

the world (age-standardised rate of 37.5/100,000) (Law et al., 2013), and this may also be true for other LMICs in Asia, but detailed studies are lacking.

Human papillomavirus infection is the most common sexually transmitted infection and there is an increased risk of acquiring the infection with multiple sexual partners. Therefore, it is important to recognise that certain populations [i.e. female sex workers (FSWs) and men who have sex with men (MSM); termed high-risks groups] are at substantially higher risk of acquiring the infection, and therefore risk of HPV-associated cancers. At the same time, they are also likely to be responsible for transmitting HPV in the community. Information regarding the burden of HPV-associated diseases in these populations would be beneficial for governing bodies to make informed evidence-based decisions about HPV vaccination policy, which might include vaccination of boys in addition to girls, as well as having vaccination campaigns for these high-risk groups. These high-risks groups are common in LMICs in Asia (Caceres et al., 2006; Pruss-Ustun et al., 2013), so the need for HPV vaccines is greater, and it may be necessary to consider specific strategies for them. The risk of anal cancer for MSM, usually due to HPV type 16, is very high and is greater among men with human immunodeficiency virus (Silverberg et al., 2012). The risk of HPV-associated cancer for FSWs is unknown, but it is likely to be very high. Although most individuals in these two high-risk groups have already been exposed to HPV, and may be actively infected with one or more types, the benefits arising from protection against types to which they are not currently infected may substantially reduce their cancer risk, especially since the higher valency 9vHPV is now available.

Barriers to HPV vaccine introduction

Several barriers and challenges against the introduction of HPV vaccines exist in LMICs. The high cost of the HPV vaccines and logistical challenges are major issues hindering the HPV vaccine introduction. These can be alleviated with the help of preferential pricing mechanisms and philanthropic organisations (although sustainable financing is needed in the long term), as well as the use of reduced-dose schedules for girls under 15 years old as recommended by the World Health Organization (WHO). For example, Gavi the Vaccine Alliance (formerly known as the Global Alliance of Vaccines and Immunization) has supported HPV immunization programs in Rwanda, Uzbekistan and Bhutan. In the case for Fiji, a middle-income country, the recent national HPV vaccine introduction in 2013 was achieved with the assistance of Australian Aid, the Department of Foreign Affairs and Trade. Countries that have initiated demonstration projects or pilot programs include Vietnam, Mongolia, and Lao People's Democratic Republic (PDR) with financial assistance from PATH, Gavi and the Millennium Challenge Corporation Fund.

Another significant barrier to HPV vaccine introduction is the perception that the HPV vaccine is not safe. To date, more than 200 million doses of HPV vaccines have been administered globally, and a review of pre- and

post-licensure surveillance for HPV vaccines support an excellent safety profile (Macartney et al., 2013). Like other vaccines, adverse reactions (i.e. fatigue, redness, swelling, pain) have been reported from HPV vaccine trials/population studies, but most were mild or moderate in intensity, are self-resolving, and only occur in a small proportion of individuals (Garland, 2016). Although more serious adverse reactions such as syncope, anaphylaxis, Guillain-Barré syndrome and venous thromboembolism have occurred following HPV vaccination, there is no evidence that these events occur at higher rates compared with those in unvaccinated individuals, and in some cases, patients who had anaphylaxis or syncope following HPV vaccination no longer had the reactions when they were re-vaccinated with HPV vaccine (Macartney et al., 2013). In Japan, medical conditions such as complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) post vaccination have led to the suspension of the HPV vaccination programme, following lobbying by the affected families and like-minded health professionals. This is despite a review by the WHO's Global Advisory Committee on Vaccine Safety (GACVS) which concluded there was no evidence to suggest a causal association between the HPV vaccine and the adverse events (GACVS, 2015). Moreover, the International Papillomavirus Society (IPVS) supports the safety of these prophylactic vaccines (Garland et al., 2016). Mongolia, which has one of the highest cervical cancer rates in Asia (age-standardised rate of 24.3/100,000) (Globocan, 2012) has also been affected by allegations that HPV vaccines are unsafe and lead to infertility. This resulted in the cessation of a pilot HPV vaccine introduction organised by the Ministry of Health in Mongolia and the Millennium Challenge Corporation, USA to vaccinate 14,063 school girls aged 11-15 years old with 4vHPV after only 9,111 girls were vaccinated.

There are also social and cultural factors that affect the uptake of HPV vaccination. The lack of knowledge and awareness of HPV associated diseases has led to refusal to take up the vaccine in Peru and countries in Sub-Saharan Africa (LaMontagne et al., 2011; Perlman et al., 2014). The fact that HPV is a sexually transmitted infection has led some parents to feel uncomfortable vaccinating their child because of religious and cultural beliefs, or simply because they fear that it will encourage the girl to become promiscuous (Joseph et al., 2012). This has also led to inconsistent HPV vaccine recommendations by some health professionals, who feel that they are promoting pre-marital sex (Krupp et al., 2010). Research has shown that there was no increase in sexual activity in girls who had received HPV vaccine compared with girls who did not in the USA (Liddon et al., 2012). These misconceptions highlight the need to create and improve awareness about HPV, including the prevention and treatment methods, both within the communities, and among health care professionals. A cross-sectional study in India, Peru, Uganda and Vietnam, and a study in Cambodia have demonstrated that increased awareness and knowledge has led to increased rates of HPV vaccine uptake (LaMontagne et al., 2011; Wadhera et al., 2015).

In addition, this approach (community education and increasing awareness of HPV vaccine) has also led to broad acceptance and uptake of the HPV vaccine in the HPV vaccine introduction campaign in Fiji (La Vincente et al., 2015).

Cost-effectiveness of HPV vaccination

The cost-effectiveness of HPV vaccination in a population depends largely on vaccine prices and are important to inform vaccination policy in a given country (Fesenfeld et al., 2013). Several studies on cost-effectiveness of HPV vaccination have been undertaken in countries of Asia. Not surprisingly, they have found HPV vaccination is most cost-effective if the vaccine is procured at a Gavi-negotiated price for LMICs, and also in settings where there is weak or no screening programmes (Fesenfeld et al., 2013). However, different assumptions (i.e. vaccine price, coverage, herd protection and outcomes) were considered for the different studies based on a three-dose schedule, which makes direct comparison of the results difficult. Furthermore, the new recommendation by WHO of a two-dose HPV schedule will increase cost-effectiveness for countries in Asia.

HPV vaccine program implementation

It is widely recognised that in order to effectively protect populations from HPV-related diseases, the HPV vaccine should be given as part of a country's national immunization schedule to young school girls (aged 9-13 years), before sexual debut, as HPV vaccine efficacy against HPV infection is the highest when given to individuals who have not had prior HPV infection (Future I/II Study Group et al., 2010; Lehtinen et al., 2012). School-based immunization campaigns increase the likelihood of reliable follow-up for administration of subsequent dose(s), and have been demonstrated to have high completion rate in not just high-income countries (i.e. Australia and Canada), but also in LMICs (i.e. Malaysia) (Brotherton et al., 2013; Malaysia Ministry of Health, 2013; McClure et al., 2015). The school-based immunization approach also been demonstrated in pilot HPV vaccine programs in Vietnam and Bhutan (LaMontagne et al., 2011; Dorji et al., 2015). However, it is important to note that school attendance may be much lower in LMICs, especially children living in rural settings, and so community outreach activities are important to achieve high vaccine awareness and uptake. Alternatively, primary school attendances are generally higher, so countries may elect to use the final year of primary school as the target group for vaccination, to minimize the need to capture out-of-school children, and thereby maximizing coverage.

However, an important point to note is that while HPV vaccines are extremely effective, they do not protect against all oncogenic HPV types. This justifies the need for continued robust cervical cancer prevention programs that encompass HPV vaccination, cervical cancer screening, education and other healthcare programs. Several cervical cancer screening methods for LMICs have also been developed (Denny et al., 2006). In addition, a new program (HPV-FASTER) has also been proposed to

expand HPV vaccination to women aged up to 45 years to minimise the number of lifetime screening visits, although more studies are needed to address the various research gaps (e.g. exact age limit for vaccination, and screening) (Bosch et al., 2016).

In conclusion, a significant burden of HPV-related disease occurs in LMICs in Asia, where HPV vaccination is not available or is not part of the national schedule. In addition, effective management of HPV diseases requires a multifaceted approach including HPV vaccination, a cervical cancer screening program with effective monitoring and strong referral systems. With Gavi support and the WHO revision of the number of recommended HPV doses (three to two doses), LMICs are now in a better position than five years ago to introduce this vaccine. Philanthropic organisations have supported pilot HPV vaccine programs in countries such as India, Laos PDR, Vietnam, Peru, Mongolia and Uganda, which may lead to a national immunization program. More LMICs, particularly those in Asia need to have improved access to crucial life-saving HPV vaccination programs. To date, only Malaysia and Bhutan have successfully introduced HPV vaccine into their national immunization schedule with high coverage (school-based program; Malaysia: current schedule of two doses of 4vHPV to all school girls aged 13 year-old girls; Bhutan: three-dose 4vHPV schedule to 12 year-old girls). The lessons learnt from establishing the Malaysia and Bhutan national HPV immunization programs are valuable for LMICs in Asia.

Statement conflict of Interest

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