Human papillomavirus update (including vaccination)

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Abstract

Human papillomavirus (HPV) is responsible for 99.7% of cervical cancer. Worldwide, cervical cancer causes more deaths than any other cancer, around one every two minutes. In the not so distant future cervical cancer may cause more deaths globally per year, (275,000 in 2008), than maternal deaths, (358,000 in 2008). Over 200 types of HPV have been identified. HPV is transmitted by skin-to-skin contact. Most HPV infections are cleared by the immune system; persistent infection may cause intraepithelial neoplasia and invasive disease.

Prophylactic HPV vaccines prevent disease caused by the included HPV types and potentially prevent 70–75% cases of cervical cancer. The UK added HPV vaccination to the national immunization programme in 2008. The vaccines are safe and well tolerated. It is likely that the benefits will be seen over a 15–20 year period.

Tests for HPV have been developed and are being evaluated as to their possible role in clinical practice.

Research is ongoing regarding therapeutic HPV vaccination and second generation prophylactic vaccines to prevent more cases of cancer.

Keywords cancer screening; cervical intraepithelial neoplasia; human papillomavirus; papillomavirus vaccines; uterine cervical neoplasms

Background

Human papillomavirus (HPV) is a small, double-stranded DNA virus containing only eight genes. It has the capability, however, to cause disease at a number of different sites in the body. Within the female genital tract, the most common association of HPV is with cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN). HPV also causes vulval, vaginal and anal intraepithelial neoplasia (VIN, VAIN, AIN), which, although less common than CIN, all have the potential to develop into invasive disease at these sites. In males, as well as anal disease, HPV causes penile intraepithelial neoplasia (PIN) and penile cancer. HPV in both sexes also causes benign genital warts. HPV can also cause disease away from the genital tract: on the skin and the mucous membranes of the head and neck where it is the causative agent of 3% mouth cancers and 12% oropharyngeal cancers.

As long ago as 1842, Rigoni-Stern observed that cervical cancer was found in married women and almost never in celibate women; but it wasn't until the 1970s that the true aetiology became known. During the 1960s and 70s evidence suggested that the likely aetiology was a sexually transmitted infection. In 1974 a review of the research by Stafl and Mattingly suggested that an environmental factor, possibly a virus, caused atypical metaplasia of cervical columnar epithelium, which could progress to cancer. In 1976 and 1977 several teams found HPV within the nuclei of abnormal squamous epithelial cells and Harold zur Hausen hypothesized that HPV was an important aetiological factor in cervical cancer. The following 30 years saw a huge expansion in HPV research leading to the knowledge we have today. In 2000 Munoz reviewed the epidemiological evidence indicating 99.7% of cervical cancers were caused by HPV.

Worldwide cervical cancer is the second commonest cancer in women, although it causes more deaths than any other cancer in the developing world. It is estimated that there are at least 500,000 new cases of invasive cervical cancer a year worldwide and over 275,000 deaths, meaning that every 2 minutes somewhere in the world a woman dies of the disease. Over 80% of cases occur in the developing world, which is least equipped to deal with the problem. However, it is not just a disease of developing countries; in the UK, approximately 1,000 women still die annually from cervical cancer or almost three a day, despite an effective cervical screening programme. Prophylactic HPV vaccines are arguably of most benefit in developing countries where there is a lack of systematic cervical screening but the high costs of vaccines limits their usage. Strategies are being developed to overcome such challenges, such as the recent GAVI (Global Alliance for Vaccination and Immunisation) initiative to provide vaccine to low resourced countries such as Sierra Leone, Ghana and Kenya (first three countries to get vaccines for school girls in 2013 aged 9–13 years).

HPV virology

Viral structure

The double-stranded DNA of HPV is circular in nature, containing only eight genes, also known as open reading frames (ORFs), Figure 1. It is a relatively small virus, approximately 55 nm in diameter. There are three regions within the genome: a relatively large, regulatory region that controls viral replication and some DNA transcription; then an early (E) and late (L) region, so called to denote where they are expressed in the viral lifecycle. There are six ORFs within the early region (E1, E2, E4, E5, E6, and E7) and two ORFs in the late region (L1 and L2).

The early region genes are expressed when the virus infects the host cell. They encode for functions that allow the infection to become established: E1 and E2 are required for, and control

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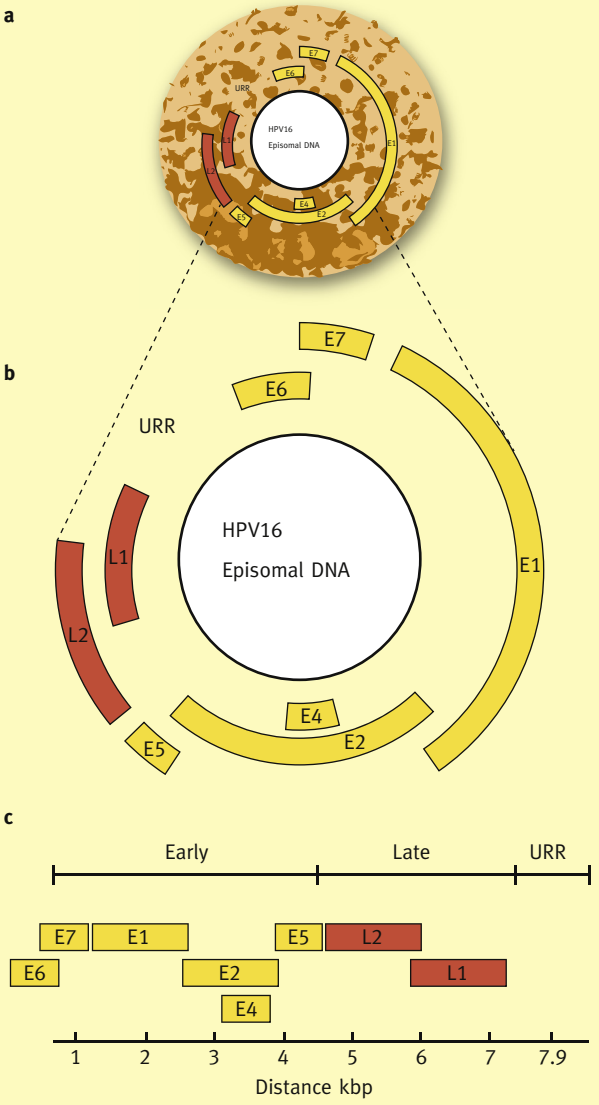
The human papillomavirus genome



a) A representation of HPV16 episomal DNA contained within the HPV capsid
b) A schematic representation of HPV16 in episomal form
c) A schematic representation of linear HPV16.

From Raybould et al (2011).

Figure 1

viral replication and also maintain the circular viral genome. E4 interacts with the host cell proteins causing instability, allowing the release of viral particles. E6 and E7 are the disease forming genes, or oncogenes that may cause a neoplastic change within a normal cell. They are thought to modify the cell cycle so as to retain the differentiating host keratinocyte in a state that allows amplification of viral genome replication and consequent late gene expression. They do this by targeting and inhibiting the tumour suppressor proteins of the host cell: p53 and retinoblastoma (pRB).

The late region of the genome, L1 and L2 ORFs encode for the capsular proteins that encapsulates the viral DNA to make the whole viral particle or virion.

HPV types

The standard virological classification of HPV includes genera of which there are 16 different groups. The alpha papillomavirus genera contain all the HPV types that cause anogenital disease.

Over 200 HPV types have now been described. The gene sequence of the L1 region encoding for the protein coat is used to classify the HPV type. A greater than 10% difference needs to be observed in order to define a new HPV type.

The HPV types can be sub-divided into groups depending on their oncogenic risk. In 2003 Munoz described high (HR) and low risk (LR) groups.

High-risk HPV types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Low risk types include HPV 6, 11, 42, 43 and 44.

High-risk HPV types 16 and 18 account for approximately 75% of cervical cancers worldwide and low risk HPV types 6 and 11 account for 90% of genital warts.

Infectious life cycle

HPV with its simple genome is unable to produce DNA polymerase and requires the host cell to permit viral replication. As an epitheliotrophic virus HPV infects only epithelial surfaces, targeting parabasal and basal cells. To access these cells a break in the surface epithelium is required, often caused by mild trauma. A possible reason for cervical disease being the most prevalent of HPV related disease is that the transformation zone with its immature, metaplastic cells is a relatively easy target for the virus.

If the infected, basal epithelial cell is mitotically active then the HPV will be reproduced and may remain in the host cell at a relatively low copy number of approximately 100 genomes per cell. This is known as **latent infection**. Latent infection does not present clinically.

Latent HPV infection may progress to **productive viral infection**, where high numbers of viral particles are produced. The reasons for this are not well understood, however the early genes promote the amplification of viral DNA. As the host cell matures, reaching the epithelial surface, the late genes encode the protein capsid and the completed virion is formed. The infected squamous cell on reaching the epithelial surface is shed (desquamation) and with the help of the E4 ORF the large number of new viral particles are released.

Carcinogenesis

When a normally replicating cell becomes damaged the host response is to induce tumour suppressor proteins, p53 and retinoblastoma (pRB). These proteins have the ability to cause programmed cell death or apoptosis to keep cellular division under control and remove damaged DNA.

It is the E6 and E7 genes that give HPV the ability to transform a normal squamous cell into a neoplastic one. It is thought that integration of the HPV DNA into the host DNA has an important role in carcinogenesis. When the circular viral genome breaks to allow integration, E6 and E7 gene expression is increased due to loss of the E2 ORF, which normally maintains regulatory control of oncogene transcription. HPV E6 and E7 inhibit the action of

p53 and pRB and therefore damaged cellular DNA is allowed to continue to replicate bypassing the usual control mechanisms. This uncontrolled replication of abnormal DNA results in genetic instability and eventually leads to cancer.

Natural history of disease

As previously noted, cervical cancer was thought to be caused by a sexually transmitted infection since the 19th century, but it is only relatively recently that HPV has been identified as the causative agent.

HPV infections are transmitted via skin-to-skin contact (including genital skin), not just sexual intercourse. HPV infection is endemic in the sexually active population. Peak exposure to HPV is following sexual debut in the late teens and early 20s, with a prevalence of 20–60%. Approximately 80% of sexually active women will have been infected with HPV by the age of 50. Therefore HPV infection should not be seen as a sign of a patient's or their partner's promiscuity or infidelity.

Epidemiological studies have shown that most (90%) infections with HPV are transient and do not cause significant disease. Studies have shown that following infection 50% of women will test negative at six months, 70% negative at one year and 80-92% will be negative at 2 years. The infection is cleared by the body's immune response.

Transient infection is much less likely than persistent infection to cause high grade CIN. Transient infection may cause low-grade CIN (CIN1) prior to clearance of the virus by the body. Approximately 50–60% of CIN1 will resolve without treatment within 2 years.

Persistent viral infection, particularly with high-risk HPV types such as HPV 16 and 18, increases the risk of high grade CIN (CIN2 or 3) and cervical cancer. High grade CIN can still regress to normal without treatment, though the rates of regression are not well documented due to current management being to treat rather than observe these lesions. Persistent infection causing high grade CIN, if left untreated may progress to cervical cancer. Studies done in the 1980s, which now would be unethical, showed that 22–27% of untreated high grade CIN progresses to cancer within 20 years with an annual risk being approximately 1–2% per year.

Overall 5% of high-risk infections progress to cervical cancer in an unscreened population of women whereas in a screened population the risk is 1–2%.

Immunocompromised patients such as those with HIV, or those on immunosuppressive medication e.g. transplant recipients, are more at risk of persisting infection and high grade CIN.

Prophylactic HPV vaccination

The current mainstay of management of cervical HPV infection in the UK is through secondary prevention by cervical screening and treatment of CIN. The aim being to pick up and treat CIN before it progresses to invasive cancer. Should cervical cancer be diagnosed it is managed by the multidisciplinary gynaecological oncology team. Attending cervical screening and any subsequent referral for further investigation or treatment is associated with a large degree of anxiety, in addition to morbidity related to the procedures themselves. It would be preferable to prevent initial HPV infection and hence the development of subsequent disease (primary prevention). Prophylactic HPV vaccination offers the opportunity for primary prevention of HPV-related disease. By immunizing girls against HPV before they get infected, the Department of Health estimates that up to 400 deaths from cervical cancer could eventually be prevented every year.

Vaccine development

The host uses both the innate and adaptive immune systems to react to HPV infection. The innate immune system, also known as the natural or non-specific immune system is already in place prior to the viral insult. The innate system includes the natural barrier produced by the skin and mucous membranes which function to contain the infection whilst the adaptive (acquired/specific) immune system is activated. The humoral immune response to HPV infection can be to either the early or late proteins which both act as antigens. The antibody response to the early proteins, made by the virus during replication is usually weak. The late proteins that form the viral capsid induce the strongest and most consistent antibody response. The neutralizing antibodies produced bind to the viral capsid thus preventing entry into the cell.

The aim of the prophylactic vaccines is to prevent HPV infection by stimulating the adaptive immune system to produce neutralizing antibodies to the HPV L1 protein and to create B-cell memory to prevent infections in the future.

As it is not possible to grow HPV in culture, a live virus vaccine cannot be made. Molecular biological techniques have been used to copy the L1 gene from specific HPV types. The sequence can be inserted into a host such as a yeast or baculovirus which then produces L1 protein in abundance. L1 proteins have the ability to self assemble into virus like particles (VLPs) that are similar in size and shape to the HPV virion but importantly, do not contain viral DNA. As there is no genetic material in the VLP there is no risk of causing an infection.

Available vaccines

Both licensed prophylactic HPV vaccines in the UK are VLP vaccines. Gardasil (Sanofi Pasteur MSD) is quadrivalent i.e. it contains VLPs of four HPV types: HPV 6, 11, 16 and 18 (20/40/40/20 μg respectively). The VLPs are produced within a yeast cell line, *Saccharomyces cerevisiae*. It is licensed for the prevention of premalignant genital lesions (CIN, VIN, VAIN), cervical cancer and genital warts caused by the four HPV types.

Cervarix (GlaxoSmithKline) is bivalent, containing VLPs of two HPV types: HPV 16 and 18; (20 and 20 μg). These VLPs are produced using an insect cell line, *Trichoplusia ni* infected with L1 recombinant baculovirus. It is licensed for the prevention of premalignant cervical lesions and cervical cancer causally related to HPV 16 and 18.

As well as the VLPs the vaccines contain an adjuvant, (a substance designed to further stimulate the immune response). Gardasil uses 225 μg aluminium hydroxyphosphate sulphate – a relatively standard adjuvant. Cervarix contains a novel adjuvant: 500 μg aluminium hydroxide with 50 μg 3-O-deacylated-4′-monophosphoryl lipid A.

Efficacy

Both vaccines have been shown to induce high titres of type specific neutralizing antibodies, with almost 100%

seroconversion rates, and mean antibody titres 10–100 times higher than those found after natural HPV infections.

Both vaccines have been subjected to double-blind randomized placebo-controlled trials and have been shown highly efficacious. After an average of three years both vaccines have shown 98% efficacy in preventing CIN2+ lesions.

The FUTURE I and II trials (international randomized double blind placebo-controlled trials in women aged 15–26 years) evaluated the prophylactic efficacy of the quadrivalent HPV vaccine (Gardasil) for preventing cervical, vulval and vaginal intraepithelial neoplasia and anogenital warts. At 42 months of follow-up, vaccine efficacy against lesions related to the HPV types in the vaccine was 96% for cervical intraepithelial neoplasia grade I, 100% for both vulval and vaginal intraepithelial neoplasia grade I and 99% for condylomata. Similarly, the PATRICIA trial was a double blind randomized controlled trial in women aged 15–25 years who were randomly assigned to Cervarix or Hepatitis A vaccine. At a mean follow-up of 35 months the vaccine efficacy against HPV16/18 associated CIN2+ was 93–98%.

Cross protection

Not only do the HPV vaccines protect against the HPV types included in the vaccine but cross protection has been demonstrated against other HPV types. The FUTURE II trial showed vaccine efficacy (Gardasil) of 30%, 75% and 48% for low-grade cervical, vulval and vaginal intraepithelial neoplasia and 83% for condyloma in the general naïve population. In the PATRICIA trial, at the end of 4 years, vaccine efficacy against CIN2+ associated with 12 non-vaccine HPV types (31,33,35,39,45,51,52,56,58,59,66 and 68) was 56% in the TVC-naïve cohort (total vaccinated *naïve* cohort) and 34% in the TVC group. Consistent cross protection by Cervarix was seen mainly for four non-vaccine HPV types (31, 33, 45 and 51).

Safety

Pain, swelling and erythema at the injection site are the most common side effects of vaccination, reported in over 10% of patients vaccinated with either vaccine. Fever is also commonly reported with Gardasil and headache, fatigue and myalgia with Cervarix. Less common (1–10%) side effects include itching at the injection site for both vaccines and nausea, vomiting, diarrhoea and arthralgia after Cervarix.

Patients are advised to delay the vaccination if they are suffering a febrile illness. The safety data gathered by the MHRA for the four-year period ending July 2012 on Cervarix concluded that the "balance of its benefits and risks remains clearly positive".

Although some patients unexpectedly became pregnant during the clinical trials and the birth outcomes were no different to a non-vaccinated population, neither company recommends vaccination in pregnancy. Gardasil is described as being safe to give to breast feeding women, though the Cervarix data sheet advises the vaccine to be given "if the possible advantages outweigh the possible risks". There has been no evidence that the vaccination reduces the effectiveness of any medication or the contraceptive pill. The vaccines can also be administered concomitantly with other booster vaccines without reducing efficacy (DPT, hepatitis A/B vaccines).

Vaccine administration

Gardasil is given as a 0.5 ml intramuscular injection, using a three dose regime at 0, 2 and 6 months. Cervarix similarly is a 0.5 ml intra-muscular injection but the three dose regime is 0, 1 and 6 months.

The FDA approved Gardasil for males and females aged 9–26 and Cervarix for use in females from 9–25 years. Gardasil is licensed in the UK for boys aged 9 to 15 years and for girls aged 9 to 26 years. Cervarix is currently licensed for girls aged between 10 and 25 years. The vaccines are not currently licensed for women aged over 26 years.

Follow up studies have shown that the duration of protection of the three dose vaccination schedule is at least 5 years and modelled data suggests a much longer period of time. These studies are currently ongoing to assess if there will be any requirement for booster vaccinations.

UK immunization programme

In September 2007 the Joint Committee on Vaccination and Immunisation (JCVI) in the UK made recommendations for the introduction of a vaccination programme to prevent cervical cancer. They recommended a routine vaccination programme for girls aged between 12 and 13 years and a catch-up programme for girls up to 18 years, 2008–11.

Following a tendering process the Department of Health chose the bivalent HPV vaccine, Cervarix, for its national immunization programme, 2008–11. The UK national vaccination programme began in September 2008 vaccinating girls aged 12–13 years and those between 13 and 18 years in the catch-up programme to 2011. In September 2012 'Gardasil' replaced 'Cervarix' in the UK HPV immunization programme.

Acceptability and uptake data

Prior to the introduction of the HPV vaccination programme there were concerns about the acceptability of a vaccine that protected young girls against a "sexually transmitted infection". Additionally, there were fears that vaccination may not be deemed necessary or suitable for some ethnic or religious groups and also fears that girls may not attend cervical screening following vaccination.

Despite a few initially publicized reports of schools or groups not participating in the programme the introduction of the immunization programme has been successful in the UK. Across the UK the uptake of all three doses of the HPV vaccine has been over 80%, though there has been a difference in uptake across different parts of the UK. Uptake for all three doses in the English catch up cohort 2010–2011 ranged from 48–81%. Modelling has indicated that if uptake is 80% year on year in the UK, there should be a two-thirds reduction in cervical cancer incidence in women aged under 30 years by 2025. Vaccine uptake data for five developed countries is shown in the table below (Table 1).

Management of HPV related anogenital neoplasia (AGIN)

Surgical treatment

The majority of HPV related disease is currently managed surgically. The standard treatment for high-grade cervical intraepithelial neoplasia is excision, most commonly using Large

Mass HPV vaccination uptake for 5 developed countries

Country	Date vaccination campaign started	Uptake – at least 1 dose	Uptake – all 3 doses	Vaccine used
Australia	2007 (Gardasil), 2008 (Cervarix); (12–13 year olds)	83%	70.8% Range: 63.7% (Tasmania) – 79.6% (Australian Capital Territory)	Gardasil and Cervarix
Canada	2007 to 2009, (9–14 year olds)	n/a	50% (Alberta and Manitoba) to 85% (Newfoundland, Nova Scotia and Quebec), for 2 or 3 doses.	Gardasil
Denmark	2009	80%	62%	Gardasil
United Kingdom	2008, (12–13 year olds)	89%	83.8%	Cervarix (changing to Gardasil in September 2012)
United States	2007, (13–17 year olds)	48.7%	32%	Gardasil and Cervarix

Table 1

Loop Excision of the Transformation Zone (LLETZ). Other methods of excision include knife cone biopsy and laser loop excision.

Ablative techniques are often used to treat low-grade CIN either if the patient does not wish conservative management and follow up or if the lesion has persisted over time. Ablation can be carried out using a number of techniques including: diathermy, laser, cold coagulation and cryocautery. Ablation can be used for high-grade lesions though this method does not permit histological examination of the lesion following treatment.

Wide local excision (WLE) is usually carried out to treat VIN, VAIN and AIN.

Topical treatment

Wide local excision, particularly of the vulval skin to treat VIN is associated with a large degree of psycho-sexual morbidity. Excision, even of small lesions, or despite plastic surgery techniques for larger lesions frequently cause distress due to the alteration of anatomy and scarring. Because of this investigators are searching for a safe and effective topical treatment for VIN.

Imiquimod cream is licensed for the treatment of anogenital warts, superficial basal cell carcinomas and actinic keratoses. A number of small trials (4–15 patients in each study) have been carried out to assess the usefulness of Imiquimod in treating high grade VIN. These trials combined show a partial response to treatment in 30% but promisingly a 42% complete response rate. 28% of patients did not respond to the treatment.

Cidofovir (1-[(S)-3-hydroxy-2-(phosphonylmethoxy)-propyl]cytosine) is an acyclic nucleoside phosphonate usually used intravenously to treat CMV retinitis in patients with HIV. It has a broad spectrum anti-viral activity with in vitro anti-tumour potential: It has the ability to decrease E6/E7 gene expression thus increasing p53 and pRB levels and it can induce apoptosis of HPV infected cells.

A small pilot study using topical cidofovir to treat high grade AGIN has been carried out. Using the topical treatment three times per week for sixteen weeks showed an 80% response rate: 40% partial response and 40% complete response.

Following the successful and promising cidofovir pilot study a phase II randomized controlled trial (RT3VIN) has been conducted to assess response rates to both Imiquimod and cidofovir in the management of biopsy proven VIN3. Recruitment to RT3VIN ceased in Jan 2013 and the trial is now in the follow-up phase. Initial response rates should be available by the end of 2013.

Future developments

Effect of HPV vaccination on the NHS cervical screening programme

The UK has a world leading cervical screening programme currently based on cervical cytology. Although it will take approximately 15–20 years for the full impact of HPV vaccination to take effect, 50% of the benefit will be seen within 10 years. The substantial reduction in abnormal smears and cases of CIN in the next 10–15 years will alter the performance of cytological cervical screening requiring adjustments to the screening programme to ensure adequate sensitivity, specificity and cost effectiveness.

HPV testing

Available assays: HPV DNA has generally been detected in the laboratory using PCR (polymerase chain reaction) and ELISA (enzyme-linked immunosorbent assay) techniques. This assay works on the principle of target amplification using type specific primers and allows identification of specific HPV types and also detection of infections involving multiple HPV types. The assay is however time consuming to perform and sensitive to contamination. Commercial testing kits are now available that make the tests simpler to perform and analyze. These include the PapilloCheck DNA microarray (PapilloCheck, Greiner Bio-One) which types 18 HR and 6 LR HPV types individually.

The LINEAR ARRAY HPV Genotyping Test by Roche is registered for use in the European Union for detection of 37 high and low-risk human papillomavirus genotypes. APTIMA HPV 16 18/45 Genotype Assay by Hologic has been approved by the FDA for use in women who test positive for HPV to assess their risk of developing cervical cancer. The Hybrid Capture 2 (HC2) assay

(Qiagen; Hilden, Germany) identifies 13 high-risk HPV types and 5 low risk types and labels the results as being HR or LR positive or negative. The HC 2 assay still requires careful laboratory protocols and trained technicians. Qiagen, in collaboration with PATH, have developed a rapid HPV test for use in developing countries. *Care*HPV covers 14 HR types, requires only basic laboratory skills and can be run without running water or electricity.

HPV testing in clinical practice

As a primary cervical screening test: the high prevalence of HPV in young women under 30 years of age, the majority of which will be cleared spontaneously prior to disease being caused, means there is no role for HPV testing as a primary screening tool in this age group. High positivity rates would lead to further investigation and intervention. In the over 30 age group, where HPV prevalence is lower, there is more potential for benefit due to the greater sensitivity of HPV testing for HG CIN than cervical cytology and a very high negative predictive value (NPV). The HART (High-risk HPV testing) study published in 2003 showed that HPV testing could be used for primary screening in women older than 30 years, with cytology used to triage HPV-positive women. However the ARTISTIC trial (A Randomised Trial of Human papilloma virus (HPV testing) in primary cervical screening) in women aged 20–64 years showed that routine HPV testing did not add significantly to the effectiveness of LBC.

Concomitantly with cervical cytology for screening: various algorithms combining cervical cytology and HPV testing have been proposed. The key fact is that if a patient has negative cervical cytology and a negative HPV test there is a high negative predictive value giving a very high degree of reassurance that she does not have CIN.

To determine the significance of a borderline or low-grade cytology result: TOMBOLA (Trial Of Management of Borderline and Other Low grade Abnormal smears) reported in 2010. This showed that 43.5% of women with these cytological abnormalities tested positive for HPV yet 70% of these did not go on to develop CIN or cancer. The trial did not find the HPV test result helpful in guiding follow up apart from possibly in the over 40 age group.

In the HPV triage (implemented in England in 2011), any women whose cervical smear shows borderline changes or mild dyskaryosis will have a HPV test. Women, who test HPV positive, will be referred for colposcopy immediately, whilst those who test HPV negative will be returned to routine recall.

Following treatment of CIN: following treatment of CIN using either ablation or excisional techniques there is a significant recurrence rate of approximately 10%. A negative HPV test post treatment has been shown to be associated with a minimal risk of recurrence and hence the suggestion that the current protocol of annual cervical cytology for ten years after treatment could be reduced.

This led to the implementation of the test of cure in England and Scotland in early 2012. An HPV test is performed at 6 months following treatment; women who have negative or low-grade cytology and test negative with HPV testing return to routine screening. Those that test HR HPV positive six months after treatment are referred back to colposcopy.

Studies have shown that the sensitivity of self-collected HPV samples by a number of differing methods is as sensitive as cervical cytology. This warrants further investigation as self-testing could potentially reduce the non-attendance for cervical screening for those women who do not wish to be examined.

Further vaccine developments

Childhood vaccination: in light of the evidence showing that prophylactic vaccination has been widely accepted, there could be a potential benefit in combining it with other early childhood vaccination programmes that have even better coverage rates. Further work needs to be carried out regarding the immunogenicity of the vaccine and its longevity in a younger population.

Vaccination of boys and older women

The current UK HPV vaccination programme excludes boys and women over the age of 18 as vaccinating these groups on a population basis is not thought to be cost effective. However the HPV vaccine is available off-licence for use in boys.

Vaccination of boys would reduce their risk of head and neck, anal and penile cancer using the bivalent vaccine and also prevent 90% of genital warts using the quadrivalent vaccine. Vaccination of boys also has the potential to reduce the prevalence of HPV in the general population and hence the incidence of HPV related disease in unvaccinated women by herd immunity. Australia has recently been the first country to introduce HPV vaccination (February 2013) for boys as well as girls. Males aged 12–13 years will receive the vaccine and those aged 14–15 years will also receive the vaccine as part of the catch-up programme until the end of the 2014 school year.

Women aged 18 or over who have not been sexually active or have not yet been exposed to HPV types contained in the vaccines also have everything to gain from HPV vaccination. General practitioners can offer, at their discretion, NHS funded HPV vaccination outside of the national vaccination programme should a patient request it. HPV vaccination is also now widely available in private clinics and more recently from high street pharmacies.

Increased coverage of HPV types in prophylactic vaccine

From September 2012, the Department of Health uses Gardasil in the UK immunization programme covering four common HPV types; 6, 11, 16 and 18.

An increase in the number of HPV types incorporated into a vaccine will prevent a higher percentage of cancers but the formulation of these vaccines is a challenge as antigens from each type need to be included in the vaccines. A number of second generation prophylactic vaccinations have been developed. A nonavalent vaccine containing L1 VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 is currently undergoing clinical evaluation. This could potentially prevent up to 85% of cervical cancers but at a higher production cost.

Therapeutic vaccines

Therapeutic vaccines have been shown to clear pre-existing cervical lesions and even malignant tumours by provoking a cellular immune response against HPV infected cells.

There are a large number of clinical trials that have investigated possible therapeutic strategies including the use of viral vectors, bacterial vectors, peptide, protein, dendritic cell, RNA and DNA vaccines. Although responses are seen in some cases the main challenge is to understand why therapeutic vaccination does not result in a reliable clinical response.

Listeria monocytogenes (gram positive bacterium), a live vector based vaccine has been shown to induce immune response by generating CD4+/CD8+ T-lymphocytes. Studies in mice have shown promising results with regression of cervical tumours. A live-attenuated Listeria monocytogenes cancer vaccine (ADXS11-001) is being evaluated in phase II clinical trial led by the Gynaecological Oncology Group (GOG) in women with persistent or recurrent carcinoma of cervix. One of the primary outcome measures is to look at the proportion of women who survive for at least 12 months. This trial commenced in September 2011 and is due to complete in October 2013. A similar trial looking at regression of CIN2+ is also being evaluated and is due to complete in April 2013.

HPV and Head & Neck cancers

Head and Neck (H&N) cancer is the sixth most common cancer worldwide with low five-year survival rates. The emergence of HPV as a causative factor in oropharyngeal cancer and the increasing incidence of HPV related H&N tumours has resulted in the establishment of various clinical trials and also to the introduction of HPV vaccination for boys. HPV 16 is the commonest causative virus. Phase I trials using a HPV DNA vaccine has been designed for established H&N cancer. Similar to cervical cancer, the E6/E7 proteins are expressed in these cancers acting as tumour specific antigens against which to direct therapeutic vaccines. The REALISTIC trial (Recombinant Listeria Monocytogenes (Lm) Based Vaccine Virus Vaccine to Treat Oropharyngeal Cancer), is a phase I trial evaluating the effect of recombinant listeria monocytoges vaccine in treatment of oropharyngeal cancers. ◆

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Practice points

- HPV is a very common, small, double-stranded DNA virus.
- HPV cannot be cultured *in vitro*.
- Over 200 HPV types have been identified and they can be divided into low and high-risk groups based on their oncogenic potential.
- 80% of sexually active women will acquire HPV during their lifetime.
- Most HPV infections are transient and are cleared by the immune system within 1-2 years.
- Persistent infection with HPV may cause intra-epithelial neoplasia and possibly even cancer if left untreated.
- HPV vaccination pre sexual debut is highly efficacious in preventing disease caused by the HPV types contained within the vaccine.
- Vaccination against HPV 16 and 18 prevents 70-75% cases of cervical cancer.
- From September 2012, Gardasil replaced Cervarix in the HPV vaccination programme.
- Australia has become the first country to introduce gender-independent prophylactic HPV vaccination.
- Continued education and screening of the vaccinated population is still required, as prophylactic vaccination does not prevent all cases of cervical cancer.
- HPV testing may have a role as a primary screening test for cervical screening in the future.
- HPV testing combined with cytology as a test of cure was implemented in England and Scotland during 2012.
- Monitoring of changes in HPV type specific prevalence post vaccination will be important both for research interest and to guide future vaccine development.
- The emergence of therapeutic vaccines is an exciting future development.