Our knowledge and understanding of the human papillomavirus and its role in cervical cancer and other ano-genital disease and infections has grown rapidly over the last 30 years. That the cause of such common and significant conditions should be identified – and a vaccine developed to prevent them – in such a relatively short space of time is remarkable. However, this has meant a steep ‘learning curve’, and educating wider medical audiences – and the public – about HPV and vaccination, has presented a great challenge. Not surprisingly, with the amount of information being disseminated from various sources, the potential for conflicting messages is high.

Since the vaccines became widely available, we have been concerned about some of the articles and reports we have seen and heard, and it is clear that there is much confusion and misunderstanding about some areas of HPV and vaccination. The purpose of this booklet is to dispel and clarify a few of these ‘myths and misconceptions’. We have also asked colleagues, whom we consider experts in the field, to contribute their knowledge and opinions and we are very grateful for their help in explaining these important points.

It would be a tragedy if – through misunderstandings or ungrounded fears – a young girl or woman was deprived of the opportunity to be protected against HPV and consequently developed cancer. This booklet aims to reduce the possibility of that happening.
Misconception about HPV vaccination and the need for subsequent cervical screening

Although vaccination against cervical cancer is highly protective, some people – especially younger women – appear to think they will have virtually total protection after vaccination, and that attending for cervical screening will no longer be necessary.

All women who have been vaccinated must have on-going cervical screening, either by conventional cytology or HPV testing, because:

- Vaccinated women may still be at risk from other HPV types not covered by the vaccines. The current vaccines aim to protect HPV-naïve women from infection with HPV 16 and 18 and, in so doing, will reduce the likelihood of those women developing cervical cancer by ~70%.

- Those women currently infected with either HPV 16 or 18 prior to vaccination will not be protected and will be still at risk from infection by other non-vaccine HPV types.

- The duration of protection given by the vaccines is not yet known, although expert opinion is that HPV vaccination will protect women for many years.

EXPERT OPINION

Chris JLM Meijer MD PhD
Chairman and Director, Department of Pathology, VUMC (Vrije Universiteit Medical Centre), Amsterdam, The Netherlands

“Health authorities, care providers and women themselves must understand that cervical screening and vaccination are complementary strategies. Women must continue with their regular screening.

A vaccination programme will not have an observable effect on cancer incidence for at least 20 years. The introduction of vaccination will reduce the burden of precursor lesions requiring follow-up and treatment in vaccinated cohorts. This may allow the commencement of screening to be delayed and may increase the screening interval. Moreover, vaccination will stimulate a change of the screening tool from cytology to HPV testing with triage by cytology with genotyping, as this will allow the actual infecting virus – and its attendant risk – to be defined. It may be expected that, in the near future, triage of HPV-positive women will be replaced by molecular disease markers.”


Misconception about cross-protection – protection against HPV types that are not represented in the vaccines

As only two of the fifteen HPV types known to cause cervical cancer – HPV 16 and 18 – are directly targeted by the vaccines, it has been assumed that vaccinated women may not have any protection against other oncogenic HPV types.

This may not be strictly true. Although, in principle, protection is type-specific, there is some evidence that cross-protection (protection against disease due to HPV types not directly targeted by the vaccine) could occur:

- Because certain HPV types are closely related phylogenetically, a degree of cross-reactivity may exist between vaccine and non-vaccine types.

- Studies have shown that immunisation with the quadrivalent vaccine (HPV types 6, 11, 16 & 18) can generate cross-reactive and cross-neutralising antibodies to HPV 45 and 31. A trial of the bivalent vaccine (HPV types 16 & 18) showed a reduction in incident infections due to these non-vaccine types.

- More recently, studies with the quadrivalent vaccine have also shown a reduction in the incidence of high-grade cervical disease (CIN 2/3) due to a number of non-vaccine types.

EXPERT OPINION

“Whilst these findings are promising, for cross protection to be truly demonstrated, a vaccine needs to show that it can prevent disease. Even if some level of cross-protection against non-vaccine types existed, the extra reduction in incidence of invasive cervical cancer in vaccinated women in western Europe would be modest.”

Stanley M, Lowy DR, Fraser I. Prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006; 24 Suppl. 3: S3/106–S3/113

Paavonen J et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like particle vaccine against infection with HPV type 16 and 18 in young women; an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007; 369: 2161–2170

Misconception about HPV type-replacement following vaccination

There is concern that, if HPV types 16 and 18 (the high-risk, oncogenic genotypes contained in the HPV vaccines) are eliminated through vaccination, the prevalence of other oncogenic types may expand to fill the gap, possibly leading to an increase in the prevalence of cervical cancer.

There is, as yet, no evidence suggesting that there will be replacement of the HPV types contained in the vaccines by other oncogenic types

- Papilloma viruses are genetically-stable DNA viruses that have co-evolved with their hosts over many millions of years. From what we understand about these viruses and their behaviour, the likelihood that immune selection would result in new variants of HPV is low.

"If elimination of some HPV types were to result in an increase in others, the different HPV types would need to be competing with each other. However, data from cell biological and epidemiological studies have not found any evidence to indicate that the presence of pre-existing HPV infection increases the risk of other HPV genotypes: this implies that competition is unlikely to exist.

On balance, the available evidence would indicate that HPV infections are independent of each other and suggests that genotype replacement is improbable. However, only in large long-term studies and post-vaccine surveillance will this question be answered definitively."

Stanley M, Lowy DR, Fraser I. Prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006; 24 Suppl. 3: S3/106–S3/113


Misconception that HPV vaccines will not provide long-term protection

There is concern that – as efficacy of the HPV vaccines has, so far, only been shown for around six years – it is not known for how much longer the vaccines will remain effective. Will there be a need for vaccinated women to be given booster doses in the future?

At the start of any vaccination programme, the duration of protection cannot be predicted. However, our knowledge of the way the HPV virus behaves – and extensive experience with other vaccines – lead us to believe that the HPV vaccines will be effective in the long-term

- The evidence at present suggests that HPV vaccines will provide long-term protection, but no one can say exactly how long this will be. We can be reassured that the vaccines have shown sustained efficacy against disease over time, and this efficacy is not going to suddenly disappear

- The demonstration of immune memory – whereby the immune response to pathogens that have been previously encountered is greatly accelerated – provides reassurance that vaccines will remain effective in the long term

EXPERT OPINION

Margaret A Stanley OBE PhD FMedSci
Professor of Epithelial Biology, Department of Pathology, University of Cambridge, UK

“What matters for long-term duration of protection – as the hepatitis B vaccine experience illustrates – is immune memory. The quadrivalent HPV vaccine generates a strong immune memory – a hallmark of long-term protection.”

Stanley M, Lowy DR, Fraser I. Prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006; 24 Suppl. 3: S3/106–S3/113


Harper DM et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against HPV type 16 and 18; follow up from a randomised control trial. Lancet 2008; 367: 1247–1255

Misconception about measuring the immune response to HPV vaccination

There has been confusing information about the value of measuring antibodies after HPV vaccination. If immune response is measured, what does this tell us – and how should it be done? Is it of any practical or clinical value?

The measurement of antibodies following HPV vaccination has only showed that there was an immune response, not how effective it was

- HPV vaccine manufacturers needed to show the regulatory authorities in the clinical trials that their vaccines could elicit an immune response (i.e. they were immunogenic) and, after the completion of the vaccination schedules, the vaccines did indeed regularly induce antibodies
- However, measuring immune responses to HPV vaccines has not told us what level of efficacy we should expect nor for how long this efficacy should last
- There is no standard way of measuring antibodies to HPV at present. Comparisons of the immune responses to HPV vaccines can be very subjective, are assay-dependent and, so far, are of no value to the clinician

EXPERT OPINION

Joakim Dillner MD
Professor of Virology, in particular Molecular Epidemiology, Department of Laboratory Medicine, Division of Medical Microbiology, Lund University, Malmö, Sweden

“The use of non-standardised HPV serological assays leads to confusion, over-interpretation of data and impairs the progress in HPV vaccinology. Establishing reliable and internationally-comparable assays, enabling meaningful definition of the correlates of protection, should be a high priority for future research. Until standardised tests and units that correlate with efficacy and/or predict duration of efficacy are developed, measurements of vaccine-induced antibody levels will be of limited value.”

Stanley M, Lowy DR, Fraser I. Prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006; 24 Suppl. 3: S3/106–S3/113
Fraser I. Correlating immunity with protection from HPV infection. Int J Infect Dis. 2007; 11 Suppl. 2: S10–S16
Misconception that the HPV vaccine only protects against one type of cancer

It is of concern that most women – and many health professionals – may not realise that HPV vaccination can protect, not only against cervical cancer, but also against other genital cancers.

The HPV vaccines offer protection against all cancers caused by HPV 16 & 18. These include most vulval and vaginal cancers. Wider knowledge of this significant, additional benefit could act as further encouragement for wider uptake of HPV vaccination.

- A small – but significant – number of women develop vulval and vaginal cancer: these account for about 6% of all gynaecological cancers.
- HPV vaccination protects against most cases of their well-defined, pre-cancerous stages – vulval intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).
- Women treated for pre-cancerous cervical lesions (CIN) also have a high risk of other ano-genital cancers developing, up to 10–20 years after their CIN was initially detected.
- Currently, there are no screening programmes for the detection of VIN or VAIN, so any vaccination programme aimed at eradicating HPV infection will have a major and beneficial impact on VIN and VAIN and the frequency of the associated malignancies.
- The efficacy of HPV vaccination against high-grade VAIN and VIN is almost 100% in women not previously exposed to the HPV types in the vaccines.

“VIN is increasingly a difficult clinical problem, in that it has a high recurrence rate after surgical treatment which can – in many cases – be extensive, mutilating and debilitating. Its link with cigarette smoking, which is prevalent in young women, means that its prevention in the form of vaccination must be an imperative. VIN is a disease of the young, sexually-active woman and it is a duty of her medical carers to protect her from developing this disease.”


PD Dr. med. Monika Hampl
Department of Obstetrics and Gynaecology, University of Düsseldorf, Germany
Misconception about vaccinating sexually-active women

One of the biggest myths – and the cause of much anguish – is the notion that young, sexually-active women cannot benefit from HPV vaccination because they may have had prior HPV infection.

This notion is wrong. From the original clinical trials, and subsequent post-marketing surveillance of the vaccines – of which millions of doses have been given – the evidence is emerging that young, sexually-active women can benefit from HPV vaccination.

- A sexually-active woman – even one who already has a CIN2/3 lesion – may well benefit from vaccination, as the HPV infection causing her lesion may have been caused by a single HPV type, such as type 18. If she had been given the quadrivalent vaccine, then she would still benefit from protection from types 6, 11 and 16 – types to which she has not yet been exposed.

- The vast majority of sexually-active young women in large clinical trials were either HPV-naïve, or harboured only one HPV type, and so would benefit from HPV vaccination.

- Overall, between 68–84% were negative to all four HPV types in the quadrivalent vaccine. Up to a third were positive for only one HPV vaccine type, and only 2–6% for two types. Only 1 in 1000 had evidence of all four types and hence would not benefit from vaccination.

“As the vaccine is prophylactic rather than therapeutic, the populations best targeted for the vaccine are young adolescents prior to sexual debut. However, even those with prior exposure to any – or one – of the HPV types in the vaccine can still benefit from vaccination against those HPV types to which they have not been exposed previously.

Recent evidence suggests that women exposed to vaccine HPV types and who have cleared their infection (seropositive, but negative for viral DNA at the cervix) may benefit from additional protection from disease manifestation from that type. This may indicate that the vaccine has boosted the naturally-acquired immunity, keeping the infection in check, rather than any re-emergence of dormant disease.

The young, sexually-active woman can definitely benefit from HPV vaccination. It is, however, the very young, sexually-inexperienced woman – and preferably before her sexual debut – that should be the primary target for vaccination.”


MMWR 2007 Vol 56 RR–2. ACIP Recommendations on the quadrivalent HPV vaccine
www.cdc.gov/mmwr/PDF/RR/RR5602.pdf
Misconception about the value of vaccinating against low-risk (non-oncogenic) HPV types

There is a perception that, because low-risk HPV types are thought not to cause cancer, they do not pose a significant risk to health and – consequently – may not be considered sufficiently important to be targeted in vaccination programmes.

This perception is incorrect. The disease burden due to HPV infections caused by low-risk HPV types is considerable. This includes a significant proportion of CIN 1 and also genital warts. Infections due to low-risk HPV types have a significant impact on health systems, as well as the affected individuals.

- As many as 10% of cases of CIN1 are due to HPV infection with low-risk HPV types. However, unless tested for HPV genotype, these women would not know whether they were at risk of developing a high-grade CIN lesion, so they would still need to undergo further monitoring.

- Low-risk HPV types – whilst not known to cause cancer – can cause clinically-serious conditions, such as the potentially-lethal condition of juvenile-onset recurrent respiratory papillomatosis (JORRP).

- HPV types 6 & 11 are responsible for around 90% of genital warts (condylomata acuminata) – a highly-contagious, often recurrent and increasingly-prevalent disease.

- Although not usually associated with long-term health problems, the burden of genital warts is considerable. This burden is both personal – psychological and psychosexual – and economic.

“...The current vaccines offer excellent protection from cervical, vulval and vaginal cancer due to HPV 16 & 18, but the quadrivalent vaccine protects, in addition, against HPV types 6 & 11-induced disease. Since the usual time interval between infection and development of the lesion is much shorter in low-risk disease compared to high-risk induced lesions, the potential benefit of the quadrivalent vaccine on the incidence of those benign lesions will occur in the vaccinated cohort within the next few years.

Although the low-risk types induce infection and disease that are not life-threatening, they still cause much discomfort, anxiety and expensive therapy because of their high risk of recurrence.”


There have been reports of adverse events related to the HPV vaccines which have generated ‘scare’ stories in the media, and consequent public concern, about the vaccines’ safety. Safety of both vaccines has been demonstrated in several large-scale trials. In addition, since becoming commercially available, there has been extensive monitoring following distribution of over 30 million doses of the quadrivalent vaccine. No significant excess of mild or severe reactions, or of long-term sequelae, has been shown.

- The commonest side effect was a self-limiting reaction at the injection site in up to 80%. Headaches and dizziness occurred but were transient.
- Fainting and panic attacks happened during the injection process and were most likely a psychological reaction to the injection.
- Severe immunological and neurological events (i.e. Guillain Barré Syndrome) were extremely rare and occurred in equal numbers in placebo and study groups. US researchers reviewed data on 190,000 girls and young women who received at least one dose of the quadrivalent vaccine during the past two years, and compared it to data on girls and young women who received other – or no – vaccines. Eight medical outcomes which could have been linked to use of the vaccine e.g. blood clots, neurological side effects, seizures and strokes were reviewed: “...there were no associations found that suggested an elevated risk.” (CDC, 2008)
- Pregnancies occurred equally in nearly 5000 women in vaccine and placebo groups. In neither group was there a difference in pregnancy outcome or live births.

“A major factor contributing to the safety of the HPV vaccines is that they are formed from virus-like proteins (VLPs) to mimic the outer coat of the virus. This means the vaccines are ‘empty’ and do not contain any active DNA.

Scientific data are essential to be able to distinguish causality from coincidence. The first data to predict vaccine scares following HPV immunisation have already been gathered and analysed. Similarly, a cohort study to define possible co-incidental associated rare neurological and autoimmune disease, and sudden death, was also carried out in the United States.

Based on these studies and on-going assessments of vaccine safety information, the FDA and Centers for Disease Control in the US continue to declare that the quadrivalent vaccine (the only one currently available in the US) is “safe to use and effective”. The types of events causing concern can also be seen – at the same frequency – in the general population. The European Medicines Agency (EMEA) has reiterated this and, in recent statements, these agencies have confirmed that the benefits of vaccination continue to outweigh the risks.

Rumours about unconfirmed side effects make people forget that, for every 700 girls vaccinated, a death from cervical cancer can be prevented.”

Siegrist C-A et al. Human Papillomavirus Immunisation in Adolescents and Young Adults; a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007; 26: 979–984
www.cdc.gov/vaccinesafety/vaers/gardasil.htm (as of 21st October 2008)
Final Thoughts...

We have covered only a few of the most commonly-raised issues concerning HPV and vaccination and, undoubtedly, more will arise as this exciting field develops.

The worldwide burden of HPV-related disease and the heavy toll it takes on the affected individuals and their families – as well as health systems and economies – is growing, especially in the developing world. However, we know that this can be addressed: the roles that cervical screening, HPV testing and HPV vaccination can play in the prevention of cervical and ano-genital disease and infection are already established.

However, it is important to continue to debate and challenge misconceptions before they can become entrenched and create barriers to achieving our goal of eradicating cervical cancer and the other diseases caused by HPV.