Scientific Impact Paper No7, 2nd edition

Second draft – August 2024

SIP 7: Progress in Cervical Cancer Prevention in the UK

LB Ellis, S Bowden, D Lyons, M Kyrgiou, on behalf of the Royal College of Obstetricians and Gynaecologists.

Correspondence: Royal College of Obstetricians and Gynaecologists, 10–18 Union St, London SE1 1SZ. Email: clinicaleffectiveness@rcog.org.uk.

Plain-language summary

Globally, cervical cancer remains a preventable yet significant healthcare problem for women. The World Health Organisation announced a call to eliminate cervical cancer in 2018, with recommendations for screening, vaccination, and treatment of pre-cancerous cervical lesions.

Screening uptake is on the decline in the UK, particularly for younger women, where the rate has now dropped below 70%. There are slight variations in the screening programme among the devolved nations; primary screening is now with high-risk Human Papillomavirus (hrHPV) testing. This test is sensitive, but not specific, meaning it is good at not missing cancers or pre-cancer, but most people who test hrHPV positive will not have cervical cancer or pre-cancer, and therefore testing positive can lead to unnecessary worry. Any samples that test positive for the virus undergo 'reflex' cytology (the process by which cells suspended in liquid are stained and examined under the microscope by those trained to perform this assessment). This means only virus-positive samples are tested, to select patients for colposcopy (visualisation of the cervix with special lenses, in a specialist gynaecology clinic). Other possibilities for this triage test which may improve the accuracy of screening including methylation (a chemical change in DNA that can be measured) testing, and testing for specific markers, are currently under investigation. HPV type 16 is the most common high-risk type found globally, including in the UK.

The UK national vaccination programme was started in 2008, and uptake in the UK is currently around 80%. Since 2021, Gardasil9 (offering protection against 7 hrHPV types and two HPV types that cause genital warts) has been offered to both boys and girls, at school, age 12-13. In 2023, new guidance from the Joint Committee on Vaccination and Immunisation (JCVI) recommended a single dose as sufficient. HPV vaccination has almost eliminated cervical cancer in those born in or after 1995.

Future directions for the screening programme in the UK include the possibility of self-sampling, adaptations in the post-vaccine era, and increasing the upper age limit of screening. Self-sampling has been shown to be similarly accurate to clinician-taken samples, and may be a good option for those who do not attend for screening, who have been shown to have increased risk of cervical cancer and worse outcomes. One in 10 women with cervical cancer in the UK is diagnosed over the age of 75.

Globally, recommendations for cervical screening exist in 139/202 countries. Of these, 48 currently recommend hrHPV testing. Efforts must be made to encourage uptake of both screening and vaccination in order to continue to reduce rates of cervical cancer in the UK.

This guidance is for healthcare professionals who care for women, non-binary and trans people. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

Introduction

Cervical cancer remains the fourth most common cancer in women worldwide. Over 300,000 women died from cervical cancer globally in 2018; more than 90% of deaths were in low and middle-income countries.[1] Primary Human Papillomavirus (HPV) testing in cervical cancer screening and HPV vaccination have been the two most impactful developments in cervical cancer prevention in the last decade. This paper discusses progress in cervical screening in the context of a UK setting, and future directions for cervical cancer prevention.

HPV is responsible for 99.7% of cervical cancer cases, and although over 80% of women will become infected with HPV at some point during their lives, the majority will clear it[2]. Thus, HPV is necessary but not sufficient for cervical cancer development; persistent infection with HPV can lead to cervical precancer over the course of around 5-10 years, and in around 20 years can develop into cancer[3]. HIV is a risk factor for persistence of HPV, and immune-altering states including rheumatoid arthritis and inflammatory bowel disease on immunosuppressive medication, smoking, and vaginal dysbiosis are risk factors for cervical cancer and cervical precancer development, respectively[4]. There are over 200 types of HPV that have been identified, and currently 12 of these types are officially classified as 'high-risk', meaning are recognised as carcinogenic[5], although 15 types have been associated with cervical cancer[6]. The list of HPV types classified as high-risk is dynamic as we may find that some rarer types can also cause cancer in the future. The long natural history of cervical cancer and the interval between HPV infection and cancer development, as well as the anatomical position of the cervix being suitable for non-invasive sampling, mean that cervical cancer screening is beneficial and cost-effective at a population level, although unfortunately this is not available to many women globally[7,8].

1.1 WHO Elimination Strategy 90-70-90

In May 2018, the World Health Organization announced a global call for action to eliminate cervical cancer. This was adopted by the World Health Assembly in 2020 under the title of the Global Strategy for Cervical Cancer Elimination[9]. Goals are divided into three pillars: vaccination, screening and treatment, with the aim of 90% of girls to be vaccinated against HPV by age 15; 70% of women to be screened for cervical cancer with a high-performance test by age 35 and again by age 45; and for 90% of cervical pre-cancer and cancer to be treated. (The definition of a high-performance test in the World Health Organization Cervical Cancer Elimination Initiative is as follows: A high-performance test refers to a test that would have performance characteristics similar to or better than an HPV test. In future, however, new technologies may become available.) The aim is for the targets to be met in each country by 2030. Elimination of cervical cancer from a public health perspective is defined by incidence rates of 4 per 100,000 or less[10].

1.2 United Kingdom screening population coverage

Cervical screening uptake continues to decline, particularly among younger women, and the national coverage in England, Scotland, and Wales has now dropped below 70% for those younger than 49 years. In England in 2020-21, 69.9% of eligible individuals aged 25-64 had last been screened within the required number of years, down from 70.2% in the previous year[11]. In Wales, coverage rates for the same year were 69.5%[12]. Scotland presented coverage figures of 55.4% for those aged 25-29 and 78.8% for those aged 50-54; the total uptake rate was 69.3% for all ages[13]. Northern Ireland coverage rate was 66.7% overall for the same year[14]. The requirement for a successful screening programme is 80% coverage.

2 Recent developments

The UK cancer prevention strategy has been modified over the last decade to reflect new and emerging technologies and evidence.

2.1 High-risk Human Papillomavirus testing in screening

After a successful pilot[15], primary HPV testing was introduced to the English screening programme in December 2019, echoing the choice of many other countries globally; as of 2022, 35% of 139 countries with an established screening program were using primary HPV testing[16].

2.1.1 Higher sensitivity of hrHPV test

High-risk HPV (hrHPV) testing as a primary screening test has a higher sensitivity for the detection of high-grade Cervical Intraepithelial Neoplasia (CIN) (CIN2 or worse; CIN2+) and cervical cancer in comparison to cytology. A meta-analysis of four European randomised controlled trials including over 175,000 women, compared hrHPV testing to cytology, and found that HPV testing conferred 60-70% greater protection against invasive cervical cancer; the incidence of cancer at 5.5 years was 8.7 per 10^5 women (95%CI 3.3-18.6) in those who underwent hrHPV testing, compared to 36 per 10^5 women (95%CI 23.2-53.5) in those who were tested with cytology[17]. In 2017, a Cochrane review and meta-analysis of 40 comparative studies found the sensitivity and specificity of conventional cytology to be 62.5% and 96.6%, respectively, and the sensitivity and specificity of hrHPV testing were both 89.9%. Therefore, the relative sensitivity (calculated by taking the sensitivity of the reference test, cytology as 1) was 1.52 (95%CI 1.24–1.86) for hrHPV testing compared to cytology for detection of CIN2+ with a corresponding relative specificity of 0.94 (95% CI 0.92-0.96)[18]. Retrospective data from the UK of over 500,000 women from the first round of screening after implementation of hrHPV testing corroborates this; baseline hrHPV testing detected more CIN2+ than cytology with an odds ratio of 1.49 (95% CI 1.43-1.55)[19]. HrHPV test has high negative predictive value (estimated to be between 93.8% and 99.7%[20]), improved cost-effectiveness once established[21], and better suitability for vaccinated cohorts[22]. There has been concerns that the introduction of primary hrHPV screening will increase the number of colposcopy referrals. Colposcopy referrals increased by 29% from 182,304 in 18-19 (latest year unaffected by the COVID-19 pandemic) to 235,223 in 21-22[11]. However, observational data over 500,000 women screening in the UK with either cytology or hrHPV testing found that although hrHPV detects high-grade CIN earlier, the cumulative rate of colposcopy over a screening round was similar.[19]

2.1.2 Triage of high-risk HPV-positive women detected at screening

The UK prevalence of hrHPV is high; up to 13% of those screened may test positive, including up to 28% of women aged 30 or less, 10.5% in women aged 30-49 and 5.6% in women aged 50-64[19]; one third of hrHPV positive women were HPV 16/18 positive. The high prevalence of hrHPV in women screened requires triage tests that could accurately select women that should be referred for a colposcopic examination in secondary care. In Great Britain, cytology is performed on high-risk HPV positive smears and women with borderline cytology or worse are referred to colposcopy. (This is referred to as ‘reflex cytology’, meaning it is performed only on samples testing positive on the primary test, which is hrHPV testing.) In the presence of normal cytology, women are referred to colposcopy after three positive hrHPV samples 12 months apart. Due to the modest sensitivity as discussed above, other potential markers are currently under investigation, including DNA

methylation[23,24], p16INK4a[25,26], and HPV genotyping[27,28]. Methylation tests using certain Cytosine-phosphate-Guanine (CpG) sites or combinations of CpG sites in a panel appear to be accurate; with some comparative studies showing this can be more sensitive and specific than cytology as a triage test[29,30]. There is currently no consensus as to the best marker or panel of markers, and many potential markers have not been directly compared [31]. There is conflicting evidence on the advantages of immunostaining with p16; although one study found an improvement in diagnostic accuracy of CIN2+ detection on histological specimens[32], others found no benefit in a colposcopic setting[33]. The IMPACT trial found dual staining with p16 and Ki67 using immunohistochemistry on cytological samples does appear to show enhanced sensitivity for CIN2+ and CIN3+ detection, although the specificity was lower than cytology[34]. Although HPV 16/18 genotyping is used as a triage in the US, in a study of 127,000 women within the UK screening programme, there was very little clinical benefit added by genotyping, given the relatively high adherence to early recall, and the high quality of cytology[35].

2.1.3 Adaptations after implementation of HPV testing

The introduction of hrHPV test led to changes in the laboratory processes and infrastructure that are now centralised in 11 laboratories. As a result, cytology training required for the British Society of Colposcopy and Cervical Pathology (BSCCP) accreditation is offered online given the distance and limited number of cytology laboratories.

The knowledge of a positive result for hrHPV may be misinterpreted and can lead to concerns and fear of a sexually transmitted infection or cancer. It is important that the language used in both the community and secondary care settings adequately addresses concerns and anxiety as result of a positive test. A survey-based study of over 1000 women in the UK found that an HPV-positive result can cause psychosexual distress[36].

2.1.4 HPV geographical genotype variation

Hr-HPV type prevalence varies globally and within different regions in the UK; one study in Wales of over 14,000 unvaccinated women found an unexpectedly high prevalence of HPV51[37], as it was the most common type after HPV16 and 18. A meta-analysis analysing HPV type in cervical cancer globally included 243 studies and over 30,000 cancer cases[38]; HPV16 was the most common type found in cancers in every continent, followed by HPV18, although the third to eighth most common varied significantly between regions. The theoretical risk of type replacement post-vaccination is

thought to be unlikely, given the low prevalence of non-vaccine covered HPV types, and the genetically stable nature of HPV as a DNA-based virus[37], although monitoring of HPV type within populations remains important.

2.2 Devolved nations variation in screening programs

The UK Cervical screening program operates with variations in each of the devolved nations. Scotland were the first to extend the screening interval length from 3 years to 5 years when hrHPV testing was implemented in 2020[39]. This was followed by Wales in January 2022[40].

Devolved nation	Screening interval	Primary screening method	Reflex test
England	Age 25-49: Every 3 years Age 50-64: Every 5 years	High-risk HPV	Cytology
Wales	Age 25-64: Every 5 years	High-risk HPV	Cytology
Scotland	Age 25-64: Every 5 years	High-risk HPV	Cytology
Northern Ireland	Age 25-49: Every 3 years Age 50-64: Every 5 years	High-risk HPV*, followed by cytology on all samples	n/a

*In Northern Ireland, high-risk HPV testing is used to prioritise samples for cytology (updated in April 2023 from primary cytology testing, followed by high-risk HPV testing for borderline and low grade abnormalities)[41].

There is an ambition to align the screening programmes across the devolved nations by introducing primary hrHPV testing in Northern Ireland and extending the screening interval to 5 years in England[42]. Observational data from the first two hrHPV-based rounds of screening in the UK included over 1 million women and found that in the second 3-yearly round, the detection of CIN3+ was significantly lower following a first-round negative hrHPV test when compared to a negative cytology test (1.21/1000 for hrHPV testing; 4.52/1000 for cytology), supporting the extension of screening intervals to 5 years[42]. Australia moved to 5-yearly intervals with hrHPV testing in 2017[43], whereas the Netherlands cervical screening programme intervals were 5-yearly even prior to hrHPV testing, which was introduced in 2016[44]; both countries have maintained low cervical cancer incidence, less than 8/100,000 women-years[45]. Providing public health information on the safety of 5 yearly intervals may help to increase its acceptability[46], as will long-term safety data after multiple screening rounds, which will start to become available from 2026/2027.

2.3 Human Papillomavirus Vaccination

There has been a national HPV vaccination campaign in the UK since 2008, delivered via education systems. Vaccination was firstly offered exclusively to females aged 12-13 (with a catch-up campaign for those aged 13-18), with the bivalent vaccine Cervarix, then updated to the quadrivalent vaccine Gardasil in 2012. In 2019, the Joint Committee on Vaccination and Immunisation (JCVI) recommended that the HPV vaccine invitation be additionally extended to males aged 12-13. In

2021, Gardasil9, a nonavalent vaccine that protects against types 6, 11, 16, 18, 31, 33, 45, 52 and 58, was introduced. High-risk types 31, 33, 45, 52 and 58 are thought to be responsible for 15% of cervical cancer; Gardasil9 protects against high-risk HPV previously responsible for 85% of cervical cancers[47]. Originally the full schedule comprised of three-doses, and this was updated to a two-dose schedule in 2014. The JCVI have now recommended single-dose regimes can be implemented from 2023[48].

Vaccination uptake rates are around 80% in the UK[49]. In the UK in the academic year 2021/2022, vaccination rates for Year 8 females were 69.6%, which was 7% lower than the previous year. In Year 8 males the uptake was 62.4%, 8.7% lower than the previous year. Cumulatively, by Year 10, one-dose vaccination coverage reached 86.5% and 81.5% for females and males respectively, which is a significant increase from previous school years[49].

Those who have missed the vaccination programme can be vaccinated for free on the NHS up until their 25th birthday[47]. HPV vaccines are licensed up to the age of 45, however vaccinating individuals older than 26 is not cost-effective at a population level[50], although there may be benefit for individuals, particularly those who have developed pre-invasive disease and have shown themselves to be susceptible to not only HPV infection but its sequelae. A small Italian study of 500 women suggested that HPV vaccination may shorten the time to clearance[51]. The value of HPV vaccination in women undergoing local treatment for CIN is under investigation[52].

HPV vaccination has almost eliminated cervical cancer in women born in 1995 or after; in a large study evaluating data from 13.7 million-years of follow-up, there were 448 fewer cervical cancers than expected, and over 17000 fewer cases of CIN3[53].

3. Future directions

3.1 Self-sampling

It has been proposed that self-sampling for hrHPV in cervical screening may improve coverage and participation, particularly for poor attenders, who are a group at particularly high risk of developing invasive cancer[54]. (Self-sampling refers to vaginal swabs inserted by the patient themselves, rather than a clinician.) Large meta-analyses found self-sampling to be as accurate as clinician-taken samples[55,56]. A meta-analysis of 33 studies found that offering self-sampling increased screening participation, with opt-in strategies being the most effective[57]. In 2017, the Netherlands became the first nation to introduce self-sampling as an option in addition to the option of a clinician-taken

sample[44]. Australia implemented a similar policy nationally in 2022[58]. Initial data of over 30,000 self-samples from the Netherlands found the relative sensitivity of self-sampling for detection of CIN3+ to be 0.94 (95% CI 0.90-0.97), and relative specificity to be 1.02 (95% CI 1.02-1.02).[59] In terms of longitudinal data, the five-year Scottish Papillomavirus Dumfries and Galloway study found the risk of CIN2+ and CIN3+ in those with HPV negative self-samples to be 0.6% and 0.2% respectively[60]. This study found the relative sensitivity of CIN3+ for hrHPV self-samples to be slightly lower in comparison to clinician-taken samples, 0.95 (95% CI 0.90-0.99). A London-based self-sampling feasibility trial for non-attenders at screening has recently been completed[61], and it is likely that self-sampling may form part of the future of cervical screening in the UK in some capacity.

While self-sampling has potential to significantly improve uptake for screening, there are multiple issues with its implementation that will inevitably arise, including how to manage those who test positive on self-samples. In the London-based feasibility trial, women who tested negative for hrHPV on self-sampling tests returned to routine recall, and those who tested positive were then invited for a clinician-taken sample[62]. The proportion of those sent a self-sample kit who returned it within 90 days was 11.6% (95%CI 11.2 to 12.1), whilst the uptake in those that were opportunistically offered a kit in primary care was 55.0% (95%CI 53.9 to 56.1), respectively. hrHPV prevalence in the self-screened cohort was 13.1%. Of those who tested positive for hrHPV on the self-sample, 84.9% (95%CI 82.5 to 87.0) attended for a clinician-taken sample within 6 months. Self-sampling resulted in a 22% (95%CI 18 to 26) increase per month in non-attenders that were screened per month in the as-per-protocol analysis. 29.9% (8338/27,840) of offered kits were returned, 91.7% (7643/8338) were suitable for analysis, and 13.1% (1001/7643) women tested positive for hrHPV positive on self-samples. Of the 87.8% (879/1001) that attended for clinician-taken samples, 50.1% (440/879) tested hrHPV positive on clinician-taken samples, 58.4% (257/440) were referred to colposcopy, and 65.8% (169/257) underwent biopsy or treatment, including two invasive cancers detected.

3.2 Screening of mixed vaccination populations

HPV vaccination has led to a major reduction in CIN3 rates and the risk of cervical cancer[53.] Cervical precancer and cancer are expected to continue to decrease over the next decade as the first vaccinated cohorts will reach the peak age of cervical cancer development. Despite the advent of vaccination, screening will need to continue. The first ever vaccinated cohort at age 12-13 will exit the screening program in 2058. Even the second-generation vaccines only offer 90% protection against cancer, whilst many individuals remain unvaccinated due to hesitancy, cultural and religious beliefs. The lack of vaccination registration and increasing international migration of those who may

have received no or differing vaccination schedules will continue to add complexity[63]. Screening of mixed populations remains a potential future public health challenge, and an increase in the screening intervals is likely.

3.3 Increasing the upper age limit of screening

In the United Kingdom, 1 in 10 cervical cancers are diagnosed after the age of 75[64] and it is projected that this will increase in the future. Factors such as an aging population, decreasing hysterectomy rates, and changes in sexual behaviours with increasing sexual partners in those over 50s[65] contribute to that increase. In 2017, Australia introduced hrHPV-based screening in 5-yearly intervals and further increased the exit age. Modelling suggested that this programme would eliminate cervical cancer within 20 years[10]. However, screening in older ages is not without challenges. The rates of insufficient cell sampling, inadequate colposcopy and discomfort during gynaecological examination are increased after menopause[66]. A study published in 2014 studied the association between screening at age 50-64, and cervical cancer age 65-83, and found that those with adequate negative screening at age 65 were at the lowest risk of cancer (8/10,000 women), compared with those not screened during that period (49/10,000). The study concluded that stopping screening between age 60 and 69 seems sensible, although further screening may be justifiable as life expectancy increases.[67] A Danish population-based study aiming to recruit 10,000 women age 65-69 will evaluate whether screening of this population will result in an increased detection of CIN2 or worse[68], and the results may help to inform cervical screening policy extension in countries including the UK.

3.4 Global developments

While this paper focuses on developments within the UK, significant global advances in cervical cancer prevention must be recognised. Recommendations for cervical screening exist currently in 69% (139/202) countries, and 35% (48/139) of those recommend primary hrHPV testing.[16] A pooled analysis published in 2016 estimated that 118 million women had been targeted by a HPV vaccination programme, although only 1% of these were in low or middle income countries[69]. All European Union countries have introduced HPV vaccination in their national programmes, and many of these have extended HPV vaccination to boys or are planning to in the near future.[70] Despite these advances, there remains a clear socioeconomic gap in cervical cancer incidence and mortality worldwide[45]; Malawi has an age-standardised incidence of 67.9 cases per 100,000 women-years [95%CI 65.7-70.1], in the context of a global age-standardised incidence of 13.3. There is an urgent

need to develop and implement feasible screening and vaccination programmes for low and middle income countries.

4 Opinion and Summary of current and future developments

Screening:

- The introduction of primary hrHPV testing in screening and HPV vaccination has and will continue to reduce the incidence of both cervical precancer and cancer. The high longitudinal sensitivity of hrHPV testing for detection of CIN2+ allows the extension of cervical screening round to 5-yearly intervals, which has already been adopted in Wales and Scotland.
- Reflex cytology is currently used to triage women with hrHPV that should be referred to colposcopy, although other tests are being investigated.
- As more women will test positive for hrHPV at screening, the communication and contextualisation of this result by clinicians and public health providers is important to prevent unnecessary anxiety for these women.

Vaccination:

- A single dose vaccine for both males and females will be recommended in the UK from 2023.
- Infrastructure and training taskforce in colposcopy should adapt to the decreasing number of women with cervical disease in the advent of vaccination.

Policy:

- Particularly as screening uptake continues to decline, it is important that national public health campaigns continue to provide accurate and comprehensive information on the safety and efficacy of screening and vaccination.
- Smoking cessation should also be encouraged as smoking remains a risk factor for cervical cancer development.
- Self-sampling strategies may further improve coverage for poor attenders, whilst increasing the age of screening exit to over 65 and adaptation in the post-vaccine era may be further developments.

References

1. World Health Organization. Cervical cancer. WHO. 2018; https://www.who.int/health-topics/cervical-cancer#tab=tab_1. [Accessed 1 August 2024]
2. Crow JM. HPV: The global burden. *Nature* 2012; **488**: S2-S3.

3. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination—Review of Current Perspectives. *J Oncol.* 2019; **2019**: 1-11.
4. Bowden SJ, Doulgeraki T, Bouras E, et al. Risk factors for human papillomavirus infection, cervical intraepithelial neoplasia and cervical cancer: an umbrella review and follow-up Mendelian randomisation studies. *BMC Med.* 2023; **21**(1): 274.
5. National Cancer Institute. HPV and Cancer. 2021. https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer. [Accessed 1 August 2024]
6. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsague X, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003; **348**: 518-27.
7. Kyrgiou M, Bowden S, Denny L, Fagotti A, Abu-Rustum NR et al. Innovation in gynaecological cancer: highlighting global disparities. *Lancet Oncol.* 2024; 25: 425-30
8. Kyrgiou M, Arbyn M, Bergeron C, Bosch FX, Dillner J, Jit M, et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). *Br J Cancer.* 2020; **123**: 510-7.
9. World Health Organization. Cervical Cancer Elimination Initiative. 2023; https://www.who.int/initiatives/cervical-cancer-elimination-initiative. [Accessed 1 August 2024]
10. Hall MT, Simms KT, Lew J-B, Smith MA, Brotherton JMI, Saville M, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. *Lancet Public Health.* 2019; **4**: e19-e27.
11. NHS Digital. Cervical screening programme - England - 2021-2022. NHS Digital. 2022; https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/england-2021-2022. [Accessed 1 August 2024].
12. Public Health Wales. Screening Division Inequities Report 2020-21. PHW. 2022; https://phw.nhs.wales/news/men-younger-people-and-those-living-in-the-more-deprived-communities-in-wales-show-lower-uptake-of-life-saving-screening-services1/screening-division-inequities-report-2020-21/. [Accessed 1 August 2024].
13. Public Health Scotland. Scottish cervical screening programme statistics. Annual update to 31 March 2022. https://publichealthscotland.scot/publications/scottish-cervical-screening-programme-statistics/scottish-cervical-screening-programme-statistics-annual-update-to-31-march-2022/#:~:text=For%20the%20financial%20year%202021,compared%20with%20the%20previous%20year. [Accessed 1 August 2024].
14. HSC Public Health Agency. Northern Ireland Cervical Screening. https://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/cervical-cancer-screening#:~:text=Currently%2C%20women%20aged%2025%2D49,of%20Human%20Papillomavirus%20(HPV). [Accessed 1 August 2024].
15. Kitchener HC. HPV primary cervical screening: time for a change. *Cytopathology* 2015; **26**: 4-6.
16. Bruni L, Serrano B, Roura E, Alemany L, Cowan M, Herrero R, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Glob Health.* 2022; **10**: e1115-27.

17. Ronco GD, Dillner JP, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet.* 2014; **383**: 524-32.
18. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPI, Mustafa RA, et al. Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database Syst Rev.* 2017; **8**: CD008587.
19. Rebolj M, Rimmer J, Denton K, Tidy J, Mathews C, Ellis K, et al. Primary cervical screening with high risk human papillomavirus testing: Observational study. *BMJ.* 2019; **364**: l240.
20. Moss S, Gray A, Legood R, Vessey M, Patnick J, Kitchener H, et al. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ.* 2006; **332**: 83-5.
21. Inge MCMdK, Joost van R, Joakim D, Arbyn M, Sasieni P, Iftner T, et al. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model. *BMJ.* 2012; **344**: e670.
22. Kitchener HC, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. *Health Technol Assess* 2014; **18**: 1-196.
23. Bowden SJ, Kalliala I, Veroniki AA, Arbyn M, Mitra A, Lathouras K, et al. The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: A systematic review and meta-analysis. *EBioMedicine* 2019; **50**: 246-59.
24. Bowden SJ, Ellis LB, Kalliala I, et al. Protocol for a systematic review and meta-analysis of the diagnostic test accuracy of host and HPV DNA methylation in cervical cancer screening and management. *BMJ Open* 2023; **13**(6): e071534.
25. Shi Q, Xu L, Yang R, Meng Y, Qiu L. Ki-67 and P16 proteins in cervical cancer and precancerous lesions of young women and the diagnostic value for cervical cancer and precancerous lesions. *Oncol Lett.* 2019; 18: 1351.
26. Giorgi Rossi P, Carozzi F, Ronco G, Allia E, Bisanzi S, Gillio-Tos A, et al. p16/ki67 and E6/E7 mRNA Accuracy and Prognostic Value in Triaging HPV DNA-Positive Women. *J Natl Cancer Inst.* 2021; **113**: 292-300.
27. Bonde JH, Sandri M-T, Gary DS, Andrews JC. Clinical Utility of Human Papillomavirus Genotyping in Cervical Cancer Screening: A Systematic Review. *J Low Genit Tract Dis.* 2020; **24**: 1-13.
28. Cuzick J, Wheeler C. Need for expanded HPV genotyping for cervical screening. *Papillomavirus Res.* 2016; **2**: 112-5.
29. Chen Y, Cui Z, Xiao Z, Hu M, Jiang C, Lin Y, et al. PAX1 and SOX1 methylation as an initial screening method for cervical cancer: a meta-analysis of individual studies in Asians. *Ann Transl Med.* 2016; **4**: 365.
30. Barrett JE, Sundstrom K, Jones A, Evans I, Wang J, Herzog C, et al. The WID-CIN test identifies women with, and at risk of, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer. *Genome Med.* 2022; **14**: 116.
31. Kelly H, Benavente Y, Pavon MA, De Sanjose S, Mayaud P, Lorincz AT, et al. Performance of DNA methylation assays for detection of high-grade cervical intraepithelial neoplasia (CIN2+): a systematic review and meta-analysis. *Br J Cancer.* 2019; **121**: 954-65.

32. Bergeron C, Ordi J, Schmidt D, Trunk MJ, Keller T, Ridder R, et al. Conjunctive p16INK4a testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. *Am J Clin Pathol.* 2010; **133**(3): 395-406.
33. Wentzensen N, Schwartz L, Zuna RE, Smith K, Mathews C, Gold MA, et al. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. *Clin Cancer Res.* 2012; **18**: 4154-62.
34. Wright TC, Stoler MH, Ranger-Moore J, Fang Q, Volkir P, Safaeian M, et al. Clinical validation of p16/Ki-67 dual-stained cytology triage of HPV-positive women: Results from the IMPACT trial. *Int J Cancer.* 2022; **150**: 461-71.
35. Rebolj M, Brentnall AR, Mathews C, Denton K, Holbrook, Levine T, et al. 16/18 genotyping in triage of persistent human papillomavirus infections with negative cytology in the English cervical screening pilot. *Br J Cancer.* 2019; **121**: 455-63.
36. Bennett K, Waller J, Mcbride E, Forster AS, Gessa G Di, Kitchener H, et al. Psychosexual distress following routine primary human papillomavirus testing: a longitudinal evaluation within the English Cervical Screening Programme. *BJOG.* 2021; **128**: 745-54.
37. Bowden SJ, Ellis LB, Kyrgiou M, Fiander AN, Hibbitts S. High Prevalence of HPV 51 in an Unvaccinated Population and Implications for HPV Vaccines. *Vaccines (Basel).* 2022; **10**: 1754.
38. Li N, Franceschi S, Howell-Jones R, Snijders PJF, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. *Int J Cancer.* 2011; **128**: 927-35.
39. Public Health Scotland. Cervical screening – HPV testing and change of routine screening intervals. Frequently asked questions for professionals. 2022; https://apps.nhslothian.scot/files/sites/2/changes-to-cervical-screening-programme-faq.pdf. [Accessed 1 August 2024].
40. Morgan E. Written Statement: Change to cervical screening interval. Welsh Government. 2022; https://www.gov.wales/written-statement-change-cervical-screening-interval#:~:text=As%20of%201%20January%202022,in%20their%20cervical%20screening%20test. [Accessed 1 August 2024].
41. HSC Public Health Agency. Cervical cancer screening. https://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/cervical-cancer-screening. [Accessed 1 August 2024].
42. Rebolj M, Cuschieri K, Mathews CS, Pesola F, Denton K, Kitchener H, et al. Extension of cervical screening intervals with primary human papillomavirus testing: observational study of English screening pilot data. *BMJ.* 2022; **377**: e068776.
43. Obermair HM, Dodd RH, Bonner C, Jansen J, McCaffery K. 'It has saved thousands of lives, so why change it?' Content analysis of objections to cervical screening programme changes in Australia. *BMJ Open.* 2018; **8**: e019171.
44. Aitken CA, Van Agt HME, Siebers AG, van Kemenade FJ, Niesters HGM, Melchers WJG, et al. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Med.* 2019; **17**: 228.
45. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *Lancet Glob Health.* 2023; **11**(2): e197-e206.

493 46. Hill E, Nemec M, Marlow L, Sherman SM, Waller J. Maximising the acceptability of
494 extended time intervals between screens in the NHS Cervical Screening Programme: An
495 online experimental study. *J Med Screen.* 2021; **28**: 333-40.
496 47. NHS. HPV vaccine. 2023; https://www.nhs.uk/conditions/vaccinations/hpv-human-
497 papillomavirus-vaccine/. [Accessed 1 August 2024].
498 48. UK Government. JCVI statement on a one-dose schedule for the routine HPV
499 immunisation programme. Published 5 August 2022;
500 https://www.gov.uk/government/publications/single-dose-of-hpv-vaccine-jcvi-concluding-
501 advice/jcvi-statement-on-a-one-dose-schedule-for-the-routine-hpv-immunisation-
502 programme#:~:text=At%20that%20time%20the%20committee,including)%2014%20years%
503 20of%20age. [Accessed 1 August 2024].
504 49. UK Health Security Agency. Human papillomavirus (HPV) vaccination coverage in
505 adolescents in England: 2021 to 2022. Health Protection Report. 2022; 16: 13.
506 https://assets.publishing.service.gov.uk/media/63a5b83be90e07048f4d598f/hpr1322-
507 HPV2.pdf. [Accessed 1 August].
508 50. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human
509 Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory
510 Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019; **68**: 698-702.
511 51. De Vincenzo R, Caporale N, Bertoldo V, Ricci C, Evangelista T, Bizzarri N, et al. HPV
512 and Cytology Testing in Women Undergoing 9-Valent HPV Opportunistic Vaccination: A
513 Single-Cohort Follow Up Study. *Vaccines* (Basel). 2021; **9**(6): 643.
514 52. Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, et
515 al. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV
516 related disease after local surgical treatment: systematic review and meta-analysis. *BMJ*
517 2022; 378: e070135.
518 53. Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Berhal J, et al. The
519 effects of the national HPV vaccination programme in England, UK, on cervical cancer and
520 grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study.
521 *Lancet.* 2021; **398**: 2084-92.
522 54. Szarewski A, Cadman L, Mesher D, Austin J, Ashdown-Barr L, Edwards R, et al. HPV
523 self-sampling as an alternative strategy in non-attenders for cervical screening – a
524 randomised controlled trial. *Br J Cancer.* 2011; **104**: 915-20.
525 55. Arbyn M, Verdoodt F, Snijders PJ, Verhoef VMJ, Suonio E, Dillner L, et al. Accuracy of
526 human papillomavirus testing on self-collected versus clinician-collected samples: a meta-
527 analysis. *Lancet Oncol* 2014; **15**(2): 172-83.
528 56. Arbyn M, Smith SB, Temin S, Sultana F, Castle P, Collaboration on Self-Sampling and
529 HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV
530 testing on self samples: updated meta-analyses. *BMJ.* 2018; **363**: k4823.
531 57. Costa S, Verberckmoes B, Castle PE, Arbyn M. Offering HPV self-sampling kits: an
532 updated meta-analysis of the effectiveness of strategies to increase participation in cervical
533 cancer screening. *Br J Cancer* 2023; **128**: 805-13.
534 58. Australian Government. Self-collection now available for cervical screening. 2022;
535 https://www.health.gov.au/news/self-collection-now-available-for-cervical-screening.
536 [Accessed 1 August 2024].
537 59. Inturrisi F, Aitken CA, Melchers WJG, Adriaan JC van den Brule, Molijin A, et al.
538 Clinical performance of high-risk HPV testing on self-samples versus clinician samples in

539 routine primary HPV screening in the Netherlands: An observational study. *Lancet Reg Healt*
540 *Eur.* 2021; **11**: 100235.
541 60. Stanczuk GA, Currie H, Forson W, Baxter G, Lawrence J, Wilson A, et al. Self-sampling
542 as the principal modality for population based cervical screening: Five-year follow-up of the
543 PaVDaG study. *Int J Cancer.* 2022; **150**: 1350-6.
544 61. ISRCTN Registry. A London HPV self-sampling pilot. 2023;
545 https://www.isrctn.com/ISRCTN23940319. [Accessed 1 August].
546 62. Lim AWW, Deats K, Gambell J, Lawrence A, Lei J. Opportunistic Offering of Self-
547 Sampling to Non-Attenders within the English Cervical Screening Programme: A Pragmatic,
548 Multicentre, Implementation Feasibility Trial with Randomly Allocated Cluster Intervention
549 Start Dates (Youscreen). eClinicalMedicine. 2024; 73: 102672.
550 63. Cruickshank M, Cubie H. Cervical screening: primary human papillomavirus testing.
551 *BJOG.* 2012; **119**: 650-2.
552 64. Cancer Research. Cervical cancer statistics.
553 https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-
554 cancer-type/cervical-
555 cancer#:~:text=Cervical%20cancer%20incidence,year%20(2017%2D2019). [Accessed 1
556 August 2024].
557 65. Dilley S, Huh W, Blechter B, Rositch AF. It's time to re-evaluate cervical Cancer
558 screening after age 65. *Gynecol Oncol.* 2021; **162**: 200-2.
559 66. Gustafson LW, Petersen LK, Bor P, Andersen B, Hammer A. Cervical cancer
560 prevention among older women – challenges in screening, diagnostic workup and
561 treatment. *Acta Obstet Gynecol Scand.* 2021; **100**: 1364-8.
562 67. Castañón A, Landy R, Cuzick J, Sasieni P. Cervical screening at age 50-64 years and
563 the risk of cervical cancer at age 65 years and older: population-based case control study.
564 *PLoS Med.* 2014; **11**: e1001585-e.
565 68. Tranberg M, Petersen LK, Elfström KM, Hammer A, Blaakær J, Holten Bennetsen M,
566 et al. Expanding the upper age limit for cervical cancer screening: a protocol for a
567 nationwide non-randomised intervention study. *BMJ Open.* 2020; **10**: e039636.
568 69. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global
569 estimates of human papillomavirus vaccination coverage by region and income level: a
570 pooled analysis. *Lancet Glob Health.* 2016; **4**: e453-e63.
571 70. Colzani E, Johansen K, Johnson H, Pastore Celentano L. Human papillomavirus
572 vaccination in the European Union/European Economic Area and globally: a moral dilemma.
573 *Euro Surveill.* 2021; **26**: 2001659.
574