



Royal College of  
Obstetricians &  
Gynaecologists

# Progress in Cervical Screening in the UK

Scientific Impact Paper No. 7  
March 2016

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## 1. Introduction

Cervical cancer prevention has been based on cervical cytology screening for the last 50 years. With rapid advances in our understanding of human papillomavirus (HPV) and its role in carcinogenesis and the clinical applications of primary prevention by HPV immunisation and secondary prevention by high-risk HPV (hrHPV) testing, the approach to cervical cancer prevention in the UK is undergoing significant change. This paper sets out the developments in cervical screening in the UK and the challenges it faces.

### 1.1 Population coverage

A major success of the English cervical screening programme has been its population coverage, which achieved 80.6% in 2004 but had declined to 77.8% in 2014 (5-year coverage).<sup>1</sup> The lowest coverage is found among those aged 25–29 years; in 2014, 63.3% of women in this group had been screened within a 3.5-year interval. Moreover, 47% of women who develop cancer have not been screened in the past 5 years or have never been screened in the UK and this group is more likely to have advanced cancer.<sup>2</sup> Several studies<sup>3–6</sup> have identified demographic groups associated with nonattendance in the UK cervical screening programmes; these include young women, older women (greater than 50 years of age), ethnic minority women and those in low socioeconomic groups. Reasons for nonattendance are variable and complex<sup>4,5</sup> and often include inconvenience, fear of cancer, apathy and concern about the actual procedure. Continued effort is required to encourage nonparticipants to attend. The UK-based STRATEGIC (Strategies to Increase Cervical Screening Uptake at First Invitation) trial,<sup>7</sup> which will report in 2016, is studying methods to increase uptake in women following their initial invitation.

### 1.2 Turnaround times

The Department of Health made a public commitment that cervical screening results would be provided within 14 days of a sample being taken by 2010.<sup>8</sup> This has been a challenge with the inclusion of additional hrHPV testing as triage and/or test of cure, but laboratory services have worked to ensure that this target is also met to provide prompt results for women. In England, this target is monitored monthly by each of the regional Screening Quality Assurance Service centres and quarterly by NHS England local patch-led screening performance monitoring meetings. In 2013–2014, 93.7% of women screened in primary care received their cytology result within 2 weeks of the sample being taken.<sup>1</sup>

## 2. Current developments

The UK cervical screening programmes need to be changed in order to incorporate advances that improve the service to women. Reliable evidence is necessary to support such changes.

### 2.1 Age range and frequency of screening

The age range for cervical screening in England is 25–64 years with 3-yearly tests from ages 25–49 and 5-yearly tests to age 64. As a result of public pressure to change the age at which screening commences to 20, a review was conducted in 2009 by the Advisory Committee on Cervical Screening. There was no evidence that cancer cases had increased in women under the age of 25 years and good evidence that screening very young women was ineffective, implying that screening below age 25 would have the potential to do more harm than good. Furthermore, the national HPV vaccination programme is likely to reduce the risk of cervical cancer further in young women. On this basis, the Advisory Committee

recommended that the onset of screening should remain at 25.<sup>9</sup> The cervical screening programmes in Northern Ireland and Wales have since adopted this same age and frequency of screening, and Scotland will change in June 2016.

## 2.2 HPV testing

Growing research evidence has indicated the potential benefits of incorporating HPV testing for high-risk genotypes into cervical screening. A number of studies have indicated that the negative predictive value (NPV) of hrHPV testing is very high at over 96%<sup>10</sup> whereas the added risk of testing positive for hrHPV in various settings merits colposcopic referral without lengthy periods of repeated cytology. Until recently Hybrid Capture 2 (HC2; QIAGEN, Hilden, Germany) was the standard HPV test in many pilot studies. Now other clinically validated commercial HPV tests have come on to the market, which have been adopted at different sites in England.

Three roles of hrHPV testing have been identified: a) triage of borderline and low-grade cervical screening tests, b) as a test of cure post treatment for cervical intraepithelial neoplasia (CIN) and c) as a primary screening test. Prior to implementation in England, these first two roles were rigorously evaluated at six sentinel NHS sites, representing around 10% of the English screening programme.<sup>11</sup>

### **Triage of borderline and low-grade abnormalities**

The Sentinel Sites study confirmed that by incorporating immediate colposcopy for women with a positive hrHPV test, triage not only reduced the number of repeat cytology tests, but facilitated earlier detection of underlying high-grade CIN and earlier return to routine recall.<sup>11-13</sup>

A Cochrane review<sup>10</sup> has confirmed that HPV triage of borderline cytology predicts the presence of high-grade CIN with greater accuracy than a repeated cytology sample. The positive predictive value (PPV) of a positive hrHPV test following low-grade cytology in detecting CIN2+ (CIN grade 2 and above) at subsequent colposcopy was 16.3%.<sup>13</sup> Although there is a high rate of hrHPV detected in samples reported as low-grade dyskaryosis (over 80%), the value of triage in the English screening programme is that it is cost-effective and avoids colposcopy for almost 20% of women with low-grade dyskaryosis who can return safely to routine recall.

The evidence from the NHS Sentinel Sites and TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears) studies has confirmed the NPV of normal colposcopy.<sup>14,15</sup> Women referred with a minor cytological abnormality and a positive hrHPV test who had a normal and adequate colposcopy examination could be discharged safely to recall of 3 or 5 years depending on the woman's age. The risk of subsequent CIN2+ in the intervening screening interval was low at 4.4%. There were no reported cases of cervical cancer in these studies.

### **Test of cure**

HPV test of cure relies on the high NPV of hrHPV testing to exclude residual CIN. A negative combined test of cytology and hrHPV at 6 months after treatment of CIN can allow return to routine 3-yearly recall in place of up to 10 years of annual cytology. The value of this approach has been confirmed in several studies.<sup>16-19</sup> A prospective test of cure study conducted in England and Scotland confirmed the safety of the HPV test of cure, which would allow 82% of women who had received treatment for CIN to return to routine recall.<sup>20</sup> This approach was incorporated into the Sentinel Sites study, combining cytology and HPV in a double test of cure, which has now been implemented nationally.<sup>12</sup> The future effects of this test of cure have been modelled using data from the same study, indicating that HPV test

of cure in cytology-negative women will avert an additional 8.4 cases of CIN3+ and reduce the cost of follow-up after treatment by £9388 per 100 women treated.<sup>21</sup> If HPV primary screening is implemented, stand-alone HPV test of cure should be considered.

### **HPV as a primary screening test**

Owing to its greater sensitivity in detecting CIN compared with cytology,<sup>10,22</sup> HPV testing could be used either as a co-test with cytology or as a stand-alone primary screening test. Its potential advantages include greater sensitivity than cytology, automated high-throughput testing and, importantly, longer screening intervals. These could be extended to 5–6-yearly screening rounds. The major disadvantage is the lower specificity compared with cytology, owing to the high rate of HPV infection, particularly in young women, in whom infection rates vary from around 40% aged 20 years to around 20% aged 30.<sup>23</sup> With HPV vaccination, there should be a reduction of hrHPV prevalence in women reaching the age of screening. This should improve the clinical utility of primary HPV screening in the 25–30-year age group.

There have been four European randomised controlled trials on HPV screening, all of which compared cytology with cytology combined with hrHPV testing.<sup>22</sup> All of these trials with the exception of ARTISTIC (A Randomised Trial In Screening To Improve Cytology) showed a significantly greater detection of CIN2+ in the first screening round and all showed a significant reduced incidence of CIN2+ in subsequent screening rounds 3 years later in the HPV screening arm. A pooled analysis of these large trials with additional follow-up demonstrated a reduction in the incidence of cervical cancer in the women who had had HPV screening plus cytology compared with cytology alone.<sup>22</sup> This body of evidence favouring HPV primary screening led to the establishment of a large HPV primary screening pilot study at the sentinel sites, prior to consideration of a national roll-out in England. In January 2016, the UK National Screening Committee issued its recommendation to adopt primary HPV testing in place of cytology for cervical screening.<sup>46</sup> Women who are hrHPV negative are routinely recalled, with the expectation of increasing the screening interval to 5 or 6 years. Women who test hrHPV positive have reflex cytology as triage and those with positive results (abnormal cells) are referred directly to colposcopy. Reflex cytology is the performance of cytological review of the patient's liquid-based cellular sample acquired at HPV testing, which is routinely stored until after HPV results are available. Women with negative cytology have early recall at 12 months in anticipation that at least half will then be hrHPV negative and can return to routine recall.

### **Use of HPV biomarkers to improve specificity**

The relatively poor specificity of hrHPV testing highlights the need for more specific triage tests, such as using molecular markers for disease. In the English screening programme, consideration has been given to increasing the viral load cut-off to determine HPV test positivity, adding a second triage test or selecting an alternative triage test. It is evident from the ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial<sup>24</sup> and other studies that the PPV for CIN3+ in women who are HPV 16/18 positive is higher than if they are HPV 16/18 negative. In the ARTISTIC trial, irrespective of the cytology result, the cumulative rate of CIN2+ over 6 years was 38.5% when the test was positive for HPV 16/18 compared with 23.9% for HPV genotypes 31/33/45/52/58 or 6.9% for the remaining cluster of hrHPV types.<sup>25</sup>

One strategy to improve the specificity of HPV testing is to add a complementary biomarker such as p16<sup>INK4A</sup> (p16)<sup>26</sup> or p16 combined with the minichromosome maintenance protein family (MCM).<sup>27,28</sup> The use of dual p16 staining in cytology (CINtec®, Roche, Basel, Switzerland) has been reported to improve specificity of triage of minor cytological abnormalities compared with HPV testing (63.2% versus 37.8% for borderline abnormalities and 37.3% versus 18.5% for low-grade dyskaryosis).<sup>28</sup> Dual testing of the

proliferation marker Ki-67 with p16 in CINtec® PLUS aims to identify CIN2+ at risk of progression. The specificity is reported as equal to cytology (95.2% versus 95.4%;  $P = 0.15$ ) in women of all ages, but more sensitive (86.7% versus 68.5%;  $P < 0.001$ ) for detecting CIN2+.<sup>26</sup> HPV testing in women 30 years or older was less specific than CINtec® PLUS (93.0% versus 96.2%;  $P < 0.001$ ) but more sensitive (93.3% versus 84.7%;  $P = 0.03$ ).

### *2.3 Automated cytology*

Liquid-based cytology was implemented across the UK by 2008 and the anticipated reduction in inadequate samples and the consequent need to repeat tests has been sustained.<sup>29</sup> Aside from reflex HPV testing in triage and as a test of cure, liquid-based cytology can facilitate automated machine cytology reading. In 2011, the MAVARIC (Manual Assessment Versus Automated Reading In Cytology) trial<sup>30</sup> reported that the sensitivity for detection of CIN2+ was 8% lower for automated cytology compared with manual reading, although there was no significant difference between the two methods for the detection of CIN3+. The Health Technology Assessment (HTA) report concluded that the significantly reduced sensitivity of automated reading, combined with uncertainty over cost-effectiveness, meant that its implementation across the screening programme could not be recommended. On this basis, manual reading was supported in England and Wales. The HTA report did, however, recommend further consideration of the 'no further review' facility for normal cytology, which was sufficiently reliable to exclude CIN2+.<sup>30</sup> In Scotland, all laboratories had changed to automated reading by 2013, following the Scottish Cervical Cytology ThinPrep® (Hologic, Bedford, Massachusetts, USA) Imager Feasibility Study,<sup>31</sup> which reported similar levels of detection of high-grade cytology between the two methods as well as an efficiency gain of 28% in terms of slide throughput.

### *2.4 Impact of HPV immunisation programme on cervical screening*

In the UK, HPV vaccination of girls aged 12–13 years started in September 2008. A catch-up campaign to target girls up to 18 years ran over the subsequent 3 years to extend the immunised cohort. The bivalent HPV 16/18 vaccine was used initially across the UK. The uptake rates for the HPV vaccine in the UK have been high: almost 90% of girls eligible for the vaccine in 2010/11 received all three doses.<sup>32,33</sup> For the school year beginning September 2012, the vaccine used in the national programme changed to the quadrivalent vaccine (HPV 6/11/16/18), which gives additional protection against genital warts.<sup>34</sup>

In Scotland and Wales, immunised women started attending for cervical screening in late 2010. In England and Northern Ireland, screening begins at age 25 and the immunised cohort started attending for cervical screening in 2015. Despite vaccination, cervical screening will remain an essential component of the programme. Linkage studies will be important to monitor rates of abnormality in vaccinated and unvaccinated women. The performance of cervical cytology in terms of PPV for CIN is likely to reduce as a result of the falling incidence of CIN and, if cytology remains the primary screen, due to challenges in maintaining skills of pattern recognition with low abnormality rates.

The Health Protection Agency (now part of Public Health England) and Health Protection Scotland have been tasked to monitor the uptake and safety of the vaccine as well as the impact of the programme on cervical screening and cervical disease. The impact was predicted to become apparent in 2015, with a noticeable decline from 2020–2025. Given high uptake levels in the UK, vaccination is predicted to result in a 50% decrease in high-grade CIN and a 70% reduction in cervical cancer.

Data from Australia,<sup>35</sup> where the quadrivalent vaccine was introduced in April 2007, demonstrated a significant decline in genital warts in young Australian women, from 11.5% in 2007 to 0.85% in 2011.

The proportion of men under 21 years of age being diagnosed with genital warts also decreased significantly from 12.2% to 2.2%. Since men were not vaccinated at that time in Australia, this is interpreted as an indicator of herd protection (where the proportion of the population immunised is sufficiently high to provide some protection to the non-immunised population by disrupting transmission of the infectious agent). Although boys and young men are vaccinated in the USA,<sup>36</sup> Australia<sup>37</sup> and some regions of Canada,<sup>38</sup> this is not current practice in the UK.

HPV vaccination in Queensland, Australia, has already been associated with a significant decrease in high-grade cervical abnormalities in girls who had not started screening prior to the introduction of the HPV vaccine.<sup>39</sup> Data are now emerging from the UK on the prevalence of HPV 16/18<sup>40</sup> and CIN<sup>41</sup> from surveillance by Health Protection Scotland. With a three-dose vaccine programme using the bivalent vaccine, the prevalence of HPV 16 and 18 has decreased in women aged 20 from 29.8% to 13.6%. A reduction was also seen in other hrHPV types, HPV 31, 33 and 45, suggesting cross-protection against closely related genotypes. A significant reduction in diagnoses of CIN1 (relative risk [RR]\* 0.71), CIN2 (RR 0.5) and CIN3 (RR 0.45) was observed in women who received three doses of vaccine compared with unvaccinated women.

The Department of Health, having considered evidence on the duration and magnitude of antibody response, announced that the vaccine schedule will change from three to two doses from September 2014. Key data came from a Canadian trial<sup>42</sup> of two versus three doses of the quadrivalent vaccine in girls aged 9–13 showing non-inferiority of geometric mean titres of antibody. In a two-dose regimen, the second dose should not be given before 6 months after the initial dose. The change in vaccine and schedule will require continued long-term monitoring of the vaccine and screening programmes.

### 3. Future developments

#### 3.1 HPV self-testing

Falling compliance with cervical screening is a recognised problem and there are several reasons that contribute to nonparticipation: service provision issues, time pressures, risk perceptions, lack of knowledge and psychological barriers. In response to this decline, a UK-based qualitative study<sup>4</sup> identified two groups of nonattenders: older women with a more negative attitude to screening who actively decided not to participate and younger women who intended to be screened but did not attend. These women were more likely to report practical issues. Recent focus has been on the use of self-collected samples to overcome these procedural barriers. Self-collected samples have already been used in bowel screening programmes and in chlamydia screening.<sup>43,44</sup> Women appear to find taking a low vaginal swab or urine samples by themselves for HPV testing acceptable. To date, most interest has been on increasing participation in nonattenders. A systematic review and meta-analysis<sup>45</sup> that included eight European studies of under-screened women reported that compliance with HPV self-testing was significantly higher than with cervical cytology (RR 2.14, 95% CI 1.3–3.52). In self-testing for HPV, it is encouraging that around 90% of those testing positive attended for colposcopic assessment.<sup>44</sup> As yet, self-testing remains in the arena of clinical research, but it would seem likely that it will evolve as an option for nonattenders.

### 4. Opinion

Each constituent country of the UK organises their own screening programme, with some differences. With more robust evidence on cervical cancer prevention now available, harmonisation between

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\* Relative risk: the ratio of the probability of an event occurring in an exposed group relative to the probability in an unexposed group.



programmes is increasing, e.g. age range, frequency of screening and introduction of HPV testing. Changes based on HPV testing are expected to increase the efficiency of the programme. The advent of the HPV vaccination programme combined with evidence-based benefits of HPV primary screening may lead to the latter being introduced before the end of the decade. Novel biomarkers, such as p16 alone or in combination with other markers, may be useful in improving the specificity of hrHPV testing when used to triage low-grade cervical cytological abnormalities. The full extent of the effect of HPV vaccination on cytological screening is currently unknown, but further evidence will become available, and will need to be reviewed, in the next few years.

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This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Dr TBR Freeman-Wang MRCOG, London; Professor ME Cruickshank FRCOG, Aberdeen; and Professor HC Kitchener FRCOG, Manchester**

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The Scientific Advisory Committee lead reviewer was: Dr IJG Harley FRCOG, Belfast.

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Professor Kitchener is Chair of the Advisory Committee on Cervical Screening (Public Health England) and any views expressed in this paper are those of the authors and in no way reflect the view of Public Health England.

*All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this Scientific Impact Paper is available from:*

<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip7/>.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2019, unless otherwise indicated.

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This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.