Report to the National Screening Committee

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1. Summary

Cervical cancer is the second biggest cancer killer in women worldwide, but due to an effective cervical screening programme in the UK, deaths have fallen by around 60% to fewer than 1,000 deaths/year since the national programme was launched in 1988. This introduced structure, standards, quality assurance and a computerised system which is still in use. Up until now, screening has been based on cytology, but the causative role of high risk human papillomavirus, together with the introduction of the HPV prophylactic vaccination programme constitute a powerful rationale for switching secondary prevention to primary HPV screening and reserving cytology for HPV positive women. This is supported by four large European randomised trials, from which a subsequent pooled analysis has confirmed that, compared with cytology, HPV screening reduces the risk of developing cervical cancer. One of these trials, the ARTISTIC Trial, was conducted in England. What primary HPV screening offers is the prospect of greater sensitivity, compared with cytology, for the detection of underlying disease, and for those women who test HPV negative, longer protection allowing extension of screening intervals from 3 years to 6 years between ages 25 to 49, and potentially from 5 years to 10 years for women aged 50 and over. An exit HPV negative result for women aged over 60 is likely to confer protection from cervical cancer into an older age than is currently the case for women regularly screened by cytology. The challenge for primary HPV screening, however, is the management of women who test HPV positive/cytology negative, amongst whom the risk of developing cervical intraepithelial neoplasia grade 3 or worse (CIN3+) is twice that of the general population. This requires early recall at 12-24 months and referral if the infection persists. A detailed cost effectiveness modelling exercise based on ARTISTIC data and other UK data concluded that HPV as a primary screen would be cost and life years saving, but that triggering referral of these HPV positive/cytology negative women at 12 months would be more cost-effective than 24 months.

In order to confirm the performance of primary HPV screening in the NHSCSP, and to address the challenge of HPV positive/cytology negative screens, as well as ensuring general acceptability amongst women and primary care, and other practical issues, a large national pilot study, at 'Sentinel Sites' has been underway since April 2013. The pilot involves the entire screening age range (25-64) and involves HPV positive women having reflex cytology on the LBC sample. Abnormal cytology triggers referral to colposcopy and negative cytology requires early recall initially at 12 months (see Appendix). A 'safety check' requires routine recall at 3 years to ensure prior to moving to the anticipated extension of the screening interval to 6 years the detection of CIN3+ is sufficiently low. Laboratories have only partially converted to primary HPV, allowing both maintenance of cytology skills and contemporaneous comparison between primary HPV and primary cytology. These data are being evaluated independently and an interim report has been provided separately to the NSC. Initial data indicated that HPV followed by cytology had not increased baseline referrals when compared with cytology triaged by HPV. Early data censored in July/August indicated that 8.5% of screened women were HPV positive/cytology negative, of whom over 50% had cleared HPV at 12 months. Detection rates of CIN grade 2 or worse and CIN3 were significantly higher amongst women who had primary HPV screening compared with primary cytology. Larger numbers with updated data will permit more reliable interim findings. The pilot appears to have been well accepted by women and primary care, due in part to careful preparation and previous experience with HPV triage.

A national switchover to primary HPV screening would require a reconfiguration of laboratories both to maximise economy of scale with tests that have high throughput platforms and to maintain adequate cytology workload in a smaller number of laboratories; overall cytology work would fall by over 80%. Staff redundancy would be an issue though cytoscreeners are skewed towards older age and some could be redeployed in HPV testing.

A final but critical point is the Exeter computerised system which is over 20 years old would not be fit for a HPV based programme, and would need to be replaced by a new system. For safety reasons the Sentinel Sites pilot could not extend without a new system, and a new system for the country should be piloted within the Sentinel Sites project before full roll out.

2. Importance of cervical screening

Worldwide, cervical cancer is thought to be responsible for around 275,000 deaths per year which ranks it as the second most common cause of cancer deaths in women after breast cancer. Screening for pre invasive changes in cervical epithelium, by means of cervical cytology, has resulted in a major fall in both incidence and deaths in the developed world, but in developing countries, most women have neither access to screening nor access to adequate treatment. As a result of screening, cervical cancer now ranks 15th in female cancer deaths in the UK and mortality has fallen from 6.4 per 100,000 population in 1988 to 2.2 per 100,000 population in 2012[1].

3. Current screening strategy

3.1. Liquid based cytology

The mainstay of screening since the inception of the National Programme in 1988 has been exfoliative cytology. This allows detection of abnormal epithelial changes which triggers referral for colposcopy, biopsy and treatment. From 2006, the Cervical Screening Programme converted from conventional to liquid based cytology which allows reflex triage testing without a second sample being needed. Treatment for the premalignant lesion, cervical intraepithelial neoplasia (CIN) grades 2 and 3, is a straightforward outpatient procedure which effects cure in 90-95% of cases by means of a single excisional procedure. Treatment failure is usually detected in follow up, and a second treatment provided, but cancer will occur despite treatment in around 1 in 200 cases[2], which actually corresponds to around five times the population risk. In recent years, there has been concern that loop excision, which is the main technique employed to treat CIN, is responsible for an increased risk in preterm labour. In a recently published case control report from England, the authors found that increased risk of preterm and very preterm labour only really applied to excisions greater than 1.5cm deep[3], which in fact accounts for a small minority of treatments.

3.2. HPV testing

The causative role of high risk human papillomavirus (HR HPV) which was confirmed in the early 1990's has provided a precise means of primary prevention through prophylactic vaccination, and more precise strategy for secondary prevention through HPV testing in cervical screening.

HPV DNA testing has been developed because HR HPV status stratifies risk which can be exploited to triage management. Essentially, being HR HPV negative places a woman at very low risk, lower than negative cytology, whereas a HR HPV positive test can select for appropriate onward investigation or early recall. HPV testing is already in place in the screening programmes in England and Northern Ireland to select colposcopy referral (triage) amongst women with low grade cytological abnormalities, and also throughout the UK as a test of cure for women treated for CIN. This approach has had the principal benefit of accelerating return to routine recall, and advancing the diagnosis of underlying CIN because of avoiding the need for repeated cytology.

4. Purpose of proposed change

The rationale of the proposed change whereby HR HPV testing would replace cytology as the primary screen is based on greater sensitivity to detect CIN, extension of screening intervals, and now that the vaccinated cohort is coming through, a more precise means of detecting women at risk of disease.

5. Epidemiology

HR HPV infection occurs rapidly after sexual 'debut', with around 50% of females acquiring infection of the cervix within six months. Thereafter the immune system will clear the infection in the majority of cases, but type specific viral persistence is seen in around 30% of infections after 2 years[4], and it is this persistent infection by high risk types that is responsible for cellular changes resulting in CIN. The prevalence of infection is very age dependent, falling from around 40% at age 20-24 to around 7% at age 50[5]. Some studies have shown a small increase in prevalence in the menopausal age range. The mean age of acquiring HPV infection and the mean age of developing CIN3 (around age 30) suggest that the process of acquiring the true cancer precursor lesion generally takes 10-15 years. Low grade CIN (CIN1) is probably best regarded simply as chronic infection and is not treated, whereas CIN3 is thought of as the cancer precursor lesion and must be treated. CIN grade 2, which is usually associated with either grade 1 or grade 3, is also treated. While there has been a trend to manage low grade CIN more conservatively, treatment of CIN grade 2 or worse (CIN2+) remains the standard of care. CIN grades 1 and 2 are regarded as potentially regressive, and though some CIN3 may regress in young women, there is no biomarker to distinguish such lesions. The concept of a transition from CIN1 through CIN2 and CIN3 is an oversimplification, and many CIN3 lesions probably arise de novo. The change made in England in 2003 to the age threshold for initiating screening from age 20 years to 25 years, was based on the demonstration that screening was ineffective in preventing cancer in that age range, and that screening would detect a very large number of low grade lesions, many of which would regress risking unnecessary treatment[6]. Due to public pressure following a small number of deaths in women under 25 years, the decision to begin screening at 25 in England was reviewed in 2009 by the Advisory Committee for Cervical Screening[7]. This has subsequently been supported by the National Screening Committee, and is also supported by IARC.

The risk of CIN3+ developing in adult women found to have a HR-HPV infection, can be determined from ARTISTIC trial data[8]. Compared with HPV negative women whose risk of being found to have

CIN3+ over a six year period was 0.28%, baseline HPV 16 infection was associated with a 100 fold increased risk. For 'any type' of HR HPV positivity, it was 20 times greater. Even amongst women with negative cytology at baseline, there was an almost 10 times greater risk for women who were HR HPV positive compared with HR HPV negative.

6. Primary prevention

The bivalent and quadrivalent HPV vaccines have been shown in pivotal randomised trials to have 98% efficacy in preventing CIN2+ related to HPV types 16/18 amongst females who were HR HPV negative at the time of vaccination. In addition, it has been recognised that there is some cross protection from other types, which provides an added effect when compared with types 16/18 alone.

Based on trial efficacy data and genotyping data from a large cross section of cervical lesions in England, vaccination would be expected to prevent at least 70% of CIN3[9]. Vaccination will also have a large impact on the incidence of HR HPV infection, which will initially be seen in the 'catch up' campaign cohort of 14-18 year olds who were vaccinated between 2008-10. Reduced prevalence of HR-HPV should be detectable in England amongst 25 year olds being screened from 2015 onwards.

Between 2008-13 the bivalent vaccine was used in the UK before switching over to the quadrivalent vaccine in 2013. Based on the published bivalent vaccine efficacy[10] for types 16/18 and 31/33/45/52/58, genotyping data from ARTISTIC[4] suggests that vaccination could reduce the prevalence of HR HPV by around 50%. A recent report from Scotland, where screening still begins aged 20 years, has shown a significant reduction in CIN3 (RR 0.45; 95% CI 0.35-0.58)[11] amongst the vaccinated cohort. In a screening programme where HPV status determines the number of women requiring any further action, the expected impact of vaccination would therefore be considerable in terms of the proportion requiring reflex cytology, referral to colposcopy and treatment for high grade CIN.

7. The HPV test

Until recently, Hybrid Capture II^{R} (HC2)[12] was the only approved test, but there are now a number of CE marked tests, which have been shown in prospective testing in the triage setting within the screening programme to be as sensitive and more specific in the detection of CIN2+ than HC2[13]. Most of these tests are based on the detection of viral DNA; one detects viral RNA. Furthermore some of these new tests can exploit high throughput platforms developed for other microbiology diagnostic tests. HPV testing therefore offers the potential to concentrate testing into a smaller number of hubs maximising the economic benefits of high throughput.

8. The evidence supporting primary HPV screening

HPV primary cervical screening has been evaluated in four large European trials which involved at least two rounds of screening. These were conducted in the Netherlands (POBASCAM)[14], Sweden (SWEDSCREEN)[15], Italy (NTCC)[16], and England (ARTISTIC)[17]. All except ARTISTIC, which used liquid

based cytology, were based on conventional cytology, and all of these trials compared cytology with cytology plus HPV testing, with interventions for cytology negative/HPV positive women. In all four trials the HPV arm showed a reduction in the detection of CIN2+ in the second screening round, as a result of greater sensitivity achieved by HPV testing in round 1. Crucially for screening, a recently published pooled analysis of all four trials involving over 176,000 women with a median of 6.5 years follow up, showed clear evidence of a reduction in the incidence of cancer in the HPV arms compared with cytology alone; the hazard ratio for developing cancer was 0.6[18].

Some of the data used in this document have been drawn from the ARTISTIC Trial of HPV primary screening which generated the largest prospective genotyped dataset developed in the UK, and allows correlation of baseline screening results with clinical outcomes over a six year period. Not only does screening for HPV provide greater protection, but it also allows screening intervals to be extended. Data from ARTISTIC over three screening rounds and a mean follow up of 72 months, indicated that the cumulative rate of CIN2+ was similar after two rounds (3 year interval) following a negative cytology result as after three rounds (6 years) following a negative HR HPV test (0.73 vs 0.87). The cumulative rate of CIN2+ over a mean of 6 years, was 1.41% (1.19-1.65) for negative cytology at baseline compared with 0.87% (0.70-1.06) over 6 years for negative HPV. The corresponding data for CIN3+ was 0.63 (95% CI 0.48-0.80) for negative cytology compared with 0.28 (95% CI 0.18-0.40) for a negative HR HPV test[8]. For HPV negative women over 50 years, the cumulative risk over six years was only 0.16% (95% CI 0.07-0.34), suggesting the potential to extend the screening interval for women over 50 to 10 years.

Although the randomised trials of HPV testing involved co-testing with cytology, there is clear evidence from the ARTISTIC trial that co-testing (cytology and HPV) would not be cost-effective compared with HPV alone. There were 20,697 HPV negative women at baseline amongst whom 1497 and 46 were found to have low and high grade cytological abnormalities respectively. Amongst these, 9 CIN3 and 28 CIN2 lesions were identified in the first screening round, and 2 CIN3 and 2 CIN2 lesions in the second round. This means that co-testing would have required 20,000 additional cytology and up to 1500 colposcopies to detect 11 CIN3 lesions (PPV<1%). Therefore HPV negative women in whom abnormal cytology was identified were at low risk with cumulative rates over six years for CIN2+ and CIN3+ of 3.24% (95% CI 2.32-4.28) and 0.83% (95% CI 0.4-1.52) respectively. Indeed, the corresponding rate for the entire ARTISTIC population was not lower for CIN2+; 3.88% (95% CI 3.59-4.17) and was in fact lower for CIN3+; 1.96% (95% CI 1.76-2.17)[4].

9. The clinical performance of HPV testing

In event of a conversion from cytology to HPV as the primary screen, it is pertinent to consider differences in clinical performance. Currently, negative cytology means a return to routine recall every three years up until age 50, and every 5 years between 50-64 years. In England and Northern Ireland, a borderline or low grade dyskaryosis involves reflex testing for HR HPV, so called triage. This allows the 30-40% who are HR-HPV negative to be returned to recall whereas women who are positive are referred immediately to colposcopy; this had a positive predictive value (PPV) in the triage pilot for diagnosing CIN2+ of around 16%[19]. Women with high grade cytological abnormalities are referred directly to colposcopy with a PPV of 75-90%[20].

In the event of conversion, HPV testing would enable an extended screening interval of six years if negative. If positive, reflex cytology would be performed and any grade of abnormality would result in referral. The PPV would therefore remain the same for the combination of HPV positive/low grade cytology. As almost all high grade cytology is HPV positive, the PPV would be expected to remain unchanged at 75-90%. The challenge for primary HPV screening is that because of the prevalence of HPV infection, particularly in younger women, it is less specific in terms of underlying CIN grade 2 or worse, than cytology. HPV testing with cytology triage will therefore produce a new class of abnormal result; those who are HR HPV positive/cytology negative, which was found in around 9% of the ARTISTIC cohort who were aged 20-64. This proportion would be expected to be lower (~8%) in a population aged 25-64, and of course far lower in a vaccinated population. Although this group are at twice the risk of the general population, referral would await evidence of persistent infection as many women clear the infection over 12-24 months. There are potential biomarkers to improve the specificity with respect to underlying CIN2+, and one of these which combine p16 and Ki67 is currently under evaluation in the Sentinel Sites primary HPV pilot project. There is no reason to believe that lesions detected by HPV triaged by cytology should be different from those detected via cytology triaged by HPV.

9.1. What is the comparative accuracy of HPV DNA tests and cytology for: CIN2 or worse (CIN2+) and CIN3 or worse (CIN3+), in women under 30 years old?

The comparative accuracy of primary HPV with cytology triage can be expected to be less specific but more sensitive than primary cytology with HPV triage, because of the high prevalence of HPV in women 25-29. Therefore the rate of referral at baseline could be expected to be higher than following primary cytology in this age group. Although the PPV for CIN2+ may be lower amongst those referred following primary HPV compared with primary cytology, the detection rate overall for CIN2+ and CIN3+ should be greater than for primary cytology in the 25-29 age group. Crucially, cytology negative/HPV positive women will harbour undetected CIN, amongst whom at least 3% will have CIN2+, which will be detected as a result of early recall. Data will be available in the report of the primary HPV pilot.

9.2. What is the accuracy of HPV DNA tests compared with liquid based cytology for these outcomes in all women and in women under 30 years old?

With respect to women below 30 and older than 30, tests should perform similarly from a purely analytical point of view. Despite the greater prevalence of HR-HPV infection, the greater prevalence of CIN2+ and CIN3+ in women under 30, should mean that the PPV for the detection of high grade CIN amongst those referred at baseline could be expected to be similar to the age group 30 and older. The proportion who are HPV positive/cytology negative will be greater in the under 30's which would therefore result in a disproportionately large number of the HPV positive/cytology negative women under 30 who require subsequent referral to colposcopy, either because of persistent infection or abnormal cytology. Around 8% of screened women are in the category of HPV positive/cytology negative. If 80% adhere to early recall and 40% of these show persistent HPV over 12-24 months, then an additional 2.5% of screened women could be referred to colposcopy, based on current data. It must be borne in mind however, that this would include a prevalence effect which will lessen for that cohort in subsequent rounds. It should also be noted that amongst 25 year olds, the impact of HPV 'catch up' vaccination programme will be felt beyond 2015, and the vaccination of 12/13 year olds beyond 2020, such that the prevalence of high risk HPV infection will

be markedly reduced. Any increase in the requirement for colposcopy should therefore be temporary. Again, data comparing HPV testing in the 25-29 and 30 and older age groups will appear in the pilot report.

9.3. What is the estimated rate of over-diagnosis of regressive lesions when current practice and HPV DNA screening are compared?

The estimated rate of regressive lesions is not possible to determine with any precision because CIN2+ is treated and not managed expectantly. Around 25% of detected CIN is CIN grade 1, which is not treated. CIN grade 2 though treated, is not widely regarded as a true precursor lesion but there have been no randomised trials of treatment versus observation to determine regression rates. It should be noted that CIN2 is not a robust diagnosis; it is often reported as CIN1/2 and CIN2/3 as it often occurs amongst areas of CIN1 and CIN3. The WHO is moving towards the reporting of CIN as low grade and high, and CIN2+ would be categorised as high grade. CIN3 may regress in a small proportion of cases but non treatment of CIN3 would be regarded as clinically negligent, even though not every case of CIN3 would progress to cancer. The most regressive lesions are CIN grade 1 which some consider to be little more than evidence of a persistent HPV infection. Amongst those women who are HPV positive and have abnormal cytology, the profile of detected CIN should be similar to primary cytology and HPV triage. It is possible that amongst women with negative cytology and persistent HPV, more CIN1 will be reported at the time of early recall.

9.4. What proportion of women with HPV positive results will be cytology negative? Can this be broken down by under 30s and over 30s?

As stated above, around 8% of screened women aged 25-64 might be expected to be HPV positive/cytology negative. In the ARTISTIC trial this proportion was 9% overall; 16% in the 20-29 and 2.6% in the 30-64 range. In the age range 25-29, the proportion is likely to be 11-12% as the HPV prevalence dropped from 37.5% to 27.5% in the 20-24 and 25-29 age ranges respectively. More precise data will be available from the report of the primary HPV pilot.

9.5. Have cut-offs for HPV testing been agreed and has the frequency of screening been agreed?

HPV tests are analysed according to manufacturer's instructions. The Hybrid Capture 2 (HC2) test did allow a variable cut off to be used and a cut off of 2pg/Co was found to be clinically more useful than the manufacturers cut off of 1pg/Co in terms of a beneficial balance of sensitivity and specificity. The recently developed tests which laboratories generally prefer for reasons of high throughput automated platforms being used for other microbiology tests, are used according to manufacturer's instructions. As stated earlier, these newer commercial tests compared favourably with HC2 at a cut-off of 2pg/Co, when tested in the triage setting. To compare the tests robustly in the primary screening setting would require very large expensive studies which cannot be justified. As stated in Section 8, there are prospective data from ARTISTIC which indicate that six yearly screening until age 50, and 10 yearly screening over 50, would be as effective as three and five yearly screening as currently used for cytology. The conversion of the Australian programme in 2016, from 2 yearly primary cytology to primary HPV screening, envisages 5 yearly HPV screening.

9.6. What is the proposed diagnostic pathway for HPV positive women?

In general, HPV positive samples are subjected to reflex cytology triage in the liquid residue, with immediate colposcopy referral for abnormal cytology. Those who are cytology negative are at twice the risk of having or developing CIN grade 2 or worse over six years compared with the general population and therefore harbour disease not detected cytologically. Early recall is therefore appropriate. In the pooled analysis of the RCT's of HPV primary screening, the incidence of cervical cancer following primary cytology began to increase relative to HPV primary screening after 2-3 years, so while there is no urgency for early recall in terms of preventing cancer, there is a balance to be struck between an interval long enough to maximise viral clearance, but not so long that women may not adhere to recall. The current pilot protocol involves early recall at 12 months and if HPV persists, again at 24 months prior to colposcopy referral. Several sites however have started to refer women who are persistently types 16/18 positive at 12 months. This is because some tests offer a 16/18 readout, and the specificity of HPV positivity can be increased by restricting referral to the highest risk types in terms of disease. If employed immediately, too many young women would be referred, on the other hand recall at 12 months for 16/18 positive and further recall at 24 months for other high risk positives will allow the highest risk women to be colposcoped and allow further clearance to occur in those with lower risk types. National programmes will vary according to follow up protocol but the economic modelling recently reported from the ARTISTIC group[21], suggested that selective referral to colposcopy at 12 months was found to be more cost effective than delaying referral for all until 24 months. This is probably related to the model predicting increased non adherence to repeated early recall. Although HPV positive/cytology negative women do not require immediate intervention, they do require early recall. To what extent this risk and need to recall is understood by women is not clearly known, however early experience from the English pilot study has indicated that adherence to early recall is encouraging, and qualitative research to address the views and experience of screened women is planned for 2015.

9.7. Have evidence based policies for the diagnostic pathway been agreed and published?

The pathway employed (see Appendix) in the national pilot broadly reflects the principal considerations above, i.e. referral with abnormal cytology and early recall with negative cytology. Of the six centres, some refer if 16/18 positive at 12 months, and other continue to defer referral until HPV persists until 24 months. This comparison will be of interest.

9.8. The treatment

This will remain unchanged. CIN1 is not treated and CIN grades 2 and 3 are treated. This is in line with worldwide practice.

9.9. Is there RCT evidence that the screening programme is effective in reducing mortality or morbidity?

As stated on page 5, the pooled analysis of the four European RCT's of primary HPV screening indicated that HPV significantly reduced the incidence of cancer. Overall the rate ratio was 0.60 (95% CI 0.40-0.89), and for negative baseline screening it was 0.30 (95% CI 0.15-0.60). There are not yet data on mortality. Reduced incidence of cancer will be cost saving and reduce cancer treatment related morbidity.

9.10. When the test produces information upon which no immediate intervention is required (eg HPV positive/cytology negative) is there evidence that this accurately measures risk, is valued and easily understood by the recipients?

The risk is accurately known from 6 year follow up data in the ARTISTIC trial. HPV positive/cytology negative women had a cumulative incidence of CIN2+ over two subsequent rounds (at three and six years) of 3.6% (1.87 + 1.73) whereas the corresponding figure for all women who screen cytology negative was 1.29% (0.42 + 0.87). We do not yet have data to show to what extent this will be appreciated by women, but the encouraging adherence to early recall in the pilot suggests it is, by the majority of women.

9.11. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

The principal harm that could accrue from HPV primary screening could be a) increased anxiety as a result of being HPV positive/cytology negative thus necessitating early recall in place of return to routine recall, b) increased morbidity from increased detection of CIN2+, some of which would not result in cancer. With respect to the latter, the pooled analysis of RCT's suggests that the overall effect is a fall in cancer incidence amongst women screened with HPV.

In general, the process of cervical screening is viewed favourably as a public health measure, with the benefits of screening, i.e. the reduction in cervical cancer deaths outweighing the harm. It should be noted that in the longer term, the observed effects of vaccination should result in a large reduction in the incidence of high grade CIN and consequently, reduced treatment-associated morbidity. The theoretical harm that could occur from the knowledge of having an oncogenic, sexually transmitted infection has not been apparent. Throughout not only the primary HPV pilot, but also the preceding pilot of HPV triage, there has not been evidence of problems either from women, GP's or sample takers. The care that has been taken to inform women, as well as sample takers and doctors has undoubtedly help to avoid distress.

10. How the screening programme would change with HPV primary screening

Given the evidence from the European trials described above, HPV based screening would be expected to save additional lives compared with current provision. If the hazard ratio from the trials were translated into population based screening there would be a significant reduction in cancer incidence with a similar reduction in deaths. With the vaccination programme in place however, primary prevention is already predicted to save a proportion of these lives; nonetheless a more sensitive HPV based programme would more precisely target women at risk and prevent cancers and deaths. It would also be more efficient and cost effective.

There would be two major changes in a HPV based programme. The first would be a reduction in the number of screens in a lifetime. Currently a woman would receive 12-13 invitations, (3 yearly intervals until age 50 and 5 yearly thereafter) but with HPV testing, this could be essentially halved due to extending screening intervals to 6 yearly and 10 yearly over the age of 50 years, based on extended follow up data from ARTISTIC. Additionally, as the vaccinated population grows older, together with the prospect of a protective nonavalent vaccine[22], there is the future prospect of de-intensifying screening further according to the evidence emerging from post vaccination surveillance

programmes. It should also be noted that an 'exit' screen at 64 years by means of HPV testing will provide longer protection into older age compared with that of cytology, which has been estimated on the basis of having been regularly screened until 64, to continue until the mid 70's.

The second characteristic of a HPV based programme that will differ is the creation of the already highlighted HPV positive/cytology negative cohort, who based on ARTISTIC data are at twice the population based risk of developing CIN2+. As stated above, it will be necessary to institute early recall of these women to maximise the benefit of the greater sensitivity of HPV testing without swamping colposcopy referral and creating unnecessary anxiety. Early recall is a key component in the national pilot.

11. Acceptability of HPV screening

There has been awareness since HPV testing was first piloted in triage and test of cure, that using a test which detects an oncogenic sexually transmitted virus could present difficulties for women. As already stated, it has been noticeable how well HPV testing appears to have been received by women and health professionals, as there has been an absence of adverse comment from women, GP's and sample takers. Throughout the piloting and implementation of HPV testing there have been no formal complaints from any quarter about the consequences of HPV testing. That is not to say that individual women have not been concerned about what a positive HPV result means to them personally, but the careful planning of information provision and training of sample takers appears to have been successful in transferring from the trusted 'smear test' to liquid based samples which have incorporated both cytology and HPV test results. A formal evaluation of the acceptability of primary HPV screened is currently planned within the primary HPV screening pilot.

12. Cost effectiveness of HPV primary screening

A number of cost effective evaluations of primary HPV screening has been performed, in the Netherlands[23], Germany[24], Norway[25] and Canada[26], all of which have determined that changing from cytology to HPV based primary screening would be favourable. International cost effective analyses may lack country specific considerations such as screening and vaccine coverage, compliance with follow-up, likely algorithms and validation of a modelling platform fitted to country specific data. In a recently published[21] cost effectiveness analysis of primary HPV screening in England, these considerations were all accounted for in a detailed analysis which concluded that switching from liquid based cytology to primary HPV screening would be both cost saving and more effective across a number of strategies, for both unvaccinated and vaccinated cohorts. The methodology for this study involved a model platform with three main components; a dynamic model of sexual behaviour and HPV transmission, a Markov cohort model of the natural history of CIN and invasive cervical cancer, and a cohort/multi-cohort model of screening, diagnosis, treatment and follow up. The model platform which had been used previously to evaluate changes to screening in Australia and the UK[27, 28], was validated against data from the ARTISTIC Trial which represents generalisable screening results in England. A number of necessary assumptions regarding sexual behaviour, vaccination data and other screening data were drawn from UK screening data sets, NATSAL II, and UK vaccination data. Because of uncertainty regarding likely final screening algorithm, particularly

with respect to women who were HPV positive/cytology negative, four screening strategies were studied.

1. HPV primary screening with a 24 month colposcopy for women with negative cytology and persistently positive HPV testing.
2. As for 1., but referring for colposcopy at 12 months on the basis of persistent HPV type 16/18.
3. Referring for colposcopy at baseline if women were positive for HPV type 16/18.
4. Screening with both HPV and cytology and referring either because of high grade cytology or managing women who are HPV positive with negative cytology, as in strategy 2.

Overall, cost savings compared with current practice, i.e. liquid based cytology, were predicted for both vaccinated and unvaccinated cohorts. These cost savings ranged from 9% (strategy 4) to 22% (strategy 1) in vaccinated cohorts and from 7% (strategy 4) to 18% (strategy 1) in unvaccinated cohorts. The most effective strategy (strategy 3) involved direct referral to colposcopy of women who screened HPV16/18 positive, however this would involve a considerable increase in colposcopy which was not considered feasible. This suggests however, that using cytology to triage HPV positive women, and referring on the basis of persistent HPV16/18 at 12 months may be more feasible and remain effective.

In general strategies using HPV as a sole primary screening test were both cost saving and life years saving. It was also determined that using 12 months rather than 24 months referral to colposcopy for persistent negative cytology/HPV positive, was more effective. Having a 12 month follow up prior to colposcopy referral resulted in an estimated 73-113 and 37-41 additional life years saved per 100,000 women in unvaccinated and vaccinated cohorts respectively, when compared with a 24 month referral. This difference is presumably due to the likelihood that more women would fail to adhere to follow up over 24 months compared with 12 months. Exploratory analyses also predicted that retaining cytology only below ages 30 or 35 years would increase costs and reduce effectiveness. This suggests that implementation of HPV as a sole screen from aged 25 years would be optimal in terms of cost and life years saving in England. In conclusion the modelled analysis predicted that primary HPV screening would be both more effective and cost saving compared with current practice. Adhering to early recall for women who test HPV positive/cytology negative is seen as of key importance if the sensitivity of HPV over cytology is not to be undermined. The analysis supports a switch from cytology to HPV based cervical screening.

13.English primary HPV screening pilot

The large pilot study of primary HPV screening, already referred to, was initiated in April 2013 across the six Sentinel Sites used previously to pilot triage and test of cure. It has been designed to assess; feasibility and practicability, to test clinical algorithms, to support an economic evaluation and assess acceptability by women. Interim data have been reported in a separate report to the NSC.

14. Consideration of infrastructure and phasing for national switchover from cytology to HPV

There are three key issues which need to be considered in the event of a decision to proceed to a national conversion from primary cytology to HPV.

1. Laboratory capacity and reconfiguration.
2. The computer system to support the changed programme.
3. The implication for staff given a massive reduction in cytology.

14.1. Laboratory capacity and reconfiguration

There are two principal drivers here. The first of these is the need to maximise cost effectiveness through high throughput testing using the capacity of the HPV testing platforms. The second, and in some respects the dominant driver, is the need to maintain laboratories with adequate workload for cytology. Current guidance supports a minimum laboratory throughput of 35,000 cytology slides per year to maintain expertise amongst 5-7 screening staff. Given that cytology would be reduced to around 15% of its current level based on the pilot experience, this would require around 200,000 HPV samples per year to generate 35,000 cytology slides. Given around 3 million screened women per year, this would equate to concentrating cervical screening to around 15 labs in England, perhaps two each in Scotland and one each for Wales and Northern Ireland. Whether this were configured as microbiology and cytology in separate but co-located labs, or HPV testing and cytology conducted in a single lab would be determined locally. Both models have been used in the pilot and both work well. Commissioning more centralised services will present some challenges.

14.2. The computer system

The current cervical screening programme uses a call/recall IT programme developed 25 years ago. Should HPV screening be introduced, the increasingly personalised screening intervals and varying results will require a modern IT system. The invitation of the cohort and management of women through a much more complex pathway without running the risk of losing women will be absolutely crucial. Failure to invite and absence of failsafes to ensure completion of the pathway (when the woman consents so to do) will result in women being lost to the system and getting cancer when they need not. An IT system that is not fit for purpose risks loss of life, massive reputational damage and loss of confidence in the programme.

14.3. Implications for staffing

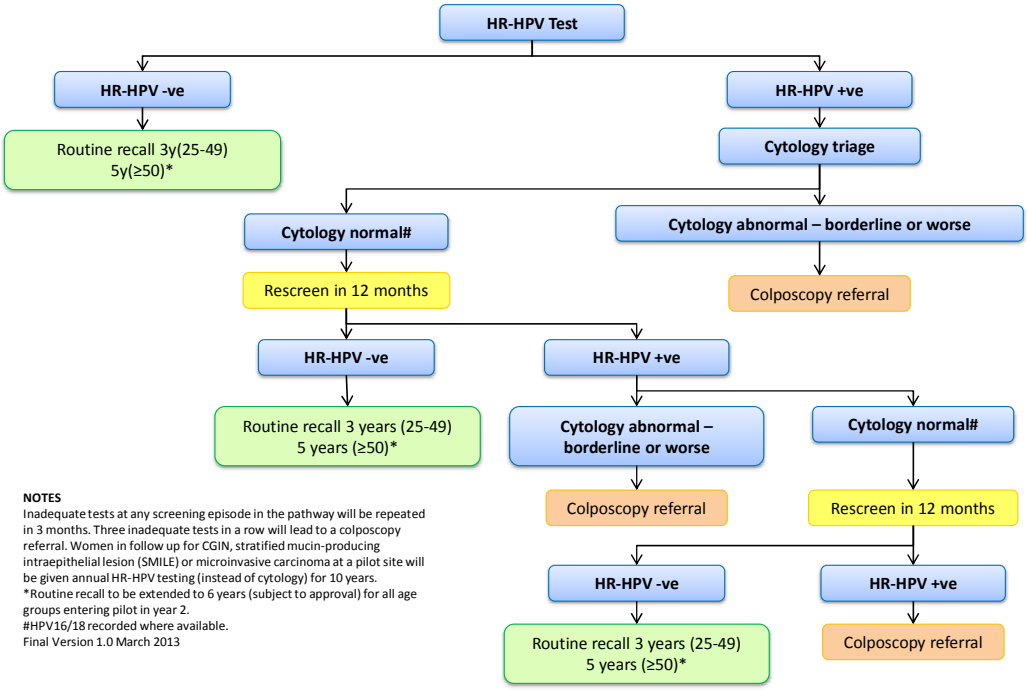
It is inevitable that a major reduction in cytology will require fewer staff, however a number of factors may mitigate this problem. These include the age range of the cytoscreeners which tends towards older staff, the potential to redeploy from cytology to HPV testing, and cytology staff seeking new posts when it becomes clear that redundancy threatens. With respect to the last point there is a need to try to clarify timescales to avoid a premature flight from cytology labs. Although laboratories have only partially converted in the pilot, once a decision to switch has been made, it would be better to plan for a total switchover in order to avoid a perceived two tier programme based partly on primary HPV and partly on primary cytology. There will be a need to consider how to mitigate a sudden move from 3 yearly to 6 yearly screening intervals in order to avoid an interval during which activity collapses. SCHARR in Sheffield University have been tasked with looking at this. Their report will be available in Q2 of 2015.

15. Conclusion

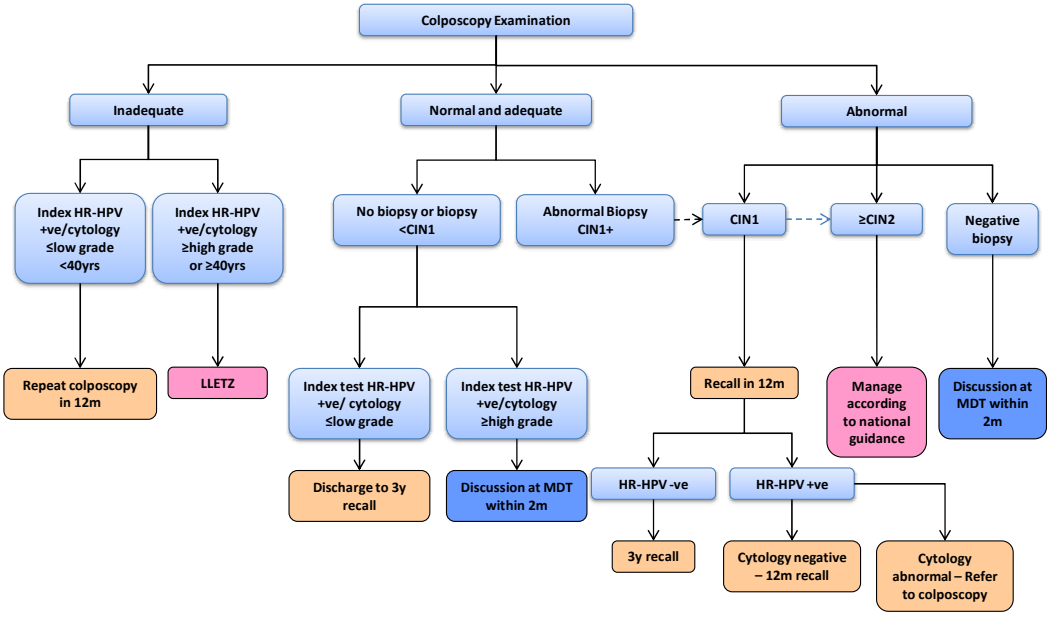
In conclusion, there is grade A evidence to support a switch from primary cytology to primary HPV testing in cervical screening. This should save life years and cost less, increasingly so as the vaccinated population grows older. A NHS pilot exercise to demonstrate feasibility, practicability and safety is reported separately. There will be some challenges in terms of laboratory reconfiguration, computer systems and staffing, but in an era of primary prevention through HPV vaccination, HPV based screening offers the prospect for a more effective, more streamlined, cheaper programme which is more tailored to individual risk.

Appendix

Algorithms for HPV primary cervical screening currently in use with the primary HPV screening pilot in England



HPV Primary Screening Algorithm – Pilot Year 1:
All women aged 25-64 on routine call/recall and early recall



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