Cervical intraepithelial neoplasia: screening and management

Globally, cervical cancer remains the fourth most common female malignancy, with over 528 000 new cases and 266 000 deaths in 2012; 84% of these occurred in low-resource settings (Ferlay et al, 2015). Cervical cancer is largely preventable through organized screening programmes, which can detect pre-malignant disease and treat it before invasive disease develops. Cervical intraepithelial neoplasia is the pre-malignant, dysplastic condition of the uterine cervix, which in a small proportion of cases will eventually progress to invasive cervical cancer if left untreated.

Aetiology and natural history

In 2008, Harald zur Hausen was awarded the Nobel Prize in Physiology or Medicine for identifying human papilloma virus as the causative agent of cervical intraepithelial neoplasia and cervical cancer. This highly prevalent, small double-stranded DNA virus is transmitted via skin-to-skin or mucosa-to-mucosa contact, with peak prevalence around 20 years of age. There are over 100 subtypes; 13 have been identified as high risk and cause cervical cancer in 100% of cases. These have also been related to other cancers to a lesser degree such as vulva, vagina, anal and oropharyngeal cancers. HPV-16 and -18 are responsible for around 70% of all invasive cervical cancers, with HPV-16 most prevalent in squamous carcinomas, and HPV-18 in adenocarcinomas (Crosbie et al, 2013). HPV-6 and -11 are low-risk subtypes but lead to the development of anogenital warts.

Data from the ARTISTIC trial in the UK (Kitchener et al, 2006) revealed that the prevalence of high-risk human papilloma virus infection before the start of the vaccination programme in the UK ranged from 40% at 20–24 years of age, and steadily declined to 6% at 55–64 years. At the peak of high-risk human papilloma virus prevalence, 12% had HPV-16 and 3% HPV-18 infection (Kitchener et al, 2006). It is estimated that by 50 years of age, 80% of sexually active people will have been infected at some point (Moscicki, 2005).

Over 90% of these human papilloma virus infections are transient, being cleared by an incompletely understood immune response within 6–18 months (Plummer et al, 2007), and persistence of the virus is required for development of high-grade cervical intraepithelial neoplasia and cervical cancer. Although the cause of persistence in some but not other individuals is unclear, factors such as age, immunodeficiency, smoking, oral contraceptives and *Chlamydia trachomatis* infection all correlate with higher persistence rates.

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Table 1. Classification of cervical intraepithelial neoplasia glandular epithelium – cytology and histology

Cytology				Histology
British Association for Cytopathology/ NHS Cervical Screening Programme		**Bethesda**		
Borderline changes in endocervical cells ? Glandular neoplasia	Endocervical Non-cervical	Atypical glandular cells not otherwise specified		Cervical glandular intraepithelial neoplasia or adenocarcinoma
		Endocervical	Endometrial	
			Glandular	
		Atypical glandular cells favour neoplastic	Endocervical	
			Glandular	
		Endocervical adenocarcinoma in situ		
		Adenocarcinoma	Endocervical	
			Endometrial	
			Extrauterine not otherwise specified	

From NHS Cancer Screening Programmes (2013)

Table 2. Classification of cervical intraepithelial neoplasia squamous epithelium – cytology and histology

	Cytology	Histology
British Association for Cytopathology/ NHS Cervical Screening Programme	**Bethesda**	
Borderline changes in squamous or endocervical cells	Atypical squamous cell of uncertain significance (ASCUS), or atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)	Human papilloma virus
Low-grade dyskaryosis	Low-grade squamous intraepithelial lesion (LSIL)	Cervical intraepithelial neoplasia 1
High-grade dyskaryosis (moderate)	High-grade squamous intraepithelial lesion (HSIL)	Cervical intraepithelial neoplasia 2
High-grade dyskaryosis (severe)	High-grade squamous intraepithelial lesion (HSIL)	Cervical intraepithelial neoplasia 3
High-grade dyskaryosis or ?invasive squamous cell carcinoma	High-grade squamous intraepithelial lesion (HSIL); squamous cell carcinoma (SCC)	Cervical intraepithelial neoplasia 3 – squamous cell carcinoma

From NHS Cancer Screening Programmes (2013)

The virus preferentially infects the basal cells of the cervical transformation zone; the area of squamous metaplasia adjacent to the squamocolumnar junction, and the area in which cervical intraepithelial neoplasia develops. Viral oncogene expression results in histological abnormalities including basal cell proliferation, nuclear enlargement and presence of abnormal mitotic figures, which define cervical intraepithelial neoplasia. These features are used to classify the severity of cervical intraepithelial neoplasia (*Tables 1* and *2*), along with the proportion of dysplastic epithelium present. CIN1 is largely appreciated to be a clinically insignificant histological marker of human papilloma virus infection, caused by low- and high-risk human papilloma virus subtypes. CIN2 and 3 are regarded as high-grade lesions, CIN2 being a more heterogeneous condition that may also be caused by both low- and high-risk human papilloma virus types, while CIN3 is considered by some to be true precancer, although regression is still possible (Ostor, 1993)(*Figure 1*). Currently it is not possible to determine which patients will develop invasive disease, so all high-grade disease must be treated.

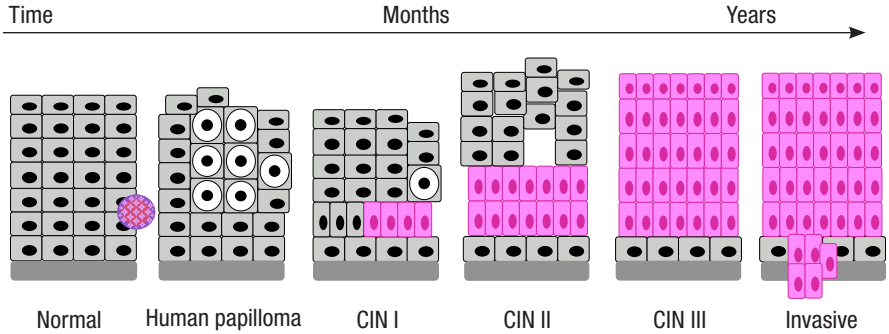
Dysplastic endocervical glandular cells may arise, referred to as cervical glandular intraepithelial neoplasia. The incidence of cervical glandular intraepithelial neoplasia is increasing, and around 30% of invasive cervical cancers are now adenocarcinomas, although their natural history is less well understood.

Population-based screening

There are no clinical features of cervical intraepithelial neoplasia, and it is largely detected through the NHS Cervical Screening Programme, based on cervical cytology, which was introduced in the UK in 1988 for women aged 20–65 years. Organized cervical screening programmes significantly reduce both incidence and mortality rates of cervical cancer (Peto et al, 2004).

In 2005, the minimum age for screening in England was increased to 25 years of age, because screening 20–24-year-olds was not shown to reduce rates of invasive cancer (Sasieni et al, 2009), and may result in young women undergoing unnecessary treatment that can have an impact on future obstetric outcomes (Kyrgiou et al, 2006, 2012, 2014). Coverage of the screening programme in England in 2013–14 was 77.8% among all women, but there are concerns that among 25–29-year-olds the attendance rate was poor at only 63.6%. A cervical smear using a liquid-based cytology system has a positive predictive value of 72–92% for detecting CIN2+ (Health and Social Care Information Centre, 2015), and is classified according to the NHS Cancer Screening Programme 2013 system in the UK and the Bethesda system in many other countries (*Tables 1* and *2*). *Figure 2* represents the current UK algorithm for management of cytology results. Of women

Figure 1. Natural history of cervical intraepithelial neoplasia (CIN) and disease progression. Quoted rates from Ostor (1993).



	Borderline	Mild	Moderate	Severe	Dyskaryosis
Regression		57%	43%	32%	
Persistence		32%	35%	56%	
Progression to CIN3		11%	22%	–	
Progression to invasive cervical cancer		1%	1.5%	12%	

Figure 2. Current management of cytology results and referral to colposcopy. From Public Health England (2016).

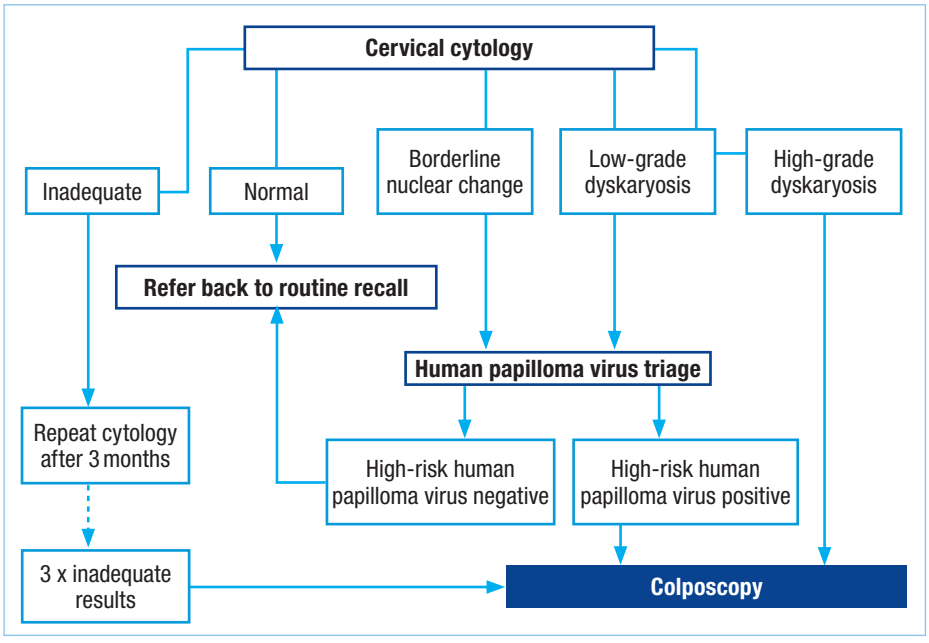
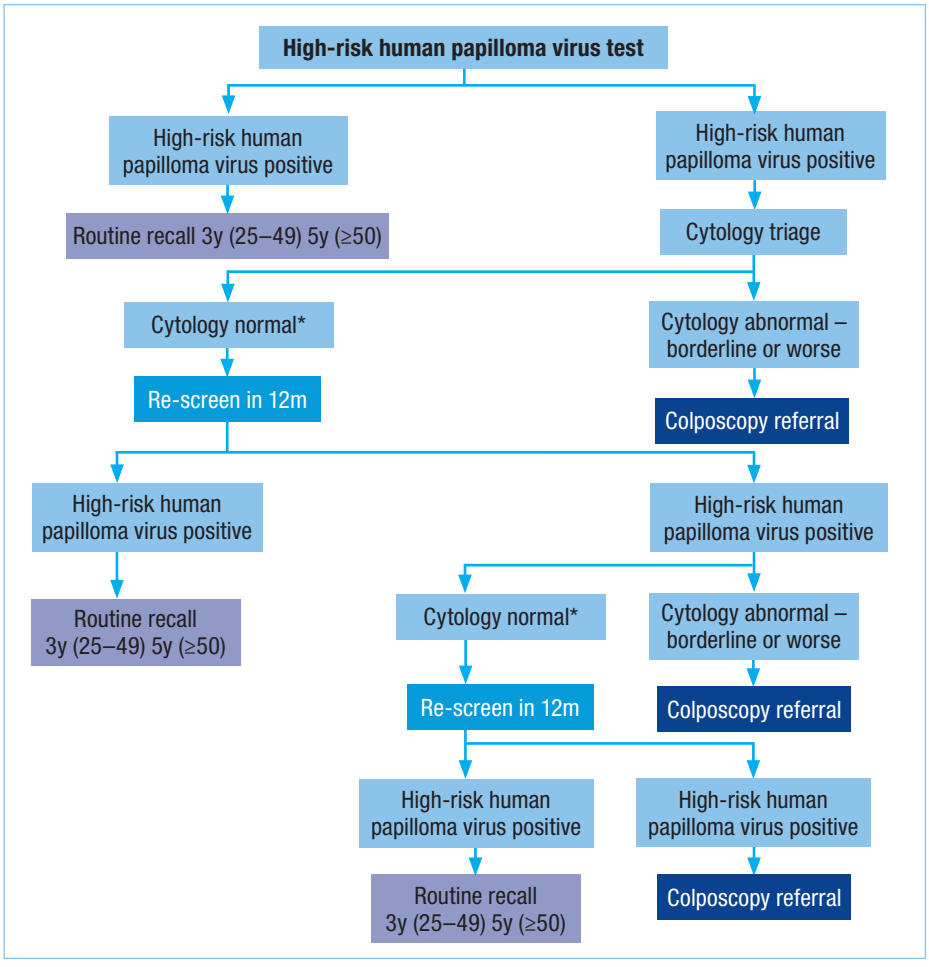


Figure 3. Proposed human papilloma virus primary screening protocol algorithm. From Public Health England (2016). HPV-16/18 recorded where available. Women testing HPV-16 or -18 positive/cytology normal at baseline and again at their first 12-month follow up test can be referred to colposcopy without further repeat tests.



screened, 6% were referred to colposcopy, the majority with either borderline changes or low-grade dyskaryosis.

There is now strong evidence from randomized controlled trials and meta-analysis that screening based on the human papilloma virus DNA test reduces the cervical cancer risk in comparison to cytology-based screening. This is currently under assessment at six sentinel sites across the UK using the algorithm in *Figure 3* (Ronco et al, 2014).

Colposcopy

A colposcope is a low-power, binocular vision microscope attached to a bright light source, which allows the clinician to directly examine the cervical epithelium for evidence of abnormalities. The objectives are to further assess abnormalities detected on cytology, guide colposcopically-directed biopsy, exclude invasive disease, help in outpatient management and treatment of pre-cancerous lesions, and help follow-up after treatment. Acetic acid is applied which produces acetowhitening as a result of reversible coagulation of nuclear proteins, the intensity of which is proportionate to the severity of the lesion. Lugol's iodine is subsequently applied and taken up by the glycogen-rich mature squamous epithelium, which becomes dark brown, but not the dysplastic tissue that contains little or no glycogen, and becomes a mustard yellow colour (*Figure 4*).

The size, location and extent of any lesion should be noted, along with the degree of any acetowhitening and iodine negativity, and the presence of abnormal vessels or vascular patterns such as mosaicism or punctuation. It is paramount that the upper limit of the lesion is visualized, with particular attention to any extension into the endocervical canal or on to the vaginal walls. Directed punch biopsies (approx. 0.5–1 cm diameter) can be taken from the area of greatest abnormality, and provide a histological diagnosis (*Tables 1* and *2*) in order to guide further management.

Conservative treatment

Conservative treatment for cervical intraepithelial neoplasia aims to destroy or remove the transformation zone, reducing the risk of future invasive cancer, and maintaining fertility, which is important to this group of patients given the average age for treatment is around 30 years. Treatment may be excisional or ablative, both methods being simple and quick to perform, and

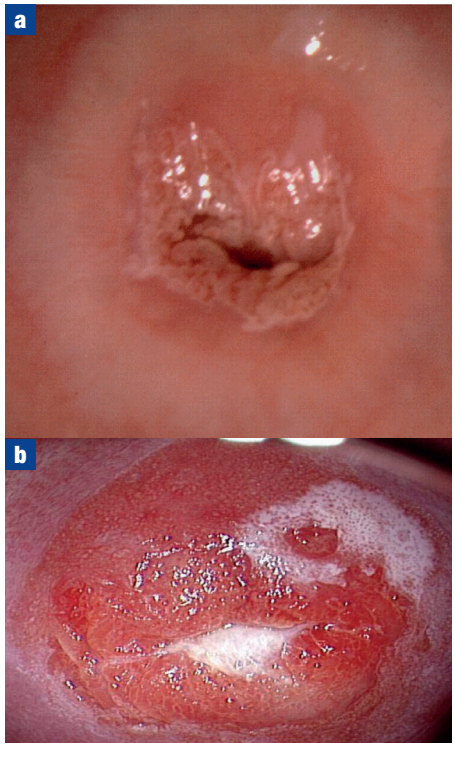
can be done under local anaesthesia in the outpatient setting. Meta-analysis suggests that both methods produce equal outcomes with respect to recurrent cervical intraepithelial neoplasia or invasive cancer (Martin-Hirsch et al, 2013). Success rates are 90–95%, and immediate complications including bleeding and infection are infrequent, rarely serious and routine antibiotic cover is not indicated. Some centres in the UK may adopt a 'see and treat' service, whereby treatment is offered at the first visit if there is colposcopic evidence of CIN2/3 or cervical glandular intraepithelial neoplasia.

Excisional treatment

Excisional treatment should be used if there is any suspicion of invasive or glandular disease. It also allows provision of a sample for histological assessment and examination of the margins to confirm whether excision is complete. Large loop excision of the transformation zone is the most frequently performed technique in the UK, being simple, easy to learn and of low cost. The choice of technique is largely dictated by user preference. Needle excision of the transformation zone offers great precision and flexibility but is more challenging than large loop excision.

Laser conisation has previously been used widely, but has largely been abandoned because of its expense. Cold knife conisation does not result in any thermal artifact, and thus offers the best option for accurate assessment of margins. However, cold knife conisation removes a larger amount of healthy tissue than other methods, with more serious adverse effects on the risk of future obstetric outcomes (Kyrgiou et al, 2006, 2012, 2014); this technique is rarely used today. Local anaesthesia containing a vasoconstrictor is injected into the cervix for pain relief and to reduce blood loss. A diathermy ball, or Monsel's solution (ferric subsulphate) are used for additional haemostasis.

Figure 4. **a.** Normal cervix on colposcopy and **(b)** cervix with high-grade cervical intraepithelial neoplasia showing dense acetowhite epithelium and punctuation.



Ablative treatment

Ablative treatments may be used in cases where the cytology, histology and colposcopic appearances are in agreement, when there is no suspicion of invasion, and when the entire lesion and transformation zone can be visualized. These are contraindicated when there is a history of previous treatment. Ablative techniques, apart from laser ablation, are cheap and easy to perform, thus ideal in resource-poor settings. Cold coagulation uses a thermo-sound heated to 100–120°C to destroy lesions up to a depth of 7 mm within 60 seconds, usually without the need for local anaesthesia. Cryocautery is another ablative technique, using a probe on a freeze–thaw–freeze cycle to destroy cells in around 2 minutes; its efficacy is lower for high-grade lesions compared to excision (Martin-Hirsch et al, 2013). Laser ablation or vaporisation using a carbon dioxide laser beam to destroy tissue can offer a great deal of precision, although it takes slightly longer than the former techniques and is expensive.

Follow up after treatment

Following treatment, women remain at higher risk of pre-invasive or invasive disease than the background population, which may be partly related to poor compliance with follow up (Soutter et al, 2012). Involved margins, a large lesion, or high-grade or glandular disease all increase the risk of recurrence, although repeat treatment is only indicated in women over 50 years of age or those with high-grade disease at the endocervical margin. A negative high-risk human papilloma virus test after treatment may have a greater negative predictive value than cytology alone, although the two together offer the highest degree of reassurance.

Current UK practice, introduced in 2012, is to invite women for cervical cytology with human papilloma virus 'test of cure' at 6 months, whereas those with normal, borderline or low grade dyskaryosis and negative human papilloma virus test are discharged back to 3-year recall. Women treated for cervical glandular intraepithelial neoplasia were previously kept under 6-monthly colposcopic surveillance for 5 years, but since 2014, UK guidelines suggest these women can also return to routine recall after a negative test of cure.

New technologies and biomarkers in colposcopy

In 2012 the National Institute for Health and Care Excellence approved the use of DySIS as a clinically and cost-effective diagnostic technology, compared to standard colposcopy. This digital video colposcope uses dynamic spectral imaging for acetowhite quantification, which can increase sensitivity of detection of high-grade lesions to 88%, compared to 55% with conventional colposcopy, and thus several UK centres now use the technology (Leeson, 2014).

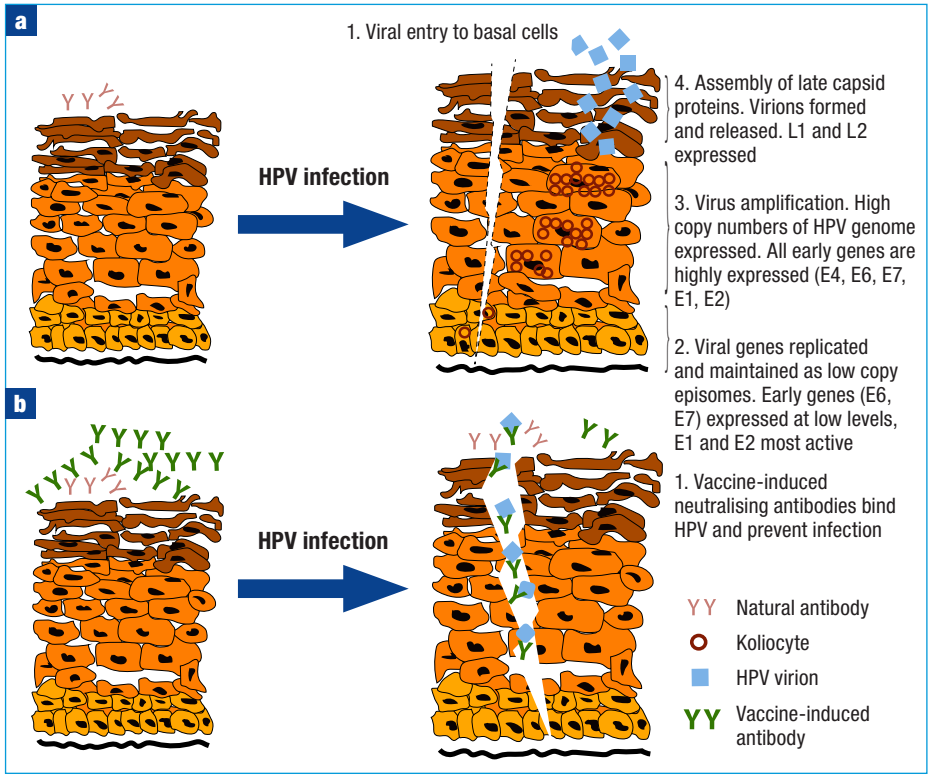
ZedScan is a handheld device that uses electrical impedance spectroscopy as an adjunct to traditional colposcopy shown to improve diagnostic accuracy and may lower intervention rates (Leeson, 2014). At least one centre in the UK has integrated ZedScan into their routine practice. Disease prevalence will decrease in the post-vaccination era, resulting in a possible decreased accuracy of traditional colposcopy. These technologies may play an important role in maintaining high standards of colposcopy practice.

Development of personalized medicine is a fast-advancing field, and the ability to personalize the management of women with cervical intraepithelial neoplasia may prevent unnecessary treatments thus reducing the risk of adverse pregnancy outcomes (Kyrgiou et al, 2006, 2012, 2014). Discovery of biomarkers could be used to stratify likelihood of disease progression but are also important for the personalized management of women with abnormalities at screening. Overexpression of viral E6/E7 oncogene mRNA and p16-Ki67 are emerging as potential tools for triaging low-grade disease

KEY POINTS

- Cervical cancer is the fourth most common female malignancy and is largely preventable through organized screening programmes.
- Cervical intraepithelial neoplasia is a pre-malignant, dysplastic condition of the uterine cervix, which can be treated to reduce the future risk of cervical cancer.
- Cervical intraepithelial neoplasia and cervical cancer are caused by high-risk, oncogenic subtypes of the human papilloma virus.
- The UK screening programme has significantly reduced morbidity and mortality from cervical cancer since its introduction in 1988.
- Human papilloma virus vaccines are now in use which significantly reduce the prevalence of cervical intraepithelial neoplasia and cervical cancer in the future, and must be given before sexual debut.

Figure 5. Natural history of human papilloma virus (HPV) infection in **(a)** unvaccinated and **(b)** vaccinated cervical epithelium. **a.** Unvaccinated epithelium may express small amounts of natural antibody against HPV, which have low efficacy against preventing future HPV infection. The virus is able to enter and begins to hijack the replication machinery of the basal epithelial cells, resulting in virion production. **b.** Vaccination provokes a strong immune response, resulting in production of antibodies, which are highly efficacious at neutralizing HPV virions, preventing infection.



but also for primary screening (Nasioutziki et al, 2011; Tsoumpou et al, 2011; Arbyn et al, 2012; Valasoulis et al, 2014).

Human papilloma virus vaccination

Development of human papilloma virus vaccines is one of the most significant medical advances in the field of gynaecological oncology of recent years. The vaccines lead to a strong and sustained IgG response to recombinant virus-like particles of the L1-capsid protein at a far higher level than that observed following natural infection (*Figure 5*). Although randomized controlled trials suggest 100% efficacy for high-grade lessions from HPV-16/18 (Dillner et al, 2010; Lehtinen et al, 2012) in women who are human papilloma virus naïve, the vaccines do not change the natural history of infections or disease present at the time of vaccination. It is therefore important that the vaccine is given before the sexual debut.

There are two human papilloma virus vaccines in use for vaccination programmes around the world. Cervarix is a bivalent vaccine against HPV-16 and -18, which are responsible for 70% of all invasive cervical cancers and Gardasil is a quadrivalent vaccine, with additional protection against the wart-causing HPV-6 and -11. Gardasil is currently used in the UK school-based vaccine programme, through which girls aged 12–13 years are given two doses, with a coverage of over 80%, significantly higher than most high-income countries. In England, a reduction in prevalence of HPV-16 and -18 from 19.1% to 6.5% has already been observed in 16–18-year-olds. Over 50% of young women infected with HPV-16 or -18 are co-infected with another high-risk human papilloma virus subtype not covered by the vaccine (Oakeshott et al, 2012). However, evidence suggests the vaccines offer cross-protection to other human papilloma virus subtypes, particularly 31, 33 and 45. If vaccination continues to have coverage of 80%, it is estimated that by 2025 there will be a 63% reduction in cases of invasive cancer, 51% reduction in CIN3 and 27% reduction in low-grade abnormalities (Cuzick et al, 2010).

In 2014 the US Food and Drug Administration approved Gardasil 9, a nonavalent vaccine which can protect against five additional high-risk human papilloma virus subtypes: 31, 32, 45, 52 and 58. This has the potential to prevent up to 90% of cases of high-grade cervical intraepithelial neoplasia and invasive cancer, but its long-term efficacy is yet to be reported.

Conclusions

Cervical intraepithelial neoplasia is a pre-malignant change of the cells of the uterine cervix which can lead to invasive cervical cancer in a small proportion of cases. The NHS Cervical Screening Programme significantly reduces the morbidity and mortality from cervical cancer, through detection of cervical intraepithelial neoplasia and treatment of high-grade disease. Excisional and ablative treatments are highly efficacious, although they increase the risk of adverse reproductive outcomes in a subsequent pregnancy. A school-based human papilloma virus vaccination programme was established in the UK in 2008 with 80% coverage. This is expected to significantly reduce the burden of high-grade cervical intraepithelial neoplasia and cervical cancer by 2025. **BJHM**

Conflict of interest: none,

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