



**Health Outcomes Research:  
How Can It Assist Decision-Making for the  
Prevention of Cervical Cancer and Other HPV  
Disease in Asia and the Pacific?**



**Symposium Proceedings**

Bangkok, Thailand  
12 February 2008

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# Introduction



Cervical cancer is the second most common cancer world-wide and is the most common cancer among women in developing countries. Globally, there are approximately 500,000 new cases and 250,000 deaths each year. Almost all cervical cancer is linked to HPV infection. 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.

In Asia and the Pacific, cervical cancer is one of the most common types of cancer with age-standardized incidence rates of 20.2, 20.9, 19.8 and 30.7 per 100,000 among women in Viet Nam, the Philippines, Thailand and India respectively.<sup>1</sup> Many countries in the region recommend prevention strategies such as safer sexual behaviors and cervical cancer screening with acetic acid visualization (VIA) followed by appropriate diagnosis and treatment. Coverage with cervical cytology is low and in many countries the Papanicolaou smear is held to be a diagnostic tool rather than a screening procedure. While HPV immunization will offer a new strategy for the prevention of cervical cancer, cervical screening will remain vital for decades, as women will continue to need screening and early detection programs. Most importantly, the 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 guidance on comprehensive programs for cervical cancer control as well as for the introduction of HPV immunization have been issued by WHO and WHO/UNFPA respectively and the process to review these at a regional or country level in Asia and the Pacific has begun. In April 2007, WHO/SEARO and WHO/WPRO convened a Bi-regional Consultation on Strategies to Prevent Cervical Cancer. The meeting was held in Pattaya, Thailand and included representatives from Ministries of Health, the pharmaceutical industry and other stakeholders including international NGOs.

It is evident that the current initial costs of large-scale HPV immunization have made decision-makers reluctant to develop strategies to incorporate HPV immunization vaccines into their programs – especially in the absence of locally applicable data on their likely impact and cost-effectiveness. The complexity of decision-making in this area is profound and without advocacy efforts to build consensus, HPV immunization will not feature prominently on the policy agenda of governments in the region for some time. The Pattaya meeting made it clear that governments of developing countries in this region consider the current vaccine price prohibitive. Without massive additional resources and a significant price reduction, few countries in the region would be able to consider even preparatory work for the introduction of HPV immunization – other than regulatory processes for approval of the vaccine in-country.

This report documents the proceedings of a regional workshop highlighting the role of health outcomes research data and modeling for future decision-making.

The meeting was sponsored by Merck Sharp and Dohme with additional support from GSK Biologicals; and planned, and hosted by Family Health International in partnership with the College of Public Health Sciences, Chulalongkorn University.

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<sup>1</sup> Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality, and Prevalence Worldwide. IARC CancerBase No. 5, Version 2.0. Lyon, France: IARC Press; 2004.



# Welcome address



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Researchers, policy-makers and implementers all face the challenge of making national public health policies as scientific and evidence-based as possible. Bridging the gap between research and programs is not easy. There is rarely the luxury of obvious or intuitive choices. The real life situation is far more complex, with multiple possible decisions. Existing programs can be challenged by new technology, rising costs and competing claims for limited financial and human resources. This is the situation today regarding decisions on how best to prevent cervical cancer and other HPV diseases, and the possible role of HPV vaccines.

The potential benefits of the HPV vaccines are enormous. However there are many lingering questions. These include:

- ❖ Are the vaccines affordable for low and middle income countries?
- ❖ To what extent and under what circumstances are the vaccines cost-effective?
- ❖ How do the vaccines compare to existing screening programs and what is the optimal use of both prevention methods?
- ❖ What are the possible resources of domestic and external funding for the HPV vaccines?

This meeting provides an opportunity to address these questions by examining the evidence from health outcomes research. It will be important for the information from presentations and the outcomes of discussions to be taken back by participants to their countries so that it can assist decision-making for the prevention of cervical cancer and other HPV disease in Asia and the Pacific.

# HPV-related diseases: epidemiologic and economic burden update from global and regional perspectives



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### HPV

HPV is a non-enveloped, double-stranded DNA virus. Over 100 types of HPV have been identified. The focus of this presentation is on the 30-40 ano-genital types of HPV, which can be divided into two groups:

- ❖ **Oncogenic types**, of which there are 15-20. Globally, the majority of cervical cancer cases can be attributed to infection with HPV types 16 and 18.
- ❖ **Non-oncogenic types** which are of lower risk. HPV types 6 and 11 are most often associated with ano-genital warts.

### Cervical cancer: global and Asian data

Cervical cancer is the second most common cancer

found in Asian women, with an incidence rate of 15.4 per 100,000. The mortality rate for cervical cancer in Asian women is 8.4 per 100,000. Cervical cancer is the fourth most common cause of death from cancer among Asian women. The estimated number of cases of cervical cancer in Asia in 2002 was approximately 266,000. Asia accounts for more than 50 per cent of the 493,000 global cases of cervical cancer. (GLOBOCAN, 2002).

Globally, it is estimated that by 2020, the number of cervical cancer cases will increase to 702,500. This is a 42% increase, compared to 2002. In less developed countries, there will be a 56% increase, compared to an 11% increase in more developed countries. These projections assume rates estimated for 2002 will hold into the future (GLOBOCAN, 2002).

In Thailand, the number of cases of cervical cancer over the last twenty years has been stable at around 5-6,000 cases per year. Deaths from cervical cancer have ranged between 2-3,000 cases per year.

The age-specific incidence rate of cervical cancer for South-Central Asia is 26.2 per 100,000 women, compared to 18.7 in South-East Asia and 7.4 in East Asia (GLOBOCAN, 2002).

The cervix is the most common site for cancer attributable to HPV infection. HPV infection can also result in cancer of the penis, vulva, vagina, anus, mouth, or oro-pharynx. However, HPV-related cancer in these sites is significantly less common, compared to cancer of the cervix. In developing countries, 7.7% of all cancers are attributable to HPV infection, compared to 2.2% in developed countries (Parkin, 2006).

Globally, 70.7% of cervical cancer cases are attributable to infection with HPV types 16 or 18. HPV type 16 is associated with 53.5% of cases of cervical cancer. A further 17.2% of cases are attributable to HPV type 18 infection (Muñoz, 2004). In common with the rest of the world, HPV

#### Key points

- ❖ Both HPV infection and cervical cancer are associated with a substantial economic burden.
- ❖ HPV types causing cervical cancer vary from one country to another. Only 70% of cervical cancer cases are attributable to HPV types 16 or 18.
- ❖ Tailor-made vaccines, including protection against HPV types 58 and 52, would be more suitable for some countries in East Asia.
- ❖ The diagnostic and treatment costs for HPV and cervical cancer vary significantly between countries and are much less in developing countries.
- ❖ Decision-making for prevention of cervical cancer and other HPV disease needs to take account of the differing contexts of sub-regions and countries.

types 16 and 18 are most frequently associated with cervical cancer cases in Asia. The third and fourth most common types of HPV associated with cervical cancer cases in Asia are types 58 and 52. Globally, HPV types 58 and 52 are the sixth and seventh most common HPV types associated with cervical cancer (Muñoz, 2007). In particular, HPV types 58 and 52 are more frequently associated with cervical cancer cases in East Asia. HPV type 58 and HPV type 52 are associated with 6.7% and 4.4% of cervical cancer cases respectively in Eastern Asia (IARC, 2007). The introduction of HPV vaccines in particular countries needs to be tailored to the HPV types most commonly associated with cervical cancer.

## HPV prevalence in Thailand

Ten studies of HPV in Thailand over the last 12 years have found prevalence rates between 61 and 97%. The variation may be largely attributable to the accuracy of laboratory testing. Three Thai studies of HPV genotypes associated with cervical cancer have found that between 73 to 75% of cases are attributable to HPV types 16 or 18 (Chichareon, 1998; Thomas, 2001; Sukvirach, 2005).

## HPV prevalence in Asia

A meta-analysis of HPV prevalence studies among general population women found rates of 13.8% in East Asia, 11.9% in South-Central Asia, and only 4.9% in South East Asia (de Sanjose, 2007). The surprisingly low prevalence rate for South East Asia may possibly be because of less extensive data collection for this sub-region. The study found significant differences in HPV prevalence between countries. The highest prevalence rates were in India (28.5%) and China (21.3%).

The meta-analysis by de Sanjose found significant variation by country and sub-region in the five most common HPV types in women with normal cytology (Table 1).

**Table 1: Five most common HPV types in Asia among women with normal cytology**

East Asia excluding Japan & Taiwan (%)	Japan & Taiwan (%)	South East Asia (%)
HPV 16: 6.7	HPV 52: 1.1	HPV 16: 1.4
HPV 18: 1.1	HPV 16: 0.8	HPV 18: 0.7
HPV 58: 0.9	HPV 51: 0.7	HPV 58: 0.6
HPV 52: 0.9	HPV 35: 0.5	HPV 81: 0.5
HPV 70: 0.8	HPV 18: 0.5	HPV 33: 0.5

Source: de Sanjose, 2007.

Tailor-made vaccines, including protection against HPV types 58 and 52, would be more suitable for some countries, compared to vaccines that only provide protection against HPV types 16 and 18.

## Medical costs

The total estimated direct medical costs of HPV in Americans aged 15-24 years is US \$2.9 billion, compared to US \$3.0 billion for HIV. The average estimated lifetime medical cost per female case of HPV is US \$1,228, compared to US \$199,800 for HIV. Compared to HPV and HIV, total estimated direct medical costs and average lifetime medical costs for other STIs (e.g. hepatitis B, genital herpes, and gonorrhoea) are significantly less (Steben, 2007).

The diagnostic and treatment costs for HPV and cervical cancer vary significantly between developed countries and also between developed and middle-income countries (Table 2).

**Table 2: HPV and cervical cancer: comparative diagnostic & treatment costs in three countries**

	USA (US \$)	Australia (US \$)	Thailand (US \$)
Colposcopy & biopsy	436	277	43
CIN 1	1,264	899	105
CIN 2, 3	2,833	905	654
<b>Cervical Cancer</b>			
Stage 1	21,533	10,617	3,595
Stage II	23,046	15,673	4,095
Stage III	27,067	15,731	5,146
Stage IV	36,912	14,158	6,336

Sources: Goldie, 2004; Kulasingham, 2007; Chulalongkorn Hospital database, 2007.

There is, however, little difference in the cost of the HPV vaccine between the USA, Australia and Thailand.

# Psychosocial burden of HPV-related diseases in three countries



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There are over 120 HPV sub-types. The different sub-types have various transmission modes and diverse manifestations. Diseases caused by the different sub-types have varying degrees of severity, different treatment methods and different health outcomes. These variations result in differences in the psychosocial burden. In particular, high-risk HPV-related diseases constitute a double psychosocial burden – the burden of stigma as a consequence of the sexually transmitted nature of the virus and the burden of its cancer causing potential.

There are very few studies in the literature on the psychosocial burden of HPV-related diseases in Asian countries. There is a need to examine levels of knowledge among women regarding the associations between HPV, STIs, pre-invasive cervical lesions and cervical cancer and what effect knowledge of these associations has on their response to a HPV-positive diagnosis and related psychosocial burden.

## **Vietnam**

Vietnam has a traditional Confucian culture with powerful social norms to guide attitudes and behavior. The community and family take precedence over self. Women are seen as subordinates of men, and their primary roles are as wives and mothers. However, Vietnam has been going through rapid social and economic changes as a result of increasing western cultural influences. Agriculture is still the major industry, but is declining relative to the growth in manufacturing industry. Per capita GDP has grown from US \$430 in 1980 to US \$3,500 in 2007. Seventy per cent of women of working age are now participating in the labor market, resulting in a triple load of wife, mother and labor. One study showed that between thirty to seventy per cent of youth engaged in premarital sex (CARE, 1997).

It was estimated that there are about one million new cases of STIs in Vietnam each year. The incidence rate of cervical cancer was 17.3 cases per 100,000 women, with 5,600 new cases and 2,500 deaths per year. HPV prevalence in the south was 11%, compared to 2% in the north of the country.

The incidence of cervical cancer was four times higher in the south, compared to the north (Anh, 2003).

A search in the major English language databases such as MEDLINE, PubMed and PsycInfo found that psychosocial data on HPV-related disease in Vietnamese women is virtually non-existent.

However, two studies on STIs were found:

- ❖ Gender gaps, gender traps: sexual identity, and vulnerability to sexually transmitted infections among women in Vietnam (Go, 2002); and
- ❖ Sexual stigma, sexual behaviors and abstinence among Vietnamese adolescents: implications for risk and protective behaviors for HIV, sexually transmitted infections and unwanted pregnancies (Kaljee, 2007).

## **Key points**

- ❖ High-risk HPV infection is associated with a heavy psychosocial burden due to sexual transmission and the fear of a lethal disease.
- ❖ Feelings of shame, being stigmatised, anger, lowered self-esteem, and blame are common reactions of women diagnosed with HPV infection. A diagnosis of HPV can have a significant impact on significant relationships.
- ❖ HPV education for health professionals and the public is much needed
- ❖ There is a need to develop policies and practices on disclosure, including the right to know and the right not to know one's HPV status, confidentiality, and how to disclose one's status to others.
- ❖ Health professionals need to consider the potential psychosocial impact of new strategies or interventions.
- ❖ There is a need for more psychosocial research on HPV, particularly in Asia.



The following findings are drawn from these papers.

Perceptions on STIs showed that they are strongly associated with promiscuity. Males with STIs were regarded as just being 'curious'. Women with STIs were regarded as being prostitutes and responsible for the spread of STIs.

If infected with an STI, both men and women were anxious about informing their partner. For women there was fear and shame, and for men embarrassment. Youths were ashamed of being infected and feared that it would reflect badly on their families.

Wives were asked what their reaction would be if their husband was infected with an STI. Responses raised included panic, worry and temporary anger. But most women said that they would ultimately remain loyal to their husbands. Wives stated that they would be expected to bear the burden of their husband's 'deviation'.

When husbands were asked what their response would be if their wife had an STI, most stated that they would divorce her or 'beat her up'. One respondent said "Frankly speaking, it is acceptable to a man to look for a love affair but not for a woman. Only a woman who wants to earn money without working hard looks for a love affair."

This indicates that it is not acceptable for Vietnamese women to have an STI as this implies they have extra-marital or pre-marital sex. STIs in women are a violation of deeply rooted social norms about gender roles and expectations of Vietnamese society.

Based on these reactions to STIs, it is expected that HPV infection in women will meet with social disapproval and stigma. Women with HPV infection will have lowered self-esteem, be ashamed and see themselves as dirty. HPV infection will have a significant negative impact on women's relationships with their families. Their social status can change if the infection affects their fertility. For asymptomatic infections, there may be an inclination not to tell others. Women may prefer not to be tested for HPV infection as they may prefer not to know.

## Hong Kong

Hong Kong also has a strong Confucian background. However, the well developed market economy and the effect of being a British colony for a long period, has resulted in strong western influences. Women enjoy comparatively high

status. Fifty per cent of university graduates are female, and 39% of women are in the workforce. There is an increasing trend of sexual permissiveness and openness among young people.

Complete surveillance data on genital warts are not available. However, 2,493 cases of genital warts were diagnosed in government clinics in 2006. Overall HPV prevalence is 7.3% (Chan, 2002). The cervical cancer incidence rate is 9.5 cases per 100,000 women.

One Hong Kong study reported on women's responses to abnormal smear results. Common responses included fear of cancer and confusion associated with sexual transmission. The majority described themselves as having only one sexual partner and not practicing 'risky' behavior. They therefore did not understand how they could have an abnormal smear (Twinn, 2006). Accordingly, they absolved themselves of responsibility for the abnormality and their self-esteem was upheld. These attitudes may have been facilitated by ignorance regarding the association between HPV, sexual transmission and pre-invasive lesions.

Another study of screened and unscreened women reported that the most frequently perceived risk for cervical cancer was having had a promiscuous life (e.g. sex at an early age and multiple sexual partners) (Holroyd, 2004).

The Gynaecological Oncology Research Team at the University of Hong Kong has conducted a number of studies on knowledge and attitudes towards cervical cancer, HPV infection and HPV immunization among Hong Kong Chinese women:

- ❖ Two focus group studies: one on adult women and one on adolescent girls.
- ❖ A large scale cross-sectional survey study involving over 1,700 adult women.

Most of the adult women in the focus group study (Lee, 2007) did not know that HPV was sexually transmitted. When this was explained to them, their reactions to HPV as an STI and precursor to cervical cancer included:

- ❖ Awe and disbelief.
- ❖ Fear of stigmatization.
- ❖ A desire to guard the diagnosis with great secrecy, including not telling family members.
- ❖ A need to find out how they became infected.
- ❖ Lowered self-esteem, with reflection on 'what I did wrong?'
- ❖ Anger and blame on sexual partners, particularly among monogamous women.
- ❖ A feeling that their future sex life will never be



the same.

- ❖ An undermining of their relationship with their husbands and family members.

The attitudes of adolescent girls expressed in focus groups (Kwan, 2008) included:

- ❖ An association between cervical cancer and promiscuity. This is likely to be because of education about risk factors and cervical cancer in relation to early sex and multiple sexual partners.
- ❖ The sexually transmitted nature of HPV raised caution about sex. Some said they would think twice before having sex.
- ❖ On the other hand, some found information on the possibility of self-healing and the asymptomatic nature of HPV infection a relief. This led to questioning about why HPV was regarded as a risk for cervical cancer.

Responses from over 1,300 women in the cross-sectional survey on what their reaction would be if they were HPV infected were:

- ❖ 65.5% would think that their HPV infection could have come from their current partner.
- ❖ 49.7% would suspect their partner of infidelity.
- ❖ 40.9% said they would terminate the relationship with their partner.
- ❖ 48.2% said their family would suspect them of 'fooling around' if they found out about their HPV infection.
- ❖ 44.8% thought their friends would keep a distance.

## United Kingdom

Data from the 1999 UK National Survey of Sexual Attitudes and Lifestyles indicated:

- ❖ The UK had the highest rate of teenage birth in Western Europe.
- ❖ An upward trend in rates of STIs among young people.
- ❖ The median age of first sex was 16 years.

Other indicators of social attitudes and sexual practices in the UK are:

- ❖ 26% of young women reported having their sexual experience before aged 16 (Wellings, 2001).
- ❖ The divorce rate in the UK was 42.6 per 100 marriages.

Genital warts are the most common STI seen at genitourinary medicine clinics in the UK. Forty per cent of women aged 20-24 years and 12% of women aged 35-49 years tested positive for HPV (Kitchener, 2006). The cervical cancer incidence rate was 8 per 100,000 women.

In a series of studies on the reactions of UK women to HPV positive results, respondents were:

- ❖ Anxious about the increased risk of cervical cancer.
- ❖ Concerned about further investigation and treatment related to CIN.
- ❖ Worried about fertility. (McCaffery et al., 2003-2006).

Responses related to the sexually transmitted nature of HPV elicited similar responses to Vietnamese and Hong Kong Chinese women:

- ❖ Shame and stigma: feeling 'dirty' and sexually unattractive.
- ❖ Guilt and blame about the cause of the infection (self or partner).
- ❖ Anxiety about disclosure. Many chose not to tell their partner as they did not know what information to convey or they saw HPV as not having an impact on males.
- ❖ Concerns about infecting others.
- ❖ Fear of rejection if they informed their partner.
- ❖ Fear of damage to their own reputation.

Women's responses varied, partly influenced by their current HPV status and history of their primary sexual relationships. These reactions included:

- ❖ Distrust and blame.
- ❖ HPV infection being attributed to a previous partner, making it easier to brush aside.
- ❖ Worries about infecting their current partner.

Another study found that immediately after an abnormal Pap smear result, general distress, anxiety and concern about the result were more prominent for HPV-positive women compared to HPV-negative women or women of unknown HPV status. However, six months later, there was no difference in distress and anxiety levels between these three groups of women. Nonetheless, HPV-positive women had higher sexual health worries and a higher self-perceived risk of developing cervical cancer compared to HPV-negative women (Maissi, 2005).

## Summary

Despite the cultural differences between Vietnam, Hong Kong and the UK, there are some commonalities in how women perceive HPV as an STI. These include feelings of shame, being stigmatized, anger, lower self-esteem, blame, and an undermining of significant relationships. For those with high risk HPV infections, there is the added burden of cancer related anxiety.

Key differences between the three countries are:

- ❖ The degree of impact
- ❖ Ways of coping

The psychosocial response to HPV is affected by:

- ❖ Cultural norms: conservative versus liberal
- ❖ The status of women.
- ❖ Societal sexual norms and attitudes, for instance monogamy versus more than one lifetime sexual partner
- ❖ Health beliefs
- ❖ HPV knowledge

### **Issues for health professionals**

The following issues need to be addressed by health professionals:

- ❖ Education for health professionals and the public.
- ❖ Developing policies and practices on disclosure, including the right to know and the right not to know one's HPV status, confidentiality, and how to disclose one's status to others.
- ❖ Consideration of the potential psychosocial impact of new strategies or interventions.
- ❖ The need for more psychosocial research on HPV, particularly in Asia.

# Regulatory and clinical update

## – MSD HPV vaccine: the quadrivalent vaccine



*Dr. John Yang*

*Asia Pacific Regional Medical Director, Merck Vaccine Division*

### Merck's quadrivalent vaccine:

#### Gardasil®

Gardasil® is a quadrivalent HPV L1 VLP vaccine for HPV types 6, 11, 16, and 18. Three doses are given within 6 months (0, 2, and 6). Gardasil® protects against the HPV types responsible for the majority of clinical HPV cases.

HPV types 16 and 18 are responsible for 70% of cervical cancers and 70% of vulvar and vaginal cancers. These HPV types are also responsible for 65% of high-grade pre-cancerous lesions in women, and 25% of low grade lesions (i.e. CIN 1). HPV types 16 and 18 are responsible for 70% of anal cancers in men and other HPV-related cancers in men.

HPV types 6 and 11 cause 90% of genital warts in both men and women, 90% of recurrent respiratory papillomatosis in men and women, and 10% of CIN 1 in women.

The quadrivalent nature of Gardasil® enables men to be brought on board in HPV prevention because of the protection it provides against genital warts in both sexes and possible block of male-to-female transmission of types 6 and 11, in addition to types 16 and 18.

### Clinical development program: overview

The primary efficacy objectives of the clinical development program for Gardasil® were to define the magnitude of its prophylactic efficacy with respect to the incidence of HPV 6, 11, 16 and 18 related:

- ❖ Cervical cancer
- ❖ Vulvar and vaginal cancers
- ❖ CIN, VIN and VaIN
- ❖ Genital warts.

The Phase II Protocol 007 study among females aged 16-23 years was completed in 2007. Two major phase III studies were also completed in 2007: Future I (females aged 16-24) and Future II (females aged 15-26). Preliminary analysis shows efficacy for Gardasil® of close to 100% in preventing infection of HPV types 6, 11, 16 and

18 and in prevention of cancer of the cervix, vulva and vagina and prevention of genital lesions.

Data on the efficacy of Gardasil® in women aged up to 45 years of age and data on the efficacy for cross-protection against HPV-related disease for non-vaccine types have been submitted to regulatory authorities worldwide.

By the end of 2008, Merck anticipates having data on the efficacy of Gardasil® in males.

### Prophylactic efficacy

Data from the 2.4 years post-dose 3 follow-up for Gardasil® in females aged 16-26 years of age for

#### Key points

- ❖ Preliminary analysis shows efficacy for Gardasil® in females aged 15-26 of close to 100% in preventing transmission of HPV types 6, 11, 16 and 18 and in prevention of cancer of the cervix, vulva and vagina and prevention of genital lesions
- ❖ Some level of protection by Gardasil® against CIN 2/3 or AIS has been demonstrated in the generally HPV-naïve population for some other HPV types in a cross-protection analysis
- ❖ The primary efficacy of Gardasil® in women aged 24-45 years of age for combined incidence of HPV 6, 11, 16 and 18-related persistent infection or cervical, vulvar and vaginal disease is 91%.
- ❖ The efficacy of Gardasil® over five years of protocol follow-up for HPV 6, 11, 16 and 18-related infection or disease is 96%.
- ❖ Gardasil® demonstrated immune memory response by antigen challenge at 60 months.
- ❖ Immunization against HPV 6, 11, 16 and 18 can dramatically reduce low- and high-grade cervical dysplasia and genital warts.

HPV 16 and 18 demonstrate efficacy of 98% for squamous cell cervical cancer, and 100% for each of cervical adenocarcinoma, HPV-related vulvar cancer and HPV-related vaginal cancer. The efficacy data are based on different HPV 16 and 18 related surrogate markers of precursor lesions (CIN 3, AIS, VIN 2/3, and VaIN 2/3).

Efficacy data also demonstrate a high degree of protection by Gardasil® for HPV 6, 11, 16 and 18-related diseases. Efficacy for females aged 16-26 years of age was 96% for CIN of any grade or AIS, and 99% for vulvar and vaginal lesions, including genital warts.

Some level of protection by Gardasil® against CIN 2/3 or AIS has been demonstrated in the generally HPV-naïve population for some other HPV types in a cross-protection pre-specified analysis. For the ten most common oncogenic HPV types excluding 16 and 18 (types 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) the efficacy of Gardasil® against CIN 2/3 or AIS was 38% (95% CI 6;60). Slightly better efficacy of 43% was demonstrated for HPV types 31, 33, 45, 52 and 58 (95% CI 7;66). Efficacy against HPV types 31 and 45 was 62% (95% CI 10;85) (Brown, 2007).

For the cross-protection analysis, composite endpoints were analyzed (primary endpoints). In analysis for the individual components of the endpoints, efficacy was variable, and the case number was not sufficient to derive affirmative conclusions. But overall, there is some level of cross-protection for HPV types (excluding HPV type 45 which caused very few cases of CIN 2/3 in our study) that are common in parts of Asia (e.g., HPV types 31, 33, 52 and 58).

In November 2007, Merck released the primary efficacy results for Gardasil® in women aged 24-45 years of age for combined incidence of HPV 6, 11, 16 and 18-related persistent infection or cervical, vulvar and vaginal disease. For all subjects, efficacy was 91%. For women aged 24-34 years of age, efficacy was 92% and for women aged 35-45 years of age efficacy was 89%. The efficacy for these age groups was somewhat lower than the efficacy observed in younger females. This is because Gardasil® was not able to offer therapeutic protection to those women in the older age group who may already have been infected with HPV. Some HPV infections may be latent or may not have been detected at the beginning of the study or at the time of immunization.

Efficacy of Gardasil® in women aged 24-45 years of age against HPV 6, 11, 16 and 18-related CIN or EGL is 92%. Efficacy for the same age group for HPV 16 and 18-related ASC-US (HR+) or worse is 94%.

## Long-term efficacy and safety

The efficacy of Gardasil® over five years of protocol follow-up was studied for Protocol 007. Efficacy for HPV 6, 11, 16 and 18-related infection or disease was 96%. There were two cases of HPV infection among immunized subjects. One subject was found to be infected with HPV-18 at 12 and 18 months, but subsequently recovered. Another subject was found to be infected with HPV-16 at 36 months and was then lost to follow-up. Efficacy in the five-year follow-up was 100% for HPV types 6 and 11, 97% for type 16, and 91% for type 18.

The five-year antibody response to Gardasil® was also measured in the Phase II Protocol 007 study. The antibody response to the first three doses of Gardasil® was very high, with antibody levels peaking at month 7. Antibody levels subsequently declined and then stabilized for the remainder of the 5 years. Another dose of Gardasil® was administered at month 60. HPV antibody levels responded very quickly. Within one month, antibody levels in subjects were very high and were higher than those found at 7 months after administration with the third vaccine dose. It can be concluded that immunized subjects demonstrated classic immune memory. This is the hallmark of long-term protection. This suggests that Gardasil® will have long-term efficacy.

## Regulatory approval

Gardasil® has been approved in 92 countries and territories. In Asia and the Pacific, Gardasil® has been approved in Australia, Hong Kong, Indonesia, Korea, Macau, Malaysia, New Zealand, the Philippines, Singapore, Taiwan, and Thailand.

The recommendations of the US Advisory Committee on Immunization Practices (ACIP) in relation to Gardasil® have been adopted worldwide (MMWR, 2007). Key aspects of these recommendations are:

- ❖ Routine immunization with 3 doses of quadrivalent HPV vaccine for females aged 11-12 years of age. The vaccine can be started in females as young as 9 years of age.
- ❖ Catch up immunization for females 13-26 years of age, not previously immunized or who have not completed the full vaccine series.

A number of countries have introduced Gardasil® into national immunization programs, with either support from public sector or private sector funding, or both. Most countries target young adolescent females as the primary cohort for HPV immunization. In Asia and the Pacific, the only country to introduce Gardasil® into its national

immunization program is Australia, where public sector funding is available for immunization of females aged 12-26 years of age.

Most of the countries that have introduced Gardasil® do this in conjunction with Pap screening.

A bivalent HPV vaccine has also been licensed in Europe. Countries now face the challenge of deciding which of the HPV vaccines they should use. In France, the recent recommendations of the High Council of Public Health (December, 2007), based on current knowledge; prefer the quadrivalent vaccine over the bivalent vaccine due to:

- ❖ the lack of prevention by the bivalent vaccine of lesions due to genotypes 6 and 11 of HPV (in particular genital condylomata and CIN);
- ❖ the absence of any demonstration of efficacy of the bivalent vaccine on grade 2 or more precancerous vulvar lesions (VIN 2 or more);
- ❖ efficacy not formally demonstrated, although probable, of the bivalent vaccine for CIN2 or more, associated with genotype 18; and
- ❖ the inadequacy of data concerning the long-term tolerance of the adjuvant ASO4.

Immunization against HPV 6, 11, 16 and 18 can dramatically reduce low- and high-grade cervical dysplasia and genital warts. The protection afforded by inclusion of HPV types 6 and 11 in the quadrivalent vaccine provides substantial additional benefits compared to the bivalent vaccine, including the immunization of males as part of HPV immunization programs.



# Regulatory and clinical update

## GSK cervical cancer vaccine



*Dr. Sally Gatchalian*

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### The importance of aggressive HPV types

Even in countries where screening programs are well established, the possible impact of HPV vaccines in preventing cervical cancer needs to be considered. Squamous cell carcinoma is the most common form of cervical cancer, followed by adenocarcinoma. HPV types 16, 18 and 45 are responsible for 75% of squamous cell carcinomas and 92% of adenocarcinomas (de Sanjose, 2007). HPV types 16, 18 and 45 are the most aggressive HPV types.

Adenocarcinoma is generally detected late in the stage of disease and associated with more severe outcomes.

Most studies have found prevalence of HPV in females is highest after sexual debut, and on the whole, before the age of 25 years. There is a

decline in prevalence for older age groups, but there remains a risk of incident infections with oncogenic HPV types throughout sexually active life, estimated at between 5 and 10%. This points to the need for long-term protection.

Persistent infection with oncogenic HPV is the necessary cause of cervical cancer. "Since persistent infection with the same high-risk type is considered a predictor for moderate or high-grade cervical dysplasia and cancer, they might represent a useful endpoint in future vaccine efficacy trials" (Pagliusi, 2004).

GSK's cervical cancer vaccine, Cervarix™, has been approved in 51 countries. In Asia and the Pacific, Cervarix™ has been approved in Australia, Hong Kong, Indonesia, Macau, Malaysia, Myanmar, New Zealand, the Philippines, Singapore and Thailand.

### GSK's development vision and vaccine design

In modern vaccinology, the main challenges for scientists are to:

- ❖ develop effective vaccines against complex pathogens such as HPV;
- ❖ develop rapid responses to new and emerging diseases; and
- ❖ provide for better immune responses in target populations in which age, chronic conditions and other factors make current vaccine prevention sub-optimal.

Since HPV types 16 and 18 are responsible for approximately 70% of invasive cervical cancers worldwide, and as these oncogenic types are the necessary cause of most cervical cancers, GSK developed a prophylactic cervical cancer vaccine based on HPV 16 and 18 L1 virus-like particles.

Because every sexually active female is at risk of oncogenic HPV, GSK's objective was to develop a vaccine which targets prevention of cervical cancer in females from 10 years of age onwards.

Antibody responses are poor after natural HPV infections because HPV is a master at evading the

#### Key points

- ❖ Persistent infection with oncogenic HPV is the necessary cause of cervical cancer.
- ❖ Cervarix™ provides protective efficacy for HPV types 16 and 18, including high levels of efficacy against persistent infection and CIN 2 lesions and worse. Efficacy is sustained at least up to 5.5 years.
- ❖ Cervarix™ provides substantial protection for HPV types 31 and 45, individually for incident infections for at least up to 5.5 years and 6 months for persistent infections.
- ❖ Cervarix™ is highly immunogenic for HPV 16 and 18, with high and sustained antibody levels and virtually 100% seropositivity up to 5.5 years. Cervarix™ demonstrated cross-protection against both incident HPV 45 and 31 infection and this continued to be evident for 5.5 years.
- ❖ Cervarix™ has a good safety profile.

immune system and the infection does not result in viremia. Thus, immunity from natural infection is not always followed by a satisfactory immune response. Therefore, the optimal vaccine must be able to induce a strong and long-lasting antibody response and elicit a good immune memory. Thus, the AS04 Adjuvant System (containing Alum plus MPL) was designed specifically to enhance the immune response, providing strong and sustained protection.

Cervarix™ consists of two components.

- ❖ HPV 16 and 18 L1 VLPs; and
- ❖ the proprietary AS04 Adjuvant System.

The L1 VLP proteins are highly immunogenic antigens and they constitute the basis for induction of specific protective immune response. The AS04 Adjuvant System contributes to enhance the immune response that is induced by the VLP 16 and 18 antigens. This combination provides for a strong and sustained immune response.

### **Clinical trials: vaccine efficacy – HPV 16 & 18**

A study was conducted to compare two vaccine formulations with the same amounts of VLPs but with:

- ❖ one adjuvanted with aluminium salt alone; and
- ❖ one adjuvanted with AS04.

The study found that the AS04-adjuvanted vaccine achieved significantly higher antibody titers in humans for HPV types 16 and 18, compared to the vaccine formulated with aluminium salt alone (Giannini, 2006).

Follow-up results after 5.5 years demonstrate Cervarix™ provides substantial protection against HPV 16 and 18 infections and CIN outcomes. Vaccine efficacy for the endpoints of 6 and 12 months persistence and CIN 1 or worse and CIN 2 or worse was 100% (Gall, 2007). This study involved a broad-based population of females with normal smears and low-grade cytology.

The 5.5 years follow-up results demonstrated vaccine efficacy for HPV 16 and 18 beyond the estimated prevalence for HPV 16 and 18 for the different endpoints of cytological abnormalities and CIN outcomes. For example, for CIN 2 or worse, the vaccine efficacy was over and beyond the estimated prevalence for HPV 16 and 18. This raises the question: where is this additional efficacy coming from? (Harper 2006).

### **Clinical trials: vaccine efficacy – other oncogenic types**

When we talk about cross-protection, this is based on real clinically demonstrated protection against infection or disease caused by HPV types not included in Cervarix™. HPV types 45 and 31 are the third and fourth most common HPV types found in cervical cancer worldwide. They are not included in Cervarix™. However, based on the results, for 5.5 year follow-up, vaccine efficacy was demonstrated against incident infection due to types 45 and 31, giving a vaccine efficacy of 88% for HPV 45 and 53.5% for HPV type 31 (Gall, 2007; Harper, 2007). Although most incident infections regress, in some of the cases, they may proceed to persistence and eventually pre-cancerous lesions and cervical cancer. Incident infection is very difficult to detect clinically.

A Phase III clinical trial involving a broad population of women examined cross-protection for HPV types 45 and 31 against 6 months persistent infections. In an interim analysis, based on the number of cases observed in the vaccine and placebo groups, we calculated a vaccine efficacy of 59.9% for HPV type 45 and 36.1% for HPV type 31 against 6 months persistent infections with these types (Paavonen, 2007).

### **Immunogenicity**

The 5.5 year follow-up data show high and sustained antibody levels and seropositivity for both HPV types 16 and 18. Increased antibody levels occur at 7 months, one month after the third vaccine dose. This is followed by a slight decline in antibody levels, and a subsequent stabilization at 18 months and this plateaus until 5.5 years. For natural infection the antibody titers are much lower compared to those found in immunized subjects. By 63-64 months, antibody levels are at least 11 times greater than antibody levels for natural infection. Seroconversion is 100% at 7 months and seropositivity is ≥98% at 5.5 years (Harper, 2006).

It is documented that the higher the level of serum antibodies, the higher the level of antibodies in the cervical mucosa. Recent research has demonstrated that there is a significant linear correlation between serum antibody levels and antibody levels of cervical vaginal secretions for both anti-HPV 16 and anti-HPV 18 and this was observed until 2 years follow-up. HPV antibodies can enter the cell very quickly. The best guarantee of immune protection is having antibodies at the site of infection (Schwarz, 2007).

Despite the ability of HPV to depress the immune response, it is noted that neutralizing antibodies are established in most cases. However, the level of neutralizing antibodies is generally very low, even at their peak titers. Uptake and internalization of HPV occurs as fast as 15 minutes to 2 hours. It is therefore important to have high antibody levels at the site of infection. If you are relying only on memory response, this will occur only after 2 days. In the meantime the HPV infection is very active (Frazer, 2004).

An efficacy study in women 15-25 years of age showed high antibody levels up to 5.5 years for both HPV 16 and 18. There was non-inferiority in the antibody levels for girls aged 10-14 years of age compared to the 15-25 years age group. In fact, the antibody levels in the younger age group were higher compared to the older age group. This is expected because younger age groups will usually have better immune responses, compared to older age groups (Rombo, 2007).

HPV 16 and 18 antibody levels for those aged from 15-55 year of age were of a similar order of magnitude compared to those aged 15-25 years of age (Harper, 2006). This is likely to result in longer antibody persistence.

### **Safety profile**

Systemic adverse events were comparable between the vaccine group and placebo group, with no statistical difference. There was no overall difference in pregnancy outcomes between the vaccine group and the placebo group (Paavonen, 2007).

### **Cervarix™: safe and efficacious**

Cervarix™ is generally safe and well tolerated. Protective efficacy for HPV types 16 and 18 has been demonstrated. In particular there is a:

- ❖ High level of efficacy against persistent infection.
- ❖ High level of efficacy against CIN 2 or worse.
- ❖ Efficacy is sustained at least up to 5.5 years.
- ❖ Efficacy has been substantiated in a broader population of women.

Substantial protection has also been demonstrated for HPV types 31 and 45 for incident infection for at least up to 5.5 years and 6 months persistent infections. This has been further substantiated in a broader population of women.

### **Cervarix™: highly immunogenic**

Cervarix™ is highly immunogenic for HPV 16 and 18 for the following groups:

- ❖ **Females 15-25 years of age:** 100% seroconversion with high and sustained antibody titers for at least up to 5.5 years, which has been further substantiated in a broader population of women.
- ❖ **Females 10-14 years of age:** mount twice the GMT level to both 16 and 18 as the 15-25 years age group.
- ❖ **Females 10-55 years of age:** 100% seroconversion with GMT levels remaining 8-fold higher than natural infection titers, and a high correlation between CVS and serum IgG antibodies.

Cervarix™ demonstrated cross-protection against both incident HPV-45 and 31 infection and this continued to be evident for 5.5 years. The vaccine also afforded cross-protection against 6 months persistent infection with other oncogenic HPV types in the interim analysis of the phase III study.

### **GSK Biologicals contribution to world health**

GSK contributes to world health in the following ways:

- ❖ As a primary supplier to international organizations such as UNICEF and GAVI.
- ❖ As a provider of vaccines to some of the most disadvantaged regions in the world at preferential prices.
- ❖ Working with policy-makers to establish immunization policies and ensuring vaccines are available to all.
- ❖ Participating in new more predictable financing mechanisms such as Advance Market Commitments.

### **Concluding proverb**

“The superior doctor prevents illness. The mediocre doctor treats impending illness. The inferior doctor treats actual sickness” – Chinese proverb.



# Key points from questions and discussion



## Vaccine comparisons

GSK was asked to specify the areas in which they believe their bivalent vaccine is superior to the quadrivalent vaccine. In response, GSK emphasised that the world is fortunate to have two HPV vaccines of proven efficacy. Having two HPV vaccines has the potential to significantly improve women's health. It was stated that the two vaccines are different, with both vaccines having distinct advantages. The approaches taken by GSK and MSD to HPV vaccine development were different. GSK's focus was on cervical cancer because it is the major burden of HPV-related disease, with HPV types 16 and 18 as the most common oncogenic HPV types. GSK's application of the innovative adjuvant system, ASO4 has shown superior immunogenicity compared to the same VLPs adjuvanted with alum alone.

## The financial cost of psychosocial burdens

It is possible to calculate the impact of psychosocial burden and translate this into financial costs in areas such as loss of earnings. This type of study has not been conducted in relation to the psychosocial burden of HPV.

## HPV as an STI

The issue of stigmatization associated with the sexual transmission of HPV was raised. The question of what is the best way to explain HPV to patients was asked and in particular whether it is necessary to inform patients that HPV is an STI. In response, Professor Hextan Ngan stated that this is a difficult issue in the Asian context, compared to western countries. As outlined in her presentation, many women in the UK take the attitude that their HPV infection was acquired from a previous partner. This means that they do not see their infection as a problem related to their current relationship. This approach is not possible for the many Asian women who have only one lifetime sexual partner. In Asia, one approach that can be taken is to explain to women that HPV is an STI, although other modes of transmission cannot be excluded. Public education should emphasize that HPV is a common STI and that all sexually active people are at risk, not just those who have multiple partners. This approach contrasts with some HPV educational materials which focus on high-risk individuals with multiple partners.

## HPV prevalence in Asia

A possible explanation of the lower HPV prevalence in Asia, compared to other regions, (as presented by Professor Wichai) is the limited number of epidemiological studies in Asia. The age groups studied across the different regions of the world were the same (18-35 years of age), so the data from different regions are comparable. Asia accounts for more 50% of global HPV prevalence because of its large population.

## Infection with non-oncogenic HPV types

The question was asked to GSK and MSD about how many cases of infection with non-oncogenic HPV types they have observed after 5 years of follow-up. GSK responded that they did not yet have these data. It was also stated that if the question was about replacement, this has not been observed since a longer-term study would be needed to observe replacement in viral strains. MSD stated that they do not have the data, particularly as it would come from the Phase II study, with a small number of subjects. From the experience of MSD's larger Phase III clinical trials, using CIN 2/3 as an endpoint, approximately 50% of cases were caused by HPV types other than 16 and 18.

## Cervical cancer prevention in Thailand

The incidence of cervical cancer in Thailand has reduced somewhat from 23 cases per 100,000 women ten years ago, to 19.5 cases per 100,000 women at present. To achieve a significant reduction in the prevalence of cervical cancer, the optimal prevention program would consist of a combination of improved cervical cancer screening and HPV immunization. Cervical cancer screening has the advantage of low cost compared to immunization.

## Impact data

Both GSK and MSD indicated that they both have ongoing large-scale effectiveness studies to measure the impact of universal HPV immunization programs on the prevalence of cervical cancer.

# Research summary: Health economic models for HPV vaccines



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## Health outcomes research

Health outcomes research studies seek to understand the end result of particular health practices and interventions. End results include effects that people experience and care about, such as change in the ability to function. In particular, for people with chronic conditions, where cure is not always possible, end results include quality of life, as well as mortality. By linking the care people receive to the outcomes they experience, outcomes research has become the key to developing better ways to monitor and improve the quality of care.

## Outcomes information for decision-making

For clinicians and patients, outcomes research provides evidence about benefits, risks and results of treatments, so they can make more informed decisions. Developing outcome instruments for specific diseases has been an especially prolific research area. Such instruments are more likely than general health survey measures to be able to detect changes in the disease due to treatment.

Health economics research, including economic modeling, is increasingly used to support the decision-making process as well as disease management, and evaluating the long-term clinical benefits and cost-effectiveness of therapies.

### Key points

- ❖ A number of economic evaluation models and mathematical disease transmission models can be used to support the decision-making process as well as disease management, and in the evaluation of the long-term clinical benefits and cost-effectiveness of therapies.
- ❖ Economic models can be powerful tools in understanding economic relationships. A primary limitation is that all models are based on certain assumptions. When these assumptions fail, the model cannot be used to draw conclusions.

## Economic models

An economic model attempts to abstract from complex human behavior in a way that sheds some insight into a particular aspect of that behavior. This process inherently ignores important aspects of real-world behavior, making the modelling process an art as well as a mathematical exercise.

The expression of a model can be in the form of words, diagrams or mathematical equations, depending on the audience and the point of the model. Theoretically, there are six types of economic models:

- 1. Stochastic models** are formulated using stochastic (random) processes. They model economically observable values over time.
- 2. Non-stochastic mathematical models** may be purely qualitative (for example, models involved in some aspects of social choice theory) or quantitative (involving rationalization of financial variables, for example, with hyperbolic coordinates, and/or specific forms of functional relationships between variables).
- 3. Qualitative models** Although almost all economic models involve some form of mathematical or quantitative analysis, qualitative models are occasionally used. One example is qualitative scenario planning in which possible future events are played out. Another example is non-numerical decision tree analysis. Qualitative models can often suffer from lack of precision.
- 4. Accounting models** are based on the premise that for every credit there is a debit. More symbolically, an accounting model expresses some principle of conservation in the following form: algebraic sum of inflows = sinks – sources.
- 5. Optimality and constrained optimization models** look at how to optimize best use of limited available resources. Other examples of quantitative models are based on principles such as profit or utility maximization.
- 6. Aggregate models** are used for macroeconomic analysis to deal with aggregate quantities such as output, the price level and the interest rate.

## Economic evaluation models for HPV

A number of economic evaluation models have been used for HPV. They are:

**Cost-benefit analysis** is an economic tool to aid social decision-making. It is typically used by governments to evaluate the desirability of a given intervention in markets. The aim is to gauge the efficiency of the intervention relative to the status quo. The costs and benefits of the impacts of an intervention are evaluated in terms of the public's willingness to pay for the benefits or willingness to avoid the costs.

**Cost-effectiveness analysis (CEA)** is a technique for selecting among competing wants wherever resources are limited. CEA is a technique for comparing the relative value of various clinical strategies. In its most common form, a new strategy is compared with current practice (the 'low-cost alternative') in the calculation of a cost-effectiveness ratio:

$$\text{CE ratio} = \frac{\begin{array}{c} \text{cost} \\ \text{new strategy} \end{array} - \begin{array}{c} \text{cost} \\ \text{current practice} \end{array}}{\begin{array}{c} \text{effect} \\ \text{new strategy} \end{array} - \begin{array}{c} \text{effect} \\ \text{current practice} \end{array}}$$

Cost-effectiveness models are used to compare the net cost of HPV immunization with the potential benefits (often expressed as years of life saved or years of disability-adjusted life saved). It is important to consider exactly what that statement means. If a strategy is called 'cost-effective'; and the term is used as its creators intended, it means the new strategy is good value.

Being cost-effective does not mean that the new strategy saves money. And just because a strategy saves money does not mean that it is cost-effective.

The very notion of cost-effectiveness requires a value judgment – what you think is a good price for an additional outcome may not be the view of others.

**Budget impact analysis model (BIA)** is an essential part of a comprehensive economic assessment of a health care technology and is increasingly required, along with cost-effectiveness analysis, prior to formulary approval or reimbursement. The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health care intervention within a specific health care setting or system context, given inevitable resource constraints.

**Decision tree analysis models** are excellent tools for helping to choose between several courses of

action. They provide a highly effective structure within which you can lay out options and investigate the possible outcomes of choosing those options. They also help you to form a balanced picture of the risks and rewards associated with each possible course of action.

**Cost of illness models** identify direct and indirect costs. Direct costs are direct medical and direct non-medical costs. Indirect costs include transportation costs, opportunity costs of patients, family members and other unpaid care givers, what the patient and others would be willing to pay to avoid the anxiety, pain and suffering associated with the illness, and costs to society.

## Mathematical Disease Transmission Models

The two main mathematical disease transmission models used for HPV are:

**Cohort or Static or Markov Model.** This model is typically probabilistic and linear. In this model, the progression of HPV disease is simulated for a single cohort over its expected life time, much as a cohort is tracked in a life-table analysis. Cohort models can underestimate in that the indirect benefits of immunization gained from herd immunity effects are not accounted for. They can also overestimate the benefits of immunization if the duration of vaccine protection is not life-long and the progression rates between disease states depend on age.

**Dynamic models** are typically deterministic and non-linear. They do not track a just a single cohort, but rather the changing population over time. Individuals constantly enter the model as they are born and exit the model as they die. These models account for herd immunity.

## Conclusion

All of these models differ both in their complexity and in the questions they answer. Economic models can be such powerful tools in understanding some economic relationships, that it is easy to ignore their limitations. These models are based on certain assumptions. When these assumptions fail, the model cannot be used to draw conclusions.

An economic model that has been established to have validity in explaining a relationship under one set of assumptions is useless if the assumptions are not valid or realistic. Model assumptions include not only those that can be expressed as predicates on model parameters but others with more qualitative or asymptotic form.

# The practical use of surveillance data and HECON modeling – a model for HPV? FHI case study: the A<sup>2</sup> Project



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Although the Analysis and Advocacy Project (A<sup>2</sup>) is an HIV program, its relevance to this meeting is that it illustrates how epidemiologic modeling and health outcomes modeling can be brought to effect policy change.

The A<sup>2</sup> Project is a regional HIV initiative that aims to build sustainable in-country capacity to:

- ❖ develop a clear understanding of the HIV epidemics in countries in Asia; and
- ❖ translate that understanding into effective policies and appropriately targeted and resourced programs.

This allows countries and international donors to move decision-making to a more empirically informed evidence base and to use that base to:

- ❖ strengthen political commitment;
- ❖ ensure adequate resources are available; and
- ❖ ensure resources are appropriately directed.

The A<sup>2</sup> Project began in 2004. The Project is currently being implemented in Bangladesh, Thailand, Vietnam and Yunnan and Guangxi Provinces in China. At the regional level, the current partners are Family Health International, the Research Triangle Institute and the East West Center. At the country level, the partners include non-governmental organizations, Ministries of Health, Communicable Disease Control Departments and Provincial AIDS Committees.

## Why is the A<sup>2</sup> Project necessary?

The A<sup>2</sup> Project was a response to frustration with the adequacy of the regional response to HIV. There is a good understanding of the dynamics of Asian HIV epidemics. New infections primarily occur in most-at-risk populations such as sex workers, their clients, injecting drug users and men who have sex with men. These populations are strongly linked behaviorally. There are many examples in the region of successful responses. For example, it is estimated that in the late 1980s and early 1990s, Thailand's prevention efforts averted approximately six million infections. However, despite this understanding and despite the examples of successful prevention responses,

prevention coverage remains low and epidemics continue to grow.

This begs the question: "what is going wrong?" The following factors were identified:

- ❖ Data gaps (e.g. population size estimates for most-at-risk populations).
- ❖ Unsystematic data collection and analysis (e.g. static data systems and 'quick and dirty' approaches to estimates and projections).
- ❖ Even when good quality data are available, they often remain peripheral to the decision-making process. The consequence is that evidence does not always inform policy.

This suggested the need to merge the traditionally separate fields of analysis and advocacy.

## The A<sup>2</sup> approach

The A<sup>2</sup> Project's approach consists of four stages:

### 1. Local teams gather and synthesize local data

Data are collected in the following areas:

- ❖ Epidemiologic, behavioral and biological data.
- ❖ Sizes of key populations.
- ❖ Responses: programs and policy.
- ❖ Program costing and coverage.

Through collecting these data, local teams develop a better knowledge of the current state of their epidemic and key trends in HIV epidemiology, behaviors and responses.

### Key points

The A<sup>2</sup> Project is a working example of how data synthesis, epidemic and health outcome modeling, and targeted engagement with key decision-makers has been used to inform evidence-based policy and resource allocation decisions for HIV programs. This type of approach can be adapted to address other health problems such as HPV.



## 2. Developing a local model of the HIV epidemic

The A<sup>2</sup> Project uses the Asian Epidemic Model (AEM), a semi-empirical process model. Inputs to the model include sizes of key populations, risk behavior data, average duration in different key populations, the start year, cofactors such as STIs, and transmission probabilities. These inputs are used to develop output data on new and prevalent HIV infections (in at-risk populations and the population overall), AIDS cases and deaths by male and female ratios and by year.

By conducting the modelling, it is possible to project the future course of the epidemic in a particular location, on an overall population basis, and in most-at-risk populations. The model enables monitoring of trends in HIV infection in particular populations over time. This is key information for decision-making on whether interventions are focused on the right populations.

## 3. Evaluating the impact of different program choices and resource allocation decisions

This assists the decision-making process on the responses and resources needed for maximum impact. Linked AEM and GOALS modeling is used. The GOALS Model consists of three modules, two of which have been successfully applied to date:

*The Resource Needs Module:* by inputting data on target population size, unit costs and the desired level of program coverage, information on the financial resources needed is generated. Estimated resource needs can then be compared with current and projected available resources and any resource gap quantified.

*Impact Module:* This module quantifies the impact of various prevention interventions on risk behaviors that influence HIV transmission.

The steps in using this module to calculate the impact of program changes on the epidemic are:

1. Desired program changes are entered into the GOALS Model.
2. The Impact module generates the associated (post-intervention) behavior changes. (Values in the model are derived from effectiveness or impact studies).
3. These post-intervention behavior changes are fed back as inputs into AEM to calculate the impact of interventions on HIV infections.

With its linkage to AEM, this module allows the impact of different program options to be modeled in terms of their impact on HIV incidence. Following on from this analysis, simple cost-effectiveness calculations can be made and the cost per averted infection calculated.

## 4. Turning strategic information into action

This starts with a mapping of key policy-makers, processes and opportunities for using strategic information, (i.e. the data from the previous three stages). This stage of the Project focuses on the development of advocacy action plans and their implementation. This includes development and dissemination of summary technical reports and policy briefings, and meetings with key decision-makers. The aim is to achieve implementation of the most effective policies and programs and mobilization of adequate resources.

## What has the A<sup>2</sup> Project achieved?

- ❖ Strong local collaborations.
- ❖ Increased local capacity for analysis and advocacy through training in the models and advocacy.
- ❖ Increased understanding of local epidemics through extensive data synthesis and AEM and GOALS modeling.
- ❖ Highlighting of data gaps through the process of data synthesis.
- ❖ Substantial engagement with decision-makers on HIV strategic planning processes.
- ❖ Effecting policy, program and funding changes in the different project sites.

## Summary

The A<sup>2</sup> Project is a working example of how data synthesis, epidemic and health outcome modeling, and targeted engagement with government and key decision-makers has been used to inform evidence-based policy and resource allocation decisions.

# Review of health economic model of a quadrivalent HPV (6, 11, 16, 18) vaccine - Taiwan data



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## Cervical cancer screening in Taiwan

The Pap smear screening program in Taiwan commenced in 1995. Pap smear screening rates have increased year by year and annual cervical cancer mortality has reduced from 11.28 to 7.44 per 100,000 women over the period 1994 to 2005. This indicates that Pap smear screening in Taiwan has been an effective program. However, cervical cancer is still a serious health problem in Taiwan. The incidence of cervical cancer in 2005 was 17.8 per 100,000 women. Cancer of the cervix is the fifth most common cancer in Taiwanese women.

## HPV vaccines

HPV vaccines are a potentially powerful tool in the prevention of cervical cancer and would be a worthwhile addition to the current screening program. However, before this public policy decision is made, we first need to know whether HPV vaccines are cost-effective.

To assess the cost-effectiveness of HPV vaccines we first need to assess:

1. The prevalence of HPV in relation to cervical cancer, precancerous lesions and warts.
2. The disease burden of cervical neoplasia and warts.
3. The medical costs of cervical neoplasia and warts.

The next steps are to:

1. Estimate the disease reduction which could be achieved by HPV immunization.
2. Estimate the cost additions and reductions related to HPV immunization.

## Epidemiology of HPV in Taiwan

In recent years, there have been nine studies of HPV epidemiology in Taiwan. These studies used different detection methods for HPV typing. Laboratory quality control methods varied between the studies. In order to address these problems, the Department of Health (DoH) conducted a new study using the central laboratory to re-test all stored specimens from these previous studies.

The findings of the DoH study using a calibration endpoint for HPV type distribution with normal cytology were:

- ❖ HPV 16: 11.4%
- ❖ HPV 18: 6.6%
- ❖ HPV 31: 1.6%
- ❖ HPV 45: 2.3%
- ❖ HPV 52: 12.4%
- ❖ Other high-risk HPV types: 29.5%.

The results using a calibration endpoint of HPV type with lesions for HPV 16 and 18 were:

- ❖ LSIL: 25.6%
- ❖ HSIL: 34.4%
- ❖ Cervical cancer – all stages: 70.9%

### Key points

- ❖ Introduction of HPV immunization in Taiwan could reduce the incidence of CIN 1 by as much as 25.6%, CIN 2 and 3 by 34.3%, and cervical cancer by 70.9%.
- ❖ The total estimated annual health care cost of treating HPV-related pre-cancerous lesions and cervical cancer in Taiwan is \$31.8 million. Introduction of routine HPV immunization could reduce this cost by as much as \$16.6 million.
- ❖ Pap smear screening is estimated to reduce HPV-related mortality by 32.9% at an annual cost of US \$25 million. HPV immunization is estimated to reduce HPV-related mortality by 67.5% at an annual cost of US \$31 million.
- ❖ The dollar/QALY ratio for routine prophylactic quadrivalent HPV immunization is US \$12,439/US \$74,773. Routine HPV immunization can be cost-effective because the cost is similar to colon cancer screening and mammographic screening.
- ❖ A prophylactic quadrivalent HPV vaccine can be cost-effective and be efficiently added to current screening programs to reduce the incidence of cervical cancer, CIN and genital warts.

For HPV type 52 the results were:

- ❖ LSIL: 19.6%
- ❖ HSIL: 19.1%
- ❖ Cervical cancer – all stages: 2.4%.

The estimated relative risk reduction of pre-cancerous lesions and cervical cancer that could be achieved by the introduction of HPV immunization in Taiwan, assuming 100% vaccine efficacy is:

- ❖ CIN 1: 25.6%
- ❖ CIN 2 & 3: 34.3%
- ❖ Cervical cancer: 70.9%

HPV types 16, 18, 58 and 52 are very important in Taiwan. However, types 58 and 52 are only predominant in CIN 1, 2 and 3. For cervical cancer the predominant types are 16 and 18, as in other countries.

The HPV type distribution in Taiwanese females with genital warts was 93.3% with HPV 6 and 11. There is a high proportion of multiple types of HPV infection for females with genital warts, with 48.8% of females testing positive to more than one HPV type (Tsao, 1994).

The theoretical relative risk reduction for genital warts that could be achieved by introduction of the quadrivalent HPV vaccine in Taiwan, assuming 100% vaccine efficacy, is 93.3%.

## Cost and disease burden of cervical cancer

Computer databases are available for:

- ❖ The Pap smear screening registration system (since 1994).
- ❖ Medical and other health costs from the National Insurance scheme (since 1995).
- ❖ The National Cancer Registration System (since 1997).

These enable analysis of health care system data, including cost and disease burden. A cost analysis study was conducted from 2003-2005 to evaluate the cost of medical care for cervical cancer, linking data from National Insurance and the National Cancer Registration System. The study population was drawn from 1.4 million randomly selected women. The enrolment criteria were CIN or new cases of cervical cancer. The average annual cost per case (in US \$) were:

- ❖ ASCUS/CIN 1: \$90
- ❖ CIN 2: \$399
- ❖ CIS: \$1,524
- ❖ Stage 1 (localized) cervical cancer: \$4,648
- ❖ Stage 2-3 (regional) cervical cancer: \$7,041
- ❖ For recurrence and terminal cases: \$9,141

These costs are similar to those in Thailand.

Estimated costs were calculated by multiplying the average cost per case with the annual disease burden. The estimated annual costs for pre-cancer and cervical cancer were (in US \$) (with the percentage of total costs in brackets):

- ❖ ASCUS/CIN 1: \$2.4 m (7.7%)
- ❖ CIN 2: \$1.9 m (5.9%)
- ❖ CIS: \$5.5 m (17.5%)
- ❖ Cervical cancer: \$22 m (68.9%)

The total estimated annual cost was \$31.8 million. The annual cost of Pap smear screening was estimated to be \$25 million. This brings the estimated annual cost to \$56.8 million. Screening accounts for 44% and CIN/cancer management for 56% of the total cost.

The CIN/cancer management costs may contain non-cancer-related medical expenses for co-existing conditions. The Department of National Medical Insurance requested that the direct medical costs be calculated. Estimated direct costs were:

- ❖ Atypia/CIN 1: \$2.4 m (8.4%)
- ❖ CIN 2: \$2.5 m (9.0%)
- ❖ CIN 3: \$4.2 m (14.9%)
- ❖ Cervical cancer: \$19 m (67.8%)

The total estimated cost was \$28.1 million.

## Cost-effectiveness analysis of HPV vaccine

The impact of HPV immunization on cost reduction on an annual basis in Taiwan is estimated to be:

- ❖ ASCUS: reduced from \$2.4 m to \$2 m.
- ❖ CIN 2: reduced from \$1.9 m to \$1.5 m.
- ❖ CIS: reduced from \$5.5 m to \$3.5 m.
- ❖ Cervical cancer: from \$22 m to \$7.9 m.

The total estimated annual cost reduction is \$16.6 million, or 29%. The cost reductions are in the area of treatment. Screening costs remain the same.

The cost-effectiveness comparison between Pap smear screening and HPV immunization is set out in Table 1.

**Table 1: Cost-effectiveness comparison – Pap smear screening & HPV immunization**

	Mortality reduction (%)	Cost per year (US \$)
Pap smear	32.9	25 m
HPV immunization	67.5	31 m

The cost of reducing mortality by 1% by use of Pap smear screening is estimated to be \$0.76 million. The cost of reducing mortality by 1% by HPV immunization is estimated to be \$0.46 million.

In 2003 42,501 women were treated for genital warts at a cost per case of \$85.60. The total cost was \$3.6 million, which is higher than the total treatment cost for CIN 1 and for CIN 2.

To assess the health and economic impact of a quadrivalent HPV vaccine in Taiwan, a Transmission Dynamic Model was used, based on a published US study (Elbasha, 2007). This is an integrated disease transmission model and cost-utility analysis, incorporating a demographic model, a behavioral model, and HPV infection and disease models. Taiwan health care system data were used.

Routine immunization of 12 year-old females against HPV types 16 and 18, assuming lifelong duration, is estimated to reduce the annual incidence of cervical cancer from around 13.5 cases per 100,000 women at the commencement of routine immunization to fewer than 1 case per 100,000 60 years later. The reduction in incidence would be progressive over this period. Routine immunization of 12 year-olds, plus catch-up immunization of 12-24 year-olds would further reduce the annual incidence of cervical cancer from year 9, post introduction of routine immunization, through to year 80. Thereafter, there would be no significant difference in cervical cancer incidence rates between immunization of only 12 year-old girls versus immunization of 12 year-old girls, plus catch-up.

Routine HPV quadrivalent immunization of 12 year-old females, assuming lifelong duration, is estimated to reduce the annual incidence of HPV 16, 18, 6 and 11-related CIN 2 and 3 from around 60 cases per 100,000 women at the commencement of routine immunization to approximately 6 cases per 100,000 60 years later. The reduction in incidence would be progressive over this period. Routine HPV quadrivalent immunization of 12 year-olds, plus catch up immunization of 12-24 year-olds would further reduce the annual incidence of HPV 16, 18, 6 and 11-related CIN 2 and 3 from year 4, post introduction of routine immunization, through to year 70. Thereafter, there would be no significant difference in CIN 2 and 3 incidence rates between immunization of only 12 year-old girls versus immunization of 12 year-old girls, plus catch-up.

Routine HPV quadrivalent immunization of 12 year-old females, assuming lifelong duration, is

estimated to reduce the annual incidence of HPV 6 and 11-related genital warts from around 97 cases per 100,000 women at the commencement of routine immunization to approximately eight cases per 100,000 60 years later. The reduction in incidence would be progressive over this period. Routine HPV quadrivalent immunization of 12 year-olds, plus catch up immunization of 12-24 year-olds would further reduce the annual incidence of HPV 6 and 11-related genital warts from year 6, post introduction of routine immunization, through to year 42. Thereafter, there would be no significant difference in genital warts incidence rates between immunization of only 12 year-old girls versus immunization of 12 year-old girls, plus catch-up.

As is shown in Table 2, a prophylactic quadrivalent HPV vaccine can be cost-effective because the cost is similar to colon cancer screening and mammographic screening.

**Table 2: Select cost-effectiveness ratios (\$/QALY)**

Program	US \$
Colon cancer screening	10,000 25,000
Mammographic screening	10,000 25,000
Type 2 diabetes screening in Taiwan	9,000 36,000
Cholesterol management: secondary prevention	10,000 50,000
<b>Quadrivalent HPV routine immunization</b>	<b>12,439</b> <b>74,773</b>
Dialysis in renal disease	50,000 100,000

## New cancer prevention program

There was a plateau in the rate of cervical cancer screening in Taiwan at between 50-55% in the period 2000-2005 (Chen, 2005). In response to this, and after much discussion, a new Cervical Cancer Prevention Program has been developed. This will include the introduction of routine HPV immunization of females aged 12-15 years of age, in addition to the current Pap smear screening program. However, as the cost of immunization is very high, the immunization program will be introduced progressively, with high priority areas or populations to be immunized first. The HPV immunization program commenced in late 2007 at Taipei city, in September 2008 at Golden Island, and all females aged 12-15 years will be immunized in around 2010 or later.

## Summary

A prophylactic quadrivalent HPV vaccine can be cost-effective and be efficiently added to current screening programs to reduce the incidence of cervical cancer, CIN, and genital warts.



# Key points from questions and discussion



## Frequency of screening

Annual Pap smear screening is not cost-effective. Screening every three years is sufficient and would result in substantial cost savings. There is, however, the possibility that less frequent screening would result in a reduction in the number of women being regularly screened. There would also be resistance from the medical profession.

## Priority groups for immunization

It was suggested that where data are available to identify cervical cancer rates in different populations over time, this could be used to identify priority groups for immunization, where HPV immunization programs are introduced progressively.

## HPV treatment costs in Thailand

The estimated HPV treatment costs in Thailand include both direct and indirect costs. The Taiwan costs in Dr. Tseng's presentation are for direct medical costs, but exclude indirect costs. Direct medical costs in Thailand are therefore likely to be somewhat less, compared to Taiwan.

## The long-term future of cervical cancer screening

The introduction of routine universal HPV immunization will significantly reduce the incidence of cervical cancer in the long-term. In forty years time, the incidence of cervical cancer may be so low that governments may legitimately consider terminating routine population-based cervical cancer screening. In the light of this, the cost of HPV immunization can be seen as a 'temporary' additional cost that would eventually allow cost savings in relation to cervical cancer screening.

### Health economic interactive tools for Gardasil® for policy and decision-makers



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#### Thinking behind developing the Gardasil® health economics tools

Policy and decision-makers often want to assess health economic information on Gardasil® immunization programs. Providing tools that do not require health economics expertise can aid informed decision-making regarding immunization program policy at the national level.

#### Key points

- ❖ Merck has developed three Gardasil® health economics tools to aid informed decision-making regarding immunization program at the national level.
- ❖ The HPV Burden of Disease Tool estimates the number of incident cases of HPV disease and associated diagnosis and treatment costs over time.
- ❖ The Health and Budget Impact Tool provides insights in the potential reduction in HPV-related disease and associated costs resulting from immunization, and the net cost of the immunization program.
- ❖ The Health and Budget Impact and Cost-Effectiveness Web Tool (under development) will provide better customization than the Health and Budget Impact Tool and will also provide cost-effectiveness assessments of the immunization program.
- ❖ The tools are designed to be easy to use and provide information in an easily understood format. The tools can provide valuable insights into the health economics of HPV disease and impact of immunization at the national level.

#### How the tools can be implemented at the national level

The tools can generally use the following data specific to a country:

- ❖ Total population size or population distribution by gender and age.
- ❖ Annual incidence of HPV disease.
- ❖ Cost to diagnose and treat an episode of HPV disease.

However, the tools also contain data from selected countries and this information can be used to inform decision-making without the need to collect additional data.

Caution is needed in interpreting data generated by the tools. As with all models, the following limitations apply to these tools:

- ❖ Models are limited by available data.
- ❖ Modelling uses assumptions.
- ❖ Models provide estimates, not precise findings.
- ❖ Models provide insights on the issues rather than definitive conclusions.

Merck has developed three Gardasil® health economics tools, which are outlined below.

#### HPV Burden of Disease Tool

The objective of this tool is to estimate the number of incident cases of HPV disease and associated diagnosis and treatment costs over time, including:

- ❖ Cervical cancer cases and deaths.
- ❖ Cervical dysplasia (CIN 2/3, CIN 1).
- ❖ False-positive abnormal Pap tests.
- ❖ Genital warts in females and males.

The HPV disease burden for the next 100 years can be estimated using the tool. The tool is available in an easy to use format on a CD-ROM.

The tool uses the population size and annual incidence of HPV disease to derive the total number of cases of HPV-related disease. Information on the

cost of diagnosis and treatment for HPV disease is then used to determine the total cost of HPV disease.

The HPV Burden of Disease Tool uses the following inputs:

- ❖ Total population size or, if available, population distribution by gender and age categories.
- ❖ Annual incidence of HPV disease.
- ❖ Cost to treat each case of HPV disease, by disease
- ❖ Time horizon for analysis up to 100 years.
- ❖ Discount rate for future costs.

The tool generates the following outputs:

- ❖ Estimated total number of incident cases overtime for genital warts, abnormal Pap smears (no CIN), CIN, and cervical cancer.
- ❖ Estimated total deaths related to cervical cancer over time by age group.
- ❖ Estimated total costs of HPV disease over time by HPV disease and age.

The tool produces slides containing these outputs that can be used in presentations to health care decision-makers.

## Health and Budget Impact Tool

The objective of this tool is to provide insights to the potential reduction in HPV-related disease and associated costs resulting from immunization. The tool assists in estimating the immunization costs. Projections can be developed for up to 100 years. The tool is available on CD-ROM.

The Health Budget and Impact Tool estimates the incident HPV disease cases and associated costs for "without immunization" and "with immunization" scenarios.

- ❖ In the "without immunization" scenario, the incidence and cost of HPV-related disease is projected assuming the current state of cervical cancer screening only.
- ❖ In the "with immunization" scenario, immunization is added to the current state of cervical cancer screening, and incidence and costs of HPV-related disease are projected.

The difference of the HPV-related disease cases and costs from "without immunization" and "with immunization" scenarios provides an estimate of the projected reduction in HPV-related health and cost impact resulting from immunization. The cost of the immunization is then added into the tool to give the net cost or budget impact of the immunization program.

The back engine of the tool is a dynamic

transmission model described elsewhere. Briefly, the dynamic transmission model describes the viral transmission and disease in a changing population over time with individuals entering the model as they are born and exiting as they die. The model also accounts for the reductions in HPV prevalence over time, due to immunization. This modelling approach captures the direct effects of immunization as well as indirect effects through herd immunity.

The Health and Budget Impact Tool has benchmark data on four countries from different regions of the world. Each country has different cervical cancer incidence and mortality rates and differs from others on the cervical cancer screening rate and whether screening rates have stabilized. The countries included are the USA, Hungary, Mexico and Taiwan.

These four countries constitute four modules in the tool. Users of the tool can select one of the modules that most closely matches their country on cervical cancer incidence, mortality and screening rates and whether screening rates have stabilized (US and Hungary: stabilized; Taiwan and Mexico: not stabilized).

Following are the inputs to the tool:

- ❖ **Population demographics:** including total population size or population by gender and age groups, and, if available, immunization cohort size (i.e., number of 11 year-old girls, number of females aged 12-24 years of age, and number of 11 year-old boys).
- ❖ **Cost of immunization:** including the price per vaccine series and administration fees.
- ❖ **Immunization scenarios:** variables are immunization gender, immunization coverage/penetration levels for different cohorts, and vaccine duration of vaccine efficacy.
- ❖ **Economic Burden Profile:** including the average cost per case of genital warts (in males and females), CIN 1, CIN 2/3, and cervical cancer.
- ❖ **Temporal variables:** the annual discount rate (if any) to apply to future costs, and the time-frame (1-100 years) for modelling the health and budget impact.

Following are the types of results that can be generated using the tool:

- ❖ Estimated annual and total incident cases and associated costs overtime for genital warts (female and male), CIN1, CIN2/3, and cervical cancer, with and without immunization.
- ❖ Estimated annual and total cervical cancer deaths overtime, with and without immunization.

- ❖ Estimated total cases of HPV-related disease and associated costs avoided over time, by disease and age, as a result of immunization.
- ❖ Estimated total immunization costs, cost offsets from immunization, and the net cost of immunization.

Results are produced in a slide format that can be used in presentations.

### **Health and Budget Impact and Cost-Effectiveness Web Tool**

This tool is currently under development. The tool would estimate the health and budget impact and cost-effectiveness of HPV immunization and will be available on a web interface. This tool allows for better customization of data, compared to the current Health and Budget Impact Tool. In addition to the inputs already available in the current health and budget impact tool, the web-based tool is planned to have the following inputs:

- ❖ Vaccine uptake rates between 1 and 100%
- ❖ Annual cervical cancer screening rates, by age
- ❖ Annual hysterectomy rates, by age.
- ❖ Sexual activity parameters (# of partners by age and gender, and population distribution in sexual activity groups).
- ❖ All-cause mortality rates, by age and gender
- ❖ Cervical cancer-specific mortality rate, by age
- ❖ Percentage treatment rates of HPV disease for genital warts, CIN and cervical cancer
- ❖ QALY weights.

### **Summary**

The Gardasil® health economic tools are designed to be easy to use and provide information in an easily understood format. The tools can provide valuable insights into the health economics of HPV disease and impact of immunization at the national level.

# Health economic outcome measures in vaccines against cervical cancer



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## Key issues

It is difficult to propose a uniform approach for health economic analysis in the Asia-Pacific region because of the wide variation of the management of cervical cancer across the region. Some countries, such as Korea, Taiwan and Japan, have well developed cervical cancer screening programs, but this is not common across the region. Therefore, there is a need to be country-specific in economic evaluations.

It is important to keep health economic models simple. Complex models are demanding in specific data and sometimes the results are difficult to understand and to interpret. However, tools exist to keep things simple. What health authorities usually want to know is how many cases of cervical cancer and pre-cancerous lesions will be avoided by immunization, annual total cost offsets and annual net costs.

A complete economic assessment of the impact of immunization includes evaluating the vaccine characteristics (cross- and sustained protection) and evaluating different vaccine scenarios (e.g. age of immunization, catch-up, and target groups).

## Outcome measures in health economics

There are four types of outcome measures in health economics:

- ❖ Costs.
- ❖ Quality of life impact.
- ❖ Survival time or life-years saved.
- ❖ Combinations of the above.

Epidemiological data, costs, quality of life impact and survival time, collectively describe the disease burden.

Costs can be direct, indirect and intangible. Direct medical costs for cervical cancer vaccines include:

- ❖ The vaccine cost, plus administrative costs. The cost will depend on coverage rates.
- ❖ Screening costs. Variables will be the type and frequency of screening and the coverage rate.
- ❖ Treatment costs for abnormal Pap smears, CIN 1, CIN 2/3, and cervical cancer.

Indirect and intangible costs for cervical cancer vaccines are hard to calculate and this area has not been the subject of very much research so far.

In relation to quality of life, no specific instruments have been developed to determine the impact of cervical cancer screening. Measurement of quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs) is the commonly used approach.

Survival time is quite easy to measure if you know the number of cancer cases, age, the stage at which cancers are diagnosed, and the case-fatality rate. Once you know the life-expectancy at the age of cancer death, it is possible to estimate the potential survival time when avoiding the cancer and the cancer death by the new intervention.

Some countries have developed economic evaluation guidelines to be used in calculating the incremental cost-effectiveness ratio and the discount, but most of the countries in Asia-Pacific do not have such guidelines, with the exception of Korea, Taiwan and Japan.

Additional information useful for health economic analysis of HPV vaccines are data on the function of age and the distribution of HPV types.

## Key points

- ❖ Simple methods exist to estimate the economic benefit of HPV immunization.
- ❖ In the absence of access to detailed data, the best option is to use simple methods as the first step.
- ❖ Results should be checked with extensive sensitivity analysis, including vaccine characteristics and vaccine strategies.
- ❖ The starting age for immunization, cross-protection and sustained protection of the vaccine are important factors that influence cost and effect results.



## Evaluation methods of outcome measures

The types of evaluation methods used for outcome measures are:

- ❖ Cost of illness studies.
- ❖ Patient questionnaires for quality of life.
- ❖ Epidemiological studies on cancer for survival time.
- ❖ Epidemiologic studies on sexually transmitted infections.
- ❖ Clinical trial data.
- ❖ Application of models.

For cervical cancer vaccines, the data that are needed are:

- ❖ Cervical cancer registry data.
- ❖ Ministry of Health unit cost data for health care procedures.
- ❖ Data from local screening programs, with retrospective data analysis.
- ❖ Prospective studies on HPV testing.
- ❖ Clinical trial data, particularly representative samples from the region.

## Specific tools

Use of models is mandatory for analysis of health economic outcomes in relation to vaccines. Randomized clinical trials (RCTs) are too short for measuring all the consequences of immunization and RCTs report data under specific conditions (i.e. the efficacy measure).

A number of models exist which range from easy to use and to understand to very complex models. The most basic model is the back of the envelope calculation. This is not a stand-alone model but rather a cross-sectional observation over one year that relates more or less to population models.

Cohort models select an age group and follow the cohort over time till everyone dies. If you have different subsequent age cohorts immunized and you conduct a cross-sectional measurement across all the cohorts at one point in time, you have an evaluation as if you are working in a population model.

We further make a distinction between static and dynamic models. In static models, all the values remain fixed. In dynamic models, values change over time. Within dynamic models, a distinction is made between compartmental and individual-based models. Compartmental models split, for example, the population into different compartments or boxes of different types of sexual behavior. Compartmental models become complicated if you have many compartments and

you need to estimate the relationship between the boxes. Because sexual behavior changes with age, dynamic models are now being developed with individual sexual characteristics for each participant in the model that change while the population ages. You can then simulate, for example, 200,000 individuals over their life-time and see what will happen over time regarding health outcomes.

The more complex models can be more accurate but they are less transparent and not readily understood by many decision-makers.

Key steps in the back of the envelope calculation method are:

- ❖ Selection of a country and the relevant endpoints to be impacted by immunization (e.g. abnormal Pap smears, CIN 1, genital warts, CIN 2/3, cervical cancer and cervical cancer deaths).
- ❖ Estimate the number of cases/events per endpoint per year.
- ❖ Estimate the cost per case/event for the follow-up and treatment of each endpoint.
- ❖ Estimate the vaccine efficacy of each vaccine type for each endpoint.
- ❖ Calculate the effect difference per endpoint and the total cost difference between vaccine strategies using simple arithmetic calculations.

No discount rate is applied because this method only calculates costs over one year after full immunization of the population (i.e. a steady state situation). The model result is a first but not a final indicator. The results are presented as an incremental analysis.

## Sensitivity analysis

It is very important to consider the different types of sensitivity analysis that can be applied:

- ❖ Univariate: every variable within a range is tested separately.
- ❖ Multiple: combines two or more variables to see the impact on the result.
- ❖ Probabilistic: stochastic variables together.
- ❖ Scenario: 'what if' conditions.

For the evaluation of cervical cancer vaccines there are multiple variables for which there are only estimates rather than proven data. For example, estimates need to be made for the following variables:

- ❖ The transmission or infection rate between two individuals.
- ❖ HPV infection as a function of age.
- ❖ The transition probability from infection to cancer.
- ❖ HPV distribution at every stage and age.

- ❖ Cost figures.
- ❖ Vaccine characteristics (cross-protection and waning of immunity)
- ❖ Vaccine scenarios (age of immunization, catch-up).

## Example of Thailand

The following is a description of how HPV health outcome analysis was conducted in Thailand. Cervical cancer registry data were available. All other data were estimated. A one-year cancer model was developed. This estimated the infection curve of HPV types 16 and 18 and also estimated the effect of HPV immunization at different ages in terms of number of cancer cases avoided and survival time gained.

A back of the envelope calculation was performed to estimate the cost offsets compared with no immunization and a sensitivity analysis on cross-protection and limited sustained protection was also performed.

The starting point for the one-year cancer model was cervical cancer. Outcomes associated with initial HPV infection, cervical cancer mortality and natural cause mortality were determined simultaneously for each patient who was simulated in the model. In that respect, the model differs from a traditional Markov state-transition model.

The model runs in Excel™, with Monte Carlo Process. The advantage of using Monte Carlo simulation is that it allows input variables to be varied simultaneously for each individual, using the entire range of possible values for each parameter:

- ❖ Age at diagnosis of cervical cancer.
- ❖ Time to progression from HPV infection to cervical cancer.
- ❖ Mortality due to cervical cancer.
- ❖ Fatal case survival.

The results reflect the variability in each of the input parameters.

Model inputs are:

- ❖ Age at immunization\*.
- ❖ Vaccine coverage rate (%)\*.
- ❖ Vaccine efficacy (%) against persistent HPV types 16 and 18 infection\*.
- ❖ Local HPV-16 and 18 prevalence in cervical cancer (%)\*.
- ❖ Current cancer registry-based cervical cancer incidence\*.
- ❖ Current cancer registry-based cervical cancer mortality.

- ❖ Current demographic data of women in Thailand.
- ❖ Time to progression between initial HPV infection and cervical cancer diagnosis.
- ❖ Mean duration of survival for fatal cases of cervical cancer.
- ❖ Minimum age at HPV infection.

A sensitivity analysis was conducted for the inputs above marked with an asterisk (\*).

The estimated time to progression from HPV infection to diagnosis of cervical cancer was 28 years with a standard deviation of 9 years.

Table 1 shows the number of cervical cancer cases avoided and number of cervical cancer mortalities avoided in Thailand from immunization of 10 year-old girls.

**Table 1: Cancer cases & mortality avoided from HPV immunization of 10 year-old girls in Thailand**

Immunization of 10 year-olds		
Years post-immunization	Cancer cases avoided	Cancer mortalities avoided
5 years	0	0
10 years	5	2
15 years	38	16
20 years	73	64
25 years	466	188
50 years	4,094	1,642
75 years	5,311	2,125
90 years	5,467	2,150

Table 2 shows the effect of immunization at different ages on the number of cases of cervical cancer avoided and the number of cases of cervical cancer mortality avoided. The greatest effect is gained from immunization at 10 years of age, compared to immunization at an older age.

**Table 2: Cancer cases & mortality avoided in Thailand from HPV immunization at different ages**

Outcome & age of immunization	Number of cases		Cases averted (% cases averted)
	No immunization	HPV immunization	
Cervical cancer cases	7,000		
10 years		1,533	5,467 (78)
15 years		1,678	5,322 (76)
20 years		2,968	4,032 (58)
25 years		4,773	2,227 (32)
Cervical cancer mortality	2,753		
10 years		603	2,150 (78)
15 years		660	2,093 (76)
20 years		1,183	1,570 (57)
25 years		1,903	850 (31)

The model also estimates survival time gain for immunization at different ages. The results for Thailand are in Table 3. There is only a small difference in terms of years of survival time gained between immunizing at 10 and 15 years of age.

**Table 3: Survival time gained (years) for HPV immunization at different ages in Thailand**

Immunization age	Survival Time Gained (Years)
Immunization at 10 years	14,582
Immunization at 15 years	14,516
Immunization at 20 years	13,940
Immunization at 25 years	7,903

Table 4 shows the estimated cost offsets for HPV immunization in Thailand, using the back of the envelope calculation.

**Table 4: Estimated cost offsets from HPV immunization in Thailand \***

	Abnormality	CIN 1	CIN 2/3	Cancer
Cases/events treated per year	50,000			7,000
Cervarix™ efficacy	95%			100%
HPV 16 & 18 %	18%			73%
Prevented	8,550			5,110
Unit cost	\$135			\$2,400
Total	1,154,250			\$12.26 million
<b>Cost offset</b>				<b>\$13.42 million</b>

\* Because cytological screening in Thailand is poor, related data are not reported in the table.

Cost impact of immunization is measured at a steady state of immunization. This is not the cost impact after one year of immunization, but rather the cost impact per year once the whole population is immunized. The model allows estimation of cost impact for cancer cases avoided as well as precursor cases. The estimates generated will vary depending on the cancer screening method put in place.

This cost estimation method is simple and straightforward. As a cost impact result, it does not tell the complete story, because life-years gained are missing in that data-set. Also the cost of the vaccine is not included in the analysis. It relates to cost-offset only.

Using the same type of cost estimation method it is possible to calculate the impact of cross-protection for non-vaccine oncogenic HPV, using a range of vaccine efficacy rates. The level of cross-protection will affect total costs and cost offsets. Finally, sensitivity analysis can also be conducted on waning vaccine efficacy at different time points.



# Key points from questions and discussion



## Estimation of the prevalence of pre-cancerous lesions

A participant from Korea stated that they have no data on the prevalence of HPV pre-cancerous lesions. Estimates of the number of cases of pre-cancerous lesions are based on the number of cases of cervical cancer. What is the best way to estimate the prevalence of pre-cancerous lesions?

In response, Dr. Standaert stated that there is a rule of thumb for estimating the number of cases of CIN 1 and CIN 2/3, based on the number of cases of cervical cancer. This will depend on the screening method used. In the cohort model being developed by GSK, there is a transition probability for progression from CIN 1 and CIN 2/3, based on assumptions. A sensitivity analysis on the transition probabilities can be performed. In a recent analysis of Irish data, performed by GSK, all kinds of distribution variables for everything that was uncertain (25 variables) were tested. The model was tested 10,000 times using Monte Carlo Simulation. It was concluded from this analysis that cross-protection is more important than vaccine waning. The reason is that waning only applies to HPV type 18, which is proportionally only a small group of patients.

Dr. Singhal said that MSD faced a similar problem when they tried to adopt the dynamic model, used in the United States, for Mexico. In Mexico, there were age-specific cancer incidence and mortality data, but no data for CIN 1 and CIN 2/3. The approach used, based on the other inputs in the model (screening parameters, treatment rates and sexual behavior parameters) was to calibrate the model for cervical cancer incidence in Mexico. If the calibration worked out, it was assumed that the estimates of CIN 1 and CIN 2/3 were close to reality.

Dr. Standaert added that data will never be available on the transition from CIN 3 to cervical cancer because all diagnosed cases of CIN 3 are treated. He also stated that the calibration process for all parameters, as mentioned by Dr. Singhal, is essential. He cautioned that there is too much focus on calibration of screening rates. Following introduction of immunization, females will be immunized at an age before screening will be necessary. HPV immunization will reduce cervical cancer prevalence by up to 70%. There will be a need to adjust cervical cancer screening programs

for the 30% of cases of cervical cancer that cannot be prevented by the HPV vaccines. It could be that the current screening programs will not be cost-effective anymore after the introduction of immunization.

## Cross-protection sensitivity analysis

Does the cross-protection sensitivity analysis use the assumption that cross-protection is independent of vaccine type protection, or do you calculate the possibility that cross-protection may come from co-infection of vaccine types and non-vaccine types, which was observed in the clinical trials? Using these two different scenarios, your sensitivity analysis may give you a large difference in cost estimation.

In response, Dr. Standaert stated that at this stage GSK gives a range rather than a fixed value. He said that it is necessary to specify the level of cross-protection by HPV type to be precise.

### Decision-making and economic modeling in vaccine adoption: the case of HPV vaccines



*Dr. Yot Teerawattananon, Program Leader, Health Intervention and Technology Assessment Program (HITAP), International Health Policy Program (IHPP), Thailand*

#### Similarities and differences between vaccines and other health interventions

There are key differences between vaccines and other health interventions:

- ❖ For vaccines, the benefits can only be observed in the future. For treatment interventions the benefits can generally be observed immediately.
- ❖ For vaccines, there are externalities in that people not immunized receive the benefit of herd immunity. For other treatment interventions, externalities are generally rare.
- ❖ Vaccines have relatively large budget impacts because of their broad population coverage. Other treatment interventions generally provide at individual level so that they have relatively small budget impacts.

There are similarities between vaccines and other health interventions in the factors considered by decision-makers on what to fund. These are:

- ❖ Affordability;
- ❖ Public support (political defensible);
- ❖ Efficiency or value for money.

However, value for money is not always a factor. For example the incremental cost-effectiveness ratio for providing renal dialysis compared to palliative care in Thailand is approximately US \$19,000/QALY. As this is more than six times greater than annual per capita GDP, renal dialysis is not cost-effective in Thailand. It is, however, publicly funded.

#### Similarities and differences between HPV vaccines and other vaccines

There are differences between HPV vaccines and other vaccines that will be considered when making a funding decision:

- ❖ For HPV vaccines, the full benefits of immunization will take 30-40 years. For most

EPI vaccines, the benefits of immunization are realized in fewer than 20 years.

- ❖ HPV vaccines are unlikely to have externalities since herd immunity is unlikely with female-only immunization. Externalities are common for other vaccines.
- ❖ The HPV vaccine is administered to older-aged children. This makes vaccine delivery more challenging, compared to childhood EPI vaccines.
- ❖ The HPV vaccine is very expensive at around US\$350.00 for one course of 3 doses in Thailand. The cost of each EPI vaccine in Thailand is generally less than \$5.00.
- ❖ A cost-effective alternative for the prevention of HPV-related disease already exists (cervical cancer screening). Cost-effective alternatives to EPI vaccines rarely exist.

#### Thai cost-effectiveness study

A World Bank-funded study compared the cost-effectiveness of HPV prevention options in Thailand. The current policy of providing Pap smear screening to all females aged between 35-60 years of age, every 5 years, provides a life-year gain of 0.002 at a cost of PPP US \$6.62 (cost saving).

The study found the most cost-effective option was to provide VIA every 10 years to females aged 30 and 40 years of age, and then Pap smear every 10 years to women aged 50 and 60 years of age. This strategy provides a life-year gain of 0.006 at a cost of PPP US \$18.72 (cost saving).

Universal HPV immunization of females aged 15 years of age provides a life-year gain of 0.031 at a cost of PPP US \$1027.17.

A combined strategy of VIA every 10 years for women aged 30 and 40 years of age, plus Pap smears every 10 years for women aged 50 and 60 years of age, plus HPV immunization of 15 year-old females, provides a life-year gain of 0.033 at a cost of PPP US \$1029.72.

The incremental cost-effectiveness ratio, comparing HPV immunization of 15 year-old girls with the current policy of Pap smears for women aged between 35-60 years every 5 years, is approximately PPP US \$35,941 per life-year saved. This is very high compared to Thailand's annual per capita GDP of PPP US \$8,677 in 2005.

### Public sector versus private sector financing

Factors to be considered in relation to the decision on public or private sector financing of HPV vaccines are:

- ❖ The ability to achieve widespread coverage, especially of high-risk groups, at an affordable price.
- ❖ The ability to improve or maintain screening programs for cervical cancer.
- ❖ The ability to answer currently unanswerable questions. For example, is there a need for booster doses and what is the optimal age for immunization?

### The role of economic modeling in decision-making

Economic modelling will help in:

- ❖ Estimating present and future costs and benefits of immunization.
- ❖ Identifying information needs for future monitoring and evaluation of the immunization program.

Economic modeling assists decision-making processes if good quality information is available at the time the decision is being made. Decision-makers need to understand and accept the method used in economic modeling. Trust and distrust are important issues. A Thai study involving in-depth interviews with 37 policy-makers in Thailand found that decision-makers wanted:

- ❖ Local information rather than international data.
- ❖ Transparent data.
- ❖ Studies conducted by impartial researchers.

Methodological issues that need to be considered in conducting economic evaluations are:

- ❖ Questions to be answered: clarity, whose perspective will be used in the analysis, and selection of comparator(s) in the model.
- ❖ Time horizon: to capture long-term costs and benefits.
- ❖ Future value of resources used and benefits: discounting rate – 0%, 3%, 5%, 10%?
- ❖ Uncertainty: about the model, methodological issues, and parameters.

The incremental cost-effectiveness ratio of HPV immunization for females aged 15 years of age versus the current practice of Pap smear every five years for females aged 35-60 years of age will be significantly effected by the discounting rate because the real effectiveness of the vaccine e.g. cancer cases averted, can only be observed in the remote future. The ICER for different discounting rates will be:

- ❖ 0% discounting: PPP US \$3,337 per life year saved.
- ❖ 3% discounting: PPP US \$35,941 per life year saved.
- ❖ 5% discounting: PPP US \$99,063 per life year saved.
- ❖ 10% discounting: PPP US \$692,341 per life year saved.

# Factors to be considered in relation to the funding and affordability of HPV vaccines



*Professor Sathirakorn Pongpanich, Ph.D.,  
College of Public Health Sciences, Chulalongkorn University, Thailand*

The following factors need to be considered in relation to the funding and affordability of HPV vaccines:

- ❖ Good, reliable health outcomes research is important in demonstrating the case for funding to governments.
- ❖ Studies need to be country specific. For example, the findings from a study done in the United States will not be applicable to Thailand.
- ❖ Affordability can be enhanced if free provision of the vaccine is means tested so that people who can afford to pay for the vaccine are not receiving immunization through government subsidy.
- ❖ Politics and connections play a big role in funding decisions. Connections with political parties and leaders should be used.
- ❖ Whether the vaccine is cost-effective or not, may not always be an important factor in the funding decision of government. A range of factors are taken into account by governments when making funding decisions. Governments may decide to support funding on other grounds, even if an intervention is not cost-effective.
- ❖ Negotiations should be held with pharmaceutical companies on price reduction for the HPV vaccines. This could be linked to a government's investment with pharmaceutical companies to manufacture vaccines locally.
- ❖ Financial support for vaccine funding may be available to some countries from international organizations such as GAVI.

# The experience of how hepatitis B vaccine and other new vaccines were integrated into EPI in Indonesia



*Dr. Julitasari Sundoro, Technical Advisory Group on Vaccines, Indonesia*

## WHO recommendation

In 1992, WHO recommended that, by 1995, and then to all remaining countries by 1997, hepatitis B immunization should be incorporated into the Expanded Programme on Immunization (EPI) of countries with an HBV carrier prevalence of 8% or greater. The prevalence of hepatitis B in Indonesia at this time was greater than 8%. In countries with a carrier prevalence of 2% or greater, it was recommended that hepatitis B immunization be incorporated into routine infant immunization schedules. In countries with a carrier prevalence below 2%, the immunization of all adolescents was recommended, as an addition or alternative to infant immunization.

## History of the Hepatitis B Immunization Program in Indonesia

In 1986, the International Task Force on Hepatitis B Immunization undertook to accelerate hepatitis B immunization in countries with intermediate and high endemicity. Indonesia was the first country chosen for implementation of a model hepatitis B immunization program. The program was implemented in Lombok and West Nusa Tenggara from 1987 to 1991, with immunization of babies at 0-7 days after birth. A total of 68,000 babies were immunized. Prior to commencement of the program, HBsAg prevalence among children aged from 9 months to 5 years of age was 6.2%. By 1991 prevalence was 1.9%, a decrease of 70% (Ruff, 1995). A cost-benefit analysis of hepatitis B immunization was conducted in Indonesia in 1992. Nation-wide immunization commenced in 1997.

Other key events in the introduction of hepatitis B immunization in Indonesia for newborns aged 0-7 days were:

- ❖ 1996: Field trial at NTB and Bali Provinces (supported by PATH).
- ❖ 2000-2001: Uniject hepatitis B vaccine administered at birth in East Java, NTB and Yogyakarta Provinces (supported by PATH).
- ❖ 2000-2002: Uniject hepatitis B vaccine administered at birth in Kendari and Buton Districts, South East Sulawesi (supported by AusAID).

- ❖ 2000-2002: Uniject hepatitis B vaccine administered at birth in 6 additional provinces (supported by ICDC-ADB).
- ❖ 2002-2003: Uniject hepatitis B vaccine administered at birth in Cirebon and Cianjur Districts (West Java), Kediri and Blitar Districts (East Java) (supported by PATH).
- ❖ April 2003: Uniject hepatitis B vaccine administered at birth nationwide (supported by GAVI).

## DTP/HB vaccine

The combined DTP/HB vaccine was launched in 2004 in four provinces which represented 20% of the national target. In 2005, the vaccine was introduced into an additional 10 provinces, with nationwide coverage occurring in 2006. DTP/HB vaccine was supplied by the Indonesian Government and operational costs were supported by GAVI.

## EPI multi-year plan: New vaccine support

Plans for the introduction of new vaccines into Indonesia are as follows:

### IPV (Inactivated Polio Vaccine) (2009):

- ❖ As part of Indonesia's polio eradication strategy, a five year demonstration project, replacing IPV with OPV (Oral Polio Vaccine), will commence over the period 2009-2011.
- ❖ A cost-benefit analysis will be conducted at the end of the demonstration project.
- ❖ The EPI is waiting for local IPV production that will be available as a combination of DTP/HB/Hib/IPV.
- ❖ Integration of IPV into Indonesia's EPI will wait until World Polio Free Status.

### Typhoid vaccine (2008):

- ❖ Target: school children.
- ❖ Three-year pilot project in high-risk areas (2 provinces).
- ❖ Funded by the International Vaccine Institute (IVI) and the Government.
- ❖ Cost-benefit analysis to be undertaken in 2011.



**Japanese B encephalitis vaccine (2008):**

- ❖ Target: children aged 9 months to less than 9 years of age.
- ❖ Pilot project in Bali (high-risk area).
- ❖ Cost-benefit analysis already done
- ❖ Funded by the Government, PATH, GAVI and IVI.

***Haemophilus influenzae* type b (Hib) (2009):**

- ❖ Hib will be integrated into EPI as a pentavalent vaccine with DTP & hepatitis B vaccine (DTP/HB/Hib)
- ❖ A pilot project was conducted from 1994 to 1996.
- ❖ Cost-benefit analysis already done
- ❖ Funding for DTP and hepatitis B is from the Government and for Hib from GAVI.

**Pneumococcus vaccine (2010):**

- ❖ GAVI and NVS (New Vaccine Support) will provide co-funding with the Government.
- ❖ Strengthening the surveillance network for pneumococcus at large hospitals (Paediatric Association / IVI)
- ❖ Planned field trial (small scale)
- ❖ For poor countries, GAVI requires a government contribution of US \$0.15 per dose, and for intermediate income level countries, US \$0.30 per dose.

**Rotavirus vaccine (2011):**

- ❖ Indonesia is planning for a pilot project of Rotavirus vaccine in 2011, with GAVI support.

**HPV vaccine:**

- ❖ HIV vaccine is currently only available in Indonesia in the private market at US \$110 per dose.
- ❖ There are no plans for government funding for the HPV vaccine.

**Government funding**

The CDC makes funding proposals for new vaccines to the Planning Bureau in the Ministry of Health. Approval is subsequently required from:

- ❖ The National Development Planning Agency.
- ❖ The Department of Finance.
- ❖ The Parliamentary Health Committee.

**Donor funding**

Donor support is for logistics and supplies including the vaccine, cold chain equipment, auto-destruct syringes and safety boxes. Donors also support operational costs through training, social mobilization, and assistance with implementation.

**Summary**

There are several new vaccines available. Recommendations on the introduction of new vaccines are made by the Indonesian Technical Advisory Group for Immunization. They take account of the following factors:

- ❖ Disease burden.
- ❖ Guidelines, such as WHO position papers.
- ❖ Pilot projects to allow modeling.
- ❖ Analysis of the results of pilot projects.
- ❖ Cost-benefit analyses.
- ❖ Availability of the vaccine.

# Key points from questions and discussion



## GAVI funding, government funding and vaccine price

Only a few countries in Asia Pacific are eligible for GAVI funding for their immunization programs. Governments should not seek support from GAVI or other external sources unless they have a commitment to take over funding of the vaccine at the time donor funding ceases.

MSD indicated that it will have a differential pricing structure for Gardasil®, and GSK also stated that its long established practice of tiered pricing for different products will apply to Cervarix™. MSD understands that an Asian health economic model using the US price for Gardasil® will almost certainly not demonstrate similar cost-effectiveness ratios, due to contextual differences in health care costs. To achieve population health benefits, HPV immunization needs to be a part of a publicly funded, universal immunization program. Privately funded immunization is only capable of achieving individual benefits for those who can afford the vaccine. The pharmaceutical companies indicated that they are committed to working with governments in the region to achieve affordable and appropriate public funding opportunities for HPV immunization.

## Decision-making processes

Because of the cost of new vaccines, health outcomes will be one of the key factors in the funding decision of policy-makers. However, cost may be a relatively minor factor if it can be demonstrated that the benefits of immunization outweigh the costs.

An issue is that health economists use a lot of technical terms which are not understood by all policy-makers. This means that key messages are not effectively communicated. There is a need to translate the findings of health economics research into simple and clear messages that can be understood by all.

Non-health ministries such as Ministries of Women's Affairs can play an important role in supporting programs such as HPV immunization.

Stakeholder engagement, such as lobbying by advocacy groups (e.g. women's groups) can have an important influence on decision-makers. Strong support by politicians and women's groups

for the introduction of publicly funded HPV immunization in Australia played a key role in the decision-making process. The results of health economics research, expressed in a simple and clear way, can be a useful resource for grass-roots advocacy groups.

There is a need for health economics models to take account of the indirect costs of HPV-related disease, borne by patients and their families.

The social value of immunization is low compared to the social value afforded to treatment interventions. This is perhaps why funding is more readily available for treatment compared to prevention. There are more advocacy groups for treatment interventions, compared to advocacy groups for immunization. More effort needs to be put into advocating for funding of immunization programs, using health outcomes research.

## Cost-effectiveness and affordability

Countries such as Korea are in the unfortunate situation that they are ineligible for GAVI support, but have difficulty in funding expensive vaccines such as HPV vaccines. It was stated that it is hard to justify spending large amounts of money on the immunization of 450,000 girls annually to prevent 2,500 cases of cervical cancer that will occur 40 years later. This is especially the case as the cost of treating precancerous lesions is quite low, and the prognosis is good. It was stated that the introduction of HPV immunization into Korea would need to wait till the prices of the vaccines are reduced.

Governments take a range of factors into account in deciding whether to fund particular health interventions, not just cost-effectiveness. Dr. Teerawattananon's presentation indicated that, in Thailand, the Government funds renal dialysis even though it is not cost-effective in the Thai context. Dr. Teerawattananon stated that there were three factors which he believed influenced the Thai Government's funding of renal dialysis:

- ❖ To prevent catastrophic impact on the household expenditure of renal patients.
- ❖ There is no alternative intervention (whereas for HPV the alternative intervention of cervical cancer screening exists).
- ❖ People with end-stage renal disease will die in 3-6 months if dialysis is not provided. In comparison, HPV immunization prevents

deaths from cervical cancer in 30-40 years time.

Dr. Teerawattananon stated that the following doubts existed regarding HPV vaccines:

- ❖ Are the HPV vaccines good value for money in developing and middle income countries, at their current price?
- ❖ Can developing and middle income countries afford HPV vaccines at their current price?
- ❖ What is the long-term efficacy of the HPV vaccines? (Efficacy data currently available are for fewer than 10 years.)

It has been calculated that the cost of the HPV vaccines would need to be reduced by 60-70% for them to be considered as good value for money in Thailand. HPV vaccines are currently sold at approximately the same price around the world. The pharmaceutical companies need to make a commitment to price reductions to address the issues of cost-effectiveness and affordability.

MSD stated that there are many examples of other new vaccines being introduced globally, where long-term efficacy data have not been available. It was, however, acknowledged that the cost of these vaccines is substantially lower, compared to the cost of the HPV vaccines.

### **Infrastructure development**

MSD stated that it has identified issues relating to the infrastructure for vaccine programs in developing countries as a potential obstacle to the introduction of HPV immunization. MSD have programs in place in Vietnam and Uganda, in partnership with PATH, which are studying the existing infrastructure and conducting pilot immunization programs. MSD is also working with the Council for Scientific Research in India on the roll-out of a major immunization program.

A Thai participant stated that the first priority should be to have a well functioning secondary cervical cancer prevention program through screening, with introduction of HPV vaccines occurring after this has been achieved. They also pointed to the difficulty of developing a vaccine program that is capable of achieving a high coverage rate of girls aged 9-12 years of age.



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