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Gender-neutral HPV vaccination

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Dr Alfred Tam

After graduating in 1977 from University of Hong Kong, Dr Alfred Tam received his training at Queen Mary Hospital and subsequently in Glasgow and London in respiratory medicine and intensive care. Afterwards he returned to set up the new PICU and NICU in Queen Mary Hospital in the early 1980's. Since his entry into private practice in 1992, he has also been interested in comprehensive infant and children health care, setting up the Celeste Child Health Centre in Canossa Hospital.

In this review

Human papillomavirus (HPV) infection is a highly transmissible virus and common worldwide, an "equal opportunity" virus that infects males and females of all ages, across socioeconomic strata, with an estimated 50% of sexually active individuals being infected with genital HPV at some point in their lives. Two HPV vaccines are available worldwide and have proven highly efficacious against cervical cancer and its premalignant condition. In particular, the quadrivalent HPV vaccine protects against HPV types 6, 11, 16 and 18, and has been highly effective in the prevention of anogenital warts and precancerous lesions of the cervix, vagina, and vulva in women not previously infected with these types. In contrast, the bivalent HPV vaccine is licensed for females only to prevent cervical cancer. At present, nationally-funded HPV vaccination programmes are for females only. However, mounting evidence attests to the benefit of vaccinating males as well, with clinical trials demonstrating good efficacy in preventing anal lesions and external genital warts associated with the 4 HPV types that are targeted by the quadrivalent vaccine. Another argument for the routine vaccination of boys is "herd immunity", i.e. the belief that it will help confer protection on unvaccinated sexual partners, for the most part girls and women.

This paper is intended as an educational resource for health professionals. It describes the burden of HPV infection and reviews the clinical evidence for the use of HPV vaccination in the treatment of this condition in males and females. It is intended to help readers stay informed of developments and advancing clinical practice in HPV infection.

The burden of HPV-related disease

HPV is a common sexually-transmitted infection in all world regions, with prevalence peaking between the late teens to early twenties,[1] shortly after sexual activity commences.[2] Worldwide, it is estimated that 10.4% of cytologically normal women have HPV infection.[1] HPV is an "equal opportunity" virus, infecting both males and females of all ages, across the spectrum of socioeconomic backgrounds. An average of 33,369 HPV-associated cancers were diagnosed annually in the United States during 2004–2008 (10.8 per 100,000): 12,080 among males (8.1 per 100,000) and 21,290 among females (13.2).[3] Of these, the US Centers for Disease Control and Prevention (CDC) estimates that approximately 26,000 can be attributed to HPV: 18,000 among females and 8,000 among males (see Table 1).

Table 1. Estimated average annual percentage and number of cancers attributable to human papillomavirus (HPV), by anatomic site and sex — United States, 2004–2008[3]

		% attributable to HPV†		No. attributable to HPV§	
Site	**Average annual no.***	**%**	**Range**	**No.**	**Range**
Cervix	11,967	96	(95–97)	11,500	(11,400–11,600)
Vulva	3,136	51	(37–65)	1,600	(1,200–2,000)
Vagina	729	64	(43–82)	500	(300–600)
Penis	1,046	36	(26–47)	400	(300–500)
Anus					
Female	3,089	93	(86–97)	2,900	(2,700–3,000)
Male	1,678	93	(86–97)	1,600	(1,400–1,600)
Oropharynx					
Female	2,370	63	(50–75)	1,500	(1,200–1,800)
Male	9,356	63	(50–75)	5,900	(4,700–7,000)

* Data are from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program, and meet criteria for high data quality.

† Source: Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113 (10 Suppl):3036–46.

§ The estimated number of HPV-attributable cancers was caclulated by multiplying the HPV-associated cancer counts (Table 1) by the percentage of each cancer attributable to HPV. Estimates rounded to the nearest 100. Female and male anal cancers do not equal the total number of anal cancers because of rounding.

HPV is a highly transmissible virus; transmission is estimated to be approximately 40% per unprotected sexual act[4] and shows high concordance between couples in many prospective studies worldwide.[5] This high transmission rate contrasts with 0.09% for herpes simplex-2 infection male-to-female transmission[6] and 0.0009% for HIV infection male-to-female transmission.[7]

HPVs are non-enveloped, double-stranded DNA viruses and to date, 130 different types have been identified; the most clinically important with the highest oncogenic potential are HPV types 16 and 18, which are jointly estimated to cause 70% of cervical cancers worldwide[8] and cancers of the head, neck, penis, anus, vagina and vulva.[9] HPV 16 is highly implicated in the malignant transformation of infected cervical cells[10] and is also causally linked with less common forms of cancer, such as vulvar and vaginal cancer in women, penile cancer in men, and cancers of the oropharynx, larynx and anus in both men and women.[11] HPV types 6 and 11 are responsible for approximately 90% of genital warts (condyloma acuminata) in both men and women.[12]

Available vaccines

Two HPV vaccines are currently available worldwide and in Hong Kong; both vaccines are highly efficacious against cervical cancer and its premalignant condition. In addition to preventing cervical cancer, the HPV quadrivalent (types 6, 11, 16 and 18) vaccine (GardasilR) prevents vaginal and vulvar cancer in females, as well as genital warts and anal cancer in both males and females. The HPV bivalent vaccine (types 16 and 18) is licensed for use in females only to prevent cervical cancer.

Female-only HPV vaccination programmes have been widely introduced in many countries for the indication of prevention of cervical cancer and anogenital warts in women. Australia has witnessed an approximately 90% decrease of genital warts (figure 1) and a 50% decrease of cervical intraepithelial neoplasia (CIN)2/3 or adenocarcinoma in situ (AIS) (figure 2), after 4 years' implementation of Gardasil vaccination programmes.[14,15] Herd immunity to males was also noted. However, boys and men are not yet included in nationally-funded HPV vaccination programmes. This may change, with recent announcements from the US CDC and Australia's Pharmaceutical Benefits Advisory Committee recommending that males should be included in national programmes.

Figure 1. The near disappearance of genital warts in young women 4 years after implementation of Gardasil vaccination programmes in Australia[14]

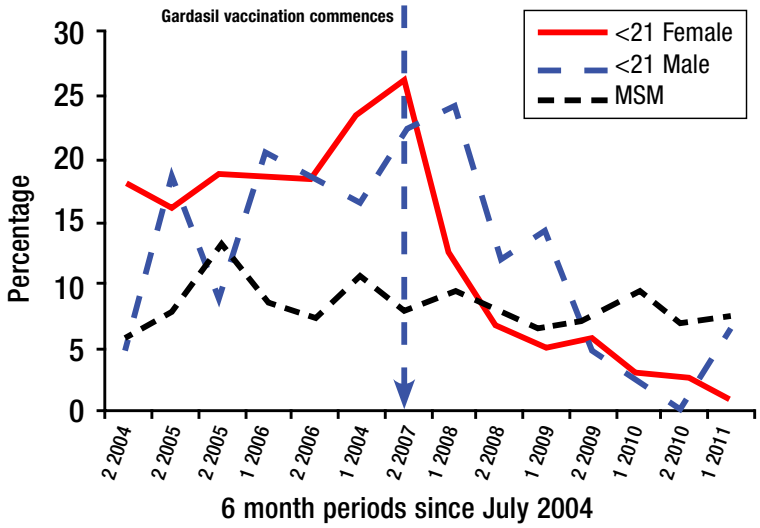
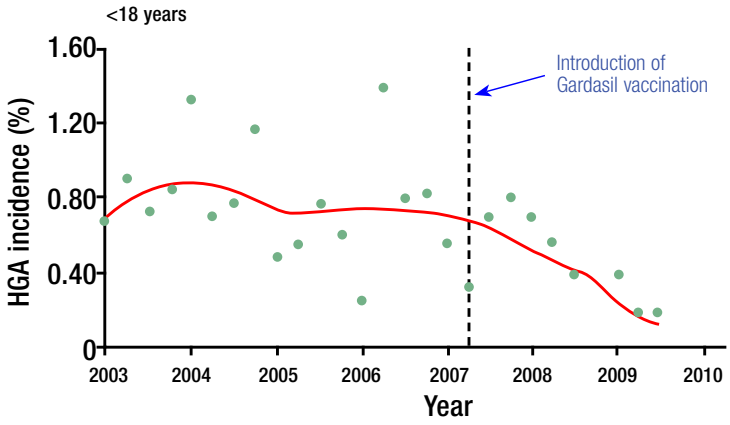


Figure 2. First report of a decrease of CIN2/3 or AIS after implementation of Gardasil vaccination programmes in Australia[15]



Incidence of high-grade cervical abnormalities (HGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Incidence trends over time are shown by Lowess smoothing (red line).

The American Academy of Pediatrics has recommended that all boys aged 11–12 years receive the full course of qHPV vaccine, and that all boys and men 13–21 years who have not been vaccinated previously should receive the vaccine.[16]

In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of qHPV vaccine in males aged 11 or 12 years.[17] They also recommended that all males aged 13–21 years who are either vaccine-naive or had not completed the 3-dose course should be vaccinated and that men aged 22–26 years may also be vaccinated. They based these recommendations on data demonstrating vaccine efficacy in the prevention of grade 2 or 3 anal intraepithelial neoplasia (AIN 2/3, a precursor of anal cancer), estimates of HPV-related cancers and their burden of morbidity and mortality, vaccine cost-effectiveness and programmatic considerations.

The HPV vaccine has been approved for use in males in many countries including the US, the UK, Australia and the UK. There have been calls in the UK for gay men to be eligible for the free vaccination programme; Lord Fowler, ex-government Health Secretary, recently claimed the exclusion of gay men from the HPV vaccine programme was "*clearly unequal and unfair*". He wrote: "*There is a clear inequity in the HPV vaccination programme offered to all 12- and 13-year-old girls. As the four strains of HPV vaccinated against are sexually transmitted, heterosexual males will eventually receive indirect protection against the related cancers and genital warts by a herd immunity effect. Men who have sex with men, meanwhile, receive no such protection, despite increasing rates of anal cancer in this group*", in a letter to Public Health Minister Anne Milton.[18]

Commentary by Dr Alfred Tam

The discovery of HPV vaccine is a crucial step towards successful primary prevention against cervical carcinoma, a common and potential deadly disease. Experience on the effects of the vaccine is accumulating rapidly worldwide and it is obvious that an effective prevention strategy should not focus on the cancer but on the prevention of the spread of the virus. Hence is it only logical that males be also vaccinated, just like giving rubella vaccine to boys. As the virus is also responsible for causing cancer in related areas and in males as well, it makes more sense to vaccinate both boys and girls. An additional benefit of preventing genital warts, which affect both sexes and is much more common, would add further weight to the universal vaccination strategy. Age 11–12 is the most appropriate and opportune time to administer the vaccine, when children are most likely to undergo a medical examination for their transition towards secondary schools. Hopefully this vaccine will be included in the national vaccination programme soon.

Cervical cancer

In 2002, approximately 493,000 women worldwide developed cervical cancer and an estimated 273,000 died from the disease.[19] Cervical cancer is the third most common cancer in women.[20] Cervical cancer primarily affects younger women than do other malignancies, with the highest incidence in women aged 35–50 years.[21]

Over 80% of the burden of cervical cancer occurs in South Central Asia, Central America and Sub-Saharan Africa, where it is the leading female cancer.[22-25] In developed countries, widespread cervical screening has reduced both the incidence and mortality from squamous cell cervical cancer over the last 30 years. However, the incidence of, and mortality from, cervical adenocarcinoma remains largely unaffected by screening. Approximately 20% of cervical cancers are adenocarcinomas, and this is reported to be increasing in Europe and North America.[25]

In the US, the estimated incidence of cervical cancer in 2010 was 12,170 with 4220 deaths.[26] In Europe, 40% of women with cervical cancer still die from the disease within 5 years of diagnosis.[27]

Cervical cancer development involves several stages:

1) The cervical epithelium is infected with certain HPV strains
2) The HPV infection persists
3) Infection progresses to CIN
4) The precancerous CIN lesion becomes invasive.

Only the first 3 stages are reversible;[28] the fourth stage takes a median of 25–30 years from infection to develop.[29]

Because the natural history of HPV infection progression to invasive cancer is so protracted, and studies of this length are not feasible, the World Health Organization (WHO) expert panel accepted that reduced incidence of CIN2 and cervical AIS or worse was an adequate surrogate clinical endpoint in HPV vaccination trials. Notably, the WHO recommends that a disease endpoint (not antibody level) is used for efficacy.[30]

While types 6, 11, 16 and 18 can all cause abnormal results on the Papanicolaou test, i.e. dysplastic cervical lesions, types 6 and 11 are not associated with cervical cancer. However, these lesions are indistinguishable from premalignant lesions caused by types 16 and 18. The costs of treatment therefore do not differ according to the oncogenicity of the lesions.

Although spontaneous clearance of HPV, particularly in younger women, does occur, cytologically identifiable intraepithelial neoplastic lesions persist in many women. The likelihood of progression of these lesions to cancer increases with duration of HPV infection, and the estimated probability of CIN3 progressing to invasive cancer is as high as 30%,[31] while the probability of progression of CIN2 lesions is much lower.

Cross-protection - waning over time

Both HPV vaccines have demonstrated some cross-protection, although with a lower level of efficacy, with lower cross-neutralising antibody titres and an unknown duration of clinical efficacy.[32] Evidence from a long-term follow-up of a phase 2b trial of bivalent vaccine suggests that the cross-protection (HPV 31, 33, 45) recorded in the clinical trials might preferentially wane over time.[32]

Thus, current HPV vaccines mainly prevent HPV 16- and 18-related cervical cancer (~70%) and Pap screening is still recommended to protect other non-vaccine types (~30% cervical cancers) after vaccination.[32]

Commentary by Dr Karen Chan:

We are very fortunate that we know the natural history of cervical cancer so well and that we have identified a single causative agent – HPV infection. The availability of a vaccine against this infection gives us a very effective way for primary prevention. The long duration of a premalignant phase that can be easily detectable by a non-invasive test, the pap smear, together with good methods to treat such premalignant lesions (e.g. by large loop excision of the transformation zone, LLETZ) makes this disease a very good candidate for screening (i.e. secondary prevention). With adequate resources and public education, cervical cancer should theoretically be one of the few cancers that can be almost eradicated.

Non-cervical HPV-associated diseases

While mortality from HPV-related cervical cancer is much higher than HPV-related disease in men in countries with limited or no screening, the numbers of HPV-related cancers in men in developed countries approaches that of cervical cancer.[33]

The economic burden of non-cervical HPV disease in the US is estimated to be approximately US$418 million (range $160 million to $1.6 billion).[34]

Head and neck cancers

HPV-associated head and neck cancers have been increasing in incidence over the last several decades, with oropharyngeal cancers disproportionately affecting men. Whilst the most prevalent risk factor is still considered to be alcohol and tobacco use, HPV has been estimated to be associated with 20–25% of all head and neck squamous cell carcinomas (SCC).[35]

Recently in the US, biopsy samples have demonstrated HPV-associated disease in 60–80% of oropharyngeal cancers; this has increased from 40% in the previous decade.[36]

A large review of 39 cross-sectional studies, comprising 1885 cases and 2248 controls with oral carcinoma, and 956 cases and 675 controls with oral potentially malignant disorders, found a significant association between HPV-DNA detection and these diseases (ORs of 3.98 and 3.87, respectively), suggesting an important causal association between HPV infection and oral cancers.[37] A recent comprehensive meta-analysis also demonstrated a strong association between HPV and oral carcinoma – especially with HPV-16.[34] Furthermore, the study estimated the total lifetime cost for oral cancers diagnosed in 2003 was US$38.1 million. The CDC estimated that oropharyngeal cancer was the second most common HPV-related cancer with approximately 7,400 cases annually (1,500 among females and 5,900 among males).[38]

Anal HPV-associated carcinoma

Eighty-four percent of anal SCC is associated with HPV infection.[39] Anal cancer is preceded by AIN2/3, but screening for AIN in the prevention of anal cancer is uncommon.[40]

The presence of anal HPV infection has been demonstrated in 60% and 100%, respectively, of HIV-negative and HIV-positive men who have sex with men (MSM);[41] the incidence of anal HPV infection in heterosexual men is estimated to be approximately 12%.[42] Anal HPV infection is also common in women; a prospective Hawaiian study found a prevalence of 42%, of which 22% was oncogenic HPV.[43]

Anal cancers have also been increasing, with a worldwide estimated annual incidence of 100,000.[40,44] Eighty-four percent of anal carcinomas (SCC) are associated with HPV infection worldwide, and the incidence of HPV-associated anal cancer is even higher in Asia at 96%.[39] The American Cancer Society estimates for 2012 are 6230 new cases (3980 in women and 2250 in men), and about 780 deaths (480 in women and 300 in men).[45]

Commentary by Dr KK Lo

Although there are no good local data on anal and penile HPV-associated carcinoma and the number of men having sex with men is still without a good estimate, the overall non-melanoma skin cancer is of rising trend and it ranks eighth place (3.1%) as one of the 10 commonest types of cancer locally. I believe that currently rare cases of AIN2/3, anal and penile carcinoma in clinical practice will increasingly be presented to clinicians in coming decades if the current trend of sexual behaviour in the homosexual population remains unchanged. A vacuum exists around this research area locally and we should expect to see more clinical cases of HPV-associated anal and penile lesions if no prompt effective preventive measures are put in place against this high risk subpopulation group in our community. Better awareness of the availability of a gender-neutral HPV vaccine against these diseases may help to abort this trend locally.

Penile cancer

Over 26,000 new cases are diagnosed annually worldwide.[46,47] While penile cancer is rare in the US and Europe, it is an important cause of morbidity and mortality in many other countries.[48] The estimated prevalence of HPV in penile cancer was found to be 46.9% by a recent large review of 31 studies published between 1986 and 2008.[49] The distribution of HPV types was 60.23%, 13.35% and 8.13% for types 16, 18, and 6 and 11 combined, respectively.

Vulvar and vaginal cancer

Vulvar and vaginal cancers, and their premalignant lesions, are also strongly associated with HPV infection with an estimated annual incidence of 40,000; 16,000 of which are attributable to HPV infection.[46] HPV was found in 85.3% of vulvar intraepithelial neoplasia 2/3 (VIN2/3) and 40.4% of vulvar carcinomas.[39] In VIN2/3 and vulvar carcinoma, HPV-16 was found in 71.9% and 32.2%, respectively, and HPV-18 in 5% and 4.4%, respectively. HPV-6, -16 and -11 were found in 22.4%, 9.8% and 9.0%, respectively, in cases of VIN1.

While rare, vaginal cancer is associated with previous hysterectomy and a past history of vulvar or cervical neoplasia. The incidence of its precursor lesion, vaginal epithelial neoplasia (ValN) is unknown, but approximately 600 new cases of vaginal cancer are diagnosed annually.[50] HPV is associated with 100%, 90.1% and 69.9%, respectively, of ValN1, ValN2/3 and vaginal carcinomas, with HPV-16 being the most predominant type.[51]

There are no screening programmes for these cancers or precursor lesions such as those that exist for breast and cervical cancer, nor are there any preventive measures. Invasive vulvar cancer is increasingly being seen in younger women; the incidence of VIN3 has increased 4-fold in the US between 1973 and 2000.[52]

Commentary by Dr Karen Chan:

Vaginal and vulval cancers are highly distressing to the patients, particularly in younger women. Treatment for vaginal cancer often involves surgery or radiotherapy that would have a long-term negative impact on sexual function, while treatment for vulval cancer often requires disfiguring surgery, such as radical local excision or vulvectomy. Since cervical, vaginal and vulval cancers or their pre-invasive lesions may share a common aetiology – HPV infection, detection of one of these would prompt the clinician to have a higher index of suspicion for the other two. As there is currently no good screening programme for vaginal and vulval cancers, primary prevention by preventing HPV infection offers one of the most effective ways to reduce the incidence.

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis, the most common laryngeal benign neoplasm in children, is also caused by HPV types 6 and 11 and affects males and females equally.[53] In the US over 5000 new cases are reported annually, with many patients requiring multiple surgeries over many years.[53] Although histologically benign, the condition is incurable, and carries a significant burden of morbidity and death.[54] HPV vaccines would be expected to reduce the incidence of this disease.

Genital warts

Genital warts are the most frequent clinical presentation of genital infection caused by HPV infection and manifest as warty growths and dysplastic areas of cellular proliferation.[55] HPV types 6 and 11 cause over 90% of genital warts.[56] In the US, it is estimated that there are over 1 million cases of genital warts diagnosed annually,[57] and this incidence is increasing.[58] Recurrence is approximately 67% and single treatment costs were estimated to be US$436 in 2000, equating to a total annual cost of US$200 million.[12,59]

The psychosocial impact of genital warts can be severe, with more than 75% of respondents in one study reporting feelings of depression and anger, and over 60% feelings of shame.[60] They also reported a negative impact on sexual enjoyment and activity. Furthermore, dissatisfaction was expressed with the diagnosing health care provider's counselling on these issues.[60]

Commentary by Dr KK Lo

All clinicians are aware of the difficulties and morbidities linked with the clinical management of genital warts. It is sometimes a big frustration to both the clinicians and the patients when facing recurrent recalcitrant genital warts that consume much of our precious health resources. With the availability of highly safe, efficacious HPV vaccine against nearly 90% of the genotypes of the genital wart locally, it is the clinician's duty to give the most updated and accurate information to at-risk groups, males and females. The recommendation regarding HPV vaccine for those who already have a history of genital warts remains unclear while more scientific information is awaited to formulate good advice. However, for those extremely anxious patients, the use of quadrivalent HPV vaccine is probably safe and not contraindicated.

Clinical efficacy

Per-protocol population analyses of data from clinical trials have demonstrated statistically significant efficacy of Gardasil for 100% of HPV 6-, HPV 11-, HPV 16- and HPV 18-related

VIN1, ValN1, VIN2/3 and ValN2/3 (see Table 2).[61] FUTURE I and II, Phase 3 trials that evaluated the efficacy of Gardasil in preventing CIN1, CIN2/3 or AIS in women aged 16–26 years, demonstrated that the vaccine was equally efficacious against HPV disease caused by each of the four vaccine HPV types.[61]

Table 2. Summary of vaccine efficacy against HPV 6-, 11-, 16- or 18-related disease for women and men aged 16–26 years in the per-protocol populations[61]

Disease	qHPV vaccine			Placebo			Observed Efficacy
	n	*Cases*	*Rate*†	*n*	*Cases*	*Rate*†	% (95% CI)
Cervical disease							
CIN1	7629	7	0.03	7632	168	0.8	95.9 (91.3 to 98.4)
CIN2	7864	0	0	7865	71	0.3	100 (94.7 to 100)
CIN3	7864	2	<0.01	7865	63	0.3	96.8 (88.1 to 99.6)
AIS	7864	0	0	7865	7	<0.01	100 (30.9 to 100)
Anal disease (males)							
All anal diseases	194	5		208	24		77.5 (39.6 to 93.3)
AIN2/3 using case-assignment methodology	194	2			24		91.7 (44.6 to 99.8)
Vulvar disease							
VIN2/3	7900	0	0	7902	13	0.1	100 (67.2 to 100)
Vaginal disease							
ValN2/3	7900	0	0	7902	10	<0.01	100 (55.4 to 100)
Condyloma (genital warts)							
Females	7665	2	0	7669	190	0.8	99.0 (96.2 to 99.9)
Males	1397	3	0	1408	28	1.00	89.4 (65.5 to 97.9)
Penile disease							
All PIN lesions	1397	0		1408	3	0.11	100 (-141.2 to 100)

Per-protocol population: subjects who received all three vaccinations were seronegative and PCR-negative at day 1 and PCR-negative through month 7 to the appropriate vaccine HPV types, and generally did not deviate from the protocol. Case counting began after month 7.

†Cases per 100 person-years-at-risk.

AIN: Anal intraepithelial neoplasia; AIS: Adenocarcinoma *in situ*; CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; PIN: Penile intraepithelial neoplasia; ValN: Vaginal intraepithelial neoplasia; VIN: Vulvar intraepithelial neoplasia.

FUTURE III enrolled 3,817 women aged 24–45 years in a multicentre, randomised, placebo-controlled study of the efficacy, immunogenicity and safety of Gardasil, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer.[61] Results of *post hoc* analyses that assessed the impact of Gardasil on the individual components of the combined endpoint were as follows: prevention of HPV 6/11/16/18-related persistent infection (80.5%; 95% CI, 68.3 to 88.6), prevention of HPV 6/11/16/18-related CIN (any grade) (85.8%; 95% CI, 52.4 to 97.3), and prevention of HPV 6/11/16/18-related genital warts (87.6%; 95% CI, 7.3 to 99.7).

An Australian group published a study in 2011 on the efficacy of the qHPV vaccine following introduction of a national vaccination programme for all women aged 12–26 years between 2007 and 2009.[15] Using data from the Victorian Cervical Cytology Registry between 2003 and 2009, they compared the incidence of high-grade cervical abnormalities, CIN2/3, AIS, and low-grade cytological abnormalities in five age groups of women at two time periods; before (2003–2007) and after the implementation of the programme (2007–2009). In girls younger than 18 years, there was a significant decrease in the incidence of high-grade cervical abnormalities (0.38%), beginning shortly after introduction of the HPV vaccination programme (see figure 2), with a reduction from 0.85% in 2006 (the year before vaccination) to 0.22% in 2009. The decrease was progressive, and significantly different to the trend in incidence before introduction of the qHPV vaccine. This decline was not seen in older age groups.

A multinational group of researchers determined the effect of the qHPV vaccine on the risk of developing subsequent lesions following excision for CIN, diagnosis of genital warts, VIN or ValN from a pooled analysis of the FUTURE I and II studies.[62] In vaccine and placebo recipients undergoing cervical surgery, the incidence of recurrence of any HPV-related disease was 6.6 and 12.2, respectively; a reduction of 46.2% (95% CI, 22.5 to 63.2) after vaccination. The vaccine was also associated with a significant decrease (64.9%; 95% CI, 20.1 to 86.3) in the risk of incidence of any subsequent high-grade disease of the cervix. The incidence of high-grade disease in those diagnosed with genital warts, VIN, or ValN in vaccine or placebo recipients was 20.1 and 31.0, respectively; a reduction of 35.2% (95% CI, 13.8 to 51.8) for vaccine recipients.

Notably, the US CDC has recently stated that protection from HPV vaccination is expected to be long-lasting; additional (booster) doses are not currently recommended after the 3-dose regimen.[63]

Efficacy in men

qHPV vaccine was granted FDA approval in October 2009 for the prevention of genital warts in boys and men 9–26 years of age. Outcomes from the Merck Protocol 020 trial demonstrated prophylactic vaccine efficacy against HPV 6/11-related genital warts of 89.4% (see Table 2).

Efficacy of qHPV vaccine in preventing HPV infection and related diseases in men has been demonstrated in a few well-designed studies.

An international, multicentre US study randomised 4065 healthy males aged 16–26 years of age to

receive either qHPV vaccine or placebo.[64] Efficacy against external genital lesions associated with HPV types 6, 11, 16, or 18 was 90.4% (see Table 2). Within 1 month of administration of the third dose of vaccine, seroconversion was 97.4%.

Injection-site pain was significantly more frequent among subjects receiving qHPV vaccine than among those receiving placebo (57% vs 51%; p<0.001).

Safety and tolerability

One recent publication summarised safety data across 5 clinical trials, comprising 21,480 females aged 9–26 years and males aged 9–16 years.[67] Treatment-related serious adverse events occurring in vaccine and placebo groups were 0.05% and 0.02%, respectively, representing 8 study participants. There were 18 deaths (0.1% in each group) considered unrelated to study treatment. New-onset autoimmune conditions were reported equally in both groups (2.4%) and there were no differences in reported serious adverse events. Placebo recipients received one of two intramuscular preparations; one containing saline only and the other saline and aluminium. Pain was the most commonly reported injection site adverse event, most frequently occurring in the vaccine group (81% vaccine; 75% aluminium placebo; 45% saline placebo). Temperature elevations of ≥38.9°C (≥102°F) were reported by 1.5% and 1.0% of vaccine and placebo recipients, respectively.

An observational study followed 189,629 women (aged mostly 9–26 years) who had received at least one dose of qHPV vaccine between August 2006 and March 2008 for 180 days.[68] The study objectives were general safety, pregnancy outcomes, and new-onset autoimmune conditions.

Autoimmune conditions of interest were pre-specified:

1) Rheumatological, including immune thrombocytopenia, autoimmune haemolytic anaemia, systemic lupus erythematosus, rheumatoid arthritis and juvenile rheumatoid arthritis
2) Endocrine autoimmune disorders, including type 1 diabetes mellitus, Hashimoto's disease and Graves' disease
3) Neurological and ophthalmic autoimmune disorders, including multiple sclerosis, acute disseminated encephalomyelitis, other demyelinating diseases of the central nervous system, vaccine-associated demyelination, Guillain-Barre´ syndrome, neuromyelitis optica, optic neuritis and uveitis.

The study identified 1014 potential new-onset autoimmune conditions, 719 of which were considered eligible for case review. No cluster of disease-onset was found in relation to vaccine timing for any autoimmune condition. Estimated incidence rate ratios (IRR) were not significantly elevated for any autoimmune conditions except Hashimoto's disease (IRR 1.29; 95% CI, 1.08 to 1.56). Further investigation of biological plausibility and temporal relationships demonstrated no consistent evidence of a safety issue for autoimmune thyroid conditions caused by qHPV.

A post-licensure safety assessment was carried out across 7 large managed care organisations in 9–26-year-old female vaccine recipients between August 2006 and October 2009.[69] A total of 600,558 qHPV vaccine doses were administered during the study period, making it the largest population-based post-licensure study.

Pre-specified outcomes included venous thromboembolism (VTE), Guillain-Barré syndrome, stroke, syncope, seizures, allergic reactions, appendicitis and anaphylaxis. For the outcomes studied, there were no statistically significant increased risks. There was a non-statistically significant relative risk (RR) for VTE of 1.98 among females aged 9–17 years. Of the 8 vaccine recipients that had VTE, only 5 met the ICD-9 standard case definition, but were confirmed to have known risk factors for VTE; smoking, oral contraceptive use, coagulation disorders, obesity or prolonged hospitalisation. The study concluded that further investigation of the possible association between qHPV vaccine and VTE was warranted.

The CDC also conducted a post-licensure safety study that reviewed post-vaccine adverse events reported through the Vaccine Adverse Event Reporting System (VAERS) from Jun 2006 to December 2008.[70] The main conclusions were that most post-vaccine adverse events were not greater than the background rates compared with other vaccines. There was, however, disproportional reporting of syncope and VTEs. They further stated that the significance of the findings should be tempered with the potential under-reporting of a passive reporting system.

Dr Karen Chan:

The availability of the HPV vaccine makes eradication of cervical cancer a possibility. Nonetheless, there are more than 100 subtypes, with at least 10–15 high-risk subtypes for cervical cancer. Current bivalent or quadrivalent vaccines target at least two of these high-risk subtypes, which account for about 70% of all cervical cancer. To improve its protection, vaccines specifically targeting more of these high-risk subtypes are being developed. We hope that in the future, at least 80–90 % of cervical cancer can be prevented by the next generation of HPV vaccines. Public education and funding then become the next big challenges.

Dr KK Lo

Quadrivalent HPV vaccine is probably of great news to people who are at high risk of acquiring ano-genital HPV-related condition including genital warts. This is a primary prevention vaccine and would be a very effective self-protective measure for those who suspect their sexual partners of high-risk sexual behaviour. Clinical efficacy for vaccine-related prevention of genital warts is higher than that of cervical cancer as about 90% of the genotyping in local genital wart studies are attributed to types 6 and 11. The only gender-neutral HPV vaccine currently available in the market is quadrivalent HPV vaccine. Regular, updated information on its status is very important for clinicians who seek to offer best management strategies to their clients.

Take home messages

- HPV is the most commonly transmitted sexually-acquired infection
- HPV prevalence rises sharply following commencement of sexual activity
- HPV infection causes most cervical cancer
- HPV infection also causes a significant proportion of other cancers including oropharyngeal, anal and genital cancers
- HPV 6 and 11 infection causes >90% of genital warts, which while benign, still carry a significant economic and psychosocial burden, and men are disproportionately affected
- The safety, tolerability, immunogenicity and efficacy of the qHPV vaccine has been extensively studied in adolescent and adult females and males
- In women aged 16–26 years, qHPV vaccine prevented 100% of CIN2 and AIS, and 96.8% of CIN3 caused by HPV 6, 11, 16 and 18
- In women aged 24–45 years, vaccine efficacy was 80.5% in prevention of persistent infection, 85.8% in prevention of CIN1, CIN2 and CIN3 and 86.7% in prevention of genital warts caused by HPV 6, 11, 16 and 18
- Vaccine efficacy against the combined incidence of persistent infection, CIN, or external genital lesions related to vaccine HPV types in the per-protocol efficacy population was 88.7%
- Vaccine efficacy by endpoint was 89.6% for persistent infection, 94.1% for CIN (any grade), and 100% for condyloma
- Vaccine efficacy in reducing the incidence of any abnormal Pap smear related to any vaccine HPV types during follow-up was 97.4% in the per-protocol efficacy population
- In men, vaccine efficacy was 91.7% in the prevention of AIN2/3 caused by HPV 6, 11, 16 and 18
- qHPV vaccine is well tolerated and safe for administration with other vaccines

References

1. de Sanjosé S et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007;7(7):453-9.
2. Winer RL et al. Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis. 2008;197(2):279-82.
3. The Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004-2008. MMWR Morb Mortal Wkly Rep. 2012;61:258-61.
4. Burchell AN et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. Am J Epidemiol. 2006;163(6):534-43.
5. Reiter PL et al. Meta-analysis of human papillomavirus infection concordance. Cancer Epidemiol Biomarkers Prev. 2010;19(11):2916-31.
6. Wald A et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA. 2001;285(24):3100-6.
7. Padian NS et al. Heterosexual transmission of human immunodeficiency virus (HIV) in northern California: results from a ten-year study. Am J Epidemiol. 1997;146(4):350-7.
8. Muñoz N et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer. 2004;111(2):278-85.
9. Muñoz N et al. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24 Suppl 3:S3/1-10.
10. Schiffman M et al. (2005). The carcinogenicity of human papillomavirus types reflects viral evolution. Virology. 2005;337(1):76-84.
11. Cogliano V et al. Carcinogenicity of human papillomaviruses. Lancet Oncol. 2005;6(4):204.
12. Lacey CJ et al. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine. 2006;24 Suppl 3:S3/35-41.
13. US Food and Drug Administration. FDA News Release. Gardasil approved to prevent anal cancer. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237941.htm
14. Read TR et al. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect. 2011;87(7):544-7.
15. Brotherton JM et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011;377(9783):2085-92.
16. Committee on Infectious Diseases. HPV vaccine recommendations. Pediatrics. 2012;129(3):602-5.
17. The Centers for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males — Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(50):1705-8.
18. Campbell D. HPV vaccination should be extended to gay men. The Guardian. 2012;34. http://www.guardian.co.uk/society/2012/jun/12/hpv-vaccination-widen-include-gay-men
19. Ferlay J et al, GLOBOCAN 2002. Cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon: IARCPress, 2004.
20. GLOBOCAN 2008. Cancer Fact Sheet. Cervical cancer incidence and mortality worldwide in 2008. http://globocan.iarc.fr/factsheets/cancers/cervix.asp
21. Yang BH et al. Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. Int J Cancer. 2004;109(3): 418-24.
22. Arbyn M et al. The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 2009;45(15):2671-8.
23. Arbyn M et al. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer. 2009;45(15):2640-8.
24. Bray F et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev. 2005;14(3):677-86.
25. International Agency for Research on Cancer. IARC Handbooks of cancer prevention. Lyon, France, IRAC Press, 2004.
26. National Cancer Institute. Cervical Cancer. 2012. http://www.cancer.gov/cancertopics/types/cervical
27. Sant M et al. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur J Cancer. 2009;45(6):931-91.
28. Bosch FX et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-65.
29. IARC Monograph Working Group on Carcinogenesis (Coglinano V et al). In: Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F editor(s). IARC monographs on the evaluation of carcinogenic risks to humans. Vol 90: Human Papillomaviruses. Lyon: IARC Press, 2007:1-670.
30. Pagliusi SR, Teresa Aguado M. Efficacy and other milestones for human papillomavirus vaccine introduction. Vaccine. 2004;23(5):569-78.
31. McCredie MR et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9(5):425-34.
32. Poljak M. Prophylactic human papillomavirus (HPV) vaccination and primary prevention of cervical cancer: issues and challenges. Clin Microbiol Infect. June 1, 2012 - Early Online.
33. American Cancer Society. Cancer Facts & Figures 2008.
34. Hu D, Goldie SJ. The economic burden of noncervical human papillomavirus disease in the United States. Am J Obstet Gynecol. 2008;198(5):500.e1–500.e7.
35. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clin Cancer Res. 2009;15(22):6758-62.
36. Mehanna H et al. Oropharyngeal carcinoma related to human papillomavirus. BMJ. 2010;340:c1439.
37. Syrjänen S et al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis. 2011;17 Suppl 1:58-72.
38. THIS HAS BECOME #3. The Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004-2008. MMWR Morb Mortal Wkly Rep. 2012;61:258-61.
39. De Vuyst H et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009;124(7):1626-36.
40. Palefsky JM. Human papillomavirus-related disease in men: not just a women's issue. J Adolesc Health. 2010;46(4 Suppl):S12-9.
41. Chin-Hong PV et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis. 2004;190(12):2070-6.
42. Nyitray A et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. J Infect Dis. 2008;197(12):1676-84.
43. Shvetsov YB et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: The Hawaii HPV Cohort Study. Clin Infect Dis. 2009;48(5):536-46.
44. Johnson LG et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. Cancer. 2004;101(2):281-8.
45. American Cancer Society. Anal cancer. 2012. http://www.cancer.org/Cancer/AnalCancer/DetailedGuide/anal-cancer-what-is-key-statistics
46. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006;24 Suppl 3: S3/11-25.
47. Hernandez BY et al. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998-2003. Cancer. 2008;113(10 Suppl):2883-91.
48. National Cancer Institute. Penile cancer. http://www.cancer.gov/cancertopics/types/penile
49. Miralles-Guri C et al. Human papillomavirus prevalence and type distribution in penile carcinoma. J Clin Pathol. 2009;62(10):870-8.
50. The Centers for Disease Control and Prevention (CDC). HPV-associated vaginal cancer rates by race and ethnicity (2010). www.cdc.gov/cancer/hpv/statistics/vaginal.htm
51. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human papillomavirus and related cancers in United Kingdom. Summary Report. 2010. www.who.int/hpvcentre
52. Judson PL et al. (2006). Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol. 2006;107(5):1018-22.
53. Harman EM, Mosenifar Z. Recurrent respiratory papillomatosis. http://emedicine.medscape.com/article/302648-overview#showall
54. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118(7):1236-47.
55. Gross G et al. (1982). Correlation between human papillomavirus (HPV) type and histology of warts. J Invest Dermatol. 1982;78(2):160-4.
56. Wiley DJ et al. External genital warts: diagnosis, treatment, and prevention. Clin Infect Dis. 2002;35(Suppl 2):S210-24.
57. Fleischer AB Jr et al. Condylomata acuminata (genital warts): patient demographics and treating physicians. Sex Transm Dis. 2001;28(11):643-7.
58. Koshiol JE et al. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. Sex Transm Dis. 2004;31(12):748-52.
59. Insinga RP et al. The health and economic burden of genital warts in a set of private health plans in the United States. Clin Infect Dis. 2003;36(11):1397-403.
60. Clarke P et al. The psychosocial impact of human papillomavirus infection: implications for health care providers. Int J STD AIDS. 1996;7(3):197-200.
61. Goldstone SE, Vuocolo S. A prophylactic quadrivalent vaccine for the prevention of infection and disease related to HPV-6, -11, -16 and -18. Expert Rev Vaccines. 2012;11(4):395-406.
62. Joura EA et al. (2012). Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ. 2012;344:e1401.
63. The Centers for Disease Control and Prevention (CDC). Vaccine Information Statement – HPV (Human Papillomavirus) Vaccine. February 2012. www.cdc.gov/vaccines/pubs/vis/downloads/vis-hpv-gardasil.pdf
64. Giuliano AR et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med. 2011;364(5):401-11.
65. Palefsky JM et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576-85.
66. Swedish KA et al. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis. 2012;54(7):891-8.
67. Block SL et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine. Pediatr Infect Dis J. 2010;29(2):95-101.
68. Chao C et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012;271(2):193-203.
69. Gee J et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011;29(46):8279-84.
70. Slade BA et al. (2009). Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA. 2009;302(7):750-7.

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