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What's next? Perspectives and future needs of cervical screening in Europe in the era of molecular testing and vaccination

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ABSTRACT

Aim: To outline the perspectives for future control of cervical cancer in Europe.
Methods: Review of current status for major cervical cancer control tools. The review was based on PubMed searches for cervical cancer prevention, Human Papillomavirus, HPV-test, HPV-vaccination, and treatment with large loop excision of the transformation zone, LLETZ.
Results: Recent studies suggest that condom use offers some but not complete protection against HPV-infection. High quality cytology screening with good population coverage reduces the incidence and mortality of cervical cancer. Randomised controlled trials have found HPV-testing to increase the detection rate of cervical intraepithelial neoplasia grade 2+, CIN2+, compared with cytology. Two studies found a decreased detection rate of CIN3+ in the HPV-testing arm at the subsequent screening. Randomised controlled trials found that women not infected with vaccine HPV-types at vaccination are well protected against CIN2+ from these HPV-types, but the vaccine does not protect against CIN2+ from other HPV-types and neither does it protect already HPV infected women. There is an increased risk of adverse obstetric outcomes following excisional treatment.
Conclusions: The future of cervical cancer control may become a diversified strategy, one for non-vaccinated birth cohorts and another for vaccinated cohorts. It will take another 50 years before the non-vaccinated cohorts have passed the screening age. With the current uncertainty concerning the long term protection from HPV-vaccination it will furthermore be precautionary to continue screening practice for the first cohorts of HPV-vaccinated women. Organised vaccination and screening programmes with good record keeping are necessary to optimise the future control of cervical cancer.

1. Introduction

The control of cervical cancer has a long and relatively successful history in countries with adequate resources and infrastructure. Surgical treatment of uterine cancer started in the 1890s, and radium treatment was added in the 1920s. However, control of cervical cancer took a new turn in the 1950s when Pap smears started to be used for screening of

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the cervical mucosa for precursor lesions. Cervical cancer screening is a well established practice in Europe, as documented in the European Guidelines for Quality Assurance in Cervical Cancer Screening.[1–3] In the 1990s, the identification of human papillomavirus (HPV) infection as a necessary step in the development of cervical cancer further expanded the possibilities for disease control. Public health authorities are now faced with the question of how to optimise disease control given the extended battery of tools. It is the purpose of this paper to discuss the future of cervical cancer control in Europe.

2. Biology of cervical cancer

The cervix uteri is only 2–3 cm long, but this small organ nevertheless harbours the second most common cancer in women.[4] At present, cervical cancer constitutes 15% of female cancers in developing countries, and 3.6% in developed countries. In the pre-screening era of the Nordic countries, cervical cancer constituted 10% of female cancers.[5] Cervical cancer originates in the mucosal layer, mainly in the transformation zone, starting with formation of dysplastic cells along the basal membrane, spreading to the entire depth of the mucosal layer, and finally invading the underlying tissue. Dysplasia, or cervical intraepithelial neoplasia, CIN, is an unstable condition which can both progress to invasive cancer, and regress to normal mucosa. CIN3 is supposed to be the last stage before invasion. In a recent 30 year follow-up study, one third of untreated CIN3 cases had progressed to invasive cervical cancer.[6]

It has been known for a long time that the risk of cervical cancer varies both geographically and by socio-economic status. The disease is common in prostitutes and rare in nuns, and the risk increases with number of sexual partners, with age at first intercourse, and with other aspects of sexual life. It is, however, only with the understanding of the essential role of HPV-infection in the disease aetiology that cervical cancer has been named a sexually transmitted disease.

In 1985, zur Hausen et al.[7] found DNA sequences of human papillomavirus in cervical carcinoma cells. In 1992, Muñoz et al.[8] published the first of a series of case–control studies showing HPV-infection to be an overwhelmingly strong risk factor for development of cervical cancer. In 1995, Bosch et al.[9] found that high risk types of HPV were present in virtually all specimens of cervical cancer collected from around the world. These findings formed the key elements when the International Agency for Research on Cancer in 1995 concluded that HPV 16 and 18 were carcinogenic to humans.[10] In 2007 this list was extended to include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66.[11] Studies of the prevalence of HPV-infection show that a large proportion of young women in the early phase of their sexual life carry an HPV-infection. However, the majority of these women clear their infection, and the prevalence decreases after the age of 30.[12] Cervical cancer will originate primarily in women with a persistent high risk HPV-infection, but only a fraction of these women will develop cancer. Persistent infection with high risk types of human papillomavirus is therefore a necessary, but not a sufficient, cause of cervical cancer. These aspects of the disease aetiology have to be taken into account in deciding on the optimal control of cervical cancer.

In the following text, the presently available cervical cancer control tools, see Fig. 1, will be described briefly, and thereafter the future combination of these tools as a public health policy in Europe will be discussed.

3. Primary prevention

The high risk types of HPV are sexually transmitted, and the question therefore arises whether transmission can be avoided or limited. While postponement of marriage age or age of onset of sexual activity may be considered in some parts of the world, the relevant tool in the European context is use of condoms.

A meta-analysis of cross-sectional studies using broad measures of condom use found condoms not to protect against infection with HPV.[13] A recent prospective study from the Unites States following 18 to 22-year-old undergraduate women at the start of their sexual life found, however, that incident HPV-infections decreased with increasing condom use by partners. Incident HPV-infection was 70% lower among those always using condoms compared with those using condoms in less than 5% of intercourses, hazard ratio 0.3 (95% confidence interval [CI] 0.1–0.6).[14] These data are supported by a randomised controlled trial undertaken in women attending a colposcopy clinic in the Netherlands. Included were women with an abnormal cervical smear and/or colposcopy and/or histology confirmed CIN, grade unspecified. Excluded were women surgically treated for their lesion and with regular condom use at baseline. Willing couples were randomised to condom use for at least 3 months or to controls. Women were followed up by colposcopy, HPV-testing, and cervical smears. The 2-year cumulative regression rate of CIN was 53% in the condom group versus 35% in the noncondom group ($p = 0.03$), and the 2-year cumulative rate of HPV clearance was 23% in the condom group versus 4% in the noncondom group ($p = 0.02$). The study thus showed that condom use promoted regression of CIN and clearance of HPV.[15] Condom use thus seems to be a method for limiting the risk of HPV-infection, and it may in this way serve as a supplementary tool for primary prevention of cervical cancer.

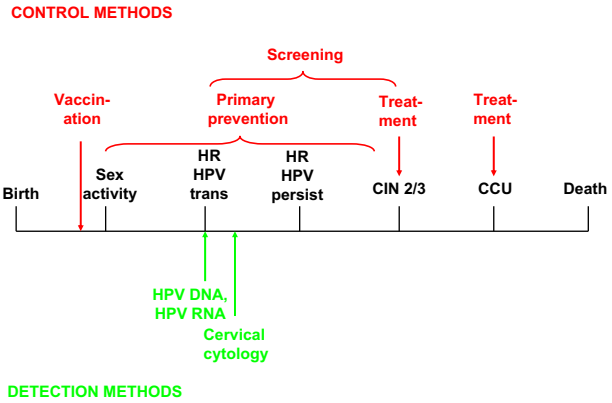

Fig. 1 – Natural history of cervical cancer. Control and detection methods at the various steps.

4. Secondary prevention (screening)

Cervical cancer screening aims at decreasing the incidence of, and the mortality from, cervical cancer by detection of abnormal cells/HPV-infection indicative of dysplasia in the cervical mucosa. Suspected findings are assessed by repeated testing and/or colposcopy, and biopsy confirmed lesions are treated. With surgical removal or destruction of the dysplasia, the potential progression towards invasive cervical cancer can be stopped. Based on follow-up studies of women with negative screening tests, it has been estimated that high quality screening with good population coverage reduces cervical cancer incidence by 80% or more.[16]

4.1. *Cytology testing*

Exfoliated cells are collected from the ecto- and endocervical mucosa. For the traditional Pap smear, cervical cells are directly fixated on a glass. For liquid based cytology, the cells are suspended in a liquid medium and cleaned before being fixated on a glass in a monolayer. Up until recently, all screening was done manually. Now, computer-assisted screening is possible. Normally a cut-off point is used where e.g. 25% of the specimens are automatically classified as normal and not further examined, whereas the remaining specimens are read manually often with the most abnormal areas highlighted by the computer. Liquid based cytology, LBC, specimens can also be handled with computer-assisted reading. Over time different classification systems have been used for cytology specimens. The systems though have two elements in common. Specimens are classified into satisfactory and unsatisfactory, and the satisfactory specimens are graded. In the presently used Bethesda 2001 classification, satisfactory specimens are for squamous cells divided into the following main groups: normal, atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesion (HSIL), and a parallel classification is used for endocervical cells.[17] LBC in general yields a lower proportion of unsatisfactory specimens than traditional Pap smears. A meta-analysis did not show significant differences in sensitivity and specificity between the two methods.[18] However, LBC with computer-assisted interpretation was recently found to have higher sensitivity than conventional cytology.[19]

4.2. *HPV-testing*

As virtually all cervical cancer cases are now known to originate from persistent high risk (hr) HPV-infections it has also become a possibility to use viral tests in the screening and management of cervical lesions. Both HPV-DNA and HPV-mRNA can be detected in exfoliated cells.

The Hybrid Capture 2, HC2, test is the most widely used HPV-DNA test. It screens for the presence of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. The result is expressed as the ratio of the sample's light emission compared with the mean of three concurrently tested controls of 1 pg/ml HPV-DNA. Normally, 1 pg/ml is used as the cut-off point for a positive test. The presence of high risk types of HPV-DNA can also be tested for by using polymerase chain reaction (PCR)-enzyme immunoassay, using general primers GP5+ and GP6+ that detect the same HPV-types as listed above plus HPV 66. Pretect HPV-Proofer is an mRNA test able to detect the presence of E6 mRNA from HPV 16 and/or E7 mRNA from HPV 18, 31, 33 and 45. These are some of the most widely used tests, but a number of other HPV tests are available.[20] However, only validated tests should be used, especially in order to have sufficient specificity and to avoid over-referral for further work-up.[21]

4.3. *HPV-testing used in triage in cytology screening*

Screening programmes have applied various policies for women with ASC-US. In some settings, all women with ASC-US are referred to colposcopy, whereas these women in other settings are referred to repeat cytology in 6 or 12 months. Combined data from trials of women with ASC-US cytology show that triage with HPV-DNA is more sensitive and equally specific as triage with cytology, when CIN2+ detection rate is used as the outcome measure.[22] Triage of ASC-US findings with HPV-DNA testing has therefore been introduced in many screening programmes. Specificity of HPV-testing is low in the triage of LSIL. In one study, specificity increased with increasing age and was shown to be acceptable in women over age 35,[23] but further data are warranted. In a recent testing of 953 women referred to colposcopy, the sensitivity and specificity for CIN3+ were 99.5% and 25.4%, respectively, when HC2 testing was used, and 82.2% and 70.4%, respectively, when Pretect HPV-proofer testing was used.[24] In some labs, for instance in Denmark, triage of both ASC-US and LSIL is undertaken using HPV-mRNA testing.

4.4. *HPV-test as the primary screening test*

In order to avoid cervical cancer it is desirable that a screening test has a high sensitivity for progressive CIN lesions. However, it is at the same time necessary to ensure a high specificity, and to avoid treatment of low grade lesions which would have regressed to normal if untreated. A meta-analysis of 25 non-randomised studies compared the sensitivity and specificity of HC2, PCR and cytology using CIN2+ as the disease cut-off point. HC2 had the highest sensitivity and the lowest specificity, and cytology with LSIL as the cut-off point for a positive test had the lowest sensitivity and the highest specificity.[25] A recent, pooled analysis of European studies using CIN3+ as the disease cut-off point and ASC-US+ as the cytology cut-off point found an overall sensitivity of 0.599 for cytology and 0.896 for HPV-testing. The specificity was 0.954 and 0.893, respectively. Both differences diminished with age.[26] In the United States, HPV-testing is accepted as an adjunct to cytology testing for women over the age of 30. This policy has not been adopted in the European guidelines since higher CIN2+detection with HPV-testing, as observed in cross-sectional studies, does not prove that these detected lesions would have progressed to invasive cancer if untreated.

The long term effect of HPV-testing is currently under study in six randomised controlled trials in Europe and one in Canada.[27] In five of these trials, the performance of HPV-testing combined with cytology testing is compared with cytology testing alone. In two trials, HPV-testing as a

stand alone test is compared with cytology testing. The control arms in the trials are offered the standard screening regime with conventional Pap smears or LBC. An overview of the design of European trials has previously been published.[28] Data from the baseline screening round have been published from five of these trials. Although the design varies slightly across the trials, the results unanimously show a higher detection rate of CIN2+ lesions in the HPV-testing arm than in the standard screening arm. In the trials with combined HPV and cytology testing the relative risks were 1.51 in Sweden[29] (age 32–38; HPV positive only: repeat HPV after 12 months, if continued HPV-type specific positive then referral to colposcopy), 1.56 (relative risk calculated from published absolute numbers) in the Netherlands[30] (age 30–60; HPV positive only: repeat both tests after 6 and 18 months and referral if cytology becomes positive or infection persists at 18 months), 1.61 for women below the age of 35 in Italy[31] (HPV positive only: repeat both tests after 12 months and referral if either are positive), and 1.47 for women at age 35 and above in Italy[32] (with direct referral to colposcopy of all HPV positives). In the trials with HPV alone testing, the relative risks were 1.44 (relative risk calculated from published absolute numbers) in Finland[33] (women age 30+, cytological triage), 1.92 for women at age 35 and above and 3.50 for women below the age of 35 (both with direct referral of all HPV positives to colposcopy) in Italy.[34] The latter result suggests that among younger women, HPV-testing with direct referral to colposcopy of all positives plausibly results in the detection of regressive lesions and should therefore be avoided. In the Netherlands with combined testing and referral of HPV positive women only if cytology was also positive or infection was persistent, the positive predictive value of the HPV-test was similar to that of cytology,[35] while the positive predictive value of the HPV-test was remarkably reduced for women over the age of 35 in Italy, where all women with a positive HPV-test were referred directly to colposcopy.[34] These results overall underline the need for adopting appropriate protocols of management of HPV positive women, in order to avoid both over-referral to colposcopy and overtreatment of regressive lesions.

As a very long term follow-up is needed in order to measure the effect of a new screening modality on the incidence of invasive cervical cancer, the effect on the detection rate of CIN3+ at the subsequent screening round has been used as a surrogate endpoint.[26] Data from the trials in Sweden and the Netherlands found HPV-testing to be associated with a reduction in CIN3+ detection at the subsequent screening round, the relative risks being 0.53 (95% CI 0.29–0.98) in Sweden,[29] and 0.45 (95% CI 0.28–0.72) in the Netherlands.[30] The reduction was particularly strong when comparing women who, at the previous screening round, were HPV-negative to those who had normal cytology. This suggests that prolonged screening intervals can be applied in HPV-negative women.

It remains to be seen whether similar results will come out from the other trials. Especially interesting are the trials using HPV-testing as a stand alone test, as a single test is a more attractive screening modality than combined testing. The trial data also need to be reported and analysed from the point of view of the cumulated burden of follow-up testing and treatment in the two trial arms.

5. Vaccination

As cervical cancer only develops in women with persistent hrHPV-infection, cervical cancer could in principle be controlled by prevention and/or treatment of persistent hrHVP-infections. So far, no therapeutic vaccine or other anti-viral treatment is available. Two types of prophylactic HPV-vaccines are available. One is the Gardasil vaccine from Merck, which protects against HPV 16, 18, 6 and 11, of which 16 and 18 are high risk types, and 6 and 11 are the types causing genital warts and benign condylomas.[35,36] The second is the Cervarix vaccine from GSK protecting against HPV 16 and 18.[37] About 70% of invasive cervical cancers derive from infection with HPV 16 and/or 18. Randomised controlled trials show consistently that women who are hrHPV-naive at vaccination are well protected against development of CIN2+ from vaccine-type HPV, the efficacy being nearly 100% for women who have followed the treatment protocol (Table 1). For the total of randomised women, i.e. including those who were vaccine-type HPV positive at entry, the efficacy for CIN2+ from vaccine-type HPV is only at the level of 44–55%, and at the level of 17–20% for CIN2+ from all HPV-types. For women being both HPV16 and 18 naive at entry, the efficacy for CIN2+ from all HPV-types was only 27%. With the presently available prophylactic HPV-vaccines, women therefore have to be vaccinated at an age where they are expected to be hrHPV-naive, this means before sexual life is normally commenced.

So far, trial results represent short term follow-up. The long term surveillance will have to clarify questions concerning the need for booster vaccinations, possible cross protection or further spread of infection with non-vaccine HPV-types. It should be noted that the trial control groups have been vaccinated later, and the trials will therefore provide limited information on the effect of vaccination on cervical cancer incidence and mortality. An official decision to include HPV-vaccination in the national immunisation schedule has been taken in some EU countries, with quite different approaches. However, the situation is rapidly evolving.[38]

6. Treatment

The treatment options for CIN have changed over time. Total hysterectomy was considered the proper treatment of detected precancerous lesions in the early era of cervical cancer screening in the 1960s, though this method was quickly replaced by the uterus-preserving cold knife conisation. Nowadays, the much more conservative treatment with large loop excision of the transformation zone, LLETZ, is the recommended and most commonly used procedure. This treatment method is also known as loop electrosurgical excision procedure, LEEP.

Cold knife conisation has been known for some time to be associated with increased risks of preterm delivery and low birth weight in subsequent pregnancies,[39,40] and the risk of these side-effects was a major reason for the transition to the more conservative treatment. However, a recent meta-analysis found that all excisional treatment procedures were associated with significantly increased risk of adverse obstetrical outcomes.[41] Serious obstetrical outcomes, perinatal mortality and extreme preterm delivery, were only associated

Table 1 – H8V-vaccination protection against CIN2+.

Study	Inclusion criteria	Outcome group	Definition	Vaccine	Placebo	CIN2+ protection Efficacy in % (95%CI)	
				N	N	HPV 16 or 18	All HPV
Future I, Gardasil[35]	16–24 y, ⩽4 sex partners, not pregnant, no history of genital wards or abnormal cytology	Per protocol	Sero and DNA negative for HPV 16 or 18 at enrolment, remained similar for 7 months, no protocol violation	2241	2258	100 (94–100)	NR
	Mean follow- up: 36 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment	2667	2684	98 (92–100)	NR
		Intention	Randomised	2723	2732	55 (40–66)	20 (8–31)
Future II, Gardasil[36]	15–26 y, ⩽4 sex partners, not pregnant, no history of abnormal cytology	Per protocol	Sero and DNA negative for HPV 16 or 18 at enrolment, remained similar for 7 months, no protocol violation	5305	5260	98 (86–100)	NR
	Mean follow-up: 36 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment	5865	5863	95 (85–99)	NR
		Unrestricted	Sero and DNA negative for HPV 16 and 18 at enrolment	4693	4703	NR	27 (4-–44)
		Intention	Randomised	6087	6080	44 (26–58)	17 (1–31)
PATRICIA Cervarix[37]	15–25 y, ⩽6 sex partners, used contraceptives, had intact cervix Mean follow-up: 14.8 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment, with follow-up	7788	7838	90 (53–99)	NR

with cold knife conisation though, while moderately, non statistically significant, elevated risks of serious side-effects were observed after LLETZ: 1.17 (95%CI 0.74–1.87) for perinatal mortality, and 1.20 (95%CI 0.50–2.89) for preterm delivery in weeks 32/34.[42] Because of possible obstetrical side-effects, it is therefore necessary to carefully monitor the treatment burden associated with different screening modalities. Gynaecologists should tailor the management of young women to minimise both residual disease and possible adverse obstetric outcomes.

The result from the Dutch trial on condom use for women with cervical dysplasia suggests the possibility for considering condom use for some months as an alternative first-line treatment in the management of women with CIN,[15] where surgery could then be reserved for persistent lesions. Larger trials on this topic are strongly recommended. Intervention on smoking cessation is also recommended, as a long term follow-up study found an excess risk of smoking related cancers in CIN-patients.[43]

7. Future cervical cancer control

All preventive measures have to be seen in a long term perspective, because a preventive intervention at one point in time will – in most instances – only affect the disease occurrence some years later. This is certainly true for cervical cancer control, and here the time perspective has been radically expanded over time. The naturally occurring incidence of cervical cancer peaks around the age of 50. When organised cervical cancer screening programmes started in the 1960s, many programmes therefore focused on screening women age 40–50. Nowadays, screening starts at a much lower age, for example at age 30 in the Netherlands, at age 25 in the UK, and at age 20 in Iceland. With the implementation of HPV-vaccination, control of cervical cancer will already start at the age of 12. The longer the time interval between costs and benefits of cervical cancer control, the more difficult the long term planning. With HPV-vaccination starting at the age of 12, and screening starting at the age of 25, it will take 13 years before the first HPV-vaccinated cohorts reach screening age, and much progress in the understanding of both cervical cancer aetiology and control is expected in the meantime. However, the length of the interval depends on the catch-up policy, and it will in some countries be much shorter than 13 years.[38]

The long time perspective also implies that a diversified strategy has to be followed in future cervical cancer control. It is common in Europe to offer cervical screening up to the age of 65. This means that if HPV-vaccination at the age of 12 is introduced now, screening of unvaccinated cohorts still has to continue for another 53 years (Fig. 2). Furthermore, vaccination coverage can not be expected to be 100% complete in the targeted cohorts. On the other hand, some sexually inactive girls above the standard vaccination age will certainly also seek HPV-vaccination, as will some sexually active

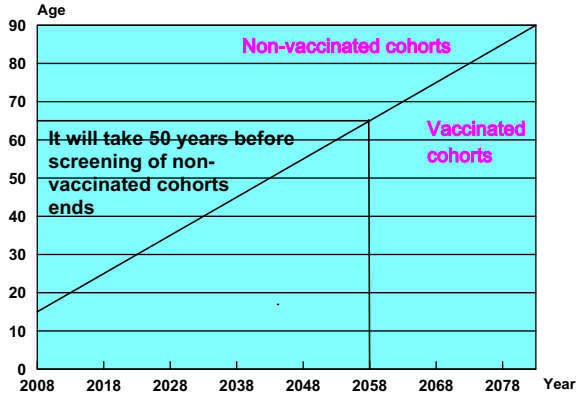

Fig. 2 – Birth cohorts by HPV-vaccination status in Denmark. *Note*: Danish cut-off points used, where girls <15 years by October 2008 will be vaccinated, and where screening stops at age 65.

women attracted by advertisements, etc. The future European population will consequently be divided into four parts: the vaccinated and non-vaccinated women in the birth cohorts targeted by vaccination, and the same two groups in birth cohorts not targeted by vaccination.

7.1. *Non-vaccinated women*

Non-vaccinated women should continue to be screened and monitored following the procedures presently established in the European guidelines for quality assurance in cervical cancer screening.[1] The same is true for women who have been vaccinated after they start sexual life. Screening is, however, as described above, a rapidly developing field. A switch to HPV-testing as the primary screening test is likely, if the screening trials unanimously point to a reduction in CIN3+ detection rates at the subsequent screening round, and if the new modality, by appropriate triage of HPV-positive women, does not increase the burden of follow-up and treatment for participating women.

Policies for HPV-testing in terms of age at start and stop of screening, screening interval, and triage of women with a positive HPV-test will have to be defined. An updated version of the European guidelines,[1] taking the long term trial results into account, are expected to be released in 2010. Further research on the optimal management of HPV positive women, including the use of biomarkers, is ongoing and is a priority.[44] Applying adequate policies will be crucial, also in order to avoid over-referral and overtreatment. The possibility of prolonged screening intervals is attractive as it might be possible in this way to reach a higher coverage. Trials are warranted to follow-up on the Dutch results on alternative strategies to the presently used surgical treatment of CIN.

To ensure optimal screening, organised programmes with good registration, with monitoring, and with quality assurance should be implemented. New parameters and standards for monitoring need to be defined. On the other hand, spontaneous screening is typically associated with overconsumption of screening and less rigorous management of screen-positive subjects. Education of professionals and of women is also an important need.

7.2. *Vaccinated women, short term policy*

'In countries with effective screening programmes with high coverage ... the benefit of adding vaccination to the screening programme will be relatively small in terms of further reducing cervical cancer related mortality'.[45] To maximise the benefit of adding vaccination, a high coverage should therefore be aimed at, in particular of subgroups with low screening participation. An active offer of the vaccine is expected to result in a higher coverage than a reimbursement policy, where there is a risk that the women who are screened will not be vaccinated either.[46]

Vaccinated women should undergo some screening in the future to protect them against lesions developing from the hrHPV infections not prevented by vaccines, and to offer a safety net for those who might not have been HPV-naive at vaccination. Screening will serve as a real life testing of the impact of vaccination in terms of reduction of high-grade CIN. Here, it should be taken into account that the trial participants were followed up much more frequently than normally recommended in screening programmes, where the intervals are of 3 to 5 years. If screening is to be based on HPV-testing it will also allow monitoring of the effect of vaccination in terms of reduction of the infections by vaccine HPV-types and of possible replacement by other types. This, however, will be feasible only in the presence of comprehensive screening registration. On the other hand, good registration of

Table 2 – Future cervical cancer control in Europe.

	HPV-vaccination status	
	Not vaccinated	Vaccinated
Birth cohort offered HPV-vaccination		
Yes	Minority born ⩾ 1993	Majority born ⩾ 1993
No	Majority born < 1993	Minority born < 1993
Screening policy		
Short term	As previously	As previously
Long term	As previously	Monitoring/research topic

Note: Danish cut-off point used, where girls born ⩾1993 will be vaccinated. Girls aged 13–15 years will be vaccinated October–December 2008, and future generations of girls will be vaccinated at the age of 12. However, it should be noted that the cut-off points will vary considerably across European countries depending on the adapted vaccination policy.

vaccination will be essential in order to allow different screening policies among vaccinated and unvaccinated women.

Even if changes of screening schedules will be plausibly appropriate in vaccinated women, the first birth cohorts of vaccinated women should preferably undergo the same screening as the previously unvaccinated birth cohorts. The European guidelines state that 'current evidence does not justify modification of the current guideline recommendations on the age groups and interval for cervical cancer screening in women who have been vaccinated for HPV'.[1] A similar statement comes from the European Centre for Disease Prevention and Control saying that 'in countries where international standards are already applied (starting screening at 25 years old and every 3 or 5 years) the screening strategy should not be changed in the short term'.[45] If this policy is followed, the standard schedule of screening will be offered to all women for approximately the next 15 years or so, i.e. 13 years before the first vaccinated cohorts reach screening age, and 5 years as a monitoring period, where the disease outcome is followed in the first vaccinated birth cohorts (Table 2). The length of this time window depends, however, very much on the chosen catch-up vaccination policy.

7.3. *Vaccinated women, long term policy*

In the long term, HPV-vaccination is, however, expected to reduce the risk of cervical cancer and high-grade CIN. This will reduce the need for screening-induced treatments. However, the detection of cytological abnormalities will be reduced much less than the detection of high-grade CIN, and this will result in a strongly decreased positive predictive value of cytological screening.[46,47] Also, the positive predictive value of HPV-testing will be reduced, as the transition from HPV-infection to high-grade lesions is lower in women infected with non-16/18 HPV-types than in those infected with 16/18 HPV-types.[47,48] This will need adequate management of screen-positive women in order to avoid over-referral and subsequent over-treatment,[49] making the need for organised programmes even more urgent.

To plan for the screening schedule of future generations, the time is shorter than it looks and research in this field is a priority. Because the incidence of high-grade CIN is lower with non-16/18 HPV-infection,[48] the interval free of high-grade lesions after a HPV negative test is expected to be longer in vaccinated than in unvaccinated women. This could allow for a further prolongation of the interval between screens with HPV tests in vaccinated women. However, population based studies are necessary to follow the rates of positive screening tests, the detection rates of CIN2+, and the incidence rates of invasive cervical cancer, in women for whom both the vaccination status and the screening histories are known. Only organised vaccination and screening programmes with systematic record keeping will allow for such studies. The aim is to avoid invasive cervical cancer and at the same time to minimise the negative side-effects such as overtreatment. The extended battery of tools may allow for longer screening intervals and for individualised control of cervical cancer, policies which can only be effectively implemented within organised and well documented programmes.

Conflict of interest statement

Elsebeth Lynge – none declared.

Ahti Antilla – none declared.

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Nereo Segnan – none declared.

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