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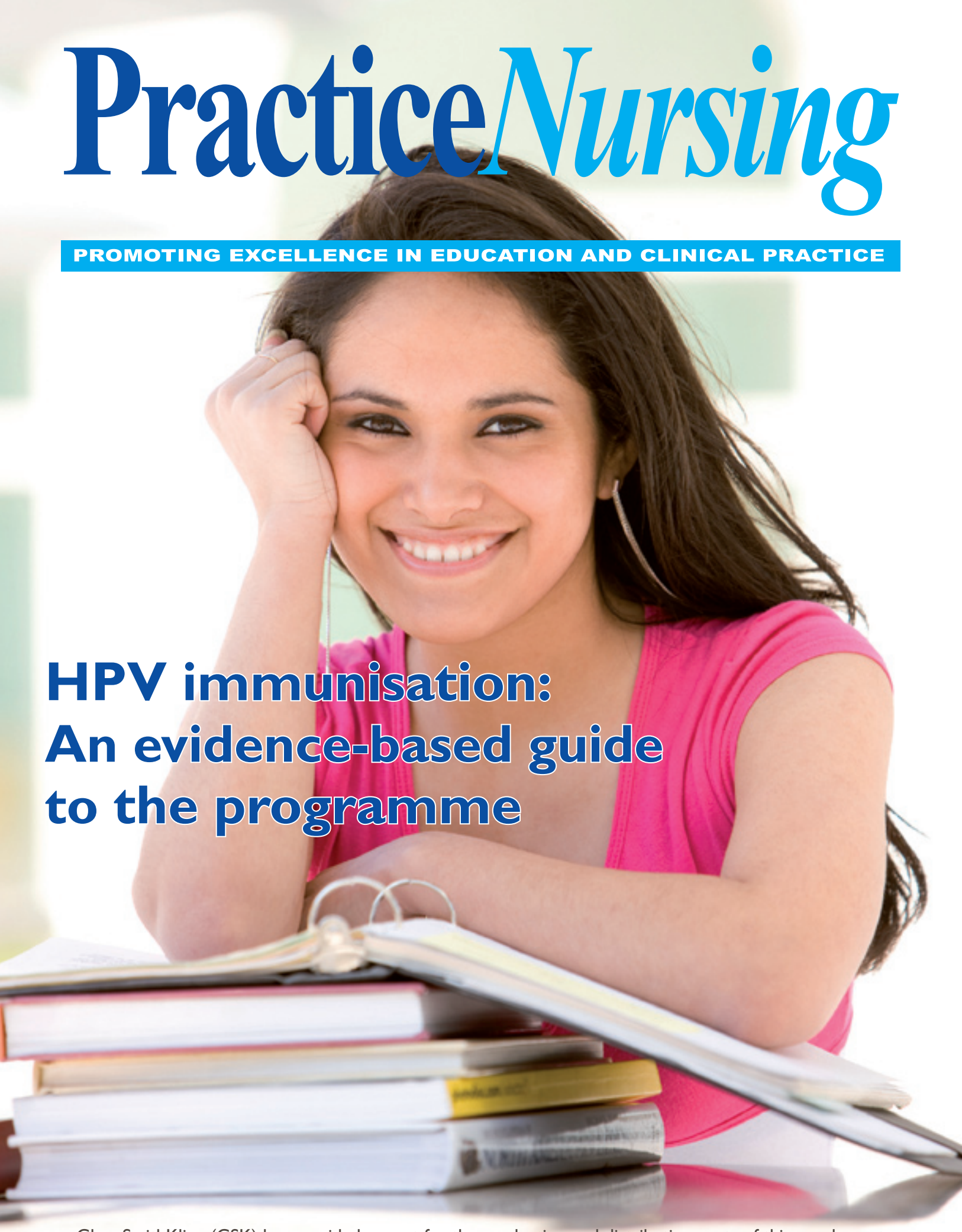

HPV immunisation: An evidence-based guide to the programme

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Changing lives

Immunisation has been one of the greatest of all health promotion successes and because of it many diseases that were once common are now rarely seen. Vaccines can and do save lives, and this year we see the introduction of a new and groundbreaking cancer vaccine.

About 2250 women were diagnosed with cervical cancer in the UK in 2005 and about 830 women died of cervical cancer in 2006 (Office for National Statistics, 2007; 2008). About 70% of cases are caused by human papillomavirus (HPV) types 16 and 18 (Smith et al, 2007). Sexual activity carries with it the possibility of transmission of HPV. It is not an indicator of promiscuity, only of sexual activity, and during our lives most of us will be sexually active at some point.

The cervical screening programme can detect women who have abnormal cell changes so that they can be treated before they develop cancer, but how much better it would be to prevent the cervical cancer and cervical pre-cancerous lesions caused by HPV types 16 and 18. Now we can.

The Department of Health decided to add the HPV vaccine Cervarix to the vaccination schedule from September 2008. When these vaccinated girls grow to be women, this vaccine will have changed the lives that many of them can then have.

This educational supplement on HPV and the immunisation campaign has been developed by *Practice Nursing* and the *British Journal of School Nursing* in collaboration with leaders in the field of HPV. Our aim is to provide you with information on all aspects of HPV and the new vaccine.

I hope that you will find it useful.

Jeannett Martin is Editor in Chief, *Practice Nursing* and Director of Nursing, BarnDoc Ltd, London

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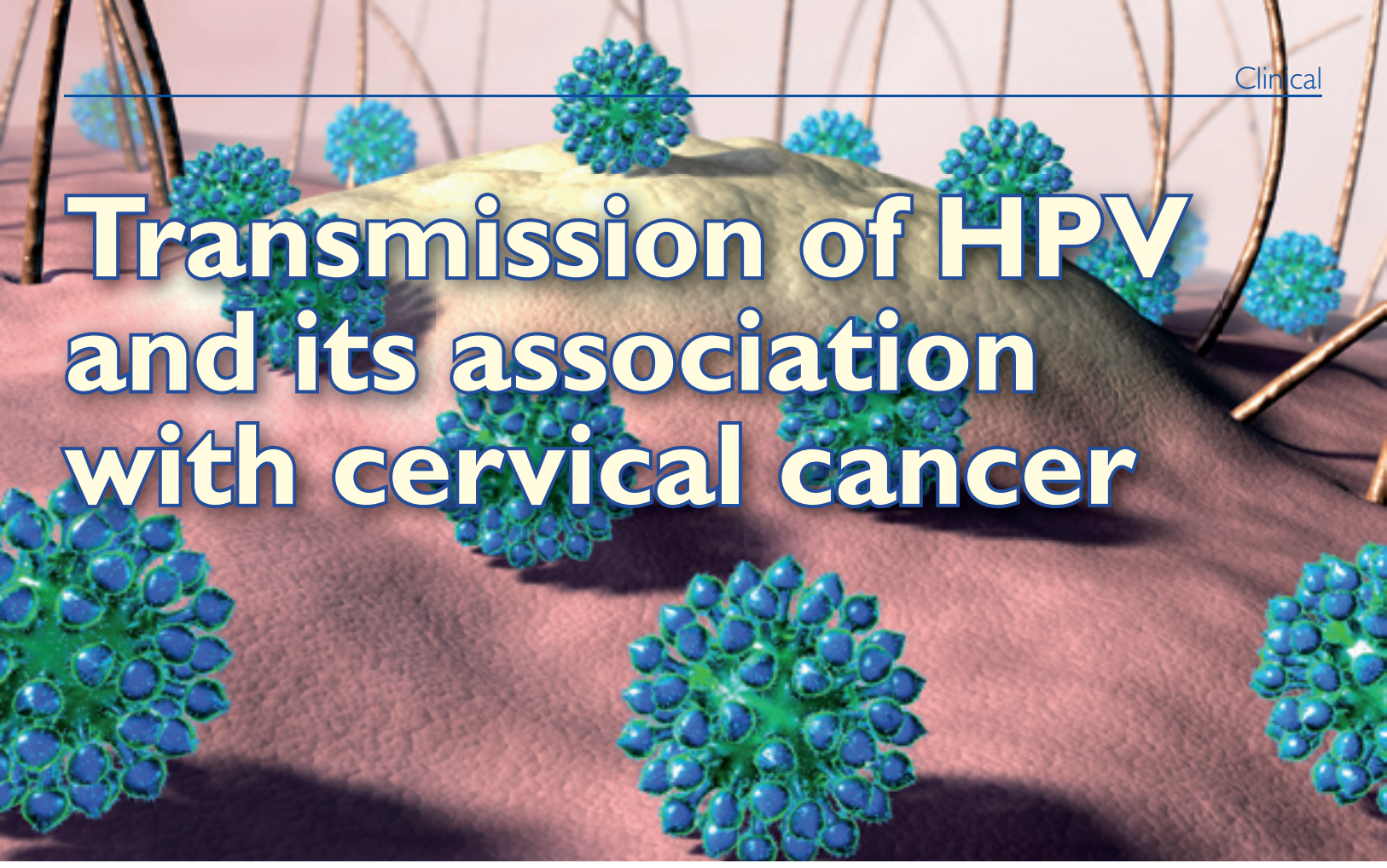

Transmission of HPV and its association with cervical cancer

The causal relationship between the human papillomavirus (HPV) and cervical cancer is well recognized and transmission of HPV is common. Louise Cadman explains how transmission occurs and the circumstances in which the risk of cervical cancer is increased.

The causal relationship between human papillomavirus (HPV) and cervical cancer is well recognised (International Agency for Research on Cancer (IARC) 1995). Knowledge about HPV is constantly evolving but, to date, it has proven hard to understand fully the way in which HPV is transmitted. HPV transmission occurs with such frequency that in many ways it behaves more like a bacterial infection such as *Chlamydia trachomatis* than other viral infections such as herpes simplex virus.

Now that the link between a sexually transmitted virus and cervical cancer is better understood, it raises many questions. In the era of the HPV vaccine it is important for parents, young people and health professionals to understand the effects of HPV and how a person becomes infected.

Types of HPV

There are more than 100 recognised types within the HPV family. Over forty of these affect the genital area, of which fifteen are referred to as being high risk for cervical cancer. These types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82. HPV 16 and 18 account for 53.5% and 17.2% of squamous cell cervical cancer respectively and the rest is caused by the remaining 13 types (Smith et al, 2007). HPV is phylogenetic and the HPV types are often referred to as making up the HPV 'family tree', with various types sharing 'branches'. This is important when considering vaccines because it explains why data are emerging about cross-protection for HPV types other than those included in the vaccine.

Non-oncogenic HPV types, referred to as low risk, include HPV 6 and 11, the cause of genital warts. Low risk HPV types act differently to the high risk types in the way that they affect the genital area and are transmitted. HPV 6 and 11 are associated with low grade cervical intraepithelial neoplasia (CIN) but this is the type of CIN which does not have the potential to develop into cancer. This is why it is important to be careful about the language used. Many women who have CIN believe they have cancer, particularly if it is CIN III, which has historically been called carcinoma in situ. CIN is referred to as 'pre-cancer' to address this misunderstanding, but this is a misnomer as very little low-grade CIN will become cancer.

Likewise, it is important that people understand that HPV causes cancer only very rarely. HPV does not aim to harm its host, as that would be self-destructive. Therefore most HPV infection eludes the body's defence mechanism, or immune system, and lives with the host quite happily.

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Relative risk and transmissibility

It has been estimated that the lifetime risk of having HPV for anyone who has ever had sex is over 70% (Koutsky, 1997). Others have looked at the probability of transmission of HPV. Burchell et al (2006) used mathematical modelling to estimate that the probability of transmission of HPV per sexual act ranged from 5% to 100% with a median of 40%. Although there are inherent problems with modelling data, taking the median of 40%, the probability of male to female transmission was estimated to be 100% with 11 acts of intercourse.

Transmission of HPV

The incidence of HPV infections in adults is associated with some degree of sexual contact. In support of this:

- The transmission of non-oncogenic HPV 6 and 11 (the cause of genital warts) between sexual partners has been well documented
- HPV type-specific concordance between male and female sexual partners (Burchell et al, 2006) has been demonstrated
- Genital HPV infections in women who have not had vaginal intercourse are rare (Koutsky et al, 1999).

It is important to note, however, that genital HPV occurs on the whole genital area both internal and external. Therefore it is possible for transmission of HPV (in particular, low risk types) without penetrative sexual contact. Indeed, genital HPVs have been detected in other mucosa such as the mouth, conjunctiva and oropharynx.

Digital or oral to genital transmission occurs but is uncommon. In a small study, Sonnex et al (1999) sampled the fingertips and tips of the fingernails as well as the genital area of men and women with genital warts. HPV DNA was detected in the finger brush samples of three out of eight women and nine out of fourteen men. Marrazzo et al (1998) detected genital HPV DNA in 19% of women who reported only ever having sex with women. Numbers in this cross-sectional study, however, were small, with only 21 out of 149 women having sex with only women reporting no prior sexual contact with men.

HPV transmission can occur from mother to child during vaginal delivery. Smith et al (2004) reported that 1.6% of oral and genital samples taken from infants after delivery (median 65 hours) were HPV DNA positive, although at 3-month follow-up no children remained positive. This indicates that persistent infection is unlikely via the perinatal route.

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Condoms do not offer complete protection against HPV. There are also some data to indicate that prolonged use of hormonal contraceptives might increase the risk of cervical cancer, although the reasons why remain uncertain.

Reasons for increased risk of exposure and transmission

A person's risk of becoming infected with HPV is increased by a number of factors.

Age at first intercourse

Intercourse at a young age has been reported as a risk factor for HPV infection (Kahn et al, 2002). It is not yet clear exactly why this is the case and it has been difficult to eliminate confounding factors such as smoking, contraceptive use or non-use of barrier methods, and number of partners. However, it may be that the cervix is more vulnerable in younger women. The immature cervix is more likely to have an ectropion (composed of vulnerable columnar epithelium) and micro-abrasions; as a result, the surface may be more susceptible to HPV infection. This supports both the likelihood of exposure to HPV and susceptibility to the virus.

It has been said that a shorter gap between the start of a young woman's periods and the time when she first has sexual intercourse leads to a greater risk of HPV infection. However, a paper by Collins et al (2005) looked closely at the gap between menarche and sexual debut and found that the longer the interval the higher the risk of HPV positivity. The hazards ratio was shown to increase with age at sexual debut (1.212 per year), partner age (1.084 per year) and a sexually experienced partner (2.794 per year). Therefore young women who are older at first intercourse are more likely to have an older more sexually experienced partner who has had more opportunity to have been exposed to HPV DNA.

Concurrent sexually transmitted infections

Infections such as *Chlamydia trachomatis* and herpes simplex virus have long been suspected of having a link with cervical cancer. It is now thought that the cervicitis these infections cause damages the epithelium (Madeleine et al, 2007). The HPV enters through the micro-abrasions and then infects basal keratinocytes. In this way the HPV infection establishes itself and the inflammation facilitates persistent infection.

Multiple sexual partners

The spread of sexually transmitted infections (STIs) other than HPV has been well studied. For example, in the 1980s, Klovdahl (1985) explored the network which led to AIDS epidemics in New York City, Los Angeles and San Francisco. The key bridges revolved around 'patient 0', an airline attendant who was a high-risk male with many and concurrent sexual partners. It is members of the 'core group' (Doherty et al, 2005) (multiple sexual partners) who contribute most to the spread of STIs. HPV is different in that it affects those who would not be considered as high risk. This could be due to the biology of the virus or because it is a 'silent' virus, i.e. people often have no symptoms and do not know that they have HPV. In addition, for those who have HPV there is no known treatment and it is also a very common, easily transmissible virus.

It is important to note that it is not solely the number of sexual partners of the female but also of the male that matters. The female takes on the risk of all her partners' previous partners and vice versa.

Having concurrent sexual partners, serial monogamy (with no interval between partners) and short intervals between partners all increase the risk of HPV. It is thought that this is because HPV infection has not been able to clear or wane before a new sexual contact and likely transmission occur.

Smoking

Smoking seems to reduce the number of Langerhahn's cells in the cervix. These are markers of immune function. Therefore smoking affects the ability to fight the virus in the cervix, increasing the risk of persistent HPV infection.

Hormonal contraceptives

Although evidence in the past has not corrected for other risk factors there are now some data to suggest that prolonged use of hormonal contraceptives over years increases the risk of cervical cancer in the presence of HPV infection. It is not clear why, but it has been hypothesised that it may be because (as in the immature cervix of the young girl) hormonal contraceptive users are more likely to have a susceptible ectropion.

Condom use

Condoms offer a degree of protection against HPV but not complete protection. This is partly because HPV is found over the whole genital area, not just in the vagina and cervix. A condom cannot therefore completely cover the areas affected by HPV. Although this is undoubtedly part of the reason, it is not the complete answer.

Complete condom use is very rare. Even the most reliable condom user reports slipped or split condoms or that a condom has been used late in proceedings. As transmissibility of HPV is several fold higher than that of other viral STIs, over multiple acts of sexual intercourse the protectiveness of condoms disappears.

Conclusions

HPV is a very common, easily transmissible virus. Although there are ways to reduce the risk of exposure and susceptibility, it is very difficult to remain completely protected if any sexual contact takes place. HPV not only affects the cervix, causing cervical cancer, but has also been linked to other genital cancers—vaginal, vulval, anal and penile.

It is unknown why HPV infection persists in some women and leads to cervical cancer. There are currently no medical treatments available for HPV infection. However, with the advent of prophylactic HPV vaccines, for the first time there is primary prevention of HPV infections.

Potential conflicts of interest: The author has received sponsorship for attendance at conferences and lecture fees from GlaxoSmithKline.

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Key Points

- There are over 100 recognised types of human papillomavirus (HPV) of which types 16 and 18 account for over 70% of squamous cell cervical cancer
- Genital HPV occurs on the whole genital area, both internal and external. Therefore, transmission is possible without penetrative sexual contact
- Intercourse at a younger age has been reported as increasing the risk of HPV infection
- Smoking increases the risk of persistent HPV infection

Why is vaccination with HPV important?

HPV immunisation provides the opportunity to prevent the development of cervical cancer in women, rather than rely on detecting cervical abnormalities during screening. Karen Ford and Sarah Lang explain the strategy for the introduction of HPV immunisation and the evidence for the effectiveness of the vaccine.

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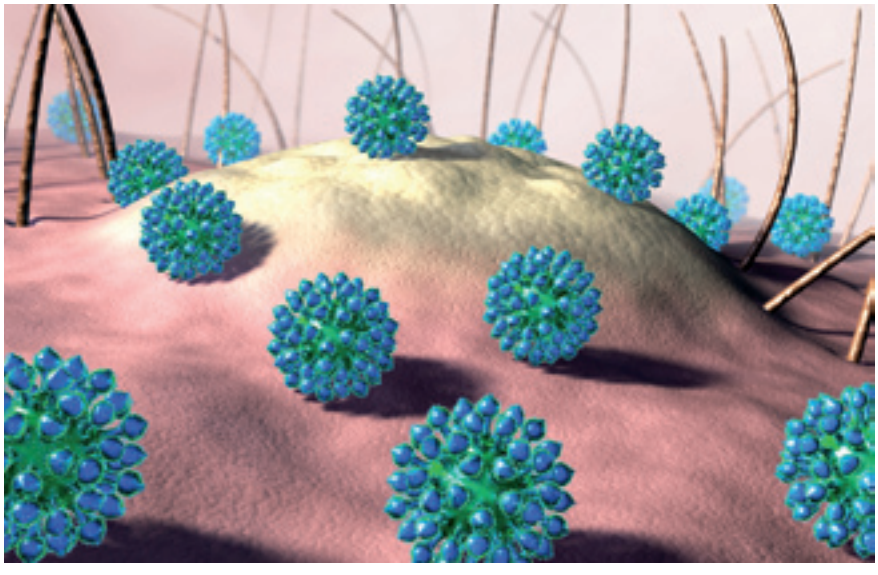
Cervical cancer kills about 830 women in England and Wales each year (Office for National Statistics (ONS), 2008) and around 2250 new cases of invasive cervical cancer are diagnosed (ONS, 2007). Until recently, cervical screening to detect and treat abnormalities of the cervix, which if left untreated could lead to cancer of the cervix, has been the main strategy to reduce risk. However, around 70% of cervical cancer is attributable to human papillomavirus (HPV) genotypes 16 and 18 (Munoz et al, 2004). Two vaccines have been developed protecting against HPV types 16 and 18.

Strategy for cervical cancer prevention

Cervical screening is offered to women at the age of 25 years and repeated every 3–5 years depending on age. This programme reduced the incidence of cervical cancer by 42% between 1988 and 1997 in England and Wales (NHS Cervical Screening Programme (CSP), 2008). However uptake of screening is declining with 79.5% of eligible women being screened in 2006/2007 (The Information Centre, 2007). Liquid based cytology has become the standard screening tool. This detects abnormalities of the cervix but does not routinely test for HPV infection. There are trials underway looking at the clinical impact of assessment of a smear sample for HPV infection.

Figure 1. Computer artwork of human papillomavirus (HPV) particles (virions) (green and blue) surrounding a raised wart (centre). The HPV virus consists of a protein capsid (green) enclosing DNA. Attached to the capsid are surface proteins (blue spikes).



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Vaccine development

HPV immunisation provides the opportunity to prevent cancer developing rather than rely solely on picking up the early signs of cervical abnormalities. The first stage of HPV vaccine development came in the early 1990s when highly purified virus-like particles (VLPs) of the major capsid (L1) protein (the viral coat of HPV) were shown to produce a strong immune response (Zhou et al, 1991) (*Figure 1*). While VLPs mimic the natural structure of the outside of the virus they are not infectious as they contain no DNA and cannot cause cancer (Crum, 2002). In 2002 the first evidence was published proving that vaccines created with this technology protected the cervical epithelium (lining of the cervix) against HPV infection (Koutsky et al, 2002).

Available vaccines

Two HPV vaccines are licensed in the UK: a bivalent vaccine (Cervarix) containing VLPs for HPV types 16 and 18, and a quadrivalent vaccine (Gardasil) containing HPV types 16, 18, 6 and 11. The additional types (6 and 11) covered by the quadrivalent vaccine are not important causes of cancer but cause genital warts.

Clinical trials of the bivalent vaccine (Harper et al, 2004; Harper et al, 2006; Paavonen et al, 2007) and the quadrivalent vaccine (Ault, 2007; Garland et al, 2007; Joura et al, 2007; The Future II Study Group, 2007) have shown both to be extremely effective at preventing infection in women with the HPV types covered by each vaccine. The vaccines have no therapeutic effect against pre-existing HPV infections and therefore must be given before the vaccine

recipient is exposed to the types of HPV against which they are targeted (Hung et al, 2008). Seroprevalence studies found little evidence of HPV infection in samples of girls below 14 years of age but a sharp increase in the mid-teens (Department of Health (DH), 2008a).

Adjuvants are added to vaccines to improve the immune response to the antigens contained within them. Both vaccines contain adjuvants and both produce a stronger immune response than natural infection. The HPV bivalent vaccine contains an innovative adjuvant ASO4, containing 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium salt (GlaxoSmithKline, 2007) to enhance antibody response and production of more specific memory B cells (Giannini et al, 2006).

Both vaccines require a course of three doses. Although the vaccines are similar there is no evidence that they are interchangeable; therefore the whole course of vaccination should be with the same vaccine. The DH has purchased the HPV bivalent vaccine for delivery of the routine and catch-up programmes over the next 3 years (DH, 2008b). As the bivalent vaccine is the vaccine to be used in the national immunisation programme, the clinical trials of this vaccine are presented in more detail (*Table 1*).

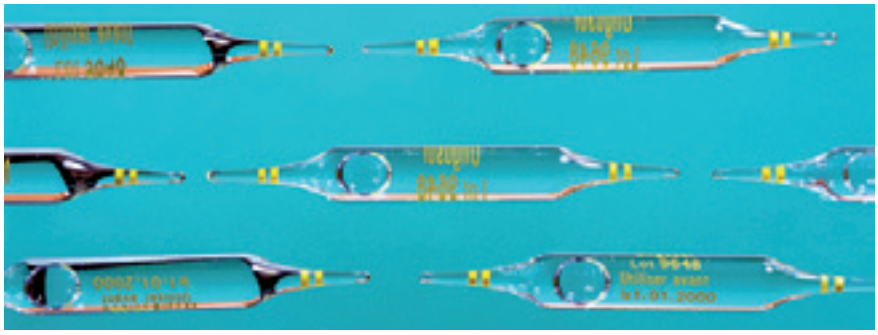
Clinical trials of HPV bivalent vaccine

More than 19 000 participants have been vaccinated with HPV bivalent vaccine during clinical trials (GlaxoSmithKline, 2007). Ideally, an HPV vaccine's efficacy would be assessed using the endpoint of a reduction in cases of cervical cancer; as it is neither feasible nor ethical to withhold treatment and allow cervical cancer to develop, surrogate markers of efficacy have been used (Kahn and Burk, 2007). These include the prevention of initial and persistent infection and the development of cervical lesions—cervical intraepithelial neoplasia (CIN), the types of abnormality that screening seeks to identify—due to HPV types covered by the vaccine (Harper et al, 2004, Harper et al, 2006, Paavonen et al, 2007).

Clinical trials show HPV bivalent vaccine to be more than 99% effective at preventing pre-cancerous lesions associated with HPV types 16 and 18 and to sustain high levels of protection against both initial (92%) and persistent (100%) infection with HPV types 16 and 18 in women aged 15–25 years (Harper et al, 2004; Harper et al, 2006; Paavonen et al, 2007). Protection is maintained for at least 4.5 years, with studies ongoing to determine the longer term immunity achieved by the vaccine (Harper et al, 2006; Paavonen et al, 2007).

Table 1. Summary of clinical trials of the bivalent HPV vaccine

Trial	Aim	Method	Summary of results
Harper et al, 2004 Phase II, randomised, double-blinded, placebo-controlled trial	To assess vaccine efficacy, safety and immunogenicity	1113 women, aged 15–25 years Vaccine group (n=560): HPV bivalent vaccine at 0, 1 and 6 months Control group (n=553): Aluminium hydroxide at 0, 1 and 6 months Follow-up: Initial phase 18 months, extension phase 27 months	➤92% protection against initial HPV 16/18 infection ➤100% protection against persistent HPV 16/18 infection ➤93% protection against cytological abnormalities associated with HPV 16/18 ➤100% seropositive (antibody response) at 18 months ➤No serious adverse events related to vaccination
Harper et al, 2006 Follow-up study of Harper et al, 2004	To assess long-term efficacy, immunogenicity and safety	776 women who participated in Harper et al (2004): 393 vaccinated, 383 controls Reported at 4.5 years. Study ongoing	➤100% protection against cervical intraepithelial neoplasia (CIN) lesions associated with HPV 16/18 ➤Sustained high protection against HPV 16/18 initial infections (97%) and persistent infections (100%) ➤Some cross-protection of non-vaccine type HPV noted ➤High HPV 16/18 antibody levels sustained (98% seropositive at 4.5 years) ➤No serious adverse events related to vaccination
Paavonen et al, 2007 Phase III double-blind, randomised controlled trial	Interim analysis assessing efficacy	18 644 women aged 15–25 years Vaccine group (n=9319): HPV bivalent vaccine at 0, 1 and 6 months Control group (n=9325): Hepatitis A vaccine at 0, 1 and 6 months Reported at 14.8 months. Study ongoing	➤90.4% vaccine efficacy against CIN 2+ containing HPV 16/18 DNA
Pedersen et al, 2007 Comparative trial	To assess immunogenicity and safety in early adolescents	773 women aged 10–14 years and 15–25 years All received HPV bivalent vaccine at 0, 1 and 6 months	➤100% seroconversion in both age groups ➤The geometric mean titres of antibodies were approximately twice as high in the 10–14 year age group compared to the 15–25 year age group



Key Points

- The cervical screening programme has reduced the incidence of cervical cancer
- Two HPV vaccines are available: a bivalent vaccine (Cervarix) and a quadrivalent vaccine (Gardasil)
- Both vaccines have been shown to be extremely effective at preventing infection in women with the HPV types covered by each vaccine
- Not all cancer causing strains of HPV are covered by the vaccines and immunisation does not offer protection for women already infected
- The cervical screening programme will continue to be an important strategy to reduce the risk of cervical cancer

Mathematical modelling based on a vaccination cohort of 12-year-olds in the UK estimates that there would be a 66% reduction in the prevalence of high grade pre-cancerous lesions and a 76% reduction in cervical cancer deaths if the national immunisation programme is successful (Kohli et al, 2007). At present there is no evidence that those not vaccinated would gain any benefit through herd immunity due to a lower circulation of HPV 16 and 18.

Why cervical screening will continue

There are several other oncogenic types of HPV. Data is accumulating on partial cross-protection against some of these other types by the vaccines. However, vaccinated women remain at risk of disease due to the types not covered by the vaccines. Therefore it is essential that young women who have received HPV immunisation attend for cervical screening at the appropriate time.

Impact of the HPV programme

The effectiveness of the HPV programme will only be measurable once the vaccinated cohort become 25 years of age and older and enter the cervical screening programme. That will not be for at least another 7 years and will take a few years of screening data to amass a substantial body of evidence. Evidence is accumulating on the longevity of protection and whether booster doses will be needed in the future.

Conclusions

Immunisation is a safe and effective way to protect against cervical cancer caused by the HPV types in the vaccines. The cervical screening programme will continue to play a pivotal role in the prevention of cervical cancer, as not all oncogenic strains of HPV are covered by the vaccines and HPV immunisation does not offer protection for women already infected.

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Evidence-based recommendations

Pauline MacDonald explains the recommendations and rationale for the HPV immunisation programme outlined by the Joint Committee on Vaccination and Immunisation, explaining why the vaccine is being offered under the programme to girls aged from 12 up to 18 years, and why cervical screening will continue.

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Once the Joint Committee on Vaccination and Immunisation (JCVI) had established that the licensed human papillomavirus (HPV) vaccines were highly effective and had good safety profiles, it considered the available published and unpublished evidence on which groups might benefit from vaccination. It made its recommendations to the Secretaries of State for Health in October 2007. Later that month the Secretary of State announced that the HPV vaccine would be introduced into the routine UK immunisation programme (DH, 2007). This statement included a summary of the JCVI's recommendations:

- The routine vaccination of girls aged 12–13 years
- A catch-up programme for girls under the age of 18 years
- Acknowledgment that the evidence that a catch-up programme for all women aged 18–25 years was unlikely to be cost-effective but could benefit some individual women. The Department of Health will consider this further.

In May 2008 the main features of the programme were summarised in a letter from the Chief Medical Officer et al (2008), and a concurrent letter (DH, 2008a) gave more detailed guidance on the strategy for implementation.

The new programme began on 1 September 2008. HPV immunisation will be offered to all girls aged 12–13 years as part of the routine childhood immunisation programme. On 21 July 2008 the DH announced that girls aged 17–18 years would be offered the vaccine from September 2008 as the first group in a catch-up campaign (DH, 2008b). The remaining catch-up campaign, for girls aged between 13 and 18 years, will take place between 1 September 2009 and the end of the academic school year in 2011.

The main features of the campaign are detailed in *Table 1*. The national cervical screening programme remains essential to the prevention of cervical cancer, and will remain unchanged following the introduction of HPV immunisation.

The rationale for the programme

The aim of the UK HPV immunisation programme is to reduce a female's risk of cervical cancer in future years.

Why not offer everyone the vaccine?

The HPV vaccine is the most expensive ever to be introduced into the UK childhood immunisation schedule. The list price is £80.50 per dose (Joint Formulary Committee, 2008: 650). Health-care interventions are becoming more costly, presenting the NHS with a dilemma. Evidence of both effectiveness and cost-effectiveness has to be considered if patients are to receive the best care (National Institute for Health and Clinical Excellence (NICE), 2008). Without a bottomless pit of taxpayers' money all health interventions need careful consideration. Funding for one intervention means the inability to fund another.

While it is recognised that everyone not already infected with HPV types 16 and 18 might benefit from HPV vaccination, some groups will benefit more than others. Scrutiny of the evidence led to the JCVI's recommendations in terms of sex and age.

Table 1. The HPV programme

Child schedule	The first cohort to be immunised will be girls born between 1 September 1995 and 31 August 1996 (school year 8 in 2008/2009) and 1 September 1990 and 31 August 1991 A 3-dose course of HPV vaccination is required over about 6 months A schools-based programme is recommended (for younger girls) Vaccine will be supplied free of charge to PCTs A range of information materials, guidance and other resources, for both professionals and the public, will be produced
Catch-up programme	A 2-year catch-up campaign will continue from the beginning of the 2009/2010 school year for all girls aged up to 18 years (i.e. 17 years and 364 days) at 31 August 2009, that is: ➤All girls born between 1 September 1991 and 31 August 1993 (school years 12 and 13 in the academic year 2009/2010) will be offered immunisation from the beginning of the 2009/2010 school year, ***and*** ➤All girls born between 1 September 1993 and 31 August 1995 (school years 11 and 12 in the academic year 2010/2011) will be offered the vaccine from the start of the 2010/2011 school year

From: Chief Medical Officer et al, 2008

The DH (2007) has estimated that the cost of the national programme to the UK taxpayer per female birth cohort will be about £100 million per year. In years 2009/2010 and 2010/2011, when older girls are offered the vaccine in the catch-up campaign, the cost may reach £300 million a year (since year 8 will be immunised as well as the two catch-up years).

These costs give an indication of the potential expenditure if the vaccine were available to all.

Why vaccinate females only?

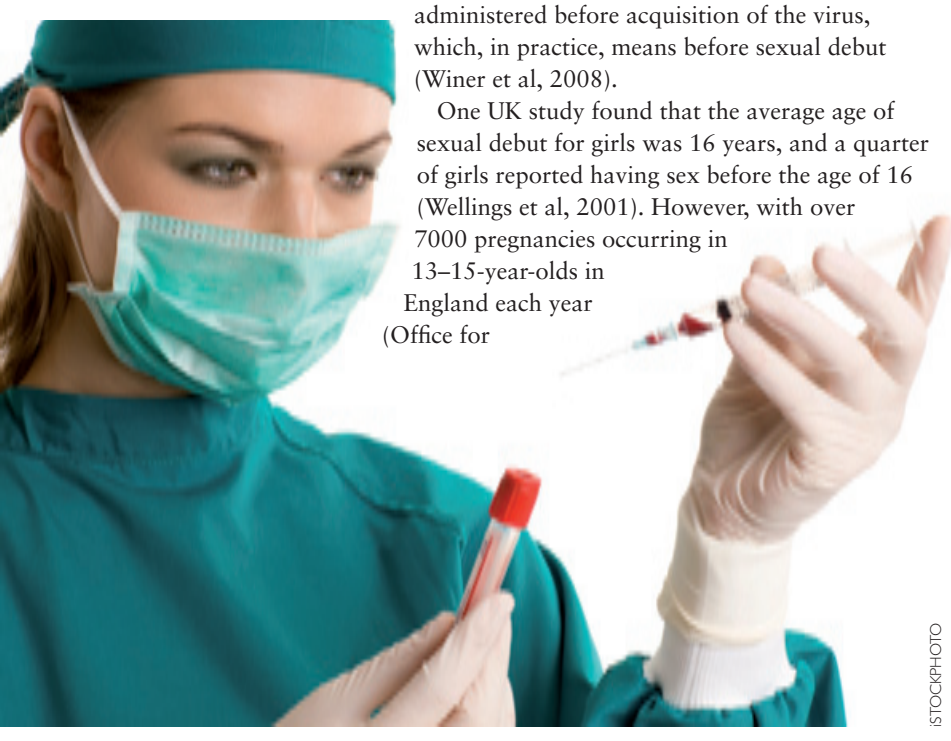
The cost–benefit analysis of using HPV vaccine in males found it not to be cost-effective, 'adding little additional benefit' to reduction of cervical cancer (JCVI, 2007a). While men do not get cervical cancer, they get other diseases caused by HPV, notably carcinoma of the anus in men who have sex with men. Males are as likely as females to be infected with HPV and may infect their sexual partners. However, the cost of immunising males far outweighs the savings to be made on preventing HPV disease in males.

It is reasonable to expect that, with the high efficacy of the vaccine, and planned high vaccine coverage in girls, there will be a corresponding fall in prevalence of HPV in both sexes. Consequently only females will be offered immunisation in the national programme.

Why only offer the vaccine to girls aged 12–18 years?

HPV infection is the most common viral infection in sexually active men and women (Centers for Disease Control and Prevention, 2004). There is no evidence that the vaccines are effective against already established infection with HPV (English, 2008). For maximum benefit the vaccine should be administered before acquisition of the virus, which, in practice, means before sexual debut (Winer et al, 2008).

One UK study found that the average age of sexual debut for girls was 16 years, and a quarter of girls reported having sex before the age of 16 (Wellings et al, 2001). However, with over 7000 pregnancies occurring in 13–15-year-olds in England each year (Office for National Statistics, 2008), the age of sexual debut is much younger for some.



ISTOCKPHOTO

Jit et al (2007) found that the percentage of women infected with HPV increased sharply after the age of 14 years. At any one time over 7% of women have HPV infection (WHO-ICO, 2007). HPV infection is greatest in women aged over 20 and under 30 years of age (Kitchener et al, 2006).

The evidence indicates that young girls, who are less likely to be sexually active, would benefit most from the vaccine. The JCVI considered the evidence from attitudinal studies of acceptance of this vaccine. The DH commissioned two qualitative studies to assess knowledge and attitudes about cervical cancer, HPV and the vaccines. One study interviewed parents of young boys and girls aged 8–10 years (Noakes et al, 2006). The second interviewed girls aged 11–12 years, their parents and health professionals (Zimet et al, 2006). Parents of younger primary school age children were uncomfortable with immunising children of this age with HPV vaccine. Parents and girls in the older groups, who were all of secondary school age felt more comfortable about the vaccine and thought it was a good idea. These studies indicated that, as a consequence of the inescapable link between the vaccine and sexual activity, parents would be more likely to accept the vaccine if it were offered to older girls, probably of secondary school age (Yarwood, 2007).

What about women over 18 years of age and men?

The JCVI reviewed the evidence on the vaccine's efficacy in women over 18 years of age and found that a nationally funded catch-up campaign was not cost-effective. The JCVI acknowledged that the studies reveal that women who were still at risk of new HPV infection with the vaccine types might benefit from vaccination (JCVI, 2007a). The DH is considering this further (2008).

The harsh reality is that the obstacle to offering the HPV vaccine to women over 18 years of age and males is the high cost of the vaccine and its delivery.

A large part of the total cost of a nationally funded vaccination campaign is spent on management, personnel and administration. This includes paying health professionals to administer the vaccine, a calling system for eligible cohorts, data collection and analysis, and education and marketing of the campaign to the public.

Deciding whether to vaccinate patients outside the programme

Some young women and men are requesting the HPV vaccine from health-care providers. The cost of vaccinating patients who present themselves may only be the cost of the vaccine itself and minimal administration, but the practitioner is obliged to ask:

- Is this patient likely to benefit clinically from the vaccine?
- Is this good use of the limited local budget?
- Could the money be better spent on other health interventions for other patients?

These are difficult ethical and moral questions and prescribers need to apprise themselves of the evidence.

Clinicians have a limited but growing body of evidence to inform their decision to prescribe the HPV vaccine, e.g. the likelihood of existing HPV infection given the patient's age, number of sexual encounters and partners. There is also growing evidence about the risk factors for cervical cancer (WHO-ICO, 2007). However, the evidence remains insufficient to determine which individual women are at risk and which are not (Dempsey et al, 2008).

Tests for the presence of HPV vary in their sensitivity and specificity (Mayrand et al, 2007) and are only available from a laboratory. A rapid test that could be used locally to reveal the presence of oncogenic types of HPV is not yet available, but may be in the future. However, a test would raise its own dilemmas, not least, which treatment to offer patients found to be infected with oncogenic HPV (Waller et al, 2007).

In the absence of more definitive evidence and tests, the decision to immunise someone with HPV vaccine has to be left to each prescriber's clinical judgment.

Conclusions

The HPV vaccines are highly effective against the oncogenic strains of HPV which they contain. The vaccines are most effective in those not already infected with the types of HPV they contain. The JCVI gave extensive consideration to the evidence of efficacy and cost-effectiveness of a programme for the UK. The DH is funding the implementation of this vaccine in specific groups based on population level cost–benefit analysis. The cost-effectiveness of this programme will be severely compromised if implementation and subsequent vaccine uptake is poor. The challenges of implementing this programme will be covered in another article in this supplement.

Two vaccines are licensed for use in UK. Individual clinicians will be required to make difficult decisions, based on efficacy, finance, ethics and morals, when considering the HPV vaccine for those outside the national implementation programme.

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Key Points

- HPV immunisation is being offered to all girls aged 12–13 years as part of the routine childhood immunisation programme
- Girls aged 17–18 years are being offered the vaccine from September 2008 as the first group in a catch-up campaign
- The cost-effectiveness of the HPV programme will be severely compromised if implementation and vaccine uptake is poor
- The decision to immunise an individual with the HPV vaccine who is outside the cohorts of the national programme has to be left to the clinical judgment of each prescriber

How to manage implementation

Pauline MacDonald outlines the key considerations for effective implementation of the HPV programme by school nurses and practice nurses in England. Details of differences in the delivery of HPV immunisation in Scotland, Wales and Northern Ireland are included. Effective communication with girls and parents, issues of consent, vaccine storage and the financial considerations are also discussed.

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The HPV vaccines are highly effective at preventing infection with the HPV types contained in them. However, if the vaccine is not delivered effectively to a sufficient number of girls in the cohort, its efficacy and cost-effectiveness will be much reduced.

Options for delivery

Primary care trusts (PCTs) in England can decide how best to deliver the programme to their local population. The possible options for delivery are:

- School health teams, including school health advisors, nurses and administrative staff
- A dedicated immunisation team employed by the PCT
- General practices, including practice nurses and GPs
- An external independent provider
- A combination of the above.

The Joint Committee on Vaccination and Immunisation (JCVI) (2007) has recommended that a school-based programme is likely to be most effective for girls in school, and the majority of English PCTs with school nursing teams are likely to deliver a school-based programme to girls in school year 8. For PCTs without a school nursing team this could be a costly service to establish, and most of these PCTs are likely to consider alternative providers.

The choice of delivery for 17- and 18-year-old girls in the catch-up cohort is more challenging (DH, 2008a). The majority of girls of this age may not be at school but in further education, training, employment or unemployed. A school-based programme for these girls is unlikely to be effective.

PCTs must ensure that all girls aged 12–13 years and 17–18 years who live in the PCT area have the opportunity to access and receive the immunisation. The PCT delivery plan must consider all possibilities of where girls may be based so that all options for delivery are explored and considered.

Scotland, Wales and Northern Ireland are following the JCVI recommendations but implementation will differ in some details (*Box 1*).

School-based delivery

A school-based programme for school-age girls is likely to be most effective. Many school nursing teams already immunise children with a school leaver booster. The mechanisms, systems, administration and goodwill of the schools are in place. The girls are a 'captive audience' and immunising them in school negates the need for them to make appointments with another provider. Any girls missed at the scheduled school immunisation sessions will have to be offered immunisation at a 'mop-up' session. School nurses may visit the school especially to immunise missed girls, provide clinics for them to attend, or they may have to go to another provider such as their general practice.

If the majority of girls are being immunised in schools, arrangements must be made for girls not at school to be offered the vaccine. This may include those who go to school outside the PCT, those

educated at home, or in hospital, and those excluded from school, in care or in youth-offender institutions.

Dedicated immunisation team

PCTs who have or intend to have a dedicated immunisation team could deliver the programme to all girls in all cohorts. The teams would have the flexibility to go into schools and colleges, run community-based clinics, visit large employers or invite girls for appointments at bases across the PCT. While such teams would provide a large degree of flexibility, they may be a costly and time-consuming resource. Girls in college may not attend every day so the team would have to visit more than once in a week to reach all girls. Community-based clinics need to be advertised, specially established and resources committed without guarantee of attendance. Health professionals in such teams, particularly nurses, are likely to get limited nursing experience; this might affect recruitment and retention in such teams.

General practices

Teenagers may be reluctant to attend general practices with their parents or guardians and may be wary of attending alone. For school-age girls, attending a general practice appointment may require absence from school, and possibly time off work for a guardian. The advantages are that each girl on a practice list could be invited for the vaccine and practices could easily re-invite non-attenders. Practice nurses already deliver the majority of immunisations in the routine childhood programme so have the necessary skills to deliver this programme. However, practices are currently being challenged to provide a range of additional services

Box 1. Implementation in Scotland, Wales and Northern Ireland

Scotland

Scotland's HPV immunisation programme started on 1 September 2008. Girls in year two of their secondary education (S2) (aged 12–13 years) will be routinely offered the vaccine on an annual basis.

The Scottish Government started its catch-up programme for girls aged 13–17 years in September 2008. This will be phased in over a 3-year period:

- Girls in S5 and S6 (and those aged 16 and 17 who have left school) are being offered the vaccine from 1 September 2008
- Girls currently in S3 and S4 will be offered HPV immunisation from September 2009
- The third year of the catch-up (2010) will focus on girls who have not completed or started their immunisation.

NHS health boards will provide a school-based programme for girls in school. Girls who have left school will be contacted by their local NHS later in the year. Although the schedule may vary slightly from school to school, the national schedule recommends five visits by the nurse. This consists of three main visits scheduled at 0, 1–2 and 6 months and two additional shorter 'mop-up' sessions for girls who have missed a dose. This will maximise the number of girls who complete the full course within the recommended 6-month period.

NHS Health Protection Scotland is responsible for coordinating the programme and has been working with local health boards to develop implementation plans.

Comprehensive training slides have been created to support nurses and these are available online at www.healthscotland.com/immunisation. A DVD has also been created to help nurses with any pre-immunisation talks. It can be viewed on the public information website (www.fightcervicalcancer.org.uk) along with the television advertisement and information materials which have been translated into the nine most commonly used languages in Scotland. A public helpline is also available 0800 22 44 88.

All girls will be given a consent form and leaflet (relevant to their age group) when they return to school from their summer holidays. Girls in S2 will also be given a Q&A booklet for their parent or carer. Girls will be asked to discuss the information in the leaflet with their parent or carer before agreeing to have the immunisation. If a girl is aged under 16, her parent or carer will be asked to sign the consent form.

If a girl is aged 16 or over she will be asked to sign and return the consent form herself. A Q&A booklet for older girls is available to view and download on the public information website. Nurses can view an example of the consent form on the NHS Health Scotland website at www.healthscotland.com/immunisation.

NHS Health Protection Scotland will evaluate the impact of HPV immunisation and monitor vaccine uptake; incidence of HPV infection, pre-cancerous cervical lesions and cervical cancer; adverse events; and attitudes to and knowledge of HPV and HPV immunisation. Routine cervical screening will continue for women aged 20–60 every 3 years. **MD**

Wales

HPV immunisation for girls in school year 8 (aged 12–13 years) started in September 2008. Parents of all 12–13-year-old girls will receive a letter advising them of the new programme. A 2-year catch-up campaign for girls up to age 18 will start in autumn 2009. Routine cervical smear tests for women aged 20–64 will continue every 3 years (NHS Direct Wales, 2008).

Leaflets, posters, information sheets and consent forms for 12–13-year-old girls and their parents also available on paper and online at the Welsh Assembly Government's Public Health Protection website: http://tinyurl.com/6hz2gr

Northern Ireland

HPV immunisation for girls aged 12–13 (school year 9) started on 1 September 2008. The catch-up campaign, beginning with girls aged 17–18 (school year 14) also started in September 2008, and will run until June 2011. School health teams will implement the routine campaign for girls in year 9, and general practices will vaccinate older girls for the catch-up campaign in 2008/2009 as a local enhanced service (LES). Arrangements for the catch-up campaign from 2009 remain to be determined.

All information materials and details of the Northern Ireland campaign are available at www.helpprotectyourself.info **LD**

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such as extended opening hours and an increasingly complex and demanding childhood immunisation programme. Some small practices may not have the capacity to deliver this enhanced service. There may be a requirement for practices to increase resources, e.g. make more clinic space or recruit extra staff. This route is likely to be more costly than using an established school nursing service.

External independent provider

Some organisations and charities are offering support to PCTs to deliver the HPV programme. Such providers would be attractive to PCTs unable to recruit staff or find an established provider willing and able to implement the programme. Quality and service provision will be strictly controlled by a contract, and expertise at PCT level would be needed for commissioning and performance monitoring of contractors. Using an independent provider would ensure that already stretched providers, such as school nurses or general practices, are not further burdened with delivering this programme. Any PCT deciding to use an independent provider must ensure robust assessment of value for money and competition rules. The complexities of data protection, transfer and production would also require strict control and expertise at local level.

Combination of providers

In practice, many PCTs may have to use a combination of two or more service providers for this programme. Using established providers would enable current systems, locations and resources to be used. With available money and resources it is likely that vaccination would best be delivered in schools for school-age children and by individual appointments for older girls, probably in general practices. Using two or more providers will make the job of the PCT programme manager or immunisation co-ordinator more difficult. As well as current standards pertaining to health records, vaccines and their storage, additional requirements for HPV data and vaccine management have been prescribed by the DH (2008b).

Finance

The DH will provide vaccine for the identified cohorts free to the NHS. Dedicated funding for the HPV programme is to enable PCTs to commission providers and implement the programme (DH, 2008c; DH, 2008a). When commissioning a service the PCT may have to consider whether the nationally provided funds will cover the delivery costs. Any shortfall in funding must be found within existing PCT resources. Some PCTs have submitted bids in their local delivery plan process and may have to continue to do so in coming years. Providers may be obliged to present business cases or submit claims to the PCT for activity under any agreed contract or service specification.

Vaccine supplies and storage

The bivalent HPV vaccine, Cervarix, will be provided by the DH for the national programme. This vaccine is the most expensive to be added to the immunisation programme in the UK; as a consequence its supply, use and storage will be strictly monitored (DH, 2008b).

Only a PCT-nominated person can order vaccine, which can be delivered to as many sites as requested but each provider site must have a delivery account number. The PCT must submit data each month to a national online database, the Health Protection Informatics (HPI) site. Providers need to report:

- The number of vaccines received from the DH
- The number administered to girls
- The number held in local storage
- The number of vaccines wasted.

There must be careful maintenance of vaccine storage, transport and cold chain to minimise wastage. An audit of cold chain standards before the programme starts will help ensure compliance with standards.

Education and training

All staff likely to be consulted or involved in delivery of the HPV programme will require training and education. This may include the school nursing teams, practice nurses, GPs, immunisation nurses, health visitors, staff in child health information departments, community pharmacists, and patient advice and liaison service (PALS) staff. Tailor-made education and training may need to be offered to different groups. Training slides and question and answer resources are available from NHS Immunisation Information, and can be downloaded from the internet (*Box 2*), but each PCT must inform all staff of local provision arrangements.

Communication

There will be a national information and publicity campaign for the public. Information will be provided at varying levels including leaflets and information packs (also available to download from the NHS immunisation websites) (*Box 2*), media and television advertising, and more detailed scientific papers and articles. PCT communications teams can help ensure information is delivered locally in a timely and appropriate manner.

Consent

As with all health interventions, the girl receiving the vaccine must give her informed consent. The following guidelines apply:

- Consent does not have to be written
- Any girl over the age of 16 years can consent for herself

Box 2. Resources online

- **NHS Immunisation Information**
  www.immunisation.nhs.uk/Vaccines/HPV
- **Northern Ireland**
  www.helpprotectyourself.info
- **Scotland**
  www.healthscotland.com/immunisation
- **Wales**
  http://new.wales.gov.uk/topics/health/protection/immunisation/leaflets/hpv/?lang=en

- A girl under 16 years of age can legally consent to vaccination so long as the nurse or other health professional administering the vaccine determines that she is competent to understand the risks and benefits (Fraser competency).

The DH (2008b) has issued detailed guidance on consent for HPV vaccine and vaccination in general (Salisbury et al, 2006). In practice, school nursing teams seek the written consent of guardians and do not immunise children in schools without it.

Uptake data

Data will be based on uptake over the academic year from September to August annually. On a monthly basis uptake data must be submitted to the HPI site. Providers may be required to enter these data themselves or submit data to the PCT co-ordinator; this will be a local decision. Nationally data are required on numbers immunised with first, second and third doses. PCTs' monthly uptake rates will be based on the cohort denominators. Annual uptake rates will be based on denominators submitted at the end of the academic year period and will account for any large movements of girls into or out of a PCT area.

Data requirements

To monitor the delivery of the programme a PCT will need to reflect on the detail of the uptake over the year. Final uptake data submitted to the HPI website will not provide the detail necessary to evaluate the local programme fully. Immunisation uptake is affected by social class, ethnicity, level of deprivation, family size, disability and level of health or social needs (DH, 2005). To assess the impact of these factors on this programme PCTs may collect some or all the information in *Table 1*.

Performance management

Each PCT will be performance managed by the strategic health authority (SHA) using the HPV standard and target identified by the DH (2008d). Although PCTs can set their own targets there is an expectation that uptake of this vaccine needs to be in excess of 90% in each cohort for it to be effective, to provide herd immunity and cost-effectiveness. The PCT must performance manage the providers to ensure the programme is delivered effectively, that data are managed correctly and that patients receive a quality service.

Conclusions

Implementation of the routine HPV immunisation for 12–13-year-old girls and the catch-up campaign for girls up the age of 18 years provides an exciting and challenging time for all those involved in immunisation provision. The vaccine is highly effective and with good uptake coverage could save about 800 deaths from cervical cancer each year.

Regardless of whether immunisation is provided in schools, general practices, by independent providers or a combination of these methods, there are challenges for data collection, vaccine supply, transport and storage, consent, education and communication. PCTs will be responsible for the effective implementation of the HPV programme, and will be performance managed by SHAs. The amount of planning and preparation required to ensure the programme's success should not be underestimated. Without effective implementation the overall effectiveness of this exciting new vaccine will be undermined.

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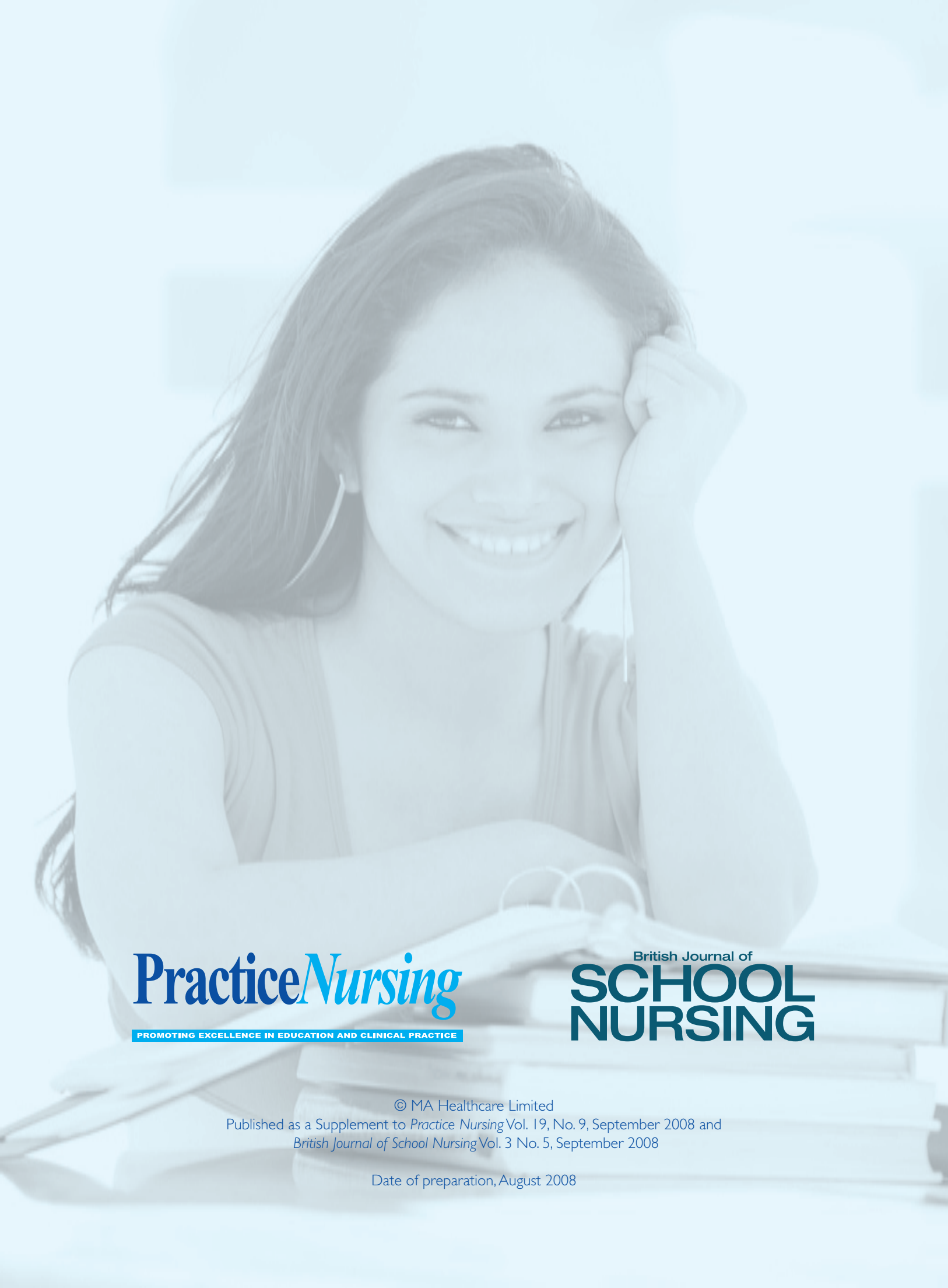
Key Points

- For school-age girls, a school-based immunisation programme is likely to be most effective where school nursing teams exist
- Vaccination of 17–18-year-old girls may be carried out by school health teams, a dedicated team employed by the PCT, general practices, an independent provider or by a combination of these methods
- All staff likely to be consulted or involved in delivery of the HPV programme will require training and education

Table 1. Data that may be collected

Ethnicity of girls receiving and refusing the vaccine
Refusal: Number of girls or their guardians refusing to consent to vaccination, and why
Failed to complete: Number of girls who started but failed to complete the three-dose course, and why
Locations where girls are immunised with each dose of the vaccine, e.g. school, clinic, general practice or private provider
Uptake rate by school, clinic, or general practice and the postcode for each
Movement of girls into or out of the PCT during the academic year and number of doses given to each before the move
Completion: Number of girls completing immunisation in the recommended timescale (6 months), within one academic year, over two academic years or longer
Ad-hoc visits: For school-based delivery, the number of ad hoc visits required to immunise girls (as opposed to scheduled sessions)
Non-attenders: For other providers, the number of girls who do not attend planned sessions, and the number who never attend despite invitation



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