Research Review™
EDUCATIONAL SERIES

Human Papilloma Virus Infection and Vaccination

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This publication presents an overview of human papilloma virus infection, its clinical consequences in both females and males, and important aspects of vaccination with its main focus being on head and neck cancer, vaccination for males, barriers to vaccination, and the importance of a healthcare provider recommendation in the decision to vaccinate.

Human papilloma virus (HPV) is established as a human carcinogen for cervical, penile, vulval, vaginal, anal, and oropharyngeal cancer, and causes about 5% of cancers globally.[1]

HPV infection and HPV genotypes

HPV is a highly transmissible virus.[2] Its transmission probability has been estimated to be 40% per unprotected sexual act, which is several-fold higher than that for other sexually transmitted viral infections such as human immunodeficiency virus or herpes simplex virus.[3] Not surprisingly, HPV is the most common sexually transmitted virus worldwide.

In terms of its clinical consequences, HPV infection is the cause of nearly all cervical cancers and high proportions of other anogenital and head and neck cancers, including anal (90%), vaginal (70%), penile (50%), vulvar (40%), and oropharyngeal (13–72%) cancers.[4]

The high-risk HPV16 and HPV18 genotypes cause 70% of cervical cancers and 80–90% of HPV-related cancers at other sites.[5,6] The other high-risk genotypes HPV45, HPV31, HPV33, HPV52, HPV58, and HPV35 are responsible for an additional 20% of cervical cancer cases. The low-risk genotypes HPV6 and HPV11 account for 90% of anogenital warts and 90% of respiratory papillomatosis, which although rare can be life-threatening.[7]

The worldwide prevalence of HPV infection in women without cervical abnormalities is 11–12%.[1] In women with cervical pathology, its prevalence increases in proportion to lesion severity reaching approximately 90% in women with grade 3 cervical intraepithelial neoplasia (CIN) and invasive cancer. In general, the HPV genotypes that cause cervical cancer are the same globally,[5] and there is no evidence of an ethnic or genetic predisposition to cervical cancer.[8] HPV infection was detected in 88.5% of NZ women with cervical cancer, with high-risk HPV types detected in 87% of women.[9] The most commonly detected high-risk HPV genotypes were HPV16 (51%), HPV18 (21%), followed by HPV31 (4%), HPV45 (3%), and HPV52 (3%).

The epidemiology of penile HPV is not well understood;[10] however, in a US study, the 12-month cumulative risk of acquiring a new HPV infection in a cohort of heterosexual males was 29% suggesting that HPV infection in men is common. Anal HPV infection is also common in MSM.[10,11]

HPV infection and head and neck cancers

There has been a rise in the incidence of head and neck cancers over the past two decades, which has been driven primarily by HPV-related oropharyngeal cancers.[12] In this context, it is interesting that the risk factors for head and neck cancer are similar to those for cervical cancer, i.e. number of sexual partners, younger age at first sexual intercourse, practice of oral sex, history of genital warts, and younger age.[13]

Three meta-analyses produced estimates of the prevalence of HPV in head and neck cancers of 31.5% (international), 40% (Europe), and 36% (Asia-pacific),[14-16] indicating that the contribution of HPV to head and neck cancers is considerable. Although this contribution is highly heterogenous by tumour site, the meta-analyses confirm an important role for HPV in oropharyngeal cancer. Estimates of HPV in oropharyngeal tumours provided by two of the meta-analyses were 41% and 46%.[14,15] However, the contribution may in fact be much higher. Two recent primary studies have produced estimates of 71% and 75% for HPV in oropharyngeal cancer.[17,18]

As the HPV serotypes implicated in head and neck cancers are the same as those included in the HPV vaccine, HPV vaccination has the potential to help prevent head and neck cancers. HPV vaccination is likely to be most effective in preventing oropharyngeal cancers given that oropharyngeal cancers are more strongly associated with HPV infection than are other types of head and neck cancer.[12]

The probability of seroconversion from an HPV infection appears to vary depending on which mucosal epithelium is infected.[19] Cervicogenital infections are associated with high rates of seroconversion in women,

and this systemic immunity may provide defence against oral infection in women. In contrast, there is evidence that men have low seroconversion rates following genital HPV infection.[20,21] Hence, men may be more susceptible than women to oral HPV infection resulting in a higher oral prevalence.[19] A recent analysis of US HPV epidemiology data (for the period 2009–2012) demonstrated a 4.4-fold higher rate of oral HPV infection in men versus women.[22] Data from the same analysis suggest that the higher prevalence of oral HPV infection in men than in women may be due, in part, to men having more sexual partners, including a higher number of oral sex partners, and thus greater opportunity for oral HPV exposure. It is also possible that HPV transmission may be more efficient when oral sex is performed on female genitalia than on male genitalia.[23]

HPV vaccination for males

Since the introduction of a government-funded national HPV vaccination programme for females in 2007, Australia has witnessed a substantial decline in the prevalence of HPV,[24] which has translated into a dramatic reduction in rates of anogenital warts and, importantly, cervical abnormalities and cancer.[25-27]

However, HPV infection in males is also associated with serious clinical outcomes, including penile, anal, and oropharyngeal cancers. In the US, the rate of HPV-related cancers diagnosed annually (during the period 2004–2008) was 8 per 100,000 among males (versus 13 per 100,000 in females).[28] Notably, the past decade has witnessed an unexpected increase in oropharyngeal cancer found to be associated with HPV, primarily in white males aged 40–55 years with limited exposure to alcohol and tobacco.[29] An analysis of NZ cancer registry data (for the period 1981–2010) demonstrated a 4-fold higher rate of oropharyngeal cancers in men (primarily in those aged ≥40 years) than in women.[30]

Countries that have not included males in national HPV vaccination programmes have done so on the premise that female-only vaccination programmes will protect males via herd immunity and that men who have sex with men (MSM) will be protected via targeted vaccination programmes.[12] However, even if herd protection is achieved with a high rate of female vaccination uptake, men will not be protected if they relocate outside the herd into populations where females are not protected. A targeted vaccination programme for MSM may not protect the majority of MSM. Most MSM are likely to have had multiple sexual partners before attending a sexual health clinic (where they would be offered the vaccination) and MSM who do not disclose their sexual activity to a healthcare professional will never be offered vaccination.

Although the most common cause of mortality related to HPV infection is cervical cancer, male HPV infection is also an important concern with respect to the risk of transmission to women in addition to the associated disease burden in men.[10] Indeed, two of the main risk factors for genital HPV infection in females are the acquisition of new male partners and having non-monogamous male partners.[31]

Moreover, even though the probability of acquiring a new genital infection is similar in males and females, males demonstrate a lower immune response to HPV infection.[32] Compared with the pattern of HPV infection in women, which peaks in the late adolescence to early adulthood period and subsequently declines, HPV prevalence in men appears to peak at older ages and remains more or less constant with increasing age, which suggests either persistent HPV infection or a higher rate of re-infection.[33]

Low seroconversion rates following HPV infection have been demonstrated in men,[20,21] which leaves them vulnerable to recurrent infections and emphasises the need for HPV vaccination in men to provide immune protection against new HPV infections and subsequent HPV-related diseases. There is also a strong argument for vaccinating males earlier rather than later in life. Early acquisition of anogenital HPV infection has been demonstrated in teenage MSM (aged 16–20 years).[34]

HPV vaccine efficacy and safety

HPV vaccine effectiveness in real-world settings is generally consistent with vaccine efficacy results in clinical trials.[4] In terms of the global effect of HPV vaccination on HPV infection and disease, maximal reductions of up to approximately 90% for HPV 6/11/16/18 infection have been reported in observational studies, including reductions of up to approximately 90% for genital warts, 45% for low-grade cytological cervical abnormalities, and 85% for high-grade histologically-proven cervical abnormalities. Within the first 5 years of its implementation, Australia's vaccination programme has produced reductions of 34% in low-grade and 47% in high-grade cervical cytological abnormalities in vaccinated cohorts of females aged 12–26 years at the start of the programme compared with unvaccinated females in the state of Victoria (**Figure 1**).

These 'real world' data are based on the 4-valent (HPV 6/11/16/18 genotypes) vaccine (4vHPV). However, a 9-valent (HPV 6/11/16/18/31/33/45/52/58) vaccine (9vHPV) has recently been launched and included in some universal vaccination programmes. In three efficacy and safety clinical trials, the 9vHPV vaccine has been demonstrated to be highly immunogenic and generally well tolerated in girls and boys (aged 9–15 years), adolescent and young adult females (aged 12–26 years), and young adult men (aged 16–26 years).[35-37] In these trials, discontinuations and vaccine-related serious adverse events were rare and injection-site adverse events were mostly of mild or moderate severity.

The 4vHPV vaccine has also been demonstrated to have a favourable safety profile observed over a decade of use.[38] Syncope, and possibly skin infections, were associated with vaccination in the post-marketing setting. Compared with background rates, there was no increase in the incidence of serious adverse events, such as adverse pregnancy outcomes, autoimmune diseases, anaphylaxis, venous thromboembolism, and stroke.

Vaccine safety represents one of the main concerns associated with the lack of acceptance of HPV vaccination.[39] HPV vaccines have a proven safety record, with a safety profile that is at least as good as any other childhood vaccine.[36,40-43]

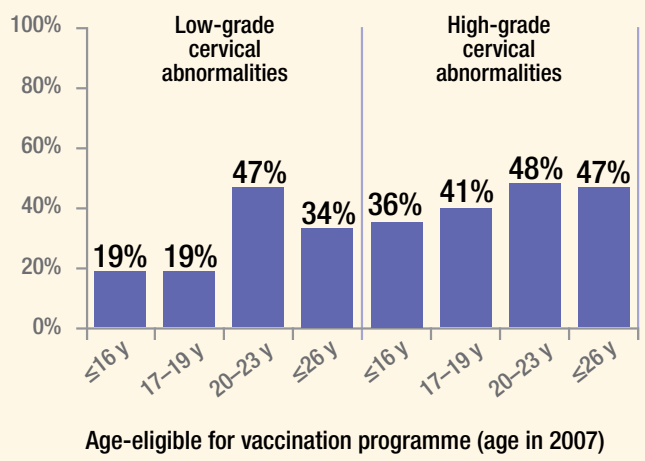

Figure 1. Reduction in cervical abnormalities since the introduction of Australia's HPV vaccination programme (4vHPV) in 2007.[4] A population-based analysis of percentage reduction in cervical abnormalities among vaccinated (≥1 dose) compared with contemporaneous unvaccinated screened females in Victoria.

Barriers to HPV vaccination

A vaccination-facilitated reduction in the incidence of HPV-related cancers will only be achieved if the offer of HPV vaccination is accepted. Globally, there is wide variation in the acceptance of the HPV vaccine. It tends to be higher in countries with school-based programmes, such as Australia (coverage rate is 72% for full course), and lower in countries that use clinic-based delivery, such as the US (32% for full course).[44,45] In NZ, which has a school-based programme, the coverage rate is 54% for the full-course.[44,46]

Cost as a barrier to vaccination is overcome through a national vaccination programme offering the HPV vaccine free at the point of delivery. Overcoming psychosocial barriers to vaccination is a more challenging proposition.

In the context of vaccination programmes targeting adolescent girls and boys, parental perceptions of the HPV vaccine are the primary determinants in vaccine uptake. A recent Australian survey reported that HPV vaccination of adolescent girls was significantly associated with their parents being the main decision maker for vaccination.[47] Parental-related psychosocial barriers to HPV vaccination include:[47-52]

- Concern that a complex (i.e. multivalent) vaccine will overload their child's immune system.
- Uncertainty about the duration of protection afforded by the vaccine. Parents who do not expect their child to be sexually active in the near future may delay vaccination to maximise the duration of protection.
- Concern about vaccine safety, especially long-term side effects. Parents who do not expect their child to be sexually active in the near future may delay vaccination until more evidence about safety becomes available.
- Perceptions of their child's sexual readiness or susceptibility to HPV infection (i.e. low perceived risk of HPV infection).
- Concerns about the effect of the vaccine on their child's sexual behaviour.
- Perceptions of a lack of direct benefit for boys.
- Reluctance to talk about sexual health with their children.
- Cultural or religious beliefs about sexual activity resulting in parents not allowing their child to be vaccinated.
- Lack of a vaccine recommendation from their physician.

Barriers to HPV vaccination also exist within the healthcare setting. Judgements by healthcare professionals about whether to recommend the vaccine may restrict a young woman's access to the vaccine irrespective of her own beliefs and preferences.[53] It is also possible that some physicians perceive discussions about HPV vaccination and sexuality to be burdensome, requiring more time and engendering less parental support than other adolescent vaccines and for this reason may recommend HPV vaccine less strongly.[54,55] Physician attitudes towards HPV vaccination and MSM may also be a factor. A lack of awareness of HPV, especially as a cause of genital warts and male cancers, has been identified as reason for poor vaccine uptake among MSM.[56]

HPV VACCINATION: TALKING TO BOYS
– remarks from Dr Sue Bagshaw

The most important point health professionals need to bear in mind when talking to young people is to be able to gauge their stage of cognitive development. As the brain develops there is a second surge at around puberty and progress continues until on average 25 years of age when the prefrontal cortex is activated more than about 10–20% of the time. Boys start puberty later than girls so their brain development also starts and finishes later.

During adolescence thinking is usually not logical, but based on emotions. The ability to future think starts to extend, thinking becomes more complex, and concrete thinking gradually becomes more abstract. These abilities are decreased when a person is stressed and increase when they feel connected, peaceful, and less stressed.

How is this knowledge applied when talking to 11-year-old boys about having the HPV vaccination? First get some context. This is an ideal situation to ask the Headss questions (ref Youth Health Resource Manual 20 www.collaborative.org.nz or Goldenring). The content of the answers is important but the two most important uses are: to engage the young person to show them you are interested in them and to hear how they answer the questions to gauge their stage of cognitive development. It is usually safe to assume they are concrete thinkers, all about me, all about now, and keep it simple until proved otherwise. Always start from an emotional base before introducing logical thinking. Many 11-year-old boys will not have started the hormonal changes of puberty, and most of them will not have thought about sex.

A good approach may be: "This is a vaccination to protect you against being infected with a virus called HPV. This virus causes warts. There are masses of different kinds of warts, caused by all the different kinds of wart virus. Some cause the ones that people get on their feet, like verrucas, some on fingers, and some affect areas in the mouth, and even your penis. Most of them aren't a problem but some can cause cancer. It's really good not to get infected with this virus so having the vaccination is a really important thing to do."

Drawing diagrams or showing pictures of different kinds of warts is an excellent thing to do and then ask for questions. If they ask if you think it is a good idea go over the top in your enthusiasm for it.

Dr Sue Bagshaw MB BS FRACShM FRNZCGP CNZM

Dr Sue Bagshaw is a legend in the field of youth health. She is the Senior Medical Officer at Christchurch's 298 Youth Health Centre, Director of the Collaborative Trust, a Senior Lecturer in Paediatrics at Otago University, and an internationally acknowledged expert in youth health.

Approaches to increase HPV vaccine uptake

A 2014 systematic review found only weak evidence for the widespread implementation of educational initiatives targeting parents and adolescents to increase vaccine uptake.[57] This finding suggests that non-educational approaches or educational approaches that are more targeted/tailored are needed to help to increase HPV vaccination.

Healthcare professional recommendation

One of the most important factors in parents' decision to vaccinate their children is recommendation by a healthcare professional.[49] In addition, having a healthcare provider as a source of factual information and positive vaccine attitudes has been cited as being associated with higher vaccine uptake among teenage girls.[58] In a recent Australian survey, 61% of unvaccinated participants (adolescent girls and young adult women) reported that a recommendation from a GP would increase HPV vaccine acceptance.[47] According to a US study, young adult women and men who received a recommendation from a physician or healthcare provider were >35-times more likely to receive at least one dose of HPV vaccine relative to those who did not receive a recommendation.[59] Provider recommendation is also associated with increased vaccine acceptability among MSM;[60,61] with MSM who received a recommendation being >40-times more likely to have been vaccinated then MSM without a recommendation.[61]

In targeting adolescent girls and boys and young women for vaccination, social norms and values related to sexual activity as well as trust in vaccination programmes and healthcare providers are key factors linked to vaccine uptake.[53,58] Issues of trust require the provision of clear, accessible, and sometimes culturally appropriate, information about HPV vaccination.[53] Central to this conversation should be an evidence-based discussion of the risks of HPV infection and related cancers against the potential side effects of the HPV vaccine (**Table 1**). Dialogue-based interventions may be the most effective strategy for addressing vaccine hesitancy.[62] The following approaches have been suggested for addressing parental anxieties or assumptions about HPV vaccination:[48]

- Concerns about vaccine safety and efficacy can be clarified by drawing on the evidence base and explaining the extensive testing has been done (pre- and post-marketing surveillance data demonstrating that HPV vaccines are safe) and why efficacy is likely to be sustained.
- Preferences to delay vaccination to maximise the time that their child is protected can be challenged by explaining that the vaccine produces a better immune response, and therefore protection from HPV invention, if delivered at a younger age.

When making the recommendation for HPV vaccination, physicians who take a presumptive approach (i.e. presupposing that a parent will vaccinate their child) or direct a parent to have their child vaccinated will be more successful in ensuring that child is vaccinated than those who take a participatory approach or merely inform a parent of the availability of the vaccine.[63,64]

Risks from HPV infection	Risks from CIN 2–3	Side effects of HPV vaccine
• Infection of partner • Development of persistent infection • Genital warts • Cervical dysplasia (CIN1–3) • Cervical cancer • Other anogenital cancers: vulva, vagina, cervix, penis, anus • Oropharyngeal cancers: mouth and throat • Recurrent respiratory papillomatosis	• Invasive treatment for precancerous lesions • Some treatments increase the risk of premature birth in subsequent pregnancies • Cervical cancer	*Common side effects:* • Mild pain, erythema, and swelling around the infection site • Syncope (as a response to being injected mainly in adolescent girls). *Uncommon side effects:* • Severe pain and swelling at infection site *Rare/very serious side effects:* • Anaphylaxis

Table 1. Summary of disease risks associated with HPV infection and moderate to severe cervical intraepithelial neoplasia (CIN) relative to HPV vaccine side effects.[65]

Recall/reminder systems

Substantial evidence exists that patient reminder and patient recall systems in primary care settings are effective in improving vaccination uptake.[66] There is increasing data indicating that patient reminder/recall systems help to improve HPV vaccination rates.[62,67,68] This is especially true for dose completion. Most failure to complete the HPV vaccine series occurs because providers expected parents to make appointments while parents expected to be reminded.[69] Recall and reminder strategies typically include telephone calls, mailed letters, and/or text messages.

Social media initiatives

Vaccination attitudes are informed and influenced not just by healthcare professionals but also by other information vehicles, including online and social media sources.[70,71] Indeed, social networks and the internet play a major role in disseminating information about vaccination and modifying the vaccination decision-making process.[71,72] Although the internet may elevate controversial issues related to vaccination, and thereby affect public opinion, it also provides new tools by which to monitor and tackle vaccine hesitancy.[72,73] As a starting point, analysis of health-related debates and sentiment on social media may help to inform the targeting and design of strategies to improve health communication and facilitate vaccine acceptance.[71,73] For example, social media could be used to track the peoples' perceptions of vaccination in real time, thereby enabling healthcare professionals to proactively engage citizens and to plan timely communication strategies.[73]

EXPERT COMMENTARY – JULIAN WHITE

The increasing rate of HPV-associated oropharyngeal cancer among men has been described as an epidemic, and has been recognised in many countries including New Zealand and Australia. This has introduced a new demographic profile to the practice of head and neck cancer. Head and neck cancers have traditionally been seen mainly in elderly male smokers. The incidence of most of these cancers has declined in recent decades along with smoking.[74] Patients with HPV-related oropharyngeal cancers tend still to be male, but more often are younger non-smokers, with fewer comorbidities.[75]

HPV-associated oropharyngeal cancers have been found to be more responsive to treatment with all modalities, compared with non-HPV-related oropharyngeal cancers. Among patients with HPV-related disease, smoking has an adverse effect on survival. Five-year overall survival for HPV-related cancer in non-smokers is approximately 90%, compared with 70% for smokers with HPV-related disease and 45% for non-HPV-related disease.[76] These survival differences are likely related to both the biological response of the cancer to treatment and the effect of increased comorbidities among older smokers. The concept of treatment de-intensification in patients with HPV-related disease is currently being explored with several ongoing controlled trials involving surgery, radiation therapy and chemotherapy, with the aim being to reduce acute and long-term toxicity of treatment, while maintaining the excellent oncological outcomes currently being seen among these patients with standard treatments.[77]

The incidence of invasive cervical cancer has declined in recent decades, largely as a result of effective screening programmes. In contrast, no reliable screening test currently exists for oropharyngeal carcinoma. It is thought that carcinoma originates in the epithelium of the posterior third of the tongue and the crypts of the palatine tonsils, areas that are relatively inaccessible to visual inspection and sampling for cytological analysis. Serological tests, for example antibodies to the HPV E6 oncoprotein, hold some promise but need to be developed further.[78] This absence of an effective screening test makes primary prevention, particularly with immunisation, especially relevant. The importance of immunising males is increasingly recognised by health funding bodies, and it is commendable that authorities in Australia and, from 1 January 2017, New Zealand have agreed to fund the vaccination of boys and young men in addition to females. The challenge now for health practitioners and associated bodies is to promote an increased uptake of HPV vaccines in both genders.

EXPERT COMMENTARY – MIN LO

It is very exciting that NZ will be commencing a new HPV vaccination programme in 2017 with the nine-valent HPV vaccine Gardasil 9, to both boys and girls, aged 9–26 years (inclusive). Those aged 9–14 years will get a two-dose schedule and those aged 15–26 years will receive a three–dose schedule. This comprehensive gender-neutral programme with the 9-valent HPV vaccine puts NZ ahead of every country in the world. NZ currently has one of the lowest rates of cervical cancer in the world and one of the best screening programmes. Together with the new vaccination programme, we will aim to be a world model of success in preventing HPV disease.

Gardasil 9 will be funded for 9- to 26-year-olds and licensed (not funded) up to (and including) age 45 years for females. Most older adolescents and adults receiving an HPV vaccine will already be sexually active and have been previously exposed to HPV infection. So, is the vaccine beneficial to people who have already been exposed to HPV? The short answer is "yes, there is some benefit to vaccinate people who may have been exposed to HPV and the decision should be made on an individual basis".

Points to consider are:

- Maximal benefit of HPV immunization is expected when individuals are vaccinated prior to onset of sexual activity or as soon as possible after sexual debut.
- All vaccines are more effective if you are younger rather than older. The 'menopause' of the immune system is around 11 years and it is all downhill from there. This is one of the main reasons for providing HPV vaccination to a young age group.
- Immune response to a natural HPV infection is poor. Seroconversion following natural infection is poor and levels of antibodies are much lower than the levels of antibodies achieved following vaccination. It is therefore possible for reinfection with the same HPV type to occur. In theory, this is one good reason for adults to get vaccinated.
- New HPV infections can occur throughout adult life; for any given person, there will be a benefit depending on their individual circumstances and HPV vaccination will provide protection against new HPV infections that they have not yet been exposed to.
- MSM have a high risk of HPV disease
- Vaccination is predominantly about protecting against future infections.
- Age is a general proxy for sexual exposure and therefore HPV exposure. I know this is a gross generalisation as some adults have been in long-term monogamous relationships with few life-time partners. However, it is fair to say that HPV vaccination becomes less effective the older you are or the more sexual partners you have had.
- If you want some figures about "how effective" HPV vaccination is in the adult population, then data comes from two sources. The very large vaccine trials all include an 'intention-to-treat (ITT) group', which is the population in the trial who are HPV positive at enrolment. Results from the ITT groups are consistently around 30–44% efficacy against all HPV-related endpoints.[79-82] Data also come from countries that are monitoring disease outcomes. The figures from Australia, Sweden, Denmark, USA, and Canada show that the risk reduction in cervical abnormalities depends on your age at time of vaccination.[4] Those vaccinated at a younger age had declines in CIN2+ and CIN3+ of about 40–70% compared to the unvaccinated cohorts while those older than 20 years showed a decline of about 20%.
- Does vaccination of persons already infected alter the trajectory of natural history of the virus, i.e. does vaccination result in faster clearance (or undetectability), reduce persistence or prevent recurrence of previous disease? The data to answer these questions conclusively is not yet available.
- While it is impossible for the GP to give patients older than 26 years an exact assessment of their potential for benefit, it is important to remember that many groups benefit from HPV vaccination and not to limit our conversations. NZ has a world-leading funded HPV vaccination programme and we should make the most of this opportunity to protect the population.

TAKE-HOME MESSAGES:

- The HPV vaccine has been highly effective in reducing the incidence of external warts and cervical abnormalities since its introduction.
- Evidence is now emerging that HPV vaccination prevents cervical cancer.
- The prevalence of head and neck cancer, oropharyngeal cancer in particular, is increasing and the HPV vaccine will likely help to prevent against these cancers as well.
- Healthcare professionals need to engage and inform parents and teenage patients to help promote broader adoption of HPV vaccination.
- Physician recommendations and patient reminder/recall systems are likely to increase HPV vaccination rates.
- Vaccination is more likely to occur if it is physician directed.
- Males remain susceptible to HPV infections throughout their lifespan, highlighting the need for vaccination of boys.
- There is a strong rationale for vaccinating boys, similar to girls, at an early age when they have had limited or no prior sexual activity.
- The benefits of HPV vaccination with regard to cancer prevention outweigh the risks and potential side effects related to administration of the vaccine.
- HPV vaccination is safe and effective for those already sexually active.
- There is a diminishing return with increasing age. However, if a patient wishes to be vaccinated there is considerable potential for individual benefit.

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