

Cervical Cancer, Human Papillomavirus (HPV), and HPV Vaccines in Southeast Asia



Key Considerations for Expanding
Vaccine Coverage and Improving
Population Health

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EXECUTIVE SUMMARY

Every year, more than 500,000 women develop cervical cancer and 270,000 women die from the disease. The vast majority of these deaths occur in low- and middle-income countries (LMICs), where high mortality rates reflect cervical cancer screening that is inaccessible or not provided in a timely manner.¹ In Southeast Asia, cervical cancer is the second most common cancer in women, and with roughly 175,000 new diagnoses annually, the region has one of the highest incidence rates of cervical cancer in the world.²

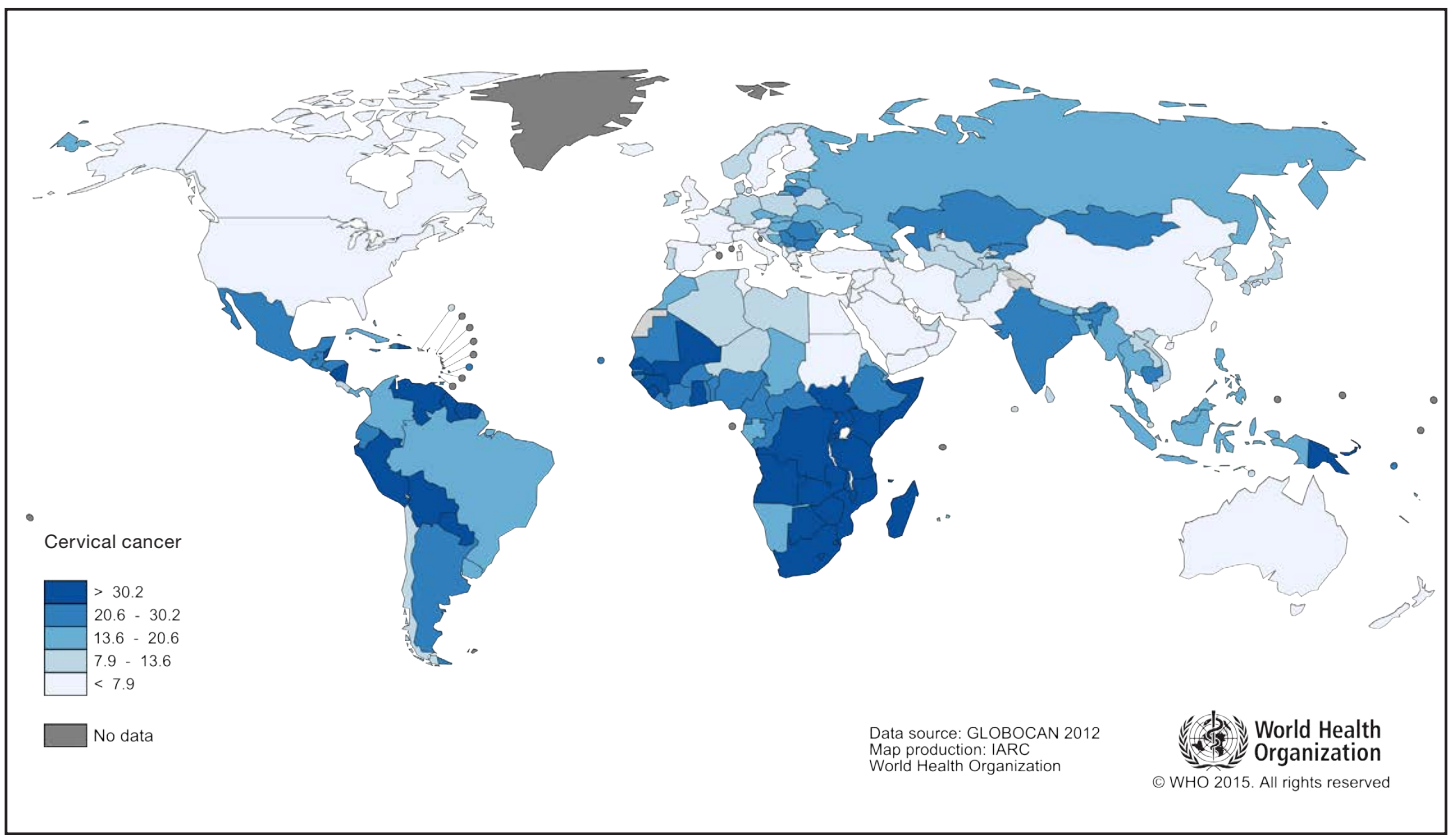
Human papillomavirus (HPV) is the cause of virtually all cervical cancer cases, as well as more than 90% of all anal cancers. The risk of developing these cancers is not

equal among populations; for example, people living with HIV (PLHIV) are at higher risk of contracting HPV and developing HPV-associated cancers. Since 2008, three HPV vaccines (Cervarix®, Gardasil®, and Gardasil®9) have been developed and approved in more than 100 countries for the prevention of select high-risk HPV types that can lead to cervical cancer. The World Health Organization recommends a two-dose HPV vaccination schedule for most children (aged 9–13) and a three-dose schedule for children living with HIV. The development of these highly effective HPV vaccines presents an opportunity to provide population protection against cervical cancer in a way that is not currently feasible in many resource-limited settings through screening alone. With the advent of the HPV vaccine as a primary prevention tool, cervical cancer is, for the first time, an eradicable disease.

KEY MESSAGES

- The HPV vaccine is a highly effective, safe, and necessary component of a comprehensive strategy to control cervical cancer in Southeast Asia and globally.
- National HPV vaccination for girls is cost-effective in 156 countries, including 11 countries in Southeast Asia.
- HPV vaccine prices remain unaffordable in some countries and are a primary reason why few LMICs have included the vaccines in their national immunization programs.
- Subsidization of vaccine costs by Gavi (a major donor providing support for eligible LMICs to purchase essential vaccines) may further improve the cost-effectiveness and affordability of HPV vaccination. However, the majority of countries in Southeast Asia are not eligible for Gavi support under current national income requirements.
- Given the higher cost of HPV vaccination and delivery compared to vaccines administered to infants, innovative methods to finance and deliver the HPV vaccine are required. This is especially important in LMICs where the health system may not routinely reach older children and adolescents with preventive care. These strategies include:
 - > Providing HPV vaccination to adolescents through non-healthcare settings, including school-based delivery systems, community-based sexual and reproductive health programs, or structured referral or outreach mechanisms.
 - > Implementing targeted vaccination programs for those most at risk of developing invasive cancers, including adolescents living with HIV.
 - > Integrating vaccination with existing cervical cancer screening programs or HIV treatment programs to increase cost-effectiveness and reach young people living with HIV.
 - > Applying for Gavi support, if eligible under country income requirements.
 - > Working with a broad range of stakeholders, including large-volume purchasers such as Gavi and UNICEF, to continue to negotiate for lower vaccine prices, and scaling up manufacturing to meet country supply needs.
 - > Establishing cross-sector partnerships with the fields of immunization, cancer control, adolescent health, sexual and reproductive health, and HIV/AIDS prevention in order to promote HPV vaccine awareness and uptake and develop strategies for vaccine delivery, financing, and monitoring.

Figure 1. Age-standardized incidence rate of cervical cancer per 100,000 females in 2012¹¹



INTRODUCTION

What is HPV? Epidemiology: General, Global, Regional

Human papillomavirus (HPV) is transmitted through intimate contact with the skin and mucous membranes of someone who has the virus.^{3,4} Transmission most commonly occurs through vaginal, anal, or oral sex, but it can also be passed between the hands and genitals.⁵ Unlike many other sexually transmitted infections (STIs), HPV can be spread through contact with skin that may not be covered by a condom. So even when used correctly, condoms do not provide 100% protection against infection.⁶ HPV is one of the most common STIs in the world, with 290 million women estimated to be infected at any one time⁷ and a lifetime risk of acquisition of over 50% for sexually active men and 80% for sexually active women.^{8,9} The prevalence of HPV in Southeast Asia is 14%, among the highest in the world.¹⁰

There are over 150 types of HPV, 16 of which are classified as “high-risk” or cancer-causing.¹² The remaining low-risk types are not associated with cancer, but can cause

genital warts. The majority of HPV cases present with few to no symptoms and are cleared by the immune system within two years of infection;¹³ as such, most individuals are unaware of their infection status. However, when symptoms do occur, the disease burden due to HPV is high. Low-risk HPV types 6 and 11 are the cause of 90% of the world’s cases of genital warts,¹⁴ and high-risk HPV types 16 and 18 have been associated with 92% of anal, 89% of oropharyngeal, 80% of both vulvar and vaginal, 70% of cervical, and 63% of penile cancers worldwide.¹⁵

Since HPV infection is considered a “necessary cause” (a factor that must be present to produce disease) of cervical cancer, reducing HPV infection is critical for reducing cervical cancer mortality.¹⁶ Addressing HPV is of high importance in Southeast Asia, where there are roughly 175,000 new diagnoses of cervical cancer annually, making cervical cancer the second most common cancer among Asian women.¹⁷ Country-specific mortality rates from cervical cancer ranged from 2.8 per 100,000 women in Japan to 12.4 per 100,000 women in India in 2012.¹⁸ By comparison, the United States reported 2.7 deaths from cervical cancer per 100,000 women during the same period.

HPV Risk Factors

Several behavioral factors are associated with an increased risk of acquiring HPV, including a higher number of sexual partners, increased age of sexual partners, and inconsistent condom use.¹⁹ While the majority of those who contract HPV will clear the virus and not develop cancer, regular screening is necessary to detect and treat precancerous lesions at an early stage. Individuals in LMICs with weak health infrastructure, inadequate health system financing, or other barriers to accessing care are less likely to be regularly screened and thus are at greater risk of being diagnosed with HPV-associated cancers at later and more dangerous stages.

A number of biological characteristics increase the risk of cancer development in people with HPV, including infection with HIV or other STIs, nutritional deficiencies, genetics, and age.²⁰ The strength of these associations is variable and in some studies contradictory; however, the positive association between HPV and HIV is well defined and of particular importance in countries with large numbers of individuals with HIV. Infection with HPV increases the risk of infection with HIV, and HIV increases the risk of developing HPV-associated cancers.²¹ HIV-positive women are estimated to be eight times more likely to develop invasive cervical cancer, which is considered an AIDS-defining illness.^{22, 23}

HPV infection increases the risk of becoming infected with HIV in multiple subgroups: heterosexually identified men, men who have sex with men (MSM), and women.^{24, 25} HPV is believed to act similarly to other STIs in disrupting the integrity of the mucosal cells that line the mouth, anus, and vagina, allowing HIV to more easily enter the body.^{26, 27} Although HPV and HIV infections are driven by many of the same types of risk behaviors, such as unprotected sex with multiple partners;²⁸ the risk of HIV infection remains more than twice as high among those with HPV than without HPV even after controlling for behavioral risk factors.²⁹

AVAILABLE VACCINES

Currently approved HPV vaccines work by generating an immunological response against HPV viral proteins, providing immune protection against future infection. These vaccines do not contain functional virus and therefore cannot cause HPV infection. There are currently three available HPV vaccines: Cervarix®, Gardasil®, and Gardasil®9. Cervarix protects against high-risk HPV types 16 and 18. Gardasil additionally protects against types 6 and 11, which cause about 90% of all genital warts, while

Gardasil 9 additionally protects against types 6, 11, 31, 33, 45, 52, and 58.³⁰ Although Cervarix and Gardasil have demonstrated efficacy in protecting against high-risk types 31, 33 and 45, in a phenomenon known as cross-protection, they are not indicated for these types.^{31, 32}

All available vaccines have demonstrated 93–100% efficacy in preventing cervical pre-cancers due to HPV types 16 or 18 in previously unexposed girls and young women.^{33, 34, 35, 36, 37} Gardasil has also demonstrated over 78% efficacy in prevention of anal pre-cancers and 90% efficacy in preventing genital warts caused by types 16 or 18 in boys and young men.^{38, 39} Additional protection provided by Gardasil 9 has proved 97% effective in preventing high-grade cervical, vulvar, or vaginal disease related to HPV types 31, 33, 45, 52, and 58.⁴⁰

HPV vaccination is shown to be safe and highly effective at successfully producing HPV protection in PLHIV, especially if individuals are also being treated for HIV with antiretroviral therapy (ART). In fact, research has shown that HPV antibody levels for types 16 and 18 in HIV-positive women after completing the three-dose series of Cervarix were higher than levels in HIV-negative females after natural HPV infection.⁴¹ This emphasizes the importance of HPV vaccination among PLHIV.

Prior to approval, all three vaccines underwent rigorous pre-licensure evaluation in several large-scale studies. In the United States, post-licensure surveillance and monitoring through the Vaccine Adverse Event Reporting System (VAERS) has classified 94% of all reported adverse events related to Cervarix and 92% related to Gardasil as non-serious,⁴² with the most common side effects being pain, redness, and swelling at the injection site.⁴³ Vaccine safety is closely monitored on a global scale by the WHO's Global Advisory Committee on Vaccine Safety (GACVS), which compiles national-level data on adverse events.⁴⁴

Licensing

In countries where the vaccines are licensed, the WHO recommends the Cervarix vaccine for girls and boys aged 9–14 and the Gardasil vaccine for girls and boys aged 9–13. HPV vaccines are typically administered along a 3-dose schedule, with the second dose occurring 1–2 months after the first, and the third occurring six months later.^{45, 46, 47} Since evidence suggests that these vaccines produce a more robust immune response in younger children,⁴⁸ in 2014 the WHO amended its guidance to recommend a 2-dose regimen for children aged 9–14, with an interval of at least six months between doses.⁴⁹ This recommendation may improve vaccine coverage and reduce

implementation barriers in LMICs by reducing the total cost of vaccination and the number of clinic visits required to complete the series.⁵⁰ The WHO continues to recommend the 3-dose schedule for children and adults aged 15 or older and immunocompromised (e.g., HIV-positive) children.⁵¹

Both Cervarix and Gardasil are licensed in more than 100 countries.⁵² Both vaccines are designated by the WHO Prequalification of Medicines Programme as prequalified vaccines, indicating that they meet high global standards for safety, quality, and efficacy.⁵³ Medications that meet these standards can be procured and distributed through international bodies such as Gavi and UN affiliates in partnership with developing countries.⁵⁴

As a newer vaccine, Gardasil 9 is not yet prequalified by the WHO⁵⁵ and has not been approved for use in any Asian country. However, its inclusion is of particular importance in Asian countries where the additional HPV strains that Gardasil 9 protects against (HPV 58, 33, 52, 45, 31) are among the most frequent types found in women (Fig. 2).⁵⁶ Indeed, one study found HPV-58 in up to 26% of cervical cancers in Shanghai and in 17% of high-grade precancerous cervical lesions in East Asia overall.⁵⁷

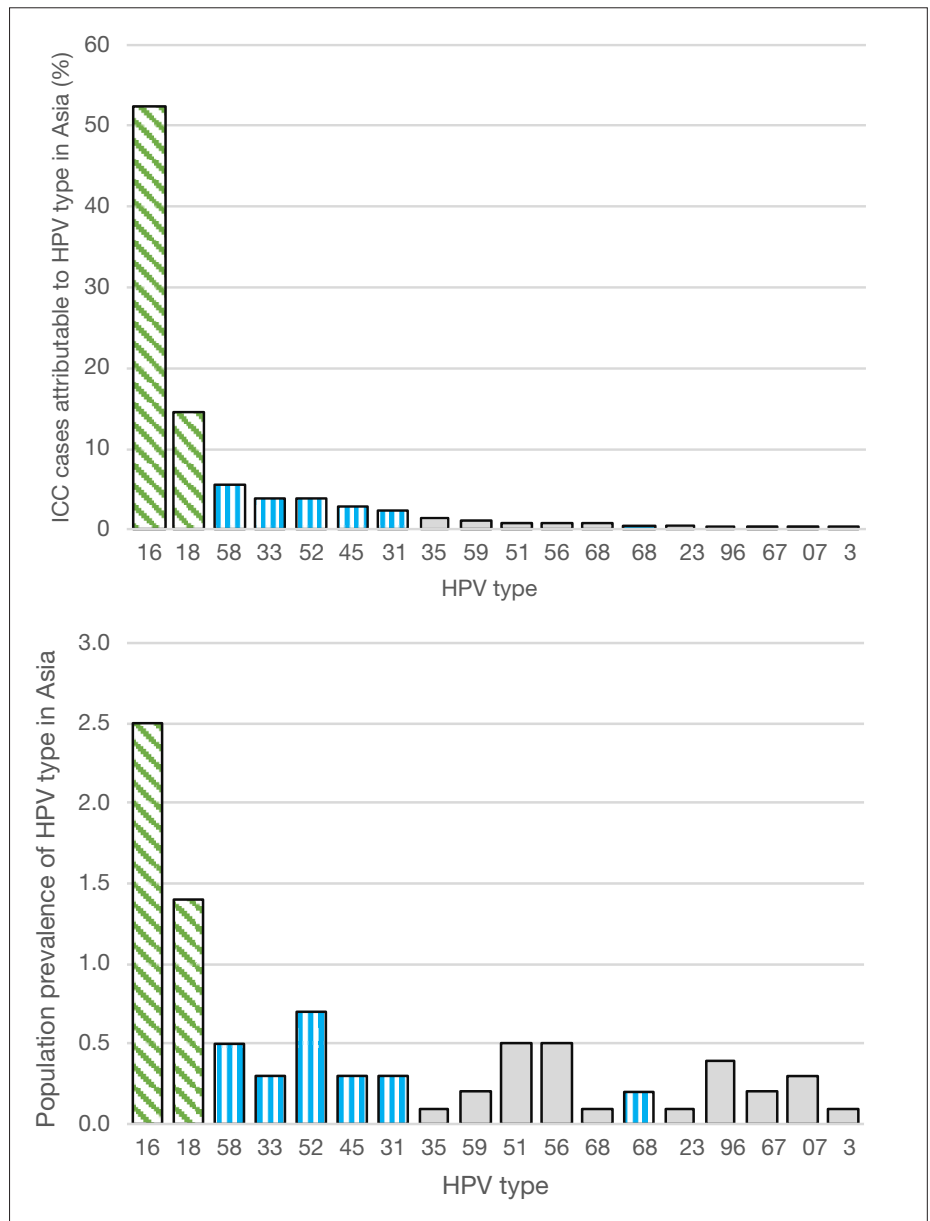
Financing

Vaccine financing is crucial to making HPV vaccines available through national immunization programs. Key issues for government consideration are the price of introducing a new vaccine, HPV disease burden, availability of cervical cancer screening, implementation capacity, and competing health priorities also requiring vaccine introduction (such as pneumococcal and diarrheal diseases).

Gavi, the Vaccine Alliance, is the major donor enabling low-income countries to procure essential vaccines, and in 2011

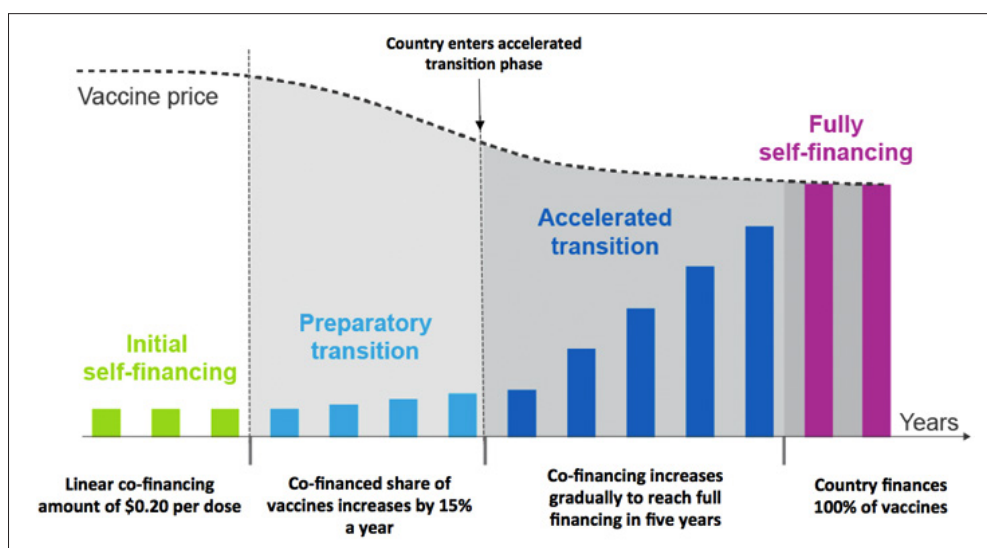
it began offering support for HPV vaccination. In general, countries with a gross national income (GNI) per capita at or below US\$1,580 on average for the past three years are eligible for Gavi support.^{60,61} Countries must also participate in a two-year HPV demonstration program and successfully deliver the HPV vaccine to at least 50% of a cohort of girls in a representative district.⁶² For applications for HPV-specific

Figure 2. Percentage of invasive cervical cancer (ICC) cases in Asia by HPV type (top)⁵⁸ and HPV type prevalence in female populations in Asia (bottom)⁵⁹



▨ HPV types preventable by Cervarix and Gardasil
▨ Additional HPV types preventable by Gardasil-9
▨ Types not included in current vaccines

Figure 3. Transition process for Gavi-eligible countries from initial self-financing to fully self-financing⁶⁴



vaccine support, countries must additionally demonstrate national diphtheria-pertussis-tetanus dose 3 (DTP3) vaccine coverage greater than or equal to 70%. Once Gavi-eligible countries surpass the economic threshold, they are known as “graduating” countries and enter a five-year accelerated transition phase toward fully self-financing their own immunization programs. After five years, these countries “graduate” and are no longer eligible to receive financial support from Gavi (Fig. 3).⁶³

Of the countries in Southeast Asia without national HPV programs, ten are eligible for Gavi support (Table 1). Four of the Gavi-eligible countries in Southeast Asia (Bangladesh, Lao PDR, Nepal, and Solomon Islands) have already applied for HPV vaccine support. Of the six remaining countries, Papua New Guinea is ineligible for HPV-specific funding based on low DTP3 coverage, and five countries (Cambodia, India, Korea DPR, Myanmar, and Pakistan) have not yet applied for funding. Five of the Gavi-eligible countries (Indonesia, Kiribati, Sri Lanka, Timor-Leste and Vietnam) are “graduating” countries and are still eligible to apply for HPV vaccine support one last time in 2016.

Middle-income countries that do not qualify for Gavi support, such as Thailand and Malaysia, must finance HPV programs through alternative financing strategies and would need to independently negotiate prices with pharmaceutical companies.

Cost-Effectiveness

Vaccine prices are an important factor influencing a country’s decision to provide HPV vaccines. The cost of HPV vaccines varies considerably worldwide, ranging from the lowest Gavi-

Table 1. 2016 Gavi-eligible countries in the Asia-Pacific region with DTP3 coverage rates⁶⁵ and GNI per capita⁶⁶ shown

COUNTRIES	HAS RECEIVED HPV VACCINE SUPPORT FROM GAVI	DTP3* COVERAGE AMONG 1-YEAR-OLDS (2014)	GNI† PER CAPITA, US\$ (2014)
BANGLADESH	YES	95%	1,080
CAMBODIA	NO	97%	1,020
INDIA	NO	83%	1,570
KOREA, DPR	NO	93%	NO DATA
LAO PDR	YES	88%	1,660
MYANMAR	NO	75%	1,270
NEPAL	YES	92%	730
PAKISTAN	NO	73%	1,400
PAPUA NEW GUINEA	NO**	62%	2,240
SOLOMON ISLANDS	YES	88%	1,830

*Diphtheria-pertussis-tetanus dose 3

†Gross national income

**Ineligible for HPV-specific funding based on low DTP3 coverage

Table 2. Cost-effectiveness (CE) of vaccinating one birth cohort of 12-year-old girls by country⁷⁰

COUNTRIES	GDP* PER CAPITA, US\$ (2011)	COHORT SIZE ('000s)	VACCINE COST (\$M)	\$/DALY [†] PREVENTED	CANCERS PREVENTED PER 100,000 GIRLS VACCINATED	CONCLUSION
AUSTRALIA	39,400	138	57.1	37,400	583	VERY CE
BANGLADESH	1,790	1,560	31.1	500	1,420	VERY CE
BHUTAN	5,810	7.0	0.2	1,100	913	VERY CE
BRUNEI	50,500	3.1	1.3	13,000	1,710	VERY CE
CAMBODIA	2,370	146	2.9	410	2,070	VERY CE
CHINA	8,470	8,210	455	3,210	603	VERY CE
FIJI	4,790	7.6	0.4	519	3,340	VERY CE
INDIA	3,650	11,700	352	509	1,950	VERY CE
INDONESIA	4,670	2,110	63.2	929	1,500	VERY CE
JAPAN	34,300	564	234	20,100	1,010	VERY CE
LAO PDR	2,810	71.7	2.2	1,110	980	VERY CE
MALAYSIA	15,600	283	15.7	2,520	1,500	VERY CE
MALDIVES	8,930	2.8	0.2	2,910	1,110	VERY CE
MONGOLIA	4,760	22.4	0.7	674	2,120	VERY CE
MYANMAR	7,360	416	8.3	394	1,550	VERY CE
NEPAL	1,260	359	7.2	346	1,740	VERY CE
NEW ZEALAND	29,900	28.4	11.8	62,300	436	CE
PAKISTAN	2,760	1,960	58.8	1,490	662	VERY CE
PAPUA NEW GUINEA	2,700	82.5	2.5	256	2,720	VERY CE
PHILIPPINES	4,140	1,060	58.7	1,590	1,270	VERY CE
SAMOA	4,570	2.2	0.1	3,840	1,350	VERY CE
SINGAPORE	61,100	33.9	14.1	24,500	1,160	VERY CE
SOUTH KOREA	30,300	273	113	35,300	811	CE
SRI LANKA	5,620	157	4.7	1,820	1,170	VERY CE
THAILAND	8,700	484	26.8	1,110	1,400	VERY CE
TIMOR-LESTE	1,590	15.9	0.5	1,250	1,270	VERY CE
VANUATU	4,630	2.8	0.2	1,980	873	VERY CE
VIETNAM	3,440	638	19.1	1,100	981	VERY CE

*Gross domestic product

†Disability-adjusted life year

procured price of \$13.50 for the three HPV vaccine doses to more than \$300 at non-Gavi market prices.⁶⁷ The additive cost to existing vaccination schedules has been the primary reason why few LMICs have included the vaccine in their national immunization programs.⁶⁸

Another key factor influencing a government's decision to introduce the HPV vaccine nationally is the cost-effectiveness of widespread vaccination. A global modeling

study found that HPV vaccination is cost-effective in 156 countries worldwide and in all countries in Southeast Asia.⁶⁹ This model estimates that in Southeast Asia, vaccinating just one birth cohort of 17 million girls would prevent 240,000 cases of HPV and 150,000 HPV-related deaths in that cohort at a net cost of \$390 million. The model assumed a full vaccine series cost per girl of \$25 and 100% vaccine coverage of the target cohort.

Vaccine price reductions would further improve cost-effectiveness calculations; however, the up-front costs of vaccine rollout may still be considered unaffordable. In non-Gavi eligible countries, where current vaccine prices make a national rollout infeasible, targeted HPV vaccination programs for high-risk subpopulations (for example, HIV-positive adolescents) may be more feasible. Such targeted vaccine campaigns can be cost-effective even at higher vaccine pricing due to the increased cancer risk in these groups; thus vaccination would provide greater potential benefit.

Furthermore, studies suggest that in countries where cervical cancer screening and testing programs are already in place, integrating HPV vaccination would increase cost-effectiveness by reducing implementation costs and increasing uptake, while also leading to a more comprehensive program for cervical cancer prevention. For example, a study conducted in Malaysia found that a combined strategy of vaccination and cervical cancer

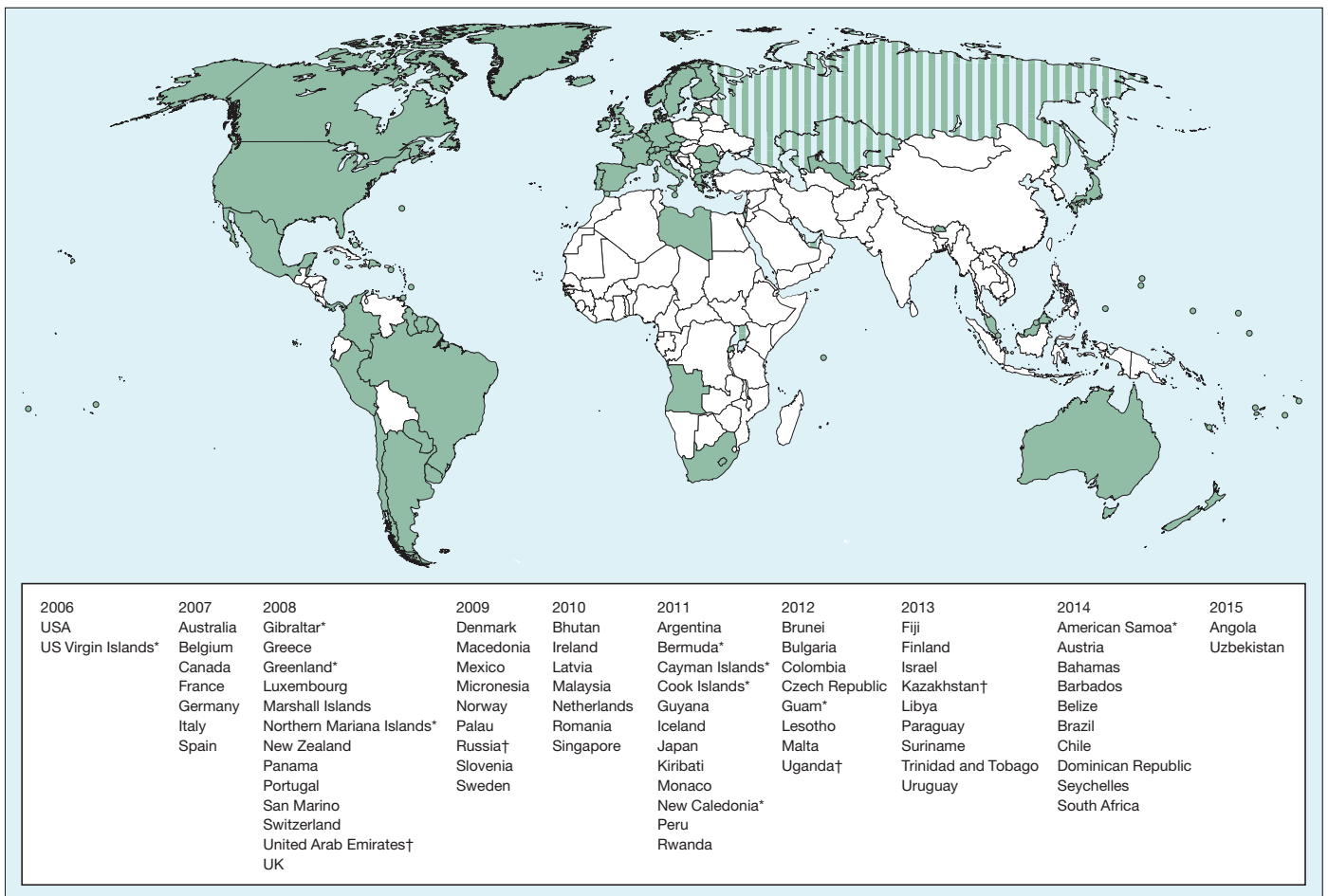
screening would be more cost-effective than screening methods alone.⁷¹

EXAMPLES OF NATIONAL AND PILOT PROGRAMS IN THE ASIA-PACIFIC

Within the Asia-Pacific region, Australia, New Zealand, Singapore, Malaysia, Bhutan, and ten Pacific islands have incorporated HPV vaccines into their national immunization plans.⁷² However, as shown in Figure 4, significant gaps remain in LMICs, despite experiencing the highest global cervical cancer burden.

Southeast Asian countries that have implemented nationwide HPV vaccination programs have done so by leveraging a variety of implementation and funding strategies (Table 3). These include financing vaccination programs through existing healthcare systems, school

Figure 4. Countries with publicly funded HPV vaccination programs⁷³



Countries with national HPV vaccination programs are in green, those with programs in only part of the country are in stripes, and those without known programs are in white.

*Special territory †Partial implementation

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Table 3. Examples of national HPV vaccine programs in the Asia-Pacific region

<p>Singapore High-Income Country</p>	<p>In 2010, Singapore adopted HPV vaccination into its National Child Immunization Schedule for females aged 9–26. The vaccination is implemented through primary care facilities and health centers. Females aged 9–14 can opt for the 2-dose schedule of Cervarix or Gardasil. The HPV vaccine is eligible for reimbursement through Medisave, the national medical savings scheme.⁷⁵ HPV vaccination in Singapore is individually initiated and voluntary; as such, vaccine uptake data are limited but estimates of coverage are as low as 4%.^{76,77} Low uptake is likely driven by lack of awareness of the vaccine and possible misconceptions about both HPV and the vaccine.^{78,79}</p>
<p>Malaysia Upper-Middle-Income Country</p>	<p>In Malaysia, cervical cancer is the third most common cancer for women.⁸⁰ The Malaysian government began vaccinating 13-year-old girls with three doses of Cervarix in 2010.⁸¹ The program is conducted through existing school clinics and financed by the school health program (SHP).⁸² The vaccine is also delivered through community health centers to reach missed or out-of-school girls.⁸³ Malaysia’s program has resulted in a 94% vaccine coverage rate among its target demographic with a 3-dose schedule in 2013.⁸⁴ The government also started a catch-up program for girls aged 18 to receive the vaccine, and has achieved 87% coverage.^{85,86}</p>
<p>Bhutan Lower-Middle-Income Country</p>	<p>Cervical cancer is the most common cancer among women in Bhutan.⁸⁷ Through a partnership between the manufacturer of Gardasil (Merck), and the Australian Cervical Cancer Foundation, Bhutan became the first developing country to implement and launch a national program to vaccinate girls against HPV in 2009.^{88,89} The six-year program targets adolescents aged 12–18 through schools and health centers with a 3-dose vaccination schedule. Merck supplied free Gardasil vaccines for the first year of the program and provided the vaccine at a discounted price for the following five years. In 2011, the government officially introduced the HPV vaccine into the routine immunization schedule for 12-year-old girls.⁹⁰ Bhutan’s program has achieved 90% vaccine coverage for girls aged 12–18 through the school-based program and 70% coverage through the health center-based program.⁹¹</p>

health systems, or partnerships with vaccine manufacturers. As seen in Malaysia and Bhutan, high rates of vaccine coverage were achieved by leveraging both school-based and community-based delivery systems to reach the target population. Integrating HPV vaccination and education into existing school or community health systems can reduce the cost of delivery and improve acceptability. Particular benefit may be seen by integrating HPV vaccination into existing cervical cancer screening programs or HIV treatment/prevention services to reach high-risk youth and young people living with HIV.

As shown in Singapore (Table 3), voluntary and individual-initiated vaccination programs may produce low coverage rates unless combined with educational outreach efforts and incentives to vaccinate. Strategies for familiarizing providers, parents, and youth with vaccination programs—including holding parent-school meetings, providing information in leaflets or on radio broadcasts, and developing partnerships with pediatric organizations, community stakeholders, and religious leaders—may be effective in

increasing acceptability. Education campaigns that clearly communicate the role of the HPV vaccine in preventing cancer, as opposed to solely preventing sexually transmitted infections, may be an effective approach, depending on the context.

Several Southeast Asian countries without national HPV vaccination programs have taken significant steps toward incorporating the vaccine into national schedules. Between 2006 and 2015, demonstration projects in India, Cambodia, Bhutan, Vietnam, Lao PDR, Bangladesh, Nepal, the Solomon Islands, Papua New Guinea, Indonesia, and Thailand have successfully delivered HPV vaccination to over 50% of girls in participating districts, with some studies achieving greater than 90% coverage rates.^{92,93,94,95} Support for these demonstration projects came from a mixture of international NGOs, vaccine manufacturers, and Gavi. Four country case examples (Table 4) demonstrate potential strategies for the implementation of subnational and national vaccination programs, and illustrate some of the obstacles to successful rollout.

Table 4. Examples of HPV vaccine pilot programs in the Asia-Pacific region

<p>Cambodia Low-Income Country</p>	<p>Cambodia is a Gavi-eligible country in the initial self-financing phase. Cervical cancer is the most common cancer among Cambodian women and is the leading cause of cancer deaths. Cambodia lacks both a national HPV vaccination program and a comprehensive cervical cancer screening program;⁹⁶ however, pilot programs are ongoing with the intent of demonstrating successful vaccine delivery.⁹⁷ In Cambodia's 2015 application to Gavi for health systems strengthening (HSS) support, the country indicated that it was considering the vaccine for possible implementation in 2016.⁹⁸</p> <p>An assessment of two pilot programs in Cambodia, rolled out by the Gardasil Access Program, found that adherence to all three doses was high, ranging from 88% (95.5% for two doses) in a mixed delivery model across 10 sites, to 95% for all three doses (97% for two doses) in a health center delivery model at one site.⁹⁹ While these programs targeted just under 12,000 girls, adherence rates for all three doses were significantly higher than the estimated rate for 13–17-year-old girls in the US, which was 40% in 2014.¹⁰⁰ These results demonstrate a high potential acceptability of the vaccine.</p> <p>A 2014 review found that a national HPV vaccination program in Cambodia would be cost-effective, compared to the subsequent costs of disease burden resulting from not vaccinating, if the cost per fully vaccinated female was less than US\$32, inclusive of service delivery.¹⁰¹ Cambodia currently delivers vaccines through a fixed facility strategy, in which vaccines are delivered in health facilities at specified times of the week; however, this strategy is poorly suited to reaching remote areas in the mostly rural country.¹⁰² Successful rollout of the HPV vaccine will require innovative strategies for reaching children in these populations.</p>
<p>India Lower-Middle-Income Country</p>	<p>A quarter (25%) of the world's new cervical cancer cases and cervical cancer deaths (26.5%) occur in India.¹⁰³ The majority of Indian women have never been screened for cervical abnormalities, and cancer patients tend to present in the advanced stages of disease.¹⁰⁴ In early 2016, Gavi awarded India US\$500 million in support for its overall national immunization program, to be implemented between 2016 and 2021, after which India will fully transition away from Gavi support.¹⁰⁵</p> <p>It is expected that a portion of the Gavi support will be dedicated to developing a national HPV vaccination program. The initiative is awaiting approval by the Indian government.^{106,107} The health ministry is urging rapid review and approval of Gardasil and Cervarix for use on a national scale.^{108,109,110} Stakeholders recommend the delivery of the vaccine through the current immunization program, i.e., in schools and health facilities.¹¹¹</p> <p>In addition to external support for an HPV vaccine program, India has recently launched a National Biotechnology Development Strategy for 2015–2020, which includes an agenda for in-country manufacture of HPV vaccines.¹¹² This would reduce costs for all vaccines included under its national immunization program.</p>
<p>Indonesia Lower-Middle-Income Country</p>	<p>Cervical cancer is the second most common cancer in Indonesian women after breast cancer.¹¹³ Cervical cancer screening is lacking in Indonesia, with only eight of the country's 34 provinces providing low-cost cervical cancer screening in 2015.¹¹⁴ Currently available research has shown that while parental acceptance of the HPV vaccine in Indonesia was high (96%), knowledge about HPV and cervical cancer was low.</p> <p>Previous efforts to provide HPV vaccination in Indonesia include a free vaccination program using Cervarix in the Bandung district in 2012.¹¹⁵ Each dose was priced at Rp. 687,500 (US\$71 at the time), and the district allocated Rp. 1.7 billion to procure vaccines, enough to vaccinate 830 girls using a 3-dose schedule. In late 2015, a partnership between the University of Gadjah Mada and the University of Melbourne began a pilot study to examine public attitudes about HPV prevention services, particularly how positive public attitudes regarding cancer prevention could be harnessed to increase HPV vaccination and screenings.¹¹⁶</p>

	<p>Indonesia's Comprehensive Multi-Year Plan for Immunization, 2015–2019, states that HPV vaccination is expected to be rolled out in some unspecified provinces in 2016 and 2017.¹¹⁷ However, there are currently no plans to expand to the rest of the country beyond those dates. Due to country classification and income status, Indonesia has one remaining chance to apply for new vaccine support from Gavi in 2016.</p> <p>Indonesia is one of the few Asia-Pacific countries that manufactures WHO prequalified vaccines. It therefore has the potential to expand production to include the HPV vaccine, thereby increasing coverage and reducing costs for a national HPV program.</p>
<p>Thailand Upper-Middle-Income Country</p>	<p>In Thailand, cervical cancer is the second leading cause of cancer deaths in women aged 15–44 years. With an incidence rate of 17.8 per 100,000 women, Thailand also has one of the highest cervical cancer rates in the Asia-Pacific region.¹¹⁸</p> <p>International NGOs and the Ministry of Public Health have implemented pilot projects to assess the feasibility of introducing the HPV vaccine countrywide. From 2010 to 2012, Jhpiego (an international nonprofit health organization affiliated with The Johns Hopkins University) partnered with Merck to integrate HPV vaccination for girls 9–13 years of age into pre-existing cervical cancer screening and treatment programs for their mothers.¹¹⁹ This project found that within the catchment area of these facilities, 50% of eligible girls received the HPV vaccine within a year. In 2014, the Ministry of Public Health implemented an HPV vaccine pilot project in Ayutthaya for female students in the fifth grade on a 2-dose immunization schedule.¹²⁰ Vaccine acceptance rate was over 90% among health staff, teachers, and parents, and the student vaccine coverage rate was 87%.</p> <p>The government plans to scale up HPV vaccination to 13 provinces in 2017, 25 provinces in 2018, 37 provinces in 2019, and nationwide by 2020.¹²¹ Although the new program is limited to females, it has been suggested that providing HPV vaccination for high-risk younger male populations, such as those with HIV or those who have sex with other males, could have substantial benefits.</p> <p>Thailand has national vaccine manufacturers that produce WHO-prequalified vaccines. Expanding production to include the HPV vaccine could reduce the cost of a national program and increase country/regional access.</p>

SUMMARY

HPV vaccination is safe and broadly cost-effective in all countries in Southeast Asia, and it produces long-term public health benefits. Countries can reduce the burden of cervical cancer by including childhood HPV vaccination as part of comprehensive cancer prevention programs and by offering vaccinations through school-based or community delivery systems. Given the higher costs of vaccination compared to other vaccines administered to infants, innovative methods to finance and deliver the HPV vaccine are required. In settings where up-front costs make national vaccine rollout infeasible, targeted HPV vaccination programs for high-risk subpopulations (for example, HIV-positive adolescents) may be achievable in the short term. Such targeted vaccine campaigns would be less cost-prohibitive, more cost-effective (even at

higher vaccine pricing), and an intermediate step toward expanding national coverage.

For countries that are Gavi-eligible and considering initiating HPV vaccination programs, submitting applications for Gavi support is an important avenue to reducing the financial burden. All countries, especially those that are not Gavi-eligible, may reduce costs by establishing or leveraging partnerships with pharmaceutical companies and international NGOs, which can work together to negotiate lower vaccine prices or advocate for increased vaccine manufacturing. By developing cross-sector partnerships, collaborative funding arrangements, and innovative delivery strategies, countries in Southeast Asia can successfully control cervical cancer and work toward a future without HPV.

Annex: HPV epidemiology, vaccine status, and associated cancer rates in Southeast Asian countries¹²²

COUNTRIES	HPV VACCINE STATUS		HPV PREVALENCE: NORMAL CERVICAL CYTOLOGY (%)	HPV 16/18 PREVALENCE: INVASIVE CERVICAL CANCER (%)	CERVICAL CANCER INCIDENCE*	CERVICAL CANCER MORTALITY†
	AT LEAST 1 LICENSED	NATIONAL PROGRAM	FEMALE	FEMALE	FEMALE	FEMALE
AUSTRALIA	Y	Y	8.5	76.1	5.5	1.6
BANGLADESH	Y	PILOT	4.4	81.2	19.2	
BHUTAN	Y	Y	5.7	81.2	12.8	7
BRUNEI	Y	Y	3	72.3	16.9	
CAMBODIA	Y	PILOT	3	72.3	23.8	13.4
CHINA	Y	N	14.33	76.1	7.5	3.4
FIJI	Y	Y	7.7	82.9	37.8	20.7
FRENCH POLYNESIA	Y	Y			8.2	5.1
INDIA	Y	PILOT	10.26	82.7	22	12.4
INDONESIA	Y	PILOT	16.4	87.7	17.3	8.2
JAPAN	Y	Y	13.53	52.1	10.9	2.8
LAO PDR	Y	PILOT	3	72.3	12.5	7.4
MALAYSIA	Y	Y	18.2	88.6	15.6	4.7
MALDIVES		N	4.4	81.2	11	6.3
MONGOLIA		PILOT	7.2	48.3	24.3	9.3
MYANMAR	Y	N	3	72.3	20.6	12.3
NEPAL	Y	PILOT	2	80.3	19	
NEW CALEDONIA	Y	Y			15.3	10.3
NEW ZEALAND	Y	Y	8.5	76.1	5.3	1.4
PAKISTAN	Y	N	2.2	88.1	7.9	4.7
PAPUA NEW GUINEA		PILOT	7.7	82.9	34.5	21.7
PHILIPPINES	Y	Y	9.3	61.1	16	7.5
SAMOA		N			17.1	
SINGAPORE	Y	Y		63.1	8.1	2.6
SOUTH KOREA	Y	N	22.3	70.3	12.4	7.2
SRI LANKA	Y	N	4.4	81.1	13.1	5
TAIWAN	Y	N	14.4	28.78*	10.5	4
THAILAND	Y	PILOT	14.07	54.42*	17.8	9.7
TIMOR-LESTE		N	3	72.3	13.3	8.1
VANUATU	Y	Y	7.7	82.9	19.2	9.8
VIETNAM	Y	PILOT	1.5*	82.8	10.6	5.2

*All incidence rates are age-standardized

†Deaths per 100,000

Y=yes; N=no

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