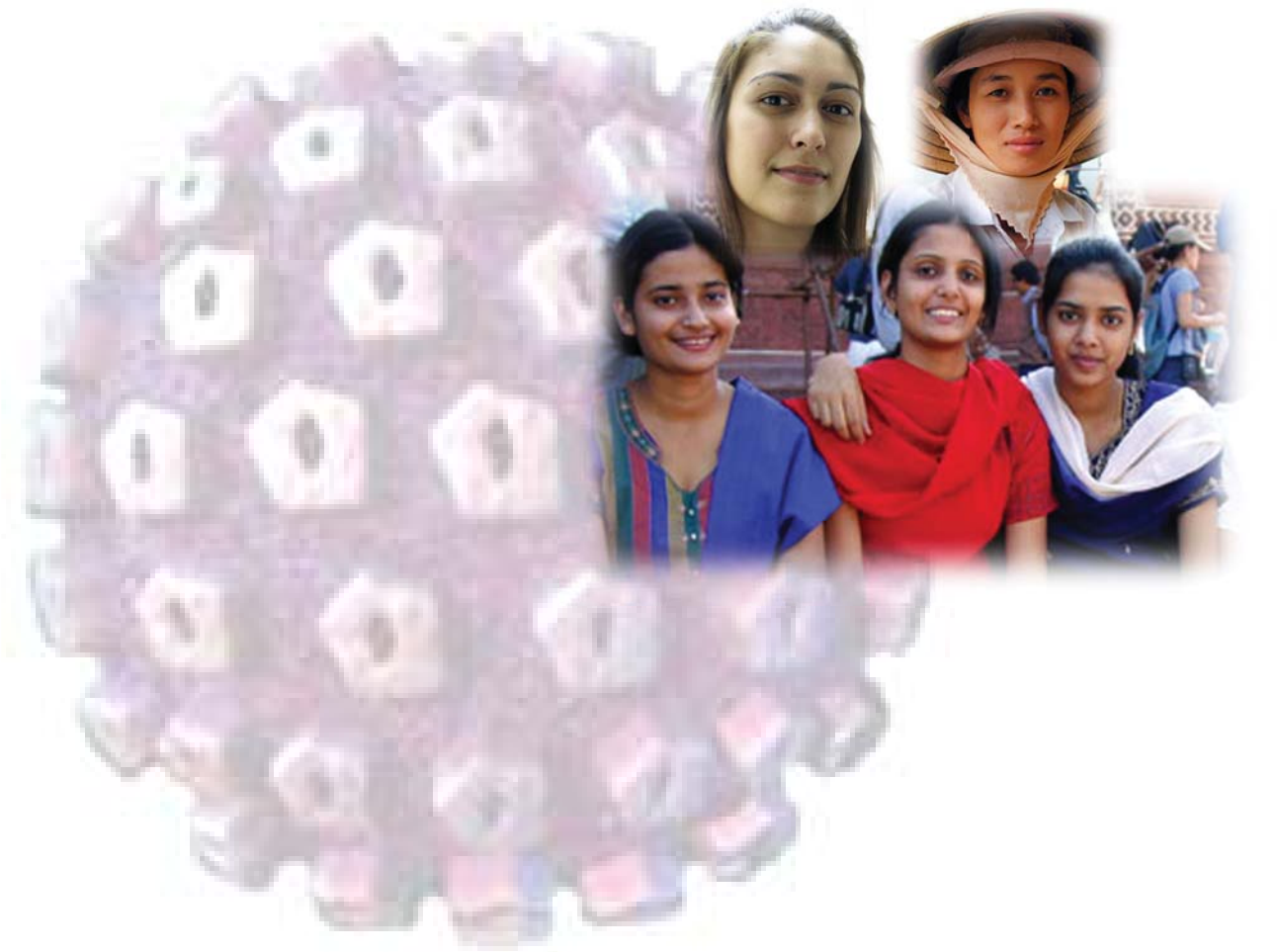
HPV VACCINES



New Tools in the Prevention of Cervical Cancer and Other HPV Disease in Asia and the Pacific

Symposium Proceedings

Bangkok, Thailand
2 November 2006

Family Health International

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Introduction

Background and Significance

Cervical cancer is the second most common cancer world-wide and is the most common cancer among women in developing countries. A comprehensive approach to cervical cancer screening and the recent advent of vaccines for oncogenic genotypes of HPV makes it the most preventable and treatable of all cancers.

While HPV immunization will offer a new tool to the prevention of cervical cancer, other tools for cervical screening will remain vital for decades, especially since women will continue to need screening and early detection programs. Most importantly, the imminent availability of HPV immunization has also opened up the dialogue on the prevention of HPV infection *per se* – whereas it was previously relatively ignored.

Global guidelines on comprehensive programs for cervical cancer control as well as guidance for the introduction of HPV immunization have recently been issued by WHO and WHO/UNFPA respectively, but there has not yet been any process to review these at a regional or country level in Asia and the Pacific.

The initial costs of large-scale HPV immunization could make decision-makers in developing countries reluctant to formulate strategies to incorporate HPV immunization vaccines into programs – especially in the absence of locally applicable data on their likely impact and cost-effectiveness. Without advocacy efforts to build consensus, HPV immunization may not feature prominently on the policy agenda of governments in the Asia Pacific region for some time.

Building partnerships to prevent cervical cancer in Asia Pacific

Family Health International (FHI) is building partnerships to advocate for comprehensive policies on adapting programs for the prevention and early detection of cervical cancer to deal with the introduction of HPV immunization. FHI will collaborate with a range of stakeholders to coordinate and provide targeted technical assistance to facilitate a process for policy and advocacy at the Asia Pacific regional level to improve programming for the prevention and early detection of cervical cancer, focused on the aim of reviewing and adapting relevant global guidelines for the region.

This meeting, *HPV Vaccines, New Tools in the Prevention of Cervical Cancer and other HPV Disease in Asia and the Pacific*, was a satellite meeting of the 3rd Asia Pacific Organisation for Cancer Prevention (APOCP) and International Union Against Cancer (UICC) Symposium, *Empowering Cancer Prevention in the Asian Pacific*. The satellite meeting brought together leading specialists in immunization, cancer prevention, and other disciplines who are essential to building consensus on programming for the prevention and early detection of cervical cancers.

The satellite meeting is the first phase in FHI's regional HPV work. The second phase will take forward a process to build consensus on regional approaches for the prevention and early detection of cervical cancer.

This meeting was organized by FHI, in close collaboration with APOCP, UICC and the National Cancer Institute of Thailand. The meeting was sponsored by Merck Sharp & Dohme (MSD), GlaxoSmithKline (GSK), and Digene.

Burden of disease: epidemiological update – HPV and cervical cancer – a global and regional perspective

Associate Professor Supannee Sriamporn
College of Medicine and Public Health, Ubon Rajathanee University, Thailand

Incidence of cervical cancer

Global: In 2002, 493,000 cases of cervical cancer were diagnosed, representing 4.5% of all cancers (Globocan, 2002). Incidence is highest in parts of Africa and Latin America (up to 87.3/100,000). Incidence of cervical cancer in Asia is lower, but varies significantly between sub-regions and also countries.

Globally, cervical cancer is the second most common cancer among women, with the burden of disease falling heavily on developing countries (Parkin, 2005). Developing countries account for 83% of global cases. The risk of cervical cancer for women aged up to 74 in developing countries is double that for women in the developed world. Cervical cancer accounts for 15% of all cancers in developing countries compared to 3.6% in developed countries.

Key points

- Globally, 500,000 cases of cervical cancer are diagnosed each year.
- 83% of cervical cancer cases are in developing countries.
- Cervical cancer incidence is highest in parts of Africa and Latin America
- Incidence of cervical cancer varies widely in Asia - by sub-region and country.
- The prevalence of cervical HPV DNA is highest in women aged below 25, compared to other age groups.
- HPV is a necessary cause of invasive cervical cancer worldwide.
- A vaccine for HPV types 16 and 18 could prevent up to 72% of cases of cervical cancer.
- Significant declines in cervical cancer incidence in some developing countries indicate the benefits of screening programs.

South-East Asia: has the widest range of incidence, from a low of 13/100,000 in Singapore to a high of 39/100,000 in Cambodia, with most countries having around 20/100,000 cases per annum (Globocan, 2002).

East Asia: has the lowest rate of any Asian sub-region. Incidence in China and Japan is very low at around 6-8/100,000, with approximately 18/100,000 in North and South Korea, and Mongolia.

South-Central Asia: incidence ranges widely from 7/100,000 cases in Pakistan to 30/100,000 in India. Half of the countries have an incidence rate of over 20/100,000.

West Asia: rates vary from a low 5/100,000 in Saudi Arabia to 17/100,000 in Georgia, with most countries below 10/100,000.

Thailand: the age-standardized incidence rate for cervical cancer is 19.5/100,000 with variation between regions from 16.5 to 25.6 for the period 1998-2000. Incidence rates in Thailand from 1990 - 2003 have been stable. Age-specific rates of cervical cancer incidence (1995-97) show the highest incidence for women aged 40 and above (Sripling, 2003).

Squamous cell carcinoma is the most common form of cervical cancer, making up between 75-95% of all cervical cancers globally. Adenocarcinoma accounts for between 5-25% of cervical cancers, with small numbers of other types of carcinoma being reported by national cancer registries (Parkin, 2002).

In addition to the 493,000 global cases of cervical cancer in 2002, 68,000 incident cases of cancer in other sites were attributable to infection with oncogenic HPV. The most common site was the anus, making up 27,360 cases, followed by vulva/vagina 16,000; penis 10,520; mouth 8,223; and oro-phar-

ynx 6,252. Ninety per cent of cases of cancer of the anus are attributable to HPV. For other sites, HPV is responsible for less than 50% of cancers (Parkin, 2006).

Survival with cervical cancer

Five-year relative survival with cervical cancer varies by stage and country:

- 77% in India for localized cancers to 93% in the USA
- 35% in India for regional cancers to 52% in USA
- 6% in India for distant metastasis to 17% in USA

(IARC, 2005)

Thai data show a similar survival rate by stage of cancer, with some variation between provinces (IARC, 1999).

HPV prevalence and incidence

In 1977, HPV was identified as the sexually transmitted etiological agent in cervical neoplasia. The first commercial HPV test was developed in 1988.

HPV infection was proven to be the cause of cervical cancer in the 1990s (Walboomers, 1999). HPV types 16 and 18 have been established as oncogenic. In addition, types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 should be considered oncogenic or high risk types (Muñoz, 2003). Types 26, 53 and 66 should be considered probably oncogenic. There is evidence suggesting types 6 and 11 are not oncogenic.

Since HPV types 16 and 18 are associated with over 70% of cases of cervical cancer, vaccines that prevent infection with these two types alone could potentially prevent over 70% of cervical cancers.

The risk of squamous cell cervical cancer is significantly higher for HPV type 16, followed, in order, by HPV types 59, 33, 18, 52, 45, 31, 58, 73, 35, 51, 68, and 56. The risk of squamous cell carcinoma for type 16 is almost 10 times higher than type 56. (Muñoz, 2003). A study of 1035 cervical cancer biopsies found the presence of HPV DNA in 99.7% of all biopsies. It was concluded that HPV is a necessary cause of invasive cervical cancer worldwide (Walboomers, 1999.)

Globally, HPV type 16 is the most common cause of squamous cell carcinoma, accounting for over 50% of cases. HPV type 18 is the next most common type in squamous cell carcinomas, with approximately 13% of cases. (Muñoz, 2003). The five most common HPV types in squamous cell carcinoma in Asia are 16, 18, 58, 52, and 45. Types 16 and 18 are responsible for approximately 60% of Asian cases of squamous cell carcinoma. (Franceschi, 2003).

In Asia, 14% of HPV infections are type 16, and 5% are type 18. A further 42% of infections are with high-risk HPV types, 7% with other types, and 33% with low-risk types (Clifford, 2005). Globally, there is some variation by region in the pattern of types of HPV prevalence, although the overall pattern is quite similar.

The prevalence of cervical HPV DNA is highest in women aged below 25, compared to other age groups (Herrero, 1997).

Studies of the prevalence of HPV DNA in sexually active women in 11 countries showed an overall age standardized prevalence of 10.5% (Clifford, 2005). There is, however, significant variation by region, and by country and within countries, including in Asia:

- Nigeria 25.6%
- India 14.2%
- Vietnam, Hanoi 1.6%
- Vietnam, Ho Chi Minh City 10.6%
- Korea 13.3%
- Thailand, Lampang 7.2%
- Thailand, Songkhla 3.6%
- Asian countries 8.7%
- South American countries 14.3%
- European countries: 5.2%

Trends in aged standardized rates of cervical cancer incidence in four Nordic countries from 1953 – 1997 show incidence declining by more than half in 3 out of 4 countries, demonstrating the benefits to be gained from screening programs (Parkin, 2002, 1997, 1992; Muir, 1987; Waterhouse, 1982, 1976; Doll, 1966, 1970).

Risk factors for cervical cancer

Dr Malcolm Moore
International Union against Cancer / Asia Pacific Organization for Cancer Prevention, Thailand

It is well established that HPV is the main risk factor for cervical cancer. It is, however, important to look at other risk factors.

Data from some Asian countries show a decrease in incidence of cervical cancer from 1982-2003. In other countries there has been little change, indicating that without screening and vaccination programs, cervical cancer will continue to be a major problem.

Socio-cultural factors

Examination of low incidence HPV countries is important for explaining risk factors associated with cervical cancer. The low incidence of cervical cancer across predominantly Muslim countries suggests that sexual and other behaviors related to STI transmission among populations of different socio-cultural backgrounds may vary considerably. For example, high rates of male circumcision in Muslim countries may lower HPV transmission from males to females.

Comparison of cumulative incidence rates (CIR) for cervical cancer by socio-cultural groups in India shows significantly lower incidence for Muslim populations compared to Hindus and Christians (Shanta, 2000). For example in Chennai, the CIR for cancer of the cervix from 1982-96 was:

- Hindus: 30.7%
- Christians: 25.1%
- Muslims: 13.9%

Key points

- Muslim countries have a low incidence of cervical cancer, possibly related to sexual and other behaviors.
- Male circumcision lowers HPV transmission rates from males to females.
- Low rates of penile cancer are associated with low incidence of cervical cancer.
- Low socio-economic status is associated with a significantly higher risk of cervical cancer.
- Persistent HPV infection and infection with multiple types of HPV increases risk of cervical cancer.
- Smoking is the most significant lifestyle and environmental carcinogen heightening cervical cancer risk.
- Physical exercise, long-term use of oral contraceptives and poor diet are risk factors.
- First intercourse at an early age may increases risk of cervical cancer.
- There is a positive association between HPV infection and infection with other STIs.
- HPV and cervical cancer control requires a range of primary and secondary prevention measures.

Sexual transmission

In countries with a low incidence of penile cancer there is a low incidence of cervical cancer, demonstrating the role of sexual transmission in HPV infection. In Iran, for example, the CIR for penile cancer is 0.1%, with a CIR for cervical cancer of 3.6%. By comparison, in Malaysia, the CIR for penile cancer is 2.9% and for cervical cancer is 19.5%.

Socio-economic factors

Indian data indicates socio-economic factors are associated with the risk of cervical cancer. The incidence rates for illiterates is over 80%, which is more than four times higher than for those with secondary and college education (Shanta, 2000).

Other risk factors

There are a number of factors which determine whether HPV infection persists and then driving the disease progression from a single initiated cell through CIN1, CIN2, and CIN 3 and subsequently cervical cancer.

Persistent HPV infection and multiple infections

It is common for young women who are infected with HPV to become HPV-negative within 6 months. Those with persistent HPV infection and those who acquire second or multiple HPV infections are at higher risk for cervical cancer.

Environmental carcinogens

Smoking is the most significant lifestyle and environmental risk factor for cervical cancer for both smokers and non-smokers (i.e. through passive smoking). Tobacco-specific carcinogens have been identified in the cervical mucus of smokers and non-smokers (Prokopczyk, 1997). Because of the significance of smoking as a risk factor, public health anti-tobacco initiatives have an important role to play in cervical cancer control. Dry cleaning solvents have been shown to increase cervical cancer risk in laundry workers (Ruder, 2001). Smegma has recently been shown not to be a carcinogen (Van Howe, 2006).

Other lifestyle factors

These include physical exercise, long-term use of oral contraceptives, and diet. There is abundant evidence of the protective effects of fruits, vegetables, vitamins C and E, beta- and alpha-carotene, lycopene, luterin/zeaxanthin and cryptoxanthin against cervical cancer. Deleterious dietary factors are alcohol, and possibly malnutrition associated with low socio-economic status.

Sexual behavior and STIs

First intercourse at an early age may be an important risk factor because the cervical transformation zone is very sensitive to trauma and HPV infection.

There are positive associations between HPV infection and infection with *Chlamydia trachomatis*, HIV, and herpes simplex virus type-2.

Trauma

Trauma to the cervix is a risk factor which may explain the positive association between parity and cervical cancer. There is, however, some evidence that the minor trauma associated with a Pap smear may be protective by stimulating the immune system and helping women clear the virus.

SCCs and Adenocarcinoma

Squamous cell carcinoma (SCC) is the much more common form of cervical cancer in Asia Pacific countries, compared to adenocarcinoma, although there is significant variation. The ratio of SCCs to adenocarcinoma varies from 11.9:1 in Mumbai Indians to 2.4:1 in Hawaiians. The Hawaiian ratio is similar to that found in developing countries. There is the possibility that Asian countries may, over time, move towards this pattern.

HPV types 16 and 18 are the main risk factors for adenocarcinoma. Co-factors are never having attended school, poor hygiene, sexual behavior-related variables, long-term hormonal contraception, high parity, and HSV-2 seropositivity (Castellsague, 2006). These risk factors are also risk factors for SCC. There is some evidence that smoking is a less important risk factor for adenocarcinoma compared to SCC. This, however, is based on a limited number of studies.

Primary and secondary prevention

Primary prevention: Key components are:

- not smoking and avoidance of smoke;
- avoidance of other environmental carcinogens;
- improved diet, including dietary supplementation;
- medication for trauma of the cervix and STIs;
- careful sexual behavior; and
- vaccination.

Secondary prevention: key components are:

- Papanicolaou smear;
- direct visual acetic acid screening and resection; and
- HPV testing.

Questions and discussion

Viral load and cervical cancer

A question was asked about whether there is a relationship between HPV viral load and progression to cervical cancer. While there has been no study to establish this, the consensus is that viral load is important and is usually associated with persistent HPV infection. Some data indicate that progression to cervical cancer is probably linked to viral load. The clinical implication is that viral load could be used as a predictor for those infections more likely to progress. There was speculation that high viral load may inhibit the immune systems ability to clear the virus, although there are no data to support this.

Quality of epidemiological data

The question of the quality of national epidemiological data was raised. The response was that the quality of data varies by country. For example, the Singapore data are considered to be quite accurate. Data for some countries are estimated. There is also high variation in cervical cancer incidence within countries, which is not apparent from national aggregated data. For example, in China, while overall incidence is low, there are some provinces with very high incidence rates. There is also variance in data quality between provinces in China. Overall, the national epidemiological data are regarded as a reasonably good broad brush indication of incidence and prevalence. Variation in incidence between countries can primarily be explained by two things: firstly, low incidence in some countries due to cultural and behavioral factors, and secondly, a reduction in incidence in developed countries due to effective screening and treatment.

Trauma

A questioner asked about whether there are any data on women who do not have intercourse suffering cervical cancer, given that trauma is a risk factor. In answer it was stated that a study of nuns had demonstrated zero HPV prevalence and no cases of cervical cancer, demonstrating that sexual intercourse is the primary mode of transmission.

Thai data do not show a significant difference in female prevalence (excluding sex workers), based on the number of sexual partners. Most Thai women, however, have low numbers of sexual partners. The route of infection for most Thai women is from their husbands, who acquire HPV infection from female sex workers. Thai data also show a significant variation in HPV prevalence between different groups of sex workers. The variation may be explained by the number of partners for sex workers in different segments of the sex industry.

Adenocarcinoma

A question was asked about why the proportion of adenocarcinomas varies between countries. In answer, it was stated that diet and obesity may be associated. This, however, needs to be tested. Another participant stated that there are countries with a low incidence of cervical cancer where the proportion (not the rate) of adenocarcinoma is quite high. The reason these countries have a low incidence of cervical cancer is because of effective screening programs. In the past, screening has been much more effective for cervical cancer compared to adenocarcinoma, due to cytology screening techniques. A higher number of adenocarcinomas may be detected at screening in future due to new molecular screening techniques. The incidence of SCCs in developed countries has declined but this has not been seen for adenocarcinoma. As the risk factors are primarily the same, the difference in the proportion of adenocarcinoma may be explained by screening techniques.

Working towards improving cervical cancer control: screening for cervical cancer – success and limitations

Dr Partha Basu,
Chittaranjan National Cancer Institute, India

Every year hundreds of thousands of women are dying of cervical cancer, which is essentially preventable. Cervical cancer is the number one cause of cancer-related years of life lost (YLL) in South Central Asia, Latin America, and sub-Saharan Africa (Yang, 2004). In developed countries, the number of YLL due to cervical cancer is dramatically below that of the developing world.

The world is divided between countries that have or do not have effective cervical cancer screening programs. Countries with well organized screening programs have seen a significant reduction in the incidence of cervical cancer and deaths from cervical cancer over the last 40 years (e.g., UK, Nordic countries) (Farley, 2002).

Key points

- Cervical cancer is the number one cause of cancer-related years of life lost in South Central Asia, Latin America and sub-Saharan Africa.
- Screening programs in some countries have resulted in a significant reduction in the incidence of cervical cancer.
- Screening programs in other countries have not resulted in a sustained decline in cervical cancer incidence. This may be because of the accuracy of cytology.
- The Pap smear is a moderately sensitive test, at best, with good results dependent on the quality of laboratories and personnel.
- VIA provides more accurate results compared to cytology.
- Combined VIA and VILI testing gives improved sensitivity, without much trade-off in specificity.
- The low specificity of VIA may offset the cost savings.
- HPV testing by hybrid capture II provides good sensitivity and reasonably good specificity, but is currently high cost.
- HPV vaccines will significantly reduce the psychosocial and health costs associated with screening.

Screening programs are not effective in all countries. For example, in Costa Rica, a population-based, government sponsored cervical cancer screening program with reasonably good coverage failed to achieve a sustained decline in the incidence of cervical cancer. This led researchers and health planners to ask what was going wrong.

Accuracy of cytology

In response to poor outcomes for some screening programs, the accuracy of Pap smear testing was objectively evaluated. A meta-analysis of the accuracy of cytology (Nanda, 2000), provided the following results:

Overall sensitivity:
Minimum: 23%
Maximum: 100%
Mean: 50%

Overall specificity:
Minimum: 6%
Maximum: 99%
Mean: 66%

The Pap smear is a moderately sensitive test, at best, with good results dependent on the quality of laboratories and personnel. A cytology-based screening program may be difficult to implement in many developing countries due to lack of proper infrastructure, logistics and trained personnel required for the test.

Alternatives to cytology

The limitations of the Pap smear led people to evaluate alternative tests. An ideal alternative test to cytology would have the following characteristics:

- A high level of accuracy
- No need for high-level infrastructure
- Can be performed in primary health care settings
- Is more objective and reproducible
- Results available immediately
- Health personnel can be easily trained
- Affordable

Accuracy of visual inspection tests

Multiple studies have found that Visual Inspection with Acetic Acid (VIA) provides more accurate test results than cytology, especially when both the tests are performed in low-resource settings. Recent analysis shows that combined use of VIA and Visual Inspection with Lugol's Iodine (VILI) tests gives improved sensitivity (VIA: 78.3%; VILI: 90.6%; combined VIA, VILI: 92.2%), without much trade-off in specificity (VIA: 87.3%; VILI: 86.9%; combined VIA, VILI: 83.5%) (IARC Multi-centric Trial, Personal Communication).

Limitations of VIA

The low specificity of VIA may offset the cost savings. It is also a highly subjective test. All results on the efficacy of VIA are from research settings. There is concern that VIA may not perform equally well outside research settings.

HPV testing by hybrid capture II

Studies in both developed and developing countries have shown consistently good sensitivity and reasonably good specificity of the test. The advantages of the HPV hybrid capture II test are:

- Reproducible and objective technique.
- Sample taking is easy.
- A high level of technical expertise is not needed.
- Self-sampling is feasible and highly acceptable.
- Rapid and cheaper tests are being developed. (Currently, the test has a high cost).

Flip side of screening

- Discomfort and embarrassment are common.
- Anxiety waiting for test results.
- False-positive and false-negative results.
- Unnecessary interventions from false positive results.
- A huge financial and logistical investment.

The annual cost of cervical cancer screening in the US is equivalent to 300 billion Indian rupees. The annual health budget of India is 26 billion rupees. Less than 1% of this budget is allocated to cancer. This raises the question of whether developing countries can afford screening programs.

Projected impact of vaccines on cervical cancer

Simulation of the projected impact of a vaccine in preventing HPV type 16 and 18-related cervical cancer indicates a decrease in the incidence of cancer, especially for women aged 45-60 years (Goldie, 2003).

Projected impact of vaccines on screening programs

It is estimated that a vaccine will potentially result in:

- A reduction of 20% in atypical squamous cells of undetermined significance.
- A reduction of 14-25% in low grade squamous intraepithelial lesions.
- A reduction of 52-60% in high grade squamous intraepithelial lesions.
- A reduction of 67-71% of cases of invasive cervical cancer.

There will be a corresponding significant decrease in the psychosocial costs associated with HPV infection, cervical cancer and associated medical interventions. The cost of health interventions following positive test results will also be reduced.

Cervical cancer screening in Thailand

Associate Professor Vasant Linasmita
Department of Obstetrics and Gynecology, Ramathibodi Hospital, Mahidol University, Thailand

The population of Thailand is approximately 63.1 million, with 14.4 million women aged 30-60 years. The majority of people live in rural areas and work in the agricultural sector.

Incidence

The ASR incidence rate of cervical cancer in Thailand in 2002 was 19.8/100,000. In that year there were 6,243 new cases of cervical cancer and 2,620 deaths (Globocan, 2002). The ASR incidence rate for all south-east Asian countries is 18.7/100,000. The annual cost of caring for cervical cancer patients in Thailand is estimated to be US$10 million. Trends in incidence of cervical cancer from 1990-2000 have been stable. However, projections of cervical cancer estimate an increase in annual incidence from 6,243 cases in 2002 to over 8,000 in 2008.

Key points

- Cervical cancer screening in Thailand, prior to 2004, has had limited success due to poor organisation and implementation of the scheme.
- Successful cervical cancer prevention programs require good screening coverage, links between screening and treatment, and effective treatment.
- A single-visit approach with VIA and cryotherapy, provided by trained nurses, is a potentially efficient method of prevention in resource constrained settings.
- The Cervical Cancer Prevention and Control Program (2004) uses a dual track Pap smear and VIA-cryotherapy strategy. Screening is performed at 5 year intervals and aims for 80% coverage.
- Coverage has increased significantly, but is below the target, pointing to the need for better recruitment.
- The dual track strategy is working well in some areas, but some problems need to be addressed.
- Women are highly satisfied with the single visit approach.

Thai screening program

Pap smears have been used to screen for cervical cancer in Thailand for the past 40 years without much public health impact. Problems with the national screening program prior to 2004 were:

- It was never implemented in an organized way.
- A lack of public awareness and knowledge of cervical cancer.
- Low screening coverage: 20-25%.
- Targeting of the wrong population.
- Delays of 1-2 months in test results.
- Management of abnormal test results was not widely available.
- Poor data collection.

Elements and characteristics of organized screening programs

For successful cervical cancer prevention programs the following key elements must be linked:

- Good screening coverage;
- Links between screening and treatment; and
- Effective treatment. (Parkin, IARC).

Characteristics of an organized screening program are:

- A defined population;
- Effective recruitment strategies to achieve high coverage;
- A health care system with capacity to screen, follow-up on positive results, and provide treatment;
- A quality assurance system;
- A health information system; and
- A management team responsible for planning and implementation

VIA and cryotherapy

From 1999-2001, a demonstration program in cervical cancer prevention, using VIA and cryotherapy, was conducted in Roi-et Province. The results showed that a single-visit approach with VIA and

cryotherapy, provided by trained nurses, is a potentially efficient method of prevention in resource constrained settings (RTCOG/JHPIEGO, 2003). The use of nurses in cervical cancer prevention is attractive, as there are a large number of nurses in Thailand compared to relatively low numbers of obstetricians-gynecologists, gynecologic oncologists, and cytopathologists.

Frequency of screening

Five-yearly screening of women aged 35-64 years will result in a 55% reduction in the cumulative rate of invasive cervical cancer, assuming an 80% coverage rate. While yearly to 3-yearly screening will result in a 60-61% reduction, it is much more resource intensive (Miller, 1992). For reasons of cost-effectiveness, the new Thai program (see below) has chosen to screen women every 5 years.

The Cervical Cancer Prevention and Control Program (2004) in Thailand

The Program's goal is to decrease the incidence of and mortality from cervical cancer by at least 50% in five years.

The target population is women aged 30-60 years. Screening by Pap smear is to be performed in women aged 35, 40, 45, 50, 55 and 60 years at 5 year intervals. VIA and cryotherapy can be performed for women aged 30-45 years in situations where Pap smear cannot be done effectively. Patients with abnormal Pap smear results, and those with positive VIA results not suitable for cryotherapy, or with suspected cancer, are sent to provincial referral hospitals for diagnosis and treatment. Providers, cytoscreeners, and colposcopists receive payment for registered cases submitted to the National Health Security Office.

The program involves a public education element to increase public knowledge and awareness of cervical cancer. Other key components are education and training of health care workers, including nurse provider competency based training, establishment of a quality assurance system, and information management system.

The Thai program aims to achieve an 80% coverage rate of the target population in five years.

Preliminary results

Pap smear (2005)

- Number screened: 405,756 (target population 600,0000
- Coverage: 67.6%
- Abnormal cytological results: 1.6%
- Patients with pathological diagnosis (pre-invasive and invasive): 0.04%

VIA-cryotherapy (2005)

- Number screened: 47,418 (target population 100,000)
- Coverage: 47.4%
- Offered cryotherapy treatment: 8-10%
- The competency of nurse providers in screening and performing cryotherapy was satisfactory.

Problems with a dual track strategy

There are some problems with the dual track strategy of Pap smear and VIA-cryotherapy:

- The target populations in some areas overlap;
- Data entering programs for the two tracks are different;
- Some health care workers do not approve use of VIA-cryotherapy;
- Shortage of public health care workers to implement the program; and
- A limited number of supervisors to train VIA providers.

Summary

- The dual-track strategy is working well in some areas of Thailand.
- Coverage has increased significantly but is still well below the target.
- Women are highly satisfied with the single visit approach.

Problems encountered can be managed by:

- Better recruitment strategies;
- More scientific evidence on the effectiveness of VIA-cryotherapy;
- Defining the role of each track more clearly and using the same data entry program; and
- Dissemination of information and education to health care workers and the public.

Future cervical cancer prevention strategies

The key words are **C**oncern, **A**ppropriate technology, **R**esearch, and **E**ducation (CARE).

Research on screening cervical cancer and implications for Thailand

Dr Saibua Chichareon
Department of Obstetrics and Gynecology, Prince of Songkla University, Thailand

Cervical cancer research in Thailand

A range of basic, clinical and prevention research has been conducted in Thailand. This presentation draws on some of the research results, especially in relation to policy and program implications.

Screening in low resource settings policy issues

Question: When to initiate screening?
Answer: Women aged 35-50 years
Question: How often to screen?
Answer: Every 3 years
When to recommend treatment & follow-up?
Answer: High-grade precancerous lesions
(PATH, 2000).

Effective Pap smear screening requirements

- Well trained Pap smear providers;
- Ongoing access to supplies and equipment;
- Linkages, including transportation, to reliable cytology laboratories;
- Strategies for ensuring the quality of Pap smear samples and the accuracy of cytological examinations;
- Proven systems for timely communication of test results to screened women; and
- Effective referral system for diagnosis and management

(Herdman, 2000)

Key points

- The single visit approach is safe and effective.
- Patient referral systems need strengthening.
- Self-administered devices for cervical cancer screening are well accepted by patients and perform well in terms of adequacy of smears.
- Combined of p16 and HPV testing may be useful in cervical cancer screening to identify high-risk patients requiring early management.

Properly organized screening programs:

- Identify the population to be screened;
- Call and recall for screening on a planned schedule;
- Have clear screening protocols;
- Have clear referral systems;
- Have process quality indicators; and
- Have outcome quality indicators.

Program monitoring and evaluation

Process indicators - screening

- Percentage of women aged 35-50 screened for the first time in the last 5 years;
- Percentage of dedicated health workers who perform or refer women for screening;
- Percentage of health facilities offering screening;
- Percentage of all screening test results that are positive for HSIL or cancer;
- Percentage of inadequate/inconclusive test results;
- Percentage of false-positive test results;
- Percentage of women aged 35-50 who know basic screening messages; and
- Percentage of women aged 35-50 with positive attitudes towards screening services.

Process indicators – diagnosis and treatment

- Percentage of women with positive screening results diagnosed within 3 months;
- Percentage of women diagnosed with HSIL treated within 3 months;
- Percentage of treated women followed-up within 1 year; and
- Percentage of women with pre-invasive lesions treated as outpatients.

Impact Indicators

- Incidence of invasive cancer; and
- Mortality rate from invasive cancer.

Process measures
- >80% of women aged 35-59 years informed about screening for cervical cancer; and
- >80% of primary health care workers instructed in taking cervical smears.

Outcome measure
- >80% of women aged 35-59 screened at least once.

Impact measures
- *Short term:* >30% reduction in proportion of cases of invasive cervical cancer with advanced (stage II+) disease;
- *Medium term:* >30% reduction in incidence of invasive cervical cancer; and
- *Long term:* >30% reduction in cervical cancer mortality.

(WHO, 1995)

Thai National Screening Program

The National Cervical Cancer Prevention and Control Program was launched in 2004. The Program has the following strengths, compared to the previous screening program:
- Improved implementation;
- A recruitment strategy;
- Better laboratory support network;
- Incentives for health care workers through payments for cases that are registered and reported;
- Free-of-charge to the patient;
- A stronger emphasis on health promotion; and
- Dual track strategy of screening: Pap smear and VIA/cryotherapy.

Cervical cancer prevention program: challenges

An appropriate test is not sufficient. An effective service delivery system is essential to provide:
- Good test coverage;
- Appropriate management of positive screens;
- Follow-up to limit loss of contact with patients; and
- Reasonable treatment cost

The single visit approach

The consensus on the single visit approach and related service delivery issues is:
- Single visits are safe and effective in resource constrained settings;
- VIA can be implemented in many settings where quality assurance is strong;
- Prevention programs based on visual screening or HPV testing can be cost-effective;
- Cryotherapy is safe and effective and can be delivered by non-physicians;
- Cervical cancer prevention programs should be sustainable; and
- Funding agencies should support costs.

(Alliance for Cervical Cancer Prevention; American College of Obstetrics and Gynecology)

Cost-effectiveness analyses of the single visit approach demonstrate:
- The single visit approach is nearly always more effective and more cost-effective than multiple visit strategies.
- A once in a lifetime test could reduce cervical cancer incidence and mortality up to 25%, dependent on coverage and targeted age group.
- Visual inspection methods combined with HPV testing is consistently more effective than Pap smear screening. However, for many developing countries screening with visual inspection will be more cost-effective.

(Goldie, 2001 and 2003. Mandelblatt, 2002)

SAFE Project results

The SAFE demonstration project in cervical cancer prevention was conducted in Roi-et Province from 1999-2001 using VIA and cryotherapy, provided by trained nurses, and a single visit approach.

Results of the test (n = 5999)
Negative: 85.9%
Positive: 13.2%
Indeterminate: 0.9%
Cancer: <0.1%

Acceptability of cryotherapy treatment (n = 630)
Accepted immediate treatment: 79.5%
Postponed treatment: 20.2%
Refused treatment: 0.3%

Types and rates of problem visits (n = 754)
Total: 4.9%
Side effects: 0.5%
Minor complications: 2.2%
Major complications: <0.1%

One year follow-up (n = 756)
VIA FU: 93.1%
Negative: 93.9%
Positive: 5.6%
Indeterminate: 0.3%
Cancer: 0.3%

Colposcopic examination of negative tests (n = 661)
Colposcopy done: 92.1%
CIN III: 0.3%

Colposcopic examination of positive tests (n = 40)
Colposcopy done: 95%
CIN II/III: 5.3%
Cancer: 2.6%

SAFE Project referral system

- Providers send women to appropriate facilities when indicated.
- OB/GYNs accept referrals at provincial hospitals and/or regional cancer centers.
- Agreement with pathology laboratories for rapid results.
- Use of health service network for follow-up.

The single visit approach is now fully operational in 5 provinces and being extended to 7 additional provinces.

Thai Cancer Registry

The Thai Cancer Registry collects data on cervical cancer incidence and prevalence and is a useful source of data for researchers.

Thai Cancer Information System

Objectives:

- To evaluate the results of cervical cancer control, focusing on screening.
- To develop policy for cervical cancer control.
- To develop an information system for the evaluation of national cervical cancer control.

Scope of research:

- Cervical cancer control policies and program;
- Indicators and appropriate methods for evaluating the results of screening policy;
- Coverage;
- Data quality; and
- Situation analysis of cervical cancer control and comparisons of the achievements, cost and resources used between the two common screening methods.

Research in southern Thailand

A situation analysis of the management of abnormal Pap smears in southern Thailand was conducted by the Alliance for Cervical Cancer Prevention and PATH. Key findings were:

- Screening is opportunistic.
- There is a lack of data on the quality of cytological services.
- Total smears performed in one year were 66,809.
- The incidence of abnormal smears was 1.24% for ASC-US and 0.36% for HSIL.
- The process of informing patients of test results is not clear.
- All 12 hospitals had colposcopy, but only one can provide a standard colposcopy service.
- Analysis of colposcopy examination workloads and coverage rates concluded that colposcopy services should be centralized.
- There are no data to indicate whether the referral system is efficient.
- Health providers thought patient lack of awareness was the biggest obstacle to providing effective management of abnormal smears.

The researchers recommended improving the referral system by allowing community hospitals, (the contracting unit for primary care), to refer patients directly to regional hospitals for tertiary care, as needed, rather than having to first refer to a general hospital, (secondary care level). The need to strengthen the capability of regional hospitals was identified.

Research in the north east

A study on patient experiences with a self-administered device for cervical cancer screening by Thai women with different educational backgrounds, found the Kato device was generally well accepted although those with a higher educational background were more skeptical of the device (Pengsa, 2004).

Another study compared the adequacy of smears collected by gynecologists with specimens collected by women using the Kato device. The Kato device performed well in terms of adequacy of smears and could be used by women who are too shy to have a pelvic examination (Pengsa, 2003).

A study of the consistency of cytology diagnosis for cervical cancer between cytologists in Khon Kaen, Thailand, and Helsinki, Finland, using the same samples, showed agreement at the level of tests requiring diagnostic follow-up or not, was only moderate (Sriamporn, 2005).

Another study concluded that the combination of p16 and HPV testing may be useful in cervical cancer screening to identify high-risk patients requiring early management (Ekalaksananan, 2006).

Thai Gynecological Oncology Group

The TGOC is conducting the following research:

Phase I: prospective study of the epidemiology of cervical cancer.

Phase II: economic burden of life-time treatment costs, quality of life and treatment satisfaction among invasive cervical cancer patients treated at university hospitals and regional cancer centers.

Phase III: Clinical trials on concurrent chemo-radiation; and management of abnormal Pap smears and treatment of CIN.

Cervical cancer screening and management of women with abnormal Pap smear Project – hospital-based experiences

Objective 1:

To determine the utility of HPV triage in high-risk women by exploring the meanings of cytological evaluation (ASC-US) and its correlation with HPV positivity.

Findings 1:

- The incidence of ASC-US by liquid-based cytology in high-risk women, (19%), increases significantly when compared with women screened by conventional smears, (0.6%).
- The rate of CIN, using HPV DNA in high-risk women with ASC-US by liquid-based cytology, is very low, (2%), when compared with women with ASC-US screened by conventional smears and managed by colposcopy, (17%).
- One-third of high-risk women with ASC-US by liquid-based cytology tested positive for HPV DNA, compared to one-half of women in the ALTS study.

Conclusions 1:

A high incidence of ASC-US is detected by liquid-based cytology in high-risk women. Two-thirds of these women can be spared from colposcopy by using HPV DNA as a triage method. A smaller number of women with ASC-US by liquid-based cytology and a positive HPV DNA test had CIN (Eurogyn, 2006).

Objective 2:

To determine outcomes for the management of women whose conventional smears revealed ASC-US by repeated cytology, using a liquid-based method.

Findings 2:

- From 2000-2001, 77% received investigation, 57% by colposcopy, and 17% by repeated smears. The incidence of CIN II/III and invasive carcinoma among women receiving colposcopy was 8.43 and 2.41 respectively.
- During 2004-2006, 92.98% received investigation, 81.08% by repeated smears (LBC). (Chichareon, 2002.)
- In ALTS, 50% of ASC-US were high-risk HPV positive; and two-year cumulative diagnosis of CIN II/III by those who tested HPV-positive was 15% compared to 1.7% by those who tested HPV-negative.
- In this study, almost 50% of repeated smears by LBC in women with ASC-US by conventional smears still revealed ASC-US. Among these, 42% were HPV positive, but none had CIN under colposcopy. Long term follow-up will be considered.
  (ALTS Group, 2003.)
- Ten percent of repeated smears by LBC in women with ASC-US by conventional smears show more than ASC-US and need colposcopy.
- Two percent of repeated smears by LBC in women with ASC-US by conventional smears had CIS.

Conclusions 2:

- Repeated liquid-based cytology in women with ASC-US by conventional cytology is able to detect significant cases of definite cytological abnormalities. These women have a possibility of harboring severe cervical pathology.
- Repeated smears by using LBC after conventional smears revealed ASC-US. Using HPV DNA testing as the triage test in women with ASC-US by LBC, can detect 1-2% of CIN III, and spare almost 70% of women from colposcopy.

Clinical endpoints for regulatory evaluation of HPV health technologies

Dr Sonia Pagliusi
Digene, Switzerland

Cancer prevention and control are among the most important scientific and public health challenges of this era. Cervical cancer continues to be a public health problem, and represents 90% of the more than 500,000 new cases of HPV-associated cancers worldwide per year.

FDA approved technologies

The HPV vaccine protects against the two most common HPV types, 16 and 18, associated with 71% of cervical cancer cases. It also protects against two low-risk types, 6 and 11, responsible for genital warts. The target population is females aged 9-26 years.

The HPV DNA test (HC2) detects 13 highly oncogenic types associated with 95% of cervical cancer cases. The test also detects 5 low-risk types responsible for genital warts. The target population is women aged 26 years and older.

The two technologies are fully complementary. The HPV vaccine is a tool for use in primary prevention. The HPV DNA test is for use in screening, or secondary prevention.

Role of regulatory authorities

In evaluating new products and interventions, the role of regulatory authorities is to ensure that products are of high quality, reliable, safe, effective, and provide benefits to individuals and populations at an economical cost. Evaluation occurs against agreed standards for quality, safety and efficacy. This presentation focused solely on efficacy.

Key points

- HPV quadrivalent vaccine efficacy is high to types 16 and 18 but not to all 13 oncogenic types.
- All vaccinated and non-vaccinated women need to be screened for cervical cancer.
- The HPV DNA test offers a consistently high sensitive method for cervical screening.
- HPV vaccines and HPV DNA testing are complementary and offer the best options for primary and secondary cervical cancer prevention respectively.

Surrogate endpoints in efficacy trials

The definition of an efficacy endpoint is a specific, measurable outcome of a clinical benefit for an illness, symptoms or quality of life. The primary endpoint for demonstration of efficacy should aim to measure the level of protection or detection achieved by interventions against cervical cancer.

Time and ethical considerations make it necessary to use a surrogate endpoint rather than invasive cervical cancer as the measurable outcome. This is because:

- ethically, clinical management requires that high-grade pre-malignant stages CIN2/3 are treated immediately; and
- malignancies develop slowly and cancer as an endpoint requires very large and lengthy studies.

(Pagliusi, 2004.)

WHO convened an international group of experts to define a globally agreed surrogate endpoint for proof of efficacy for HPV vaccines. The agreed primary endpoint was cervical lesions of moderate and high grade, (CIN 2/3), combined with virologic data (Pagliusi, 2004). Four other possible endpoints were rejected for the following reasons:
Incident HPV infection: most infections resolve and infection is sub-clinical.
Persistent HPV infection: it is difficult to distinguish transient and persistent infection.
CIN 1: most low-grade lesions regress.
Cervical cancer: lengthy studies which may not be feasible.

Published vaccine efficacy trial results

In the general trial population of females 15-26 years old, and HPV naïve, the Gardasil™ HPV vaccine has shown a reported 98.8% efficacy for HPV types 16 and 18 in preventing CIN2/3 or worse (MITT1 analysis, package insert). The FDA concluded that the efficacy, safety and 'bridging' immune response data support licensing of Gardasil™ in females 9-26 years of age, naïve to the relevant vaccine HPV type.

While HPV types 16 and 18 are associated with the majority of cervical cancer cases, vaccinated women will still be at risk of cervical cancer from other HPV types which make up 30% of all cancer cases. HPV types 16 and 18 are less prevalent in pre-cancerous lesions. Fifty-two percent of cases of CIN2/3 and HSIL are associated with HPV types other than 16 and 18 (Goldie, 2003). Vaccination therefore needs to be combined with screening to offer full protection against cervical cancer, as vaccinated women may acquire other carcinogenic HPV types.

Females naïve to the four vaccine HPV types are expected to benefit most from the vaccine. Some women may not be naïve to one or more HPV types at vaccination and they may develop cervical dysplasia. Trial data indicated that 25-32% of enrolled women 15-26 years were or had been infected with HPV types 16 or 18 at day 1 (Barr, ACIP). Gardasil™ is a prophylactic vaccine and has no protective effect on the course of infections already present at vaccination.

Evaluation of HPV DNA test efficacy

The four applications of the HPV DNA test are:

1. As a primary screening test, alone or as an adjunct to Pap smear: primary HPV test and cytology triage; or a screen and treat approach.
2. HPV DNA reflex testing: triage of borderline/ smears prior to colposcopy.
3. Post-treatment follow-up test.
4. Epidemiological studies and vaccine monitoring.

This presentation focused only on the primary screening application.

Tests for the presence of HPV viral DNA in a sample of epithelial cells have been established as a step toward identifying potentially pre-cancerous conditions. The IARC concluded that there is sufficient evidence that the HPV DNA test can reduce mortality from cervical cancer (IARC, 2004).

Sensitivity

The HPV DNA HC2 has a high clinical sensitivity and is able to detect infections, in women who have asymptomatic infection and are, thereby, at risk of developing CIN lesions (Snijders, 2003).

Six independent studies in a range of developed and developing countries demonstrated that the clinical sensitivity of the HPV DNA test to detect high grade cervical lesions is always higher than Pap alone, and that even higher sensitivity can be achieved by combining the HPV DNA test and Pap.

A recent overview of European and North American studies on HPV DNA testing in primary screening concluded that the HC2 test has a clinical sensitivity of 96% in detecting CIN 2 or 3, compared to 53% clinical sensitivity for cytology (Cuzick, 2006).

Negative predictive value

The HPV DNA test HC2 has good negative predictive value. For instance, a negative test result can identify those women at low risk of developing cervical lesions over the next 10 years, allowing time intervals for screening to be increased (Khan, 2005). Therefore, it has been proposed that the HPV test be used as a screening test for women over 25 years and cytology methods for triage of women positive in the primary screening (Cuzick, 2006).

Integrating vaccination and screening

Modeling work on the impact of the HPV types 16 and 18 vaccine on a population suggests that, without screening, vaccinating females aged 12 years with a 70% coverage rate, it will take 50 years to achieve a 50% reduction in cervical cancer mortality. Screening at similar coverage can achieve at least a 50% reduction in mortality over 10-20 years. Adding vaccination will further reduce mortality by 50% (Garnett, 2006).

HPV DNA screening is a necessary complement to vaccination:

- to prevent disease due to types not covered by the vaccine;
- to prevent disease in women already infected with types 16 or 18 at vaccination; and
- to accelerate and monitor vaccination effectiveness.

Introducing novel HPV vaccines: results of clinical trials (GlaxoSmithKline-GSK)

Dr Genara Manuel-Limson
Department of Obstetrics and Gynecology, University of the Philippines

The development of HPV vaccines is an exciting development, especially considering the difficulty of achieving changes in lifestyles and behavior to prevent infection with HPV.

Rationale for the use of vaccines

Prophylactic vaccines rationale

- HPV infection precedes and plays a major role in the genesis of cervical cancer.
- Cervical cancer is associated with HPV infection in 99.7% of cases worldwide.
- A vaccine protecting against HPV 16 would prevent around half of the cases of cervical cancer. Two-thirds of cases would be prevented by a vaccine protecting against types 16 and 18. A vaccine protecting against the 6 most prevalent types would prevent 80% of cases.
- In animal models, VLP prophylactic vaccines protected against viral challenge.

Therapeutic vaccines rationale

These vaccines have not yet been developed. Their rationale is:

- Globally, millions of women are already infected with HPV, and their infection could lead to invasive cancer. Progression to cancer could be prevented by a therapeutic vaccine.
- Tumors and their precursor epithelial lesions, including persistent HPV infection, express papillomavirus non-structural proteins.
- In animal models, therapeutic vaccination controls growth of tumor expressing virus non-structural proteins.

Key points

- Immunisation with HPV 16/18 L1 VLP vaccine adjuvanted with AS04 induces sustained antibody levels that could provide protection against HPV 16/18 associated end-points for up to 4-5 years.
- These findings set the stage for wide-scale adoption of HPV vaccination for prevention of cervical cancer.

(Harper, 2006.)

GSK vaccine

The GSK HPV 16/18 candidate vaccine contains HPV L1 virus-like particles. L1 is a unique protein that can self-assemble into virus-like particles, which do not contain DNA, and are therefore not infectious. In terms of presenting HPV antigens to the immune system, it resembles intact virus and generates immunity. The vaccine also contains AS04 which increases antibody levels protective against HPV infection.

History of HPV vaccines

In 1983, Zur Hausen established HPV type 16 as a leading candidate in the pathogenesis of pre-invasive and invasive cervical neoplasia.

In 1991, the first generation of HPV virus-like particles (VLPs) was produced. They contained no DNA and were therefore not infectious, but resemble virions and were shown at that time to generate a potent immune response.

In 2002, Koutsky *et al* reported on a phase II randomized, double-blind, multi-centric trial of HPV 16 VLPs, involving 2,392 females aged 16-23 who were given 3 doses of either placebo or HPV 16 VLPs. Genital swabs and cervico-vaginal lavage specimens were tested for HPV 16 DNA at enrolment, at one and six months after the third vaccination, and then every 6 months. The outcome measure was persistent HPV infection (i.e. two or more positive HPV DNA samples). The median follow-up was 7.4 months. The incidence of HPV infection was 3.8 per 100 woman-years in the placebo group and zero percent in the vaccinated group (100% efficacy). All nine cases of HPV 16-related CIN occurred in the placebo group.

Harper trial

The Harper *et al* double-blind, randomized controlled trial assessed the safety, efficacy and immunogenicity of a bivalent L1 VLP vaccine against

HPV 16 and 18 incident and persistent infections. Three doses of vaccine, formulated with AS04 adjuvant, or placebo, were given to 1,113 women aged 15-25 years at 0, 1 and 6 months. They were followed up for 27 months and assessed for HPV infection by cytology and HPV infection through self-obtained cervico-vaginal samples. The vaccine efficacy for HPV types 16 and 18 was 91.6% for incident infection and 100% for persistent infection. In intention to treat analysis, vaccine efficacy against persistent infection was 95.1%, and against cytological abnormalities was 92.9%. The conclusions of the trial were:

- The vaccine is generally safe, well tolerated and highly immunogenic.
- The bivalent HPV vaccine is efficacious in preventing incident and persistent HPV 16 and 18 cervical infection and associated cytological abnormalities and lesions.
- The vaccine could substantially reduce incidence of cervical cancer.

(Harper, 2004).

Extended follow-up

The Harper trial did an extended follow-up of 776 women for up to 53 months and found sustained sero-positivity and antibody levels up to 4.5 years. The level of antibody in vaccinated women was much higher than that generated by natural HPV infection (Harper, 2006).

Conclusions from the Harper trial in relation to immunogenicity and safety in women 15-55 years were:

- The candidate vaccine was generally safe and well tolerated in all age strata, with a safety profile comparable to licensed vaccines.
- 100% of initially sero-negative subjects were anti-HPV 16/18 sero-positive at all post-vaccination time points.
- HPV 16 and 18 antibody levels at one year were at least 18-30 times higher than those associated with natural HPV infection; and greater than or equal to antibody levels associated with protection against HPV infection and its associated outcomes.

The extended follow-up in the Harper trial:

- Confirmed sustained long-term vaccine efficacy against incident and persistent infections and lesions associated with HPV 16 and 18.
- Provided evidence of broader protection against cytological outcomes.
- Confirmed efficacy beyond types 16 and 18, largely due to cross-protection against HPV 31 and 45.
- Confirmed the vaccine's good safety record.

The HPV vaccine is a major breakthrough in cervical cancer prevention. Cervical cancer may be a disease of the past in 10-20 years, or perhaps sooner.

Introducing novel HPV vaccines: results of clinical trials (Merck Sharp & Dohme-MSD)

Dr Efren Domingo
Department of Obstetrics and Gynecology, University of the Philippines

Core objectives of MSD's HPV Vaccine Program

1. Prevention of major HPV-related disease objectives

Administration of Gardasil™, the brand name of MSD's HPV vaccine, will reduce overall risk of:

- Cervical cancer;
- Cervical intraepithelial neoplasia (CIN);
- Vulvar intraepithelial neoplasia (VIN) and cancer;
- Vaginal intraepithelial neoplasia (VaIN) and cancer; and
- Genital warts

in proportion to the distribution of vaccine types in such lesions.

2. Public health and socio-economic goals

Gardasil™ will reduce the incidence of:

- Low-grade and high-grade lesions: Pap smear abnormalities that lead to colposcopy;
- Colposcopy;
- Definitive therapy (loop electrosurgical excision procedure, conization, cryotherapy, genital wart excision); and
- Infection with vaccine HPV types (to prevent transmission).

3. Immunogenicity/duration of efficacy objectives

Gardasil™ will result in:

- Detectable anti-HPV responses in >90% of all subjects vaccinated, at the completion of vaccination;
- Long-term duration of protection; and
- Robust anti-HPV responses when administered with other common vaccines.

4. Safety/tolerability objectives

To characterize the vaccine's safety profile with regard to:

- Overall rates of adverse events;
- Rates and intensities of injection site adverse events;
- Rates and intensities of fever;
- Long-term health status;
- Pregnancy outcomes; and
- Outcomes of lactation.

Key points

- Anogenital dysplasia/cancer and genital warts represent significant public health problems.
- The quadrivalent vaccine is well tolerated and effective and should prevent infection with pathogenic HPV types and, thereby, should greatly reduce the burden of HPV disease.
- In Phase II studies, HPV L1 VLP vaccines were generally well tolerated, immunogenic, and effective against HPV infection and disease.
- Combined Phase II/Phase III efficacy studies showed that Gardasil™ was 100% efficacious against high-grade precancerous and non-invasive cancerous cervical lesions related to HPV 16 and 18 in a population naïve to these types until completion of vaccination.

Vaccine overview

Gardasil™ is a quadrivalent HPV L1 VLP vaccine for HPV types 6, 11, 16, and 18. Three doses are given within 6 months.

For males and females, the types 6 and 11 parts of the vaccine are capable of preventing more than 90% of genital warts, and in women around 10% of low-grade cervical lesions. The types 16 and 18 components of the vaccine are capable of preventing around 25% of low grade cervical lesions, 50% of high grade lesions, 70% of cervical cancer, and 70% of other genital cancers. The vaccine can prevent up to 60% of anal cancer in men.

Phase I vaccine studies

The studies of L1 prototype monovalent vaccines of HPV types 11, 16, and 18 demonstrated that:

- Administration of vaccines was generally well tolerated.
- All formulations were immunogenic.
- Anti-HPV 11 antibodies generated by vaccination appear to be a surrogate marker for neutralization of type 11 virions.
- In studies of 3 year follow-up, persistence of detectable antibodies in 96.8% of HPV 11 vaccines, and 93.5% of HPV 16 vaccines.

HPV 16 vaccine: proof-of-principle efficacy study

This study compared results of administration of HPV 16 L1 VLP vaccine against placebo. Efficacy of the vaccine in preventing persistent HPV 16 infection and CIN was 94%. HPV 16 infection was observed in seven of the vaccinated group at their last visit. There was no evidence of CIN or Pap smear abnormalities. As these cases were not followed-up, it is not possible to determine whether or not they had persistent infection. Their positive results may be due to contamination. The efficacy of the vaccine in preventing HPV 16-related CIN 2/3 was 100% (Koutsky, 2002).

Gardasil™ Phase II Dose-Ranging Immunogenicity and Efficacy Study

This study was designed to guide dose selection for Phase III studies and to determine the efficacy of Gardasil™ in preventing incident and persistent HPV infection; and disease related to HPV 6, 11, 16, and 18.

The result was a dramatic and robust increase of mean titer anti-HPV levels for the vaccinated group, compared to placebo. These levels were far higher than the level of antibody associated with natural HPV infection.

The combined incidence of persistent infection or disease associated with HPV 6, 11, 16, or 18 fell by 90% in the vaccinated group, compared with the placebo group, in subjects naïve at baseline for the corresponding type. None of the vaccinated group experienced HPV types 6-, 11, 16 or 18-related genital warts or CIN during the 30 months of follow-up after completing vaccination. Gardasil™ was generally well tolerated (Villa, 2005).

Gardasil™ Phase III Adolescent Immunogenicity Sub-Study

The objective was to demonstrate that administration of Gardasil™ to adolescent boys and girls aged 10-15 years generates anti-HPV responses at least as robust as those generated in vaccinated females 16-23 years. The proportion of subjects who seroconverted was comparable in all three groups - adolescent boys, adolescent girls, and females 16-23 years. Seroconversion to anti-HPV 6, 11, 16 and 18 occurred in 100% of subjects. Rates of seroconversion to anti-HPV 18 ranged from 99.1% to 100% across the three groups. Higher antibody responses to each HPV type were observed in adolescent males and females compared with adult women. Younger adolescents showed higher antibody GMT responses (1.67-2.7-fold higher) compared to older adolescents or adult females. Gardasil™ was generally well tolerated, and was similarly well tolerated among the three study groups (Schiller, 2004).

Gardasil™ Phase III Efficacy Trials: Future I and II combined analysis

The study's primary aim was to demonstrate protection with Gardasil™ against biopsy-confirmed precancerous and cancerous lesions. Results show that Gardasil™ was 100% efficacious against high-grade pre-cancerous and non-invasive cancerous cervical lesions to HPV 16 and 18 in female subjects naïve to these types until completion of vaccination.

In a secondary analysis, Gardasil™ was 97% efficacious against high-grade pre-cancerous and non-invasive cancerous cervical lesions related to HPV 16 and 18, in an analysis conducted on a prespecified modified intention-to-treat population, and starting 30 days after the first vaccination.

Combined Phase II/Phase III efficacy studies

The combined Phase II/Phase III efficacy studies enrolled 20,541 women 16-26 years of age from 33 countries. Results from the combined studies show that Gardasil™ was 100% efficacious against high-grade precancerous and non-invasive cancerous cervical lesions related to HPV 16 and 18 in a population naïve to these types until completion of vaccination. Results also show that the vaccine is 99% efficacious against high-grade precancerous and non-invasive cancerous cervical lesions related to HPV 16 and 18 in subjects who received at least one dose of the vaccine and were naïve to the relevant HPV types at enrolment.

Safety

Gardasil™ is safe and generally well tolerated. Vaccination was generally well tolerated. The most

common vaccine-related adverse event reported was local discomfort at the injection site. There were no discontinuations due to serious vaccine-related events.

Nordic Cancer Registry Extension

Nordic countries have organized mass cervical cancer screening programs. Enrolling patients from four Nordic countries in Phase III studies provides an opportunity to evaluate duration of effectiveness, interaction of vaccination with cervical screening programs, and long-term safety. Nordic females will be followed for at least 10 years through the cancer registries.

Other ongoing studies

The Mid-Adult Women's Efficacy Study is a trial of the efficacy and tolerability of Gardasil™ in women aged 14-45 years of age.

Genital warts are common in sexually active men. While men suffer less pathology from HPV infection, 85% of cases of anal cancer are attributable to HPV infection. Men also serve as the vectors of HPV transmission.

Gender-specific vaccination programs have an unfavorable track record. MSD's HPV vaccine program in men includes evaluation of the immunogenicity and tolerability of Gardasil™ in young men, and an ongoing efficacy trial is evaluating its efficacy and tolerability in men.

Cross protection potential of HPV vaccine

A recent study detected HPV neutralizing antibodies in the sera of the vaccines using Gardasil™ against HPV types 31, 45, 52, and 58. However, the concentration of the cross-reacting neutralizing antibodies were 1.5 to 2.0 $\log_{10}$ lower than HPV antibodies to HPV 6, 11, 16, and 18 (Smith, 2006). It is currently not known what level of antibody is protective against HPV infection.

HPV vaccination strategies for Asia, Africa and Latin America

Scott Wittet
PATH, USA

PATH's Cervical Cancer Vaccine Project

PATH's demonstration project will operate in 4 countries from 2006-2011. It will generate and disseminate necessary evidence for informed, public-sector introduction of HPV vaccines.

Funding for the project by the Bill and Melinda Gates Foundation allowed for one year of planning to develop country selection criteria, conduct country assessments, reach agreement with partners on research questions and to develop active partnerships.

Country selection criteria

1. Need

- Disease burden (age-standardized cervical cancer incidence >20/100,000);
- Low to middle income; and
- Reasonable life expectancy.

2. Significance

- Large population size;
- Degree to which the country represents a region or group of countries;

Key points

For maximum impact, HPV vaccine introduction will require:

- Clear understanding of the health need (disease burden).
- Safe, effective, acceptable, and affordable products.
- Demonstrated pilot project success.
- Health system strengthening (expanding EPI or establishing new vaccine programs).
- Engagement of and support among stakeholders at various levels.
- Global and regional advocacy.

3. Capacity to conduct research and introduce vaccine

- Capability to complete necessary studies;
- Vaccination capacity;
- Access to girls 10-13 years of age in school;
- Ability of different parts of government to work together;
- County presence of key collaborators/partners;
- Regulatory capacity;
- Country is GAVI-eligible;
- Experience with cervical cancer prevention; and
- Political stability

4. Political commitment

- To cervical cancer prevention;
- To introducing new vaccines; and
- To programs for youth.

The four countries selected for formative and operations research are India, Peru, Uganda, and Vietnam.

Country-level research: overview

Country-level research will provide evidence for:

- National decisions about adoption of HPV vaccine (disease burden, cost-effectiveness, and feasibility);
- Development of communication materials for different audiences;
- Selection of effective vaccine delivery approaches;
- Identification of key health system areas that need strengthening;
- Selection of appropriate target group(s) - i.e. age range and gender (girls only vs. girls + boys);
- Multi-year vaccine forecasts;
- Program financing decisions, based on real costs; and
- Integration of HPV vaccine with related services.

PATH's research will complement and contribute to the efforts of others such as clinical research by industry and others, IARC's epidemiological

studies, WHO's advocacy strategies, Harvard's decision-science modeling of health impact and cost-effectiveness, global forecasting and financing decisions, and development of WHO practice guidelines.

Formative research: socio-cultural

1. Information needs for informed use/vaccine provision

- Understanding of cervical cancer burden and secondary prevention options; and
- Understanding of the HPV-cervical cancer link.

2. Acceptability of HPV vaccine

- Community views;
- Best ways to represent the vaccine (as a cancer vaccine, STI vaccine, or women's health vaccine?); and
- Potential resistance to a girls-only vaccine.

3. Young adolescent health care utilization

- How does youth view and use health care services?
- Who are the primary decision-makers about young people's health care?
- What are young people's health priorities?

Formative research: health system capacity

- Current services available for young adolescents and the cost for users;
- Cold chain capacity; and
- Adjustments needed for health information systems.

Formative research: delivery strategies

- Routine vs. periodic.
- Site: school, clinic, and/or community?
- Age group: single-year, multi-year, or catch-up?
- Link with cervical cancer screening or with other vaccines?
- Link with other services: health education, anti-helminthics, nutrition, hygiene?

Clinical research

The primary interest will be alternate vaccination schedules. Not all countries will be able to follow the recommended 0, 1, 6 or 0, 2, 6 month schedules. In Vietnam, alternative schedules will be tested (0, 3, 9; 0, 6, 12; and 0, 12, 24; vs. standard 0, 2, 6 months). The primary outcome will be antibody titer 1 month after final dose. The secondary outcomes will be antibody titer just before the third dose; and acceptability of various schedules. A weakness is that the correlates of protection against HPV are not yet known. These may be known within a few years. The rationale for doing this research now is that when the correlates of infection are known, researchers and program staff will be able to compare with the results of older studies.

Demonstration Project issues

1. How to maximize acceptability?

- Target age for optimal acceptability, operational feasibility, and vaccine effectiveness;
- Incremental benefit for acceptability of adding boys to the target group; and
- Effective communication strategies for girls, families, and communities.

2. Effective delivery strategies

- Is a school-based strategy effective in countries with high primary school attendance?
- Can HPV vaccines be integrated into existing community outreach programs such as child health days?
- Can a supplemental strategy for out-of-school girls increase coverage over a school-based approach? Is it cost-effective?
- Is a facility-based approach more cost-effective than a school-based approach?

3. Impact on the health care system

- Logistical barriers and their solutions.
- What training is needed for health care workers regarding the vaccine and patient education?
- Incremental costs of vaccine delivery, community education, and program administration.

4. Information for vaccine production planning

- Typical size of vaccination sessions. (For planning multi-dose vials); and
- Likely uptake rates over time. (For use in demand forecasting).

Demonstration Project research

The following are illustrative examples of research questions which are currently being negotiated with the four countries.

1. Best age for maximum acceptability in India?

- *Objective*: to select a target age that maximizes acceptability and operational feasibility in a community outreach vaccination strategy
- *Method:* Developing strategies tailored to the needs of younger (e.g. 11-12 years) vs. older (e.g. 14-15 years) adolescent girls. Cluster-ran-

domize selected communities to the two strategies.
- *Primary outcome:* vaccine coverage rate in each group.

2. Impact on acceptability by including boys in Peru?
- *Objective:* to compare a primary school-based vaccination strategy that targets boys and girls, to one that targets girls only.
- *Method:* cluster-randomized comparison of the two approaches.
- *Primary outcome*: vaccine coverage rate among girls.
- *Secondary outcome:* vaccine coverage rate among boys; coverage with 1 or 2 doses among girls.

3. Feasibility of adding HPV vaccine to semi-annual health days in Uganda?
- *Objective*: To compare a primary school-based strategy with a school plus community outreach approach for reaching girls aged 11-12 through existing semi-annual child health days.
- *Method:* cluster-randomized comparison of the two approaches.
- *Primary outcome:* vaccine coverage rates with three doses in each group.
- *Secondary outcome:* cost of each strategy.

4. Best strategy to reach 14 year-old girls in Vietnam?
- *Objective:* to identify the most cost-effective strategy for reaching 14 year-old girls.
- *Method:* compare (1) school-based strategy with (2) a facility-based strategy; and (3) a combination strategy. Three-arm cluster-randomized approach.
- *Primary outcome:* coverage.
- *Secondary outcome:* partially vaccinated subjects, resource use, costs, acceptability, and cost-effectiveness data.

Guiding principles for research

- Work with stakeholders in the planning stage and throughout.
- Collaborate with national authorities to translate findings into action.
- Share results regionally and globally as rapidly as possible.

From vaccine trials to vaccination programs: applying the lessons learned

Dr Somsak Lolekha
Thai Medical Council

This presentation examines the introduction of the hepatitis B virus (HBV) vaccine in Thailand and draws upon the lessons learned so that they may be applied to the introduction of the HPV vaccine.

Hepatitis B in Thailand

Thailand is the second leading country in the world for HBV immunization, following Taiwan. The driving reason for this is the very high incidence of HBV infection. HBV infection is the leading cause of liver cancer in Thailand. In 1996, liver cancer was the leading type of cancer in males (37.6/100,000), and the third most common type of cancer in females (16.0/100,000). At that time, 10-15% percent of the Thai population were carriers for HBV.

Where pregnant women are HBV infected, the virus is transmitted to their babies in 40-50% of cases. Carrier rates after infection for specific population groups are:

- New born: 90-95%
- Infants: 80-90%
- Ages 1-6 years: 20-50%
- Adults: 1-5%

Forty to fifty percent of HBV carriers acquired the infection at a pediatric age. The HBV carrier rate in infants born to HBsAg-positive and HBeAg-positive mothers can be significantly decreased with administration of HBIG or HBV vaccine at or shortly after birth. The following compares infant carrier rates that result from no prophylaxis versus administration of HBIG and/or HBV vaccination of infants at different time intervals after birth:

- No prophylaxis: 90% infant carriers
- HBIG 1 dose after birth: 51% infant carriers
- HBIG 3 doses: 23% infant carriers
- HBV vaccine 3 doses start 1 month: 40% carriers
- HBV vaccine 3 doses start 1 week: 25% carriers
- HBV vaccine 3 doses start 1 day: 10% carriers
- HBIG at birth + HBV vaccine 3 doses: 5% carriers

Key points

Key factors that resulted in the introduction of HBV vaccination in Thailand provide lessons that can be applied to the introduction of HPV vaccination. They are the need for:

- Good epidemiological data demonstrating the burden of disease being used to develop government, health professional and public awareness of the importance of prevention.
- Developing awareness of the effectiveness of prevention measures, including vaccination, and creating a demand for intervention.
- Demonstrating cost-effectiveness of vaccination.
- Pilot projects to establish the best approach to vaccination on a national basis.

From research to practice

The steps that led to the national HBV immunization program in Thailand were:

- Discovery of hepatitis surface antigen in the late 1960s;
- Good epidemiological data demonstrating the burden of disease;
- HBV vaccine development in the 1980s, with proven efficacy and safety;
- Health care worker awareness of the burden of disease and the effectiveness of vaccination;
- Public awareness of the burden of disease and prevention measures, including availability of the vaccine;
- Priority being accorded to HBV prevention by society, health professionals and government;
- Cost-effectiveness of HBV immunization was demonstrated;
- Pilot projects conducted; and
- Development of a national program, building on the pilot projects.

Cervical cancer

The ASR incidence of cervical cancer in Thailand is 20.7/100,000, with over 6,000 incident cases per year. Thailand has the fourth highest incidence rate of cervical cancer among ASEAN nations.

The relative risk association between infection with HPV sub-type 16 and cervical cancer for Bangkok females is 500 times greater than baseline. This compares with a ten-fold relative risk association between cigarette smoking and lung cancer (Bosch, 2002).

In Asia and the Pacific there are around 245,000 cases of cervical cancer per year. Around 73% of all cases are associated with HPV sub-types 16 or 18, (HPV 16 – 50% of cases; HPV 18 – 23% of cases). Around 90% of all cases of cervical cancer in Asia and the Pacific are associated with eight HPV subtypes.

Persistence of infection

Most HPV infections are transient. The median duration of infection is 8 months. Most infections clear within two years. The gradual development of an immune response is the presumed mechanism for clearing HPV infection. However, infection can persist for decades. High-risk HPV types are more likely to persist. Persistent HPV infection is the most important risk factor for pre-cancerous developments and invasive cervical carcinoma.

HPV vaccines

Gardasil™, the MSD HPV vaccine, has been approved in USA, Australia, Mexico and the Philippines. It has been submitted for approval in other countries, including in Asia.

Cervarix™, the GSK vaccine, has fast-track designation for approval by the US FDA. Approval is forecast by mid-2007. Cervarix™ has also been submitted for approval in other countries, including most Asian countries.

When to vaccinate?

As with HBV vaccine, timing of the administration of HPV vaccine is important to maximize outcomes.

HPV infection occurs soon after first contact with an infected sexual partner. The median time from first intercourse to first detected infection is three months. Prevalence is 39% two years following first intercourse and 46% at three years following first intercourse. Vaccination should be administered before first exposure.

From research to practice: HPV vaccines

The steps that led to the national HBV immunization program in Thailand can be applied to the development and introduction of an HPV vaccination program. We can compare those steps to see how far we have advanced in taking HPV vaccine research and putting it into practice:

- Discovery of hepatitis surface antigen in the late 1960s/Discovery of HPV ten years ago;
- Good epidemiological data demonstrating the burden of HBV and related liver disease/Good epidemiological data demonstrating a high incidence of HPV infection and cervical cancer;
- HBV vaccine development in the 1980s, with proven efficacy and safety/HPV vaccines developed, with proven efficacy and safety, but awaiting regulatory approval in Thailand;
- Health care worker awareness of the burden of liver disease and the effectiveness of HBV vaccine/Growing health care worker awareness of the burden of HPV-related disease. More limited, but growing health care worker awareness of the forthcoming availability of HPV vaccines;
- Public awareness of the burden of liver disease and prevention measures, including availability of the HBV vaccine/Comparatively limited, but growing public awareness of HPV, screening and prevention. Very limited public awareness of the forthcoming availability of vaccines;
- Priority being accorded to HBV prevention by society, health professionals and government/Increased priority has been accorded to HPV through the new national screening program. Compared to HBV, Thai society has not, as yet, accorded as high a priority to HPV and cervical cancer prevention;
- Cost-effectiveness of HBV immunization was demonstrated. This has yet to be demonstrated with HPV vaccines. The high (initial) cost of the vaccine may limit its use in Thailand;
- Pilot projects for HBV immunization conducted/HPV is not yet at the pilot project phase; and
- Development of a national HBV vaccine program, building on the pilot projects/HPV is not yet at this stage.

Modeling health outcomes: experience with HIV models

Dr David C Sokal
Associate Medical Director, Family Health International, USA

The purpose of this presentation was to provide an overview of HIV models and to consider their implications for HPV modeling.

Why do modeling?

HIV is very different from HPV in that it is a new pandemic, and its eventual prevalence in a particular country is relatively unpredictable, especially in its early stages. The main purposes of HIV modeling are to (1) make rough predictions of potential epidemic scenarios, and (2) estimate the impacts of the epidemic. HIV modeling is also used to estimate HIV incidence rates, to compare prevention strategies and to estimate health care costs and coverage.

Good epidemiological data for HPV exist. It is an endemic, highly prevalent world-wide infection with relatively stable prevalence and incidence, so there is not as great a need, compared to HIV, to predict the course of the epidemic. The higher priority modeling needs for HPV are:

- Evaluating the impact of vaccination;
- Comparing different combinations of vaccination and screening strategies;
- Estimating costs and impacts of different strategies;

Key points

- High priority modeling needs for HPV are:
  1. Evaluating the impact of immunization;
  2. Comparing different combinations of vaccination and screening strategies; and
  3. Estimating costs and impacts of different strategies.
- Two stage modeling may be preferable for most HPV modeling, especially at the national program level, as it is easier to use compared to dynamic simulation modeling.
- To ensure modeling is focused, always keep in mind 'what question are you trying to answer?'

Types of HIV models

- *Extrapolation models* to predict the number of AIDS cases;
- *Cohort models* to estimate the number of AIDS cases based on the number of people with HIV infection; and
- *Simulation models*, similar to dynamic hybrid models used by Dasbach for HPV modeling, are also used in HIV.

History of HIV modeling

- *Extrapolation models* were used prior to the identification of HIV as the cause of AIDS.
- *Cohort models* were used following development of HIV serology and identification of the incubation period. This allowed prediction of the number of cases of AIDS, based on estimates of cases of HIV infection (e.g., EpiModel).
- *Simulation models* were subsequently developed, using data on transmission probabilities for different risk practices and populations (e.g., Asia Epidemic Model, iwgAIDs)

HIV models: selected examples

1. Thailand: EpiModel

The model was developed by WHO in the late 1980s. It provides simple projections of the number of AIDS cases and deaths from AIDS, based on estimates of the number of HIV infections. The model was very influential in Thailand and led to introduction of the 100% Condom Use Program in brothels. Thailand is recognized as one of the more successful countries in effectively responding to HIV.

2. Malawi: EpiModel + AIDS Impact Model

The EpiModel was used to estimate HIV incidence and prevalence. These data were fed into the AIDS Impact Model (AIM). AIM calculates AIDS cases and deaths, based on HIV prevalence data. AIM was also used to predict the number of cases of

tuberculosis and the number of orphans resulting from the HIV epidemic. The models were used to project adult HIV prevalence for 1991-2000, in two scenarios, low and high.

Projections can be validated over time by comparing estimates with observed cases. Comparing our 1992 projections to official estimates published in 2003, the 1990 prevalence in the official data was lower than the baseline prevalence used for the projections. The 1990 baseline estimation of prevalence may have been too high due to an overestimate of rural cases of HIV. If the high scenario projection is adjusted downwards to take account of the lower baseline prevalence, that projection and the official data for HIV prevalence for 1991-2000 are almost identical. This suggests the high scenario estimate of 2% incidence per year was very close to what actually occurred. The high-scenario projection for adult HIV prevalence, annual AIDS deaths, number of AIDS orphans, and number of TB patients in 2000 was similar to official estimates for 2000, made in 2003. This indicates that even if projections made by a model are not exactly on target, estimates of impacts may still be reasonably accurate and useful.

HIV models for health outcomes

1. HIV prevalence => AIDS cases
Simulation models are difficult to validate due to their complexity, the need for many years of data, and the unpredictability of HIV epidemics.

The EpiModel is no longer used by UNAIDS. UNAIDS has developed the Estimates and Projections Package (EPP) for use by national AIDS programs to estimate HIV prevalence and then predict the number of AIDS cases and deaths. AIM is still used by UNAIDS. The models can be used to estimate the number of people who will need antiretroviral therapy (ART), the quantity of drugs needed, and set related coverage targets.

2. Focused evaluation of strategies
HIV models can estimate outcomes such as:

- The number of infections averted by condom use;
- Mother-to-child infections prevented by ART, contraception and infant formula;
- The number of TB cases prevented;
- The number of children who would have been orphans, but for interventions; and
- The health care costs avoided by prevention and mitigation interventions.

A^2 Project: Integrated Analysis and Advocacy

The A^2 (A-squared) Project in Asia is a joint activity of Family Health International, the East-West Center and the Health Policy Initiative of Constella Futures. The Project uses two models:

Asia Epidemic Model (AEM): AEM models HIV transmission dynamics, taking account of the size of different risk groups and behavioral trends in those risk groups. Projections of HIV incidence and prevalence are generated by risk group and for the general population.

Goals Model: looks at the cost of interventions in relation to their impact, as modeled using AEM. This allows cost-effectiveness analysis and formulation of better policies and disease control strategies.

Examples of policy questions the Goals Model is uniquely suited to address are:

- What is the cost of reducing HIV incidence by 50% or keeping HIV prevalence below 1%?
- What is the cost of implementing the targets set in the National Strategic Plan?
- How can we justify to policy-makers the importance of continuing the current level of HIV investment?

Relevance for HPV models

Global dynamic simulation models that include sexual transmission dynamics are valuable, but very complex, requiring extensive training.

Two stage modeling (e.g., EPP and AIM) uses one model to make epidemiological projections and a second model to forecast outcomes and costs. These models can be less complex than simulation models, and are designed for use at the national program level. Their ease of use is dependent on the software being user-friendly.

HIV models have had difficulty in measuring differential infection levels between urban and rural areas. HPV modelers should keep this in mind in case there is a similar differential in the geographic distribution of infection.

Always keep in mind what question you are trying to answer so that the modeling activities remain focused.

HPV epidemiology and health economic models

William Gerth
Outcomes Research, Merck & Co, USA

The purpose of the presentation was to review:

- Parameters important to understanding the health and economic benefits of a HPV vaccine;
- HPV Markov (cohort) and dynamic transmission models; and
- Incorporation of herd immunity and HPV 6/11 in HPV health economic modeling.

Burden of HPV-related disease

It is important to take account of the full burden of HPV-related disease when considering the potential benefits of vaccination. Cervical cancer (0.5 million cases per year), while important, is just the 'tip of the iceberg'. High-grade pre-cancerous lesions (10 million cases per year), low-grade cervical lesions (30 million cases per year), and genital warts (30 million cases per year), impose a tremendous burden to the health care system, even though they may not have direct consequences in terms of mortality.

Key points

- Vaccination against high and low-risk HPV types offers substantial health benefits by reducing the incidence of cervical cancer, CIN, and genital warts, but at a cost.
- Vaccinating a female-only population (primary cohort and primary plus catch-up) with a quadrivalent HPV (6, 11, 16, and 18) vaccine has the most favourable cost-effectiveness profile, relative to other vaccination strategies, with the lowest incremental costs and greatest health benefits.
- The estimated cost-effectiveness of vaccination is more favourable when transmission effects and the prevention of genital warts are included (versus no transmission and HPV 16/18 only).

Burden of HPV over time

A vaccine that protects against oncogenic and non-oncogenic HPV types can demonstrate immediate benefits in the short-term by preventing HPV-related low-grade cervical lesions and genital warts; in the medium term by preventing pre-cancerous cervical lesions; and in the long-term by preventing cervical cancer.

Prevalence of HPV types in cervical cancer

We know that Gardasil™ has a 100% efficacy in protecting against infection with HPV types 16 and 18, which in turn are responsible for around 70% of all cases of cervical cancer. The potential to reduce incidence of cervical cancer will only be realized with effective use of the vaccine. The partnership that is represented by this kind of forum is critical to set the stage for effective roll-out.

Vulvar and vaginal cancers

Vulvar and vaginal cancers represent about 4-7% of all US gynecological cancers (Ries, 2002). The proportion of vulvar and vaginal cancer relative to cervical cancer in the US is higher than in many Asian countries due, in part, to low screening coverage in these countries leading to higher cervical cancer incidence rates. Nearly 50% of these cancers are related to HPV and, of these, 70% to HPV 16 or 18 (WHO, 1999).

Economic burden of HPV in US

The annual direct medical costs associated with HPV-related disease in the US are at least US$4 billion. Approximately half of this cost is from routine cervical screening (Insinga, 2005). As HPV screening and vaccination programs will be complementary, it is not anticipated that there will be any reduction in costs associated with screening following the introduction of HPV vaccines. Anticipated savings from vaccination will, however, occur from a reduction in the incidence of genital warts, CIN, and cervical cancer.

Age distribution of cervical cancer deaths

Over 70% of deaths in the US from cervical cancer occur in women aged 30-59 years (Insinga, in press). The estimated US productivity loss in 2000 due to cervical cancer mortality in all age groups is estimated to be US$1.3 billion. While this may be a significant economic loss in a developed country like the US, more importantly, this represents a huge loss to the social fabric of society regardless of a countries socioeconomic standing.

Genital warts: frequency, costs and burden

The incidence of genital warts has been increasing significantly over time. The estimated lifetime risk of developing genital warts is around 10% (Franco, 1997). Warts have to be removed by surgery, cryotherapy, laser or chemically. Treatment can be painful and embarrassing. The recurrence rate is around 30%. HPV 6 and 11 are responsible for more than 90% of anogenital warts (Jansen, 2004).

A US study of the characteristics of episodes of care for genital warts showed each episode of warts required a mean number of physician visits of 3, at mean cost of US$434 (Insinga, 2003). The magnitude of this cost is large when one multiplies the costs out by the population affected.

Psychosocial Burden of HPV

A number of studies have documented the psychosocial factors (e.g., anxiety, depression) related to HPV and related interventions. Preliminary results from an ongoing US study to quantitatively measure psychosocial impact of HPV infection and disease using the HPV Impact Profile found that women with genital warts had the highest (worst) psychosocial burden scores. Their scores were similar to women with high-grade cytological abnormalities and pre-cancerous cervical lesions (Mast, 2006).

HPV models: importance and inputs

A number of variables can affect the costs and benefits of HPV vaccination. Variables relevant to HPV are:

- Sexual behavior, HPV exposure and transmission rates;
- Natural history of HPV infection;
- Cervical cancer screening (e.g. coverage, frequency);
- Cervical dysplasia and cancer treatment;
- Timing of incident cases, costs, quality of life weights; and
- Vaccine efficacy, HPV types covered, coverage, duration.

These factors can vary across health care systems. Models can take relevant factors into account and project the possible health and economic impact of HPV vaccines.

HPV models: strategies and outputs

Models enable policy-makers to compare and contrast varying vaccination strategies. The different strategies examined by models are typically:

- Vaccine versus no vaccine;
- Target age and gender for vaccine administration; and
- Primary cohort and catch-up populations.

The typical outputs of these models are:

- Costs;
- Life-years saved;
- Quality adjusted life years (QALYs); and
- Incremental cost-effectiveness ratios (ICER).

HPV quality adjusted life years (QALYs)

QALYs are a unifying health outcome measure that capture:

- mortality and life expectancy; and
- survival time and quality of life.

QALYs are an important outcome measure for HPV as the consequences of precursor lesions, cancer staging and survival, and genital warts need to be taken into account in addition to cervical cancer mortality and associated reductions in years of life.

A quality adjusted life year of 1 represents one year of the best possible quality life (i.e. QALY = 1). If quality of life is reduced by half for one year, the QALY score would be 0.5. The following quality of life weights have been applied to those with the following diagnoses in the health economic evaluations for Gardasil™ (Elbasha, 2006):

- CIN 1 – 0.91
- CIN 2/3 – 0.87
- Genital warts – 0.91
- Cervical cancer:
    - invasive local – 0.76
    - regional – 0.67
    - invasive distant – 0.48
    - cervical cancer survivor – 0.84

These weights are multiplied by the age and sex adjusted weights of individuals without these

conditions and applied for only as long as the condition lasts and then return to normal.

Models in HPV vaccine literature

There are two types of models:

- *Markov (or cohort) Models:* look at the natural history of HPV infection in a cohort of individuals; and
- *Dynamic Transmission Models:* also look at the natural history of HPV. In addition they model the transmission of HPV in a dynamic population. These models take into account that a person who has been vaccinated is unable to transmit HPV infection (i.e. contribution to herd immunity).

Markov Models used to evaluate HPV vaccines

A number of models have been used to evaluate the cost-effectiveness of HPV vaccination in the US. These models all found that vaccination against HPV 16 and 18 is highly cost-effective (Goldie, 2004; Sanders, 2003; Kulasingam, 2003).

Markov models: sensitivity analyses

In modeling cost-effectiveness, these models are most sensitive to:

- Cervical cancer screening: frequency and age of initiation; and
- Duration of vaccine efficacy.

For cost-effectiveness, Markov models are least sensitive to:

- Natural history parameters; and
- Screening test characteristics.

Merck Dynamic Transmission Model

Merck has modeled the epidemiologic and economic impact of prophylactic HPV vaccination strategies on a backdrop of cervical cancer screening covering different population groups. The epidemiologic component of the model simulates HPV transmission by age and sex and the occurrence of CIN, cervical cancer, and external genital warts. The population size for the model is 100,000 persons divided equally between females and males and stratified into 17 age groups.

Vaccination strategies modeled

The vaccination strategies modeled were:

- No vaccination;
- Routine vaccination of females up to 12 years old;
- Routine vaccination of females up to 12 years old, plus female catch-up (12-24 years);
- Routine vaccination of females and males up to 12 years old;
- Routine vaccination of females and males up to 12 years old, plus female catch-up (12-24 years); and
- Routine vaccination of females and males up to 12 years old, plus females and males catch-up (12-24 years).

Model Parameters: transmission, coverage, unit costs

1. Transmission Probabilities

Since this type of model takes into account herd immunity, it is important to understand the transmission parameters used in the model. The per-partner transmission probability is assumed to be 0.8 for male–to-female transmission, and 0.7 for female-to-male transmission, making it more likely that men will be the vectors of HPV. Transmission probability also varies by age and the number of new sexual partners per year (Elbasha, 2006).

2. Vaccination penetration rates

The coverage assumptions used for the vaccination strategies are:

- *Routine vaccination of up to 12 years:* the coverage rate will increase linearly from 0% at program commencement to 70% in year 5 and thereafter.
- *Catch-up group (12-24 year olds):* the coverage rate will increase linearly from 0% at program commencement to 50% in year 5. This arm of the program will stop after 5 years.

3. Estimates of cost inputs

The following US$ (2005 US dollars) unit cost inputs were used in the modeling.

Liquid-based cytology	$99
Colposcopy	$165
Colposcopy w/cervical biopsy	$318
CIN 1	$1,554
CIN 2/3	$3,483
Local invasive cervical cancer	$26,470
Reg. invasive cervical cancer	$28,330
Distant invasive cervical cancer	$45,376
Genital warts	$489

The cost of the HPV vaccine for 3 doses and administrations is assumed to be US$360, consistent with previous analyses. Costs and quality-adjusted life years (QALYs) were discounted at 3%.

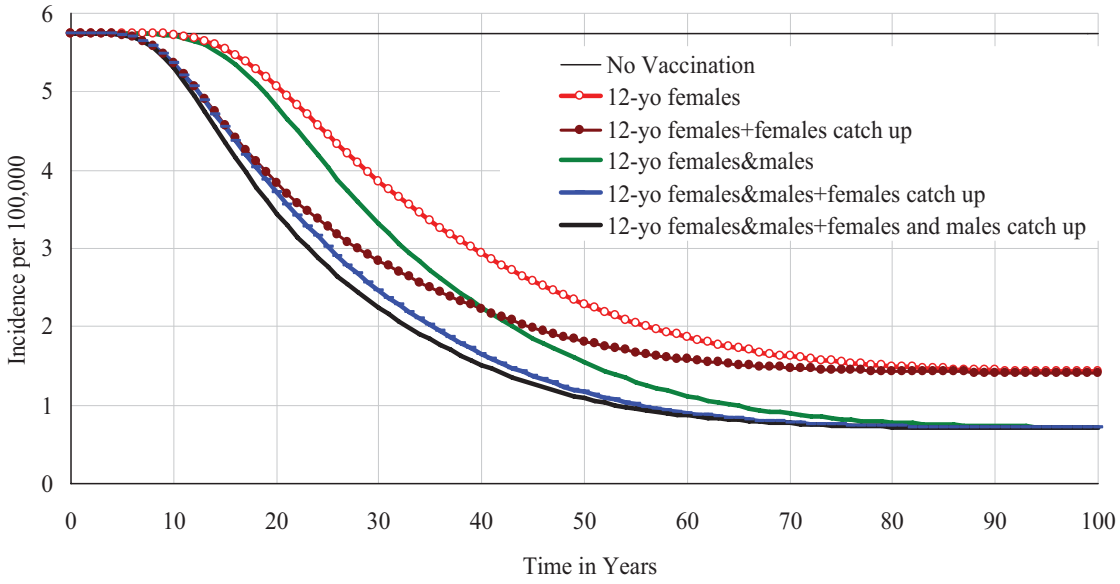
4. Degree of protection

The degree of protection against HPV 6/11 or 16/18 related disease was 100%. Lifetime protection is assumed in the model.

Impact of vaccination strategies: results

The modeling examined the impact of these different vaccination strategies on incidence for different manifestations of HPV-related disease for females 12 years and older on a lifelong duration basis. A planning horizon of up to 100 years is modeled. The modeling uses US data, where incidence of HPV-related diseases is lower compared to many countries, due to screening. The results of the modeling were as follows:

1. Impact on HPV *16/18-related cervical cancer* incidence – females (>12 years) lifelong duration
Vaccinating both females and males and using a female and male catch-up program is the most effective strategy. As shown in the figure below, by year 50, cancer cases will be 88% lower (a reduction in incidence from approximately 6/100,000 pre-vaccination to just over 1/100,000). Females-only vaccination does well. Quicker and greater reductions are achieved through catch-up vaccination.



2. Impact on HPV *16/18-related CIN2/3* incidence – females (>12 years) lifelong duration Again, vaccinating males and females, plus female and male catch-up vaccination, is the most effective strategy (a reduction in incidence from 200/100,000 pre-vaccination to around 40/100,000 within 20 years). The reduction in CIN is more quickly realized compared with the reduction in cancer. Even sooner results are achieved with catch-up.

3. Impact on HPV *6/11/16/18-related CIN 1* incidence – females (>12 years) lifelong duration
Vaccinating males and females, plus catch-up vaccination is the most effective strategy, resulting in a reduction of incidence from around 46/100,000 pre-vaccination to around 13/100,000 in ten years. The impact is sooner because CIN precedes the events of CIN2/3 and cervical cancer.

4. Impact on HPV *6/11-related genital warts* incidence – females (>12 years) lifelong duration
Once again, vaccinating both females and males, with a female and male catch-up is the most effective strategy. Incidence among females declines from more than 160/100,000 pre-vaccination to around 12/100,000 in 10 years. HPV 6/11-related genital warts will almost be eliminated if the both sexes are vaccinated. The reduction in genital warts occurred sooner than for CIN and cervical cancer.

5. Impact on HPV *6/11-related genital warts* incidence – *males* (>12 years) *ten years* duration
Although vaccinating males and females, plus a catch-up strategy is most effective, (reduction in incidence from 160/100,000 to around 28/100,000 in 10 years), female only vaccination also reduces the incidence of genital warts in males, indicating a herd immunity effect.

The modeling demonstrates that:

- The magnitude in the reduction in incidence of disease is affected by the different strategies.
- A vaccine that protects against oncogenic and non-oncogenic HPV types can demonstrate benefits in the short-term by preventing HPV-related low-grade cervical lesions and genital warts.

The impact of different vaccination strategies was modeled using US data. The findings will be similar in all countries, with some variance in the magnitude of the benefits of vaccination. These differences will be driven largely by the extent to which screening currently takes place and the incidence

of HPV and related diseases.

Cost-effectiveness analysis of HPV vaccination strategies

The table below ranks the modeled vaccination strategies by QALY gains. The greatest incremental QALY gain is for vaccination of females up to 12 years. The strategy of vaccinating females and males up to 12 years is said to be 'dominated' because there is another strategy below that is less costly and has more benefit. That is the strategy of vaccinating females up to 12 years with a female catch-up. As you go down the strategies in the table, more health benefits are added by vaccinating additional population groups. The largest cumulative gain in QALYs is from a strategy of vaccinating both females and males up to 12 years plus female and male catch-up. The balance between incremental costs and benefits varies. The incremental cost-effectiveness ratio of vaccinating 12 year old females was US $2,946 per QALY, increasing to US $4,666 per QALY by adding a female catch-up. The additional value of preventing HPV 6/11 infections improves the cost-effectiveness ratio by 59% compared to the cost-effectiveness of protection against HPV 16/18 alone (US$11,254/QALY). The strategy of vaccinating all population groups has a cost-effectiveness ratio of US$45,056. By US standards, this is still very good, but possibly not as attractive as some of the preceding strategies.

	Incremental	
Strategy	**QALY**	**US$/QALY**
No vaccination	-	-
Females up to 12	467	2,964
Females + males up to 12	149	Dominated
12 year females + female catch-up	16	4,666
12 year females/males + female catch-up	118	41,803
12 year females/males + female/ male catch-up	45	45,056

Dynamic models sensitivity analysis

Cost-effectiveness of female-only vaccination is sensitive to:

- Duration of vaccine efficacy; and
- Vaccine cost.

Cost-effectiveness of other vaccination strategies (e.g., male vaccination) may be sensitive to:

- Utility weights;
- Vaccine coverage; and
- Transmission probability.

Limitations

Factors not taken into account in the impact of vaccination strategy modeling are:

- Uncertainty about transmission dynamics of HPV, duration of acquired immunity, and other parameters.
- Not all possible effects of vaccination are addressed:
  - Decreased positive predictive value of Pap;
  - Adverse effects;
  - Behavioral issues (sexual, health-seeking, etc.);
  - Other HPV-related cancers (e.g., vaginal and vulvar cancer); and
  - Indirect costs/productivity losses.
- Other issues:
  - What if the women not vaccinated are the ones not screened?
  - The actual cost-effectiveness ratio of vaccinating may vary from the base-case estimates.

Questions and discussion

In relation to Bill Gerth's presentation, one participant commented that the conclusions drawn might be sensitive to particular cultures. The presentation mentioned that the findings are sensitive to the different weightings applied, particularly for QALYs. Genital warts being regarded as one-third as important as cervical cancer in quality adjusted life years implies that people regard genital warts quite seriously. If you are working in a society where genital warts are not regarded as seriously, especially in relation to cervical cancer, and the relative QALY weightings are different, what difference would that make to the findings?

In response, Bill Gerth indicated that reason for the weighting for genital warts relates to the large number of people affected. Part of what you are seeing is a small weighting applied to a large number of people who are infected with HPV types 6 and 11 and as a consequence have genital warts. In addition, many people with genital warts read all sorts of things into their condition and have substantial fears, not based on science. This affects the QALY weight.

The issue of the QALY weight of 0.48 for invasive distant cervical cancer was raised. A participant asked for clarification on how the weighting is applied given that a woman's health status might change over time, especially if she responds to treatment. The question of whether this weighting is applied as a constant from the time of diagnosis through to death was raised. In response, Bill Gerth stated that the modeling done by Merck does not use a constant QALY weight for cervical cancer. The modeling reflects changes in health status, by applying different weights over time.

A participant commented that two factors that are critical in HPV modeling are:

- age of sexual debut and, more broadly, risk of HPV infection; and
- whether cervical cancer screening was available or not.

Coverage is another important variable in modeling.

Vaccine licensing status and global guidance

Dr Graham Neilsen
Asia Pacific Office, Family Health International, Thailand

The purpose of the presentation was to give an overview of the:

- current status for HPV vaccines; and
- WHO's policy and program guidance.

US CDC recommendations

The recommendations adopted by CDC in June 2006 for the MSD quadrivalent HPV vaccine are:

- Universal routine vaccination of 11-12 year old girls.
- Universal catch-up vaccination of 13-26 year old females.
- 9-10 year olds may be vaccinated at the physician's discretion.
- Neither Pap testing or HPV testing are needed prior to vaccination.
- Girls and women should be vaccinated regardless of whether they have or previously had an abnormal Pap test, a positive HPV test, or genital warts.
- The vaccine should be included in the Vaccines for Children Program, a US Federally funded program for children in uninsured and indigenous populations.

Key points

- The overarching consideration is to position HPV vaccines within a comprehensive, integrated service delivery structure.
- Because HPV vaccines 'fit' in several different programs, partnerships are key to successful introduction.
- HPV vaccines are one element of cervical cancer control strategy.
- Because of the cost of the vaccines, critical issues of equity associated with the new vaccines must be addressed.
- HPV vaccines provide an exciting opportunity to improve global health, if their introduction is managed well.
- More data is needed to guide the development of HPV immunization programs.

Licensing of the quadrivalent HPV vaccine

MSD has submitted applications for licensing of Gardasil™ in over 90 countries. Approvals have been obtained in over 30 countries. In Asia Pacific, approval has been granted in Australia, Hong Kong, Macau, Malaysia, New Zealand, the Philippines, and Taiwan, as of the beginning of November, 2006.

There are variations in licensing approvals. Some countries have approved Gardasil™ for use in boys, as well as girls (e.g. Australia, EU countries, Mexico, Togo).

Some governments are considering possible funding support for Gardasil™ in public sector vaccination programs. [1]

Licensing of the bivalent HPV vaccine

GSK has submitted applications for licensing of Cervarix™ in a number of countries, including in Asia. An application for US FDA licensing is expected to be submitted by early 2007.

WHO guidance and tools for comprehensive cervical cancer programs

WHO has produced two sets of guidelines:

1. Comprehensive Cervical Cancer Control: A Guide to Essential Practice
Provides guidance on education, counseling, performing procedures to standard, screening, diagnosis, treatment for pre-cancer and cancer, including palliative care. It is a generic manual which can be adapted to different settings.

1 Gardasil™ is now approved in more than 50 countries and will be supported by federal government funding in both the USA and Australia .

2. Planning and Implementing Cervical Cancer Prevention and Control Programs: a Manual for Managers
Aimed at mid-level program planners and managers to assist them design, implement and monitor a program. It addresses systems necessary for service delivery, ensuring clients' rights and providers' needs are met.

WHO, in conjunction with partners, has also produced three training tools:

1. Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: a Beginner's Manual
This is an introductory manual for gynecologists, pathologists, general practitioners, and nurses. It provides information on the principles of colposcopy and outlines basic skills needed to colposcopically assess cervical intraepithelial neoplasia and provide basic treatment.

2. Digital Uterine Cervix Histopathology and Cytopathology Atlas
A digital basic reference atlas for practicing pathologists, cytotechnologists and technicians.

3. A Practical Manual on Visual Screening for Cervical Neoplasia
A training manual on VIA and VILI for physicians and nurses.

All these documents are available for download or ordering from the WHO web site.

WHO-UNFPA guidance on HPV vaccines

In March 2006, WHO and UNFPA held a broad-based consultation meeting on sexual and reproductive health programs and HPV vaccines. A guidance note, *Preparing for the Introduction of HPV Vaccines: Policy and Program Guidance for Countries*, provides background and conclusions of the consultation meeting on key issues. It is a guidance note rather than a technical reference.

Promise and reality

HPV immunization holds great promise for improving global health. But availability of the vaccine will not result in automatic acceptance and uptake. Issues of equitable access and affordability will need to be addressed.

Access to HPV vaccines is a critical public health need for all women. This is particularly the case for poorer women in less developed countries, where the prevalence of HPV and related diseases is much higher than is the case in the developed world. Policy questions that need to be addressed are:

- How can poor women in developing countries get equitable access to affordable, quality vaccines?
- Will there be adequate quantities of vaccines available at an affordable price for developing countries?
- What will be the role of existing programs and services?

Features of HPV vaccines: unique opportunity

Opportunities and challenges posed in planning for HPV vaccination programs include:

- National immunization programs will need to deal with the socio-politically charged environment of sexual health among pre-teenage girls (and boys).
- Cancer control programs will confront difficult decisions regarding prioritizing interventions for preventing cervical cancer (e.g. the balance of resources put into screening programs and vaccination programs).
- Sexual and reproductive health programs will need to develop new strategies for counseling young people and women receiving the vaccine.
- Experience with HPV vaccine introduction may serve as a model for eventual introduction of HIV vaccines and microbicides.

Features of HPV vaccines: an expensive product

At least initially, HPV vaccines will be expensive. Even if the price is reduced significantly, it is likely the cost will still be much higher than the cost of vaccines currently included in EPI programs.

There is the risk that a badly handled introduction of the HPV vaccine will increase health inequities. As with all new medical technologies, wealthier countries will adopt the vaccine before developing countries. In middle income and poor countries it is likely that, at least initially, HPV vaccines will be used more in the private sector compared to the public health sector.

Cost is important, but should not be the sole criterion. Additional benefits of HPV vaccines are also important.

Features of HPV vaccines: introduction challenges

Priority will need to be given to developing country-specific recommendations on the affordability, accessibility, feasibility and acceptability of HPV vaccines.

National cervical cancer control strategies will need to be updated and policy statements on HPV vaccines developed.

There is the potential for a harmful backlash against sexual and reproductive health programs and adolescent reproductive health programs given sensitive socio-political issues relating to administering a vaccine which prevents sexually transmitted infections to adolescents. Program planning will need to anticipate and manage this challenge.

Features of HPV vaccines: not business as usual

Partnerships will be essential to success. New partnerships will need to be forged. Partnerships will be needed between what are often vertically oriented health programs (e.g., immunization, adolescent and reproductive health, cancer prevention, cancer registries, women's and neonatal health, and child health).

Public-private sector partnerships will also be needed, as will partnerships with civil society, especially to ensure good communication with the community.

Advocacy, information and communication

Up-to-date and accurate information needs to be provided to decision-makers. There has already been some negative feedback on HPV vaccines, sometimes based on cost, and on other occasions based on ignorance.

HPV vaccines will need to be promoted with clear and non-confusing health messages, adapted to each country's socio-cultural norms.

In the community, a lack of understanding, especially relating to the link between HPV and cervical cancer, will result in a lack of community demand for the vaccine. Without such demand, there will be a lack of political will to make HPV vaccines available.

There will also be a need to manage possibly unrealistic expectations regarding vaccine availability.

The potential for community myths about HPV vaccines, such as conspiracy theories, will also need to be managed.

Service delivery: reaching target populations

School-based strategies may seem attractive as a first option, yet this could result in limited coverage in many settings. Adolescent sexual and reproductive health programs have experience in reaching out-of-school youth. However, they lack service delivery experience and capacity required for HPV vaccines.

Community programs can increase awareness and create linkages with services in both the public and private sectors. Referral schemes will be needed, with possible use of vouchers.

Sexual and reproductive health programs can reach women, especially through family planning, maternal and child health, and cervical cancer programs, and educate them about the need for HPV immunization of younger women and girls.

Service delivery: partnerships between programs

HPV vaccine delivery should be built on structures already in place rather than the creation of new vertical organizations. It is likely that national immunization programs will assume leadership in most settings. Delivery strategies require will require coordination mechanisms between programs. These will need guidance and support to avoid bureaucratic politics.

Service delivery: monitoring and evaluation

Attention needs to be given to data needs through both routine national immunization program surveillance and cancer registries. Monitoring of vaccine coverage and data on the outcomes of post-marketing surveillance will be needed. Dissemination of the results of pilot and demonstration studies will be important to guide the development of national programs.

Health systems: stewardship and financing

A broad range of partners, at national and international levels, should be involved in developing a strategy for comprehensive introduction of HPV vaccines.

Models should be developed at country level to forecast demand and estimate the financing and coverage needed to have an impact on the disease at a population level.

Developing countries have concerns about their ability to pay for the vaccine and other costs associated with a new vaccination program. Securing international funding commitments for HPV vaccines will be needed. (e.g., GAVI, UNICEF, revolving funds, and foundations).

Exciting possibilities but more data needed

- Areas for additional data needs are:
- Can the vaccines be given to 4-6 year olds? Trials are needed to see if the vaccine is suitable for school-entry age groups.
- The marginal benefits of vaccinating males.
- Cross protection against persistent infection and CIN 2 or worse lesions due to HPV 31 and 45?
- Duration of immunity - will a booster be required in 5-10 years?
- Safety and efficacy of the HPV vaccine in immuno-compromised persons, especially those with HIV, and in pregnant women.
- Safety of simultaneous administration with other vaccines.
- Logistical issues such as stability of the vaccines, the real need for a cold-chain, and the potential for administration by the Uniject™ system.
- Cost of the vaccine over time.

Acknowledgment: Dr. Nathalie Broutet, WHO.

Country-level perspectives on the role of cervical cancer vaccines

Professor Cecilia Ladines-Llave
Cancer Institute of the Philippines

This presentation reviews the key issues and challenges that developing countries need to address in introducing HPV vaccines.

HPV and cervical cancer

"The causal role of persistent oncogenic HPV infections in cervical cancer has been documented beyond reasonable doubt. The association is present in virtually all cervical cancers (99.7%) worldwide. This has paved the way for the development of a vaccine that prevents persistent oncogenic HPV infections and therefore has the potential to prevent cervical cancer. It is the right time for medical societies and public health regulators to consider this evidence and to define its preventive and clinical implications." (Bosch, 2002.)

Key points

- The cost of HPV vaccines will be problematic for developing countries.
- National cervical cancer prevention and control strategies need to be updated to incorporate HPV vaccination.
- A comprehensive approach to cervical cancer prevention and control requires a combination of screening linked to vaccination and establishing service delivery models integrating this combination with routine basic reproductive health services and healthy lifestyle programs.
- Attention needs to be given to organisational development issues to ensure that national cervical cancer control programs are being fully implemented.
- Religious and conservative resistance to the introduction of HPV vaccines, and community misconceptions, need to be anticipated and managed through effective communication.

Impact of vaccination

The vaccines have the potential to result in a tremendous decrease in the incidence of cervical cancer. This news has excited Filipino women, as demonstrated by this statement:
"How long will we have to wait for the HPV vaccine? Ten Filipino women die each day from cervical cancer. And given the ease of diagnosis and 10 year 'window' to treat it, these deaths are certainly unnecessary and wasteful. How many women will have to die before we start protecting our daughters?" (Rina Jimenez-David, Philippine Daily Inquirer.)

The opportunity

The greatest opportunity now exists to control cervical cancer, especially in developing countries where this is most needed. However, because of a lack of funds, HPV vaccine introduction will be much more difficult in developing countries, compared to industrialized countries. Vaccines that cost $10 per child are already seen as a major problem. A vaccine that costs $360 per child, in a country with a minimum wage of $7 day will be much more problematic.

Are we really ready?

Before we can start using HPV vaccines widely, we need to update national health strategies for cervical cancer prevention and control. These strategies need to be based on country-specific considerations and the perspectives of community members. National strategic plans need to:

- Analyze the socio-cultural, political environment, including the burden of cervical cancer to the national economy.
- Assess barriers and opportunities for both primary and secondary prevention, on a multidisciplinary basis.
- Plan advocacy, service delivery, education and training, and monitoring of progress towards cervical cancer control.
- Sustain the effort continuously.
- Identify approaches to make the vaccine affordable.
- Establish service delivery models for integrating immunization routinely as part of healthy

lifestyles and basic reproductive health services.

Vaccination linked to screening

HPV vaccination in uninfected women will prevent most cervical cancers. Cervical screening and treatment of precancerous lesions will prevent cervical cancer among women who are already infected. We need a comprehensive approach to cervical cancer control and prevention. This requires a combination of screening and vaccination (Renshaw, 2004).

HPV vaccination is not a stand-alone approach to cervical cancer prevention. In a comprehensive cervical cancer control program, the measure of success is the number of women not developing the disease. Screening will continue to play an important role in the detection of early cervical cancer.

Global burden of cervical cancer

Of the half million new cases of cervical cancer each year, around half come from Asia. Worldwide, a woman dies of cervical cancer every 2 minutes. Eighty percent of the 270,000 deaths from cervical cancer each year occur in developing countries. Projections indicate a four-fold increase in global cases of cervical cancer by 2050 (Ferlay, 2002).

Burden of cervical cancer in the Philippines

In the Philippines, the incidence and mortality of cervical cancer has remained unchanged for the past 20 years. Incidence is 22/100,000, with 4,600 new cases per year. Two thirds of diagnoses are made in late stages, resulting in 73% of cases dying within 5 year of diagnosis.

Systematic data gathering for cervical cancer is inadequate. The Philippines Cancer Registry covers only 25% of the nation, mostly in urban areas. Most women live in rural areas. The Philippines data on cervical cancer may be an underestimate.

The total population of the Philippines is 87.85 million people. Women aged 15-64 make up 60.6% of the total population. Sexual debut occurs between the ages of 15-24 years for 23% of Filipino women. The target population for cervical cancer prevention and control amounts to 20 million females aged 25-55 years, or 35 million females aged 10-64. Currently, only 12% have been screened (National Statistics Office, 2000; 2004).

Issues and challenges in the Philippines

The National Cervical Cancer Control Program has not been fully implemented due to changes in government and loss of dedicated and sustained leadership. The program is chronically underfunded. This is reflected in undeveloped facilities for service delivery. Monitoring and audit are poorly performed. The devolved health system is managed by local government offices that accord low priority to health. There is a lack of awareness of cervical cancer.

Recommendations that have been made to address this situation include:

- An organized cervical cancer control and prevention program;
- A sustained information campaign;
- Establishing a national database;
- Advocacy for responsible leadership at the national and local levels;
- Sustained funding based on need; and
- Effective monitoring and audit.

Religious and political mindsets

The Philippines is a conservative country. It is possible that the HPV vaccination could be seen by some as promoting sexual promiscuity, as reflected in the following statement:
"Giving the HPV vaccine to young women could be potentially harmful because they may see it as a license to engage in premarital sex." (Bridget Maher, Family Research Council, New Scientist.)

Anti-vaccination groups may create misconceptions about the HPV vaccine. Rumors that other vaccines were plots to sterilize girls or use them as guinea pigs for anti-fertility vaccines, have seriously damaged programs in many countries. A vaccine targeted to females only may revive and exacerbate these rumors. It is possible that an anti-STI vaccine, such as HPV vaccines, will become a target of fundamentalist groups. These issues will need to be managed through effective communication.

The Cervical Cancer Prevention Network Program

In January 2006, the Cervical Cancer Prevention Network Program was launched in the Philippines. The program is an initiative of the Cancer Institute of the Philippines, the University of the Philippines, in collaboration with Johns Hopkins University. The program's vision is for Filipino women to be free of cervical cancer. The mission is to eradicate cervical cancer by:

1. *Primary prevention* promoting healthy lifestyles through education and information campaigns and immunization.
2. *Secondary prevention* through cervical cancer screening with an emphasis on VIA, linked to cryotherapy, in a single visit approach.
3. *Research* on cervical cancer and HPV vaccines.

The initial program objectives are to:

- Increase country readiness for implementation of expanded cervical cancer prevention efforts.
- Build capacity to sustain and expand large-scale, coordinated cervical cancer prevention efforts.
- Expand access to high quality VIA and cryotherapy at service delivery points and improve program performance.

The program will be implemented in the following phases:

1. Country receptiveness;
2. Capability development;
3. Program performance support ; and
4. Service expansion.

Expected initial program results are:

- Sufficient rate of screening coverage;
- A core group of advocates and supporters;
- A training team;
- Service delivery model established;
- A management team; and
- Strengthened Alliance Network.

WHO Guidelines:Global Immunization Vision and Strategy

In line with the WHO guidelines, the Philippines is committed to:

- A world where immunization is highly valued;
- A world where every child, adolescent and adult has equal access to immunization provided for in their national schedule;
- A world where more people are protected against more diseases;
- A world where immunization is seen as crucial for the wider strengthening of health systems and a major element of efforts to attain the Millennium Development Goals.;
- A world where vaccines are put to best use in improved health and security globally.; and
- A world where solidarity among the global community guarantees equitable access for all people to the vaccinations they need.

Social impact of the introduction of cervical cancer vaccines

Dr Aree Prohmmo,
Institute of Population and Social Research, Mahidol University, Thailand

Social features of cervical cancer in Thailand

There is a high level of fear associated with cancer among Thai people. Cancer is seen as a fatal disease that cannot be prevented or adequately treated. The fear of cancer appears to be associated with high cancer incidence rates.

Thai women often link any gynecological problem they are experiencing with cervical cancer. Although there is an awareness of cervical cancer, knowledge of the causes and how to prevent cervical cancer is low.

Social features of the cervical cancer screening program in Thailand

Cervical cancer screening in Thailand has had a low coverage rate. Around 38% of women aged 35 have been screened at least once for cervical cancer. This is despite the long-term availability of Pap testing in Thailand. Women usually only seek Pap testing if they have a gynecological complaint. There is a low level of awareness of the need for routine screening. Many women are very shy and are reluctant to be examined by male physicians.

Key points

- HPV vaccines are very likely to be acceptable in Thailand, although some opposition to an 'STI-vaccine' for adolescents is possible.
- HPV vaccines should be promoted as 'anti-cancer' vaccines.
- Adolescents are best reached through school-based vaccination.
- There is a need to raise public awareness about HPV and its link with cervical cancer, HPV vaccines and existing screening programs.

Young Thai women are more likely to be screened for cervical cancer. Fifty per cent of women aged 20-29 years have been screened at least once. This is not the most effective use of resources as women in this age group are at lesser risk of cervical cancer compared with older age groups.

The higher rate of screening of younger women may be because screening is offered in family planning and at post-partum check-ups. The recently released national guidelines for cervical cancer screening focus on screening women aged 35-60 years. These guidelines need wider dissemination.

Social barriers to introducing HPV vaccines overseas

Research in the UK, Mexico and Vietnam found:

- Most parents (70%) are willing to have their girls immunize for HPV.
- A small number of vocal parents are reluctant to immunize young girls against STIs in case this encourages early sexual activity and promiscuity.
- 74-89% of young adults would agree to vaccination.

Social barriers to introducing HPV vaccines in Thailand

There has been no research in Thailand on the introduction of HPV vaccines. Based on previous experience in Thailand it can be postulated that some parents and members of the public are likely to have negative reactions to HPV vaccination of adolescents. For example, there has been opposition to condom vending machines in schools and also to sex education for young students. There is also a history of misinformation and confusion about new vaccines.

Most Thai parents and young people are, however, very likely to support the introduction of HPV vaccines. They are familiar with immunization from experience with existing immunization programs. They would also support an anti-cancer vaccine, particularly given community fears of cancer.

Program barriers to introducing HPV vaccines

Issues that will need to be considered are:

- How to reach pre-adolescents and adolescents;
- Drop-out rates for multiple-dose vaccinations, and a possible booster;
- How to reach mobile populations; Lack of knowledge and misconceptions about
- vaccination; and
- the high cost of vaccination.

Gender issues: overseas

Issues that have been identified are:

- Men have a low level of knowledge about HPV infections.
- HPV vaccines tested to date have not targeted men.
- Problems with a female-only vaccination strategy.
- Men and women should share responsibility.

Recommendations for program implementation

- Position HPV vaccines as 'anti-cancer' vaccines. Information, education and communication should emphasize the link between HPV and cervical cancer. (Awareness of the link is low.)
- To reach adolescents, vaccination programs should target primary or lower secondary schools where enrolment levels are higher. HPV vaccination should be linked with existing school health programs.
- Continue to provide cervical cancer screening.

Next steps in regional cancer prevention – building awareness and advocacy: Panel discussion

The moderator of the panel discussion suggested the focus of thinking needs to be on what happens next.

Cost

The issue of the cost of the vaccine has been raised repeatedly. The representatives of the two pharmaceutical companies were asked to give an indication of how they proposed to deal with the issues of cost and equitable access.

The representative from MSD stated that many barriers can be encountered in the introduction of new vaccines. MSD is fully committed to ensuring access to its HPV vaccine. Clearly, there will be a need to look at the economic situation of a country and differential pricing. Cost is important, but it is not the only challenge. There is a need to work in broad partnerships with governments and NGOs to address affordability and also the capacity of national immunization programs to ensure that the benefits of the vaccine are realized in a relatively short time frame.

The representative of GSK indicated that they would be taking a similar approach to MSD. In principle, the aim would be to make the HPV vaccine affordable to developing countries.

A participant commented that the price of the HPV vaccine may come down with higher production volumes. They asked the pharmaceutical companies whether they were looking at innovative production techniques that may be significantly cheaper. The representative from MSD indicated that they are committed to improving the efficiency of vaccine production, including possible development of new technologies.

A participant commented that it is now common for multinational drug companies to reduce the cost of vaccines for developing countries in relatively short-time intervals. While price reductions as much as ninety percent for the HPV vaccine may not be enough for the poorest countries, the willingness of companies to address global access issues is a very positive development.

Another participant suggested the price of the vaccine should be set on a country-by-country basis, based on affordability.

Regional guidelines / guidance notes

The moderator asked which groups need to be engaged over the next 3-6 months at the regional and country level in adapting the WHO guidelines and WHO/UNFPA guidance note.

One participant commented that in many countries, poor people have limited access to private health care. They are reliant on government services. Engagement with governments in adapting guidelines will be essential.

Another participant stated that many health professionals responsible for cervical cancer screening programs have not yet received sufficient information on HPV vaccines to make decisions on how to integrate screening and vaccination. Education of this group will be important.

A participant commented that HPV vaccine research has been a fast moving area, with many new developments. This is likely to be the case for the next couple of years. These rapid changes have presented a challenge to WHO. Because things have been changing so quickly, WHO has had to develop 'guidance notes' rather than more definitive guidelines or recommendations. There will be a continuing need to educate health professionals on new information, as it comes to hand. More guidance notes will be needed. It may, however, be premature to develop guidelines or recommendations as emerging knowledge will not allow such a definitive approach.

Another participant stated that education of health professionals and the community will generate demand for HPV vaccines. Key target groups for education are women and the general population, medical practitioners, health planners and NGOs.

Role of professional associations

A participant emphasized the need to first educate health professional associations on issues relating to HPV vaccine introduction as Ministries of Health often rely on these associations for advice. Accordingly, professional education should precede general community education and advocacy to Ministries.

Another participant said that it is important to have diagnostic and treatment services in place before public education campaigns commence, so as to be able to respond to demand.

Advocacy by women with cervical cancer

The moderator asked about the role of women with cervical cancer as advocates in the Philippines. The response was that members of patient cervical cancer support groups have taken on this role. For example, the Rotary Association developed a video promoting screening, and this included survivors of cervical cancer speaking of their experiences. They are one of the best advocate groups for promoting prevention.

Another participant said that involvement in health promotion campaigns by well known people who had experienced cervical cancer could be very powerful in generating demand for services.

Role of nurses

The moderator asked panel members about the role of nurses in cervical cancer control and prevention. A participant from the Philippines said that midwives have been trained to undertake cervical cancer screening, under the guidance and supervision of medical practitioners. Midwives also give childhood vaccinations. Another participant said that midwives in the Philippines are responsible for delivering 28 different services. This is a heavy workload which needs to be managed. There is a need to train other health care professionals so that there is a balance in workload. This needs to be addressed in integrating HPV vaccination into current services.

Another participant encouraged broad scale education of the medical profession so that practitioners can promote cervical cancer screening and HPV vaccination when patients seek health care for other reasons.

HPV vaccination programs

A Thai participant suggested that HPV vaccination be incorporated into school health programs as this is an easy way of vaccinating adolescents. It was also suggested that the vaccine be promoted as an anti-cancer vaccine, and not as an STI vaccine. This would be more acceptable to the community.

Marketing of vaccines

Another participant asked MSD how it intends to promote its quadrivalent vaccine, given that it protects against genital warts, in addition to cervical cancer. In response, MSD said the primary focus of its promotional activities will be on cancer prevention. There will be some additional focus on the additional advantage of MSD's vaccine in preventing genital warts.

Another participant noted that there may be segmented marketing strategies for different audiences. For example, MSD may choose to emphasize the genital warts aspect of its vaccine in direct marketing to medical practitioners.

A participant mentioned that attempts by conservative groups to oppose HPV vaccination of adolescents, on the basis of promoting promiscuity, has not got much traction. Most of the current opposition to introduction of HPV vaccines is based on traditional myths about vaccination, and not related to prevention of STIs in adolescents. This experience could vary from country to country.

Despite the lack of traction for conservative concerns about HPV vaccines and STI prevention in adolescents, it was stated that the media may focus on this to play up controversy. It was suggested that alternative controversies could be developed to focus the attention of the media. For example, 'the poorest women who are most in need of HPV vaccination will miss out.'

One participant said that many women were already aware that HPV is a sexually transmitted infection and would not be influenced by misreporting or hysterical reporting in the media.

Another participant asked 'is it realistic to think we can fool the media into believing that HPV is not a sexually transmitted disease?' There was some debate on the content of key messages to use in promotion of HPV vaccines, focusing around the issue of the cancer prevention or use of other messages.

Vaccination strategies

A participant recommended that HPV vaccination should be provided to children at as young an age as possible. That is, as soon as they can produce immunity. It was acknowledged that there are no data on younger age groups at present. An advantage of early immunization is that parents already accept childhood vaccination. Adolescent vaccination may be more difficult. Early vaccination also protects children before they are exposed to infection.

A participant recommended that both females and males should be vaccinated as this would lead to higher levels of herd immunity. Experience has shown that universal vaccination works best.

Taking issues forward?

The moderator said the panel had identified two broad issues:

1. The need to educate health professionals, especially so they can influence policy-makers and service planners.
2. Communication strategies need to be developed that will shape debates on HPV vaccines.

The question of who should take these issues forward over the next 6 months and how they should do this was posed.

Participants identified the following groups:

- women's groups;
- family doctors;
- obstetricians and gynecologists;
- developers of curricula for health professionals; and
- service planners and policy-makers.

A participant stressed the need to be honest with the public and patients in relation to fact that HPV is usually transmitted sexually. HPV vaccines can prevent up to 70% of cases of cervical cancer. Primary prevention, in the form of changes in sexual behavior, is needed to protect women against infection with other HPV sub-types.

A participant stated that, for communication to be effective, it has to be targeted to the audience. Communication strategies for policy-makers will be different, compared to women living in villages. The level of technical information needed will vary by audience.

A participant said that, in Thailand, the main motivating factor for vaccination against hepatitis B at the time the vaccine was introduced was the high prevalence of liver cancer. The vaccine was seen by the community as protecting against liver cancer. A similar approach can be taken with the HPV vaccine and cervical cancer prevention.

There is a need to identify the source of information women use for health issues and to use these sources to ensure that patients can access accurate information. Village health volunteers were identified as potential key sources of information for HPV vaccines.

Participants

Dr Thiravud Khuhaprema
President, 3rd Asia Pacific Organization for Cancer Prevention General Assembly
National Cancer Institute
Thailand
nci_apocp@yahoo.com

Dr Malcolm Moore
Secretary General and APJCP Chief Editor
UICC/APOCP
Thailand
apocp2000@yahoo.com

Khunying Kobchitt Limpaphayom
Department of Obstetrics & Gynecology, Faculty of Medicine
Chulalongkorn University,
Thailand
lkobchitt@csloxinfo.com

Dr Partha Sarathi Basu
Head, Department of Gynecological Oncology
Chittaranjan National Cancer Institute
India
basupartha@hotmail.com
ceds@vsnl.com

Dr. Saibua Chichareon
Department of Obstetrics and Gynecology,
Faculty of Medicine
Prince of Songkla University
Thailand
saibua.c@psu.ac.th

Professor Efren Domingo
Manila Doctors Hospital
University of the Philippines
Philippines
efrendomingo@hotmail.com

Ms Sunun Duangchan
Planned Parenthood Association of Thailand and Thai Women Watch
Thailand
soonaad@yahoo.com
info@ppat.or.th

Dr Supanee Jivasak-Apimas
Siriraj Reproductive Health Research Centre,
Department of Obstetrics and Gynecology
Siriraj Hospital
Thailand
neepasu@hotmail.com
sisjv@mahidol.ac.th

Associate Professor Vasant Linasmita
Department of Obstetrics and Gynecology,
Ramathibodi Hospital
Mahidol University
Thailand
ravln@mahidol.ac.th

Professor Cecilia Llave
Cancer Institute of the Philippines
Philippines
cesll@yahoo.com
cecap_phil@yahoo.com

Dr Somsak Lolekha
President, Pediatric Society of Thailand
Department of Pediatrics
Ramathibodi Hospital
Thailand
slolekha322@yahoo.com

Dr Ricky Lu
Senior Reproductive Health Advisor
FP/RH COE
JHPIEGO
USA
rlu@jhpiego.net

Professor Genara A. Manuel-Limson
Department of Obstetrics & Gynecology
University of the Philippines & Philippine General Hospital
Philippines
genara_limson@yahoo.com

Dr. Maxwell Parkin
Clinical Trials Service Unit and Epidemiological Studies Unit, University of Oxford
United Kingdom
parkin_iacr@iarc.fr
iacr@iarc.fr

Mrs. Waranya Pitaktepsombat
Clinic Manager
Planned Parenthood Association of Thailand
Thailand
info@ppat.or.th
ppat@samart.co.th

Dr Aree Prohmmo
Institute of Population and Social Research
Mahidol University
Thailand
prapr@mahidol.ac.th

Dr You-Lin Qiao
Department of Cancer Epidemiology, Cancer Institute/Hospital
Chinese Academy of Medical Sciences and Peking Union Medical College
China
qiaoy@public.bta.net.cn

Dr Dusadee Sakonlaya
Director of Pathology, Faculty of Medicine
Thammasat University
Thailand

Associate Professor Rudiwilai Samakoses
Department of Pediatrics
Phramongkutklao Hospital
Thailand
srudi@mozart.inet.co.th

Dr Hai-Rim Shin
Research Institute for National Cancer Control and Evaluation
National Cancer Center
Korea
cmkim53@ncc.re.kr
hrshin@ncc.re.kr

Assoc. Prof. Supannee Sriamporn, Ph.D.
(Epidemiology)
College of Medicine and Public Health
Ubon Rajathanee University
Thailand
supannee0911@yahoo.com

Sukhon Sukvirach
Research Division
National Cancer Institute
Thailand

Dr Krittika Suwanrungruang
Khon Kaen University
Thailand
krisuw@kku.ac.th

Nawarat Tungsrithong
Faculty of Medicine Science
Naresuan University
Thailand

Dr Surapon Wiangnon
Thailand

Dr Scott Wittet
Advocacy and Communication, Cervical Cancer Vaccine Project
PATH
USA
swittet@path.org

Dr. Punee Pitisuttithum
Mahidol University,
Thailand.
tmppt@mahidol.ac.th

Linda Distlerath
Vice President, Health Policy, Asia Pacific Human Health
Merck Sharp & Dohme (Asia)
Hong Kong
linda_distlerath@merck.com

Vince Docherty
Director, Public Affairs
Merck Sharp & Dohme, Hong Kong
vince_docherty@merck.com

Dr John R. Elton
Senior Director Vaccines, Asia Region
Merck Sharp & Dohme
Australia
john_elton@ merck.com

Sonthinee Chatchawalchonteera
Business Unit Manager
Merck Sharp & Dohme, Thailand
Thailand
sonthinee_chatchawalchonteera@merck.com

Dr William (Bill) C. Gerth
Senior Director, Outcomes Research
Merck Sharp & Dohme
USA
william_gerth@merck.com

Dr Yanee Hutagalong
Director, Clinical R&D/Medical Affairs
GlaxoSmithKline, (Thailand)
Thailand
yaneehutagalong@gsk.com

Mrs. Chantanee Sarawanagong
GlaxoSmithKline (Thailand)
Thailand
chantanee.sarawanawong@gsk.com

Dr Derrick Sim
GlaxoSmithKline
Thailand
derrick.k.sim@gsk.com

Dr Sonia R. Pagliusi
Director, International Public Affairs
Digene Switzerland
Switzerland
sonia.pagliusi@digene.com

Dr Jeanine Bardon
Senior Director, Asia Pacific Office
Family Health International
Thailand
jbardon@fhibkk.org

Dr Gary West
Senior Vice President, Research and Strategic Coordination
Family Health International
USA
gwest@fhi.org

Dr Steve Wignall
Director, Technical Division, Asia Pacific Office
Family Health International
Thailand
swignall@fhibkk.org

Dr David Sokal
Associate Medical Director
Family Health International
USA
dsokal@fhi.org

Dr Graham Neilsen
Associate Director, Asia Pacific Office
Family Health International
Thailand
gneilsen@fhibkk.org

Dr Somchai Sriplienchan
Country Director
Family Health International
Thailand
somchai@fhibkk.org

David Lowe
Rapporteur
Thailand
davidbkkth@yahoo.com

Family Health International

Asian Pacific Organization for Cancer Prevention

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THE NATIONAL CANCER INSTITUTE
DEPT. OF MEDICAL SERVICE., MIN. OF PUBLIC HEALTH

MSD

gsk GlaxoSmithKline

DIGENE

Family Health International
Asia/Pacific Regional Office

19th Floor, Tower 3, Sinthorn Building
130-132 Wireless Road, Lumpini,
Pathumwan, Bangkok 10330 Thailand
Tel: 662.263.2300
Fax: 662.263.2114
www.fhi.org