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EUROGIN 2010 roadmap on cervical cancer prevention

Silvia Franceschi[1], Lynette Denny[2], Kathleen L. Irwin[1*], José Jeronimo[3], Pier Luigi Lopalco[4], Joseph Monsonego[5], Julian Peto[6], Guglielmo Ronco[7], Peter Sasieni[8] and Cosette M. Wheeler[9]

[1] International Agency for Research on Cancer, Lyon, France
[2] Department of Obstetrics and Gynaecology, University of Cape Town and Groote Schuur Hospital, Observatory, Cape Town, South Africa
[3] Program for Appropriate Technology in Health (PATH), Seattle, WA
[4] European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
[5] EUROGIN and Institut of the Cervix, Paris, France
[6] Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
[7] Centre for Cancer Prevention, Turin, Italy
[8] Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics, Queen Mary University of London, London, United Kingdom
[9] House of Prevention Epidemiology (HOPE), Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM

Mini Review

The EUROGIN 2010 roadmap represents a continuing effort to provide and interpret updated information on cervical cancer screening and vaccination against the cause of the disease, high-risk human papillomavirus (HPV). Contrary to the two previous reports in 2008 and 2009, the present roadmap gives equal room to HPV-based screening and HPV vaccination, as a result of the recent strengthening of the evidence on the efficacy and feasibility of both approaches. The superiority of HPV testing in primary screening compared to cytology (in more developed countries) and to cytology or visual inspection methods (in less developed countries) has been demonstrated in several randomised trials. High vaccine efficacy has been confirmed up to 7 years after vaccination; school-based programmes in some countries have been able to reach over 70% coverage among adolescent girls. Demonstration projects have indicated that the delivery of HPV vaccines in less developed countries is feasible and favourably received by populations where cervical cancer is very common. HPV-based screening can diminish cervical cancer incidence more quickly than HPV vaccination, but vaccination can eventually facilitate screening efforts, especially if new vaccines against a greater number of HPV types are introduced. The availability of two highly complementary prevention tools such as HPV testing and HPV vaccination makes it possible to conceive integrated strategies for the elimination of cervical cancer that have no precedent in the cancer field. HPV tests and HPV vaccines remain, however, too expensive, and large-scale financing of screening and vaccination in less developed countries is sorely lacking.

Key words: cervical cancer, human papillomavirus, screening, vaccination

Abbreviations: CIN: cervical intraepithelial neoplasia; CIN2+: CIN2 or worse; EMA: European Medicines Agency; EU: European Union; GAVI: the Global Alliance for Vaccines Immunisation; HC2: Hybrid Capture 2; HDI: human development index; HIV: human immunodeficiency virus; HPV: human papillomavirus; ICC: invasive cervical cancer; PPV: positive predictive value; VIA: visual inspection acetic acid; WHO: World Health Organization

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Correspondence to: Dr. Silvia Franceschi, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France, Tel.: +33-472738402, Fax: +33-472738345, E-mail: franceschi@iarc.fr

This report represents the third edition of the Eurogin roadmap. The aim of the roadmap is to highlight selected issues that emerged from the most recent Eurogin meeting. The first edition was published in 2008[1] soon after the publication of decisive trials on quadrivalent and bivalent human papillomavirus (HPV) vaccines. It mainly included the discussion of crucial decisions (*e.g.*, age for HPV vaccination,[2] need for viral status before vaccination,[3] changes in cervical cancer screening[4] and vaccination monitoring[5]) related to the introduction of mass vaccination programmes. The second Eurogin roadmap[6] mainly dealt with the progress and the gaps in HPV vaccine introduction. It also included an overview of the most promising second-generation vaccines and the endpoints to be used for their evaluation.

The present Eurogin 2010 roadmap gives equal room to the application of HPV-based intervention in the field of primary screening and vaccination, as in the last 2 years the efficacy and feasibility of both types of interventions in both high-resource and medium- and low-resource countries have been proven. Screening and vaccination will be considered separately in high-resource countries (referred to as more developed countries) and in medium- and low-resource countries (referred to as less developed countries). Finally, in a scenario where inexpensive polyvalent vaccines become available, a completely new combination of infection avoidance, recognition and selective treatment of persistent infections would be conceivable. This issue will be explored further at the end of the present roadmap.

Screening in More Developed Countries

A large number of studies in which women were screened with both cytology and HPV testing, and referred to colposcopy if either test was positive, showed that HPV DNA has higher sensitivity, but lower specificity than cytology for detecting cervical intraepithelial neoplasia Grade 2 or worse (CIN2+).[7] Importantly, whereas the sensitivity of HPV testing was uniformly high across all studies, the sensitivity of cytology was highly variable.[7] At its best, cytology can be as good as HPV testing, but maintaining such high-quality cytology is extremely difficult.

European randomised controlled trials comparing women who were screened and managed according to different strategies with and without HPV testing were conducted in Sweden (SWEDESCREEN),[8,9] the Netherlands (POBASCAM),[10] England (ARTISTIC),[11] Italy (NTCC)[12–15] and Finland.[16] Four of these trials (SWEDESCREEN,[8] POBASCAM,[10] ARTISTIC[11] and NTCC[15]) have published results on the first two screening rounds. Baseline results from the Finnish trial have also been published.[16]

Three of these studies[8,10,15] showed greater detection of CIN2 and CIN3 with HPV-based testing compared to cytology-based screening at the first round. All four studies with longitudinal data showed fewer CIN2 and CIN3 at the second round of screening (after 3–5 years) in the group initially screened by HPV, compared to the one screened by cytology. Taken together, these two results suggest that HPV-based screening provided earlier detection of cervical lesions that would have persisted at the second screening round (*i.e.*, clinically relevant lesions). No increase in CIN3 detection at the first round with HPV testing was observed in the ARTISTIC trial. However, this is likely to be due to a lack of investigation of HPV-positive, cytology-negative women[17] and overdiagnosis of regressive lesions with liquid-based cytology.[18]

The NTCC study showed for the first time a lower occurrence of invasive cervical cancers (ICCs) after HPV-based testing compared to cytology-based screening. During the second round of screening, no ICC was detected among HPV-screened women *versus* nine among cytology-screened women.

The reduced detection of high-grade CIN in the second round shows that prolonged screening intervals are safe in HPV-negative women. This is also consistent with results of cohort studies that indicate very low detection of high-grade CIN for several years after a negative HPV test.[19–21] Short intervals should be discouraged to avoid overreferral for recent and often regressive HPV infections. Intervals of between 5 and 7 years seem advisable for the moment. With these intervals, HPV testing would plausibly have even better long-term specificity than cytology screening every 3 years (*i.e.*, the number of false positives from one round of HPV testing may be fewer than from two rounds of cytology).

The aforementioned randomised trials applied substantially different protocols. Cytology and HPV were used together as primary screening tests (meaning that all women were tested for both) in SWEDESCREEN, POBASCAM, ARTISTIC and in the first round of NTCC, whereas HPV alone was used in the second round of NTCC. All HPV-positive women were directly referred to colposcopy in NTCC (except women aged 25–34 years in the first round), whereas cytological triage was applied to all the other trials. Cytological triage consisted in performing cytology on HPV-positive samples and referring women who showed cytological abnormalities directly to colposcopy, whereas the others (HPV-positive, cytology-normal women) were retested after some time and referred to colposcopy only if the infection persisted or, in some studies, if cytology became abnormal.

The decrease in the detection of high-grade CIN in HPV-screened (approximately half) compared to cytology-screened women at the second round was similar in all studies (and among women over age 35 years in the two rounds of NTCC) independently of the protocol used (Table 1). In addition, the relative sensitivity of HPV testing *versus* cytology for CIN2+ or CIN3+ at the first round was also similar in most studies.[8–16] The protection provided by HPV-based screening appears to be independent from whether HPV testing is used alone or together with cytology, and from whether all HPV-positive women are referred to colposcopy or whether cytological triage is applied.

On the other hand, different screening strategies in different trials entailed very different rates of referral to colposcopy and different positive predictive value (PPV) for the entire

Table 1. Detection ratio of cervical intraepithelial neoplasia Grade 3 (CIN3) or worse between human papillomavirus (HPV) and cytology groups in the second screening round in randomised controlled trials

Study	No women randomised (HPV:cytology)	Screening interval (years)	Detection ratio for CIN3 or worse (HPV *versus* cytology)
SWEDESCREEN[8,9]	12,527 (1:1)	3	0.53 (0.29–0.48)
POBASCAM[10]	17,155 (1:1)	5	0.45 (0.28–0.72)
ARTISTIC[11]	24,510 (1:3)	3	0.53 (0.28–0.97)
NTCC 35–60 years[15]	68,835 (1:1)	3	0.48 (0.21–1.11)[1]

[1]It does not include cervical cancer (0 in the HPV arm and 9 in the cytology arm).

screening and triage process. In POBASCAM[10] and SWEDESCREEN,[8] which used double testing with cytological triage, the PPV was similar in the two arms. In the Finnish trial, which used stand-alone HPV testing for the primary screen with cytological triage, the PPV of the HPV arm was even greater than that of the cytology arm (relative PPV 1.34; 95% CI: 1.04–1.72).[16] By contrast, among women aged 35–60 years in NTCC (direct referral of all HPV-positive women to colposcopy), the relative PPV compared to cytology was 0.67 (95% CI: 0.52–0.87) in the second round (HPV DNA alone as primary test)[14] and just 0.34 (95% CI: 0.21–0.54) in the first round (HPV + cytology as primary test).[12]

The trials demonstrated clear advantages of using HPV DNA testing alone for primary screening and applying cytological triage to HPV-positive samples and no or only limited increase in the overdiagnosis of regressive lesions with HPV testing. However, results of the NTCC study suggested that among women younger than 35 years HPV-based screening can lead to overdiagnosis (and consequently overtreatment) of CIN2 that would have spontaneously regressed. Indeed, three times more CIN2 were detected during the first two screening rounds with HPV-based than with cytology-based screening.[15] An association between excisional treatment of CIN and preterm delivery in subsequent pregnancies has been reported in some,[22] although not all[23] studies on the topic. HPV-based screening, therefore, should be avoided among women below a certain age (which would need defining).

Further research is needed to determine optimal screening intervals and to optimise the management of HPV-positive women, particularly younger women. It is clear that not all HPV-positive women should be directly referred to colposcopy, but some kind of triage is needed. Cytological triage, as previously defined, was tested in the randomised controlled trials and showed good cost-effectiveness. However, it entails short-term recalls of HPV-positive, cytology-negative women and, hence, it requires high levels of compliance to follow-up. Even in the trials, loss to follow-up represented a problem. A number of biomarkers, including p16INK4A overexpression,[24] genotyping[25] and HPV mRNA,[26] showed promising results and may reduce the number of repeated visits, but further research and comparison between different biomarkers are needed.

Screening in Less Developed Countries

The enormous difficulty in adequately following-up screen-positive women in less developed countries has led to the study of "screen-and-treat" approaches, *i.e.*, immediate treatment of screen-positive women. Cryotherapy has been the first-choice treatment with excisional treatment, after colposcopy-guided biopsy, being reserved to more advanced lesions or lesions not suitable for ablative therapy.[27,28]

The performance of visual inspection with acetic acid (VIA) has been evaluated in multiple cross-sectional studies that included over 150,000 women. Reported sensitivity for detecting high-grade intraepithelial lesions greatly varied from one study to another (37–96%), as did specificity (49–98%).[27–29] Overestimation of VIA sensitivity (verification bias) was especially strong when colposcopy (another visual method), rather than random cervical biopsies, was used as a gold standard.[30] In addition, VIA sensitivity declined substantially in women aged 40 years or older.[29,31]

Sankaranarayanan *et al.*[31,32] evaluated VIA efficacy in two large cluster-randomised trials performed in India (49,311 and 131,746 women, respectively). A reduction of 25% (95% CI: 5–45%) in cervical cancer incidence and 35% (95% CI: 11–53%) in cervical cancer mortality were found among women randomised to receive VIA compared to the control group (standard of care, no screening) in the earliest trial.[31]

Conversely, no significant reductions in the number of advanced cancers or deaths were observed in the VIA and cytology groups compared to the control group in the other randomised trial that included four groups: HPV testing, cytology, VIA and control group.[32] There is no clear explanation for the difference in the efficacy of VIA to reduce cervical cancer mortality in the two trials[31,32] except, possibly, higher compliance to treatment in the earlier trial.[31]

Even though there are some limitations associated with VIA, including its low sensitivity, specificity and PPV (resulting in inevitable overtreatment) and the difficulty to provide quality control, VIA has some advantages in low-resource settings. It makes screen-and-treat strategies possible (as the result is immediately available), and it aids in creating the infrastructure and knowledge required for future introduction of new better screening tests.

In respect to HPV test-based screening, trials in less developed countries have shown consistently that HPV DNA testing followed by cryotherapy for women with positive test results reduced the incidence of CIN2+[33] and cervical cancer.[32] Denny *et al.*[33] showed that HPV DNA testing followed by cryotherapy was twice as effective in reducing CIN2+ over a 36-month follow-up period compared to VIA followed by cryotherapy.

In the previously mentioned large four-arm trial from India,[32] only HPV testing (using Hybrid Capture 2, HC2, QIAGEN, Gaithersburg, MD) was associated with significant reductions in advanced cervical cancer incidence (0.47; 95% CI: 0.32–0.69) and mortality (0.52; 95% CI: 0.33–0.83).

Shortcomings of HPV testing include its low specificity for CIN2+, which in the screen-and-treat approach may lead to overtreatment of spontaneously regressive HPV infections, and high costs. In addition, the HPV tests commercially available at the moment are too expensive for less developed countries, and the laboratory infrastructures required are too sophisticated. However, a new test (careHPV, QIAGEN, Gaithersburg, MD), more suitable for low-resource settings, has been developed to detect 14 high-risk HPV types in about 2.5 hr and can be performed onsite.[34] A large cross-sectional study from China showed that the sensitivity and specificity of careHPV for detecting high-grade squamous intraepithelial lesions (90 and 84%, respectively) were comparable to those of HC2.[34] These results are very encouraging and may enable "screen-and-treat" protocols to use HPV test in low-resource settings at an affordable cost.

Screening in HIV-Infected Women

An important consideration in regards to the best screening modality in human immunodeficiency virus (HIV)-infected women and populations with high prevalence of HIV infection is necessary. There is no doubt of the equal importance in these circumstances of high coverage and follow-up of screening-positive women,[35] but no evidence-based recommendations exist for the use of HPV testing for primary screening or triage in HIV-infected women.[36] Concerns have been raised about the low specificity of HPV testing in HIV-infected women.[37,38]

Support for the use of HPV testing to screen HIV-infected women has recently been provided, however, by the already mentioned randomised trial from South Africa.[33,39] The study included 956 HIV-infected women and relied on robust endpoints: CIN2+ or CIN3+ detected by colposcopy and biopsies at month 6 and, in a subset of study women, at months 12, 24 and 36. Screen-and-treat approach using HPV testing was as feasible, safe and effective in HIV-infected women as it was in HIV-uninfected women. As expected, HPV test specificity was lower in HIV-infected women, but sensitivity, and PPV and negative predictive values were not compromised. The number of cases of CIN2+ prevented per 100 women screened was actually greater among HIV-infected women (11.9) than among HIV-uninfected (3.1) women. Screen-and-treat based on VIA was substantially less beneficial than that based on HPV testing, mainly on account of the low sensitivity of visual methods even in skilled hands.[39]

Vaccination Experience in More Developed Countries

Decisions on the introduction of the bivalent or quadrivalent HPV vaccines in national immunisation programmes have been taken in many more developed countries faster than decisions on the introduction of other new vaccines in the past.[40] A few unique features of HPV vaccines represent special challenges even in more developed countries: (*i*) they are more expensive than most other vaccines; (*ii*) they target adolescent girls for whom no delivery platform is readily available anywhere; and (*iii*) they are meant to prevent a cancer for which an effective secondary prevention strategy already exists.[6]

At the end of 2007, two HPV vaccine products were granted marketing authorisation in the European Union (EU).[41,42] By the end of 2007, seven EU countries (Austria, Belgium, France, Germany, Italy, Spain and the United Kingdom) had integrated HPV vaccination of female adolescents in their national immunisation programme.[40] By the end of 2009, ten additional EU countries had started HPV vaccination (Denmark, Greece, Ireland, Latvia, Luxemburg, the Netherlands, Norway, Romania, Slovenia and Sweden). HPV vaccination programmes have also been rapidly implemented in several more developed countries outside Europe: Australia,[43] the United States[44] and Canada.

For HPV vaccination of adolescent girls, the majority of more developed countries chose to target 12-year-olds, whereas others chose a range of ages between 11 and 18 years.[40,43,44] Large between-country differences are also found for the upper age limit of catch-up vaccination (from 16 to 26 years).

The cost of HPV vaccination still represents the main obstacle to the implementation of HPV vaccination in many countries in the EU, and a clear correlation exists between socioeconomic levels and implementation of organised HPV vaccination programmes. Most of the countries that started HPV vaccination programmes in the EU have a human development index (HDI)[45] equal to or higher than 0.9. The highest mortality rates for cervical cancer, however, are reported in countries with HDI less than 0.9 and where organised screening programmes are not in place (Fig. 1). Therefore, even in the EU HPV vaccination is not reaching the populations that would benefit from it the most—at least in terms of reducing the death toll from cervical cancer. Of note, the EU has little influence on health decisions in its Member States, in particular in respect to vaccination programmes, as these are under the exclusive competence of national authorities.

Data on HPV vaccine coverage are available from seven EU countries and from Australia and the United States (Fig. 2). Only three countries achieved a coverage for three

doses of 70% or higher.[40,44,46] For catch-up vaccination programmes, vaccination coverage was well below 60% except in Denmark (73%).[40] Also importantly, there is evidence from England that school-based HPV vaccination shows little inequality in coverage amongst 12-year-olds by deprivation level of the areas where they live. This contrasts with a persisting correlation with deprivation level for cervical screening uptake.[47]

Low uptake of HPV vaccination was reported in all more developed countries where HPV16/18 vaccination is recommended, but it is distributed through the private sector, regardless, to some extent, of reimbursement policies (Fig. 2). In the United States, where vaccine delivery is mainly through family doctors, the uptake of three doses amongst 13- to 17-year-old girls in 2009 was 27%.[44] In addition, at a state level, vaccination rates in the United States were strongly and inversely correlated with cervical cancer mortality rates and median income.[48]

The first evidence of high efficacy of HPV vaccination at a population level was reported in Australia, the first country to provide in 2007 free vaccination against HPV 6/11/16/18 to all women aged 12–26 years.[46] Genital warts diminished by 59% among women below age 27 years. A significant decline in genital warts was also observed in heterosexual men in the same age group.

In conclusion, a variety of obstacles still prevent the effective implementation of HPV vaccination programmes also in more developed countries. These obstacles are due not only to budgetary but also to organisational and communication issues. Of great concern is the possibility of low vaccine coverage especially in the subsets of the female population who might be less adequately screened in adult age.[48]

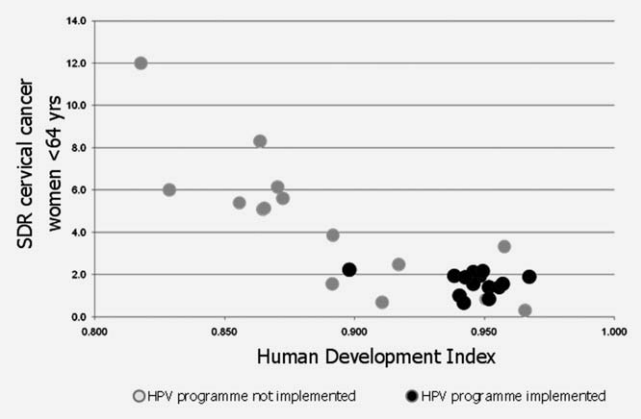

Figure 1. Human development index (HDI), standardised death rates (SDR) for cervical cancer and human papillomavirus (HPV) vaccination in European Union (EU) countries. Each dot represents an EU member state.

Vaccination in Less Developed Countries

Since the publication of the past two EUROGIN roadmaps,[1,6] some advances have occurred regarding HPV vaccine introduction in less developed countries, where more than 80% of cervical cancer cases occur.[49] In April 2009, the WHO recommended routine use of vaccines for young adolescent girls in countries where prevention of cervical cancer is a public health priority, introduction is feasible, sustainable financing can be secured and cost-effectiveness is considered.[50] WHO's 2009 review of global vaccine safety data was reassuring as it concluded that marketed vaccines were generally safe in several less developed countries, HIV-infected children and pregnant adolescents.[51]

WHO's recommendations strongly influence public-sector vaccine introduction decisions in less developed countries and agencies that procure and subsidize vaccines for these countries. By mid-2009, WHO had also prequalified both vaccines: a process that assures vaccines meet the quality standards of United Nations agencies that purchase bulk

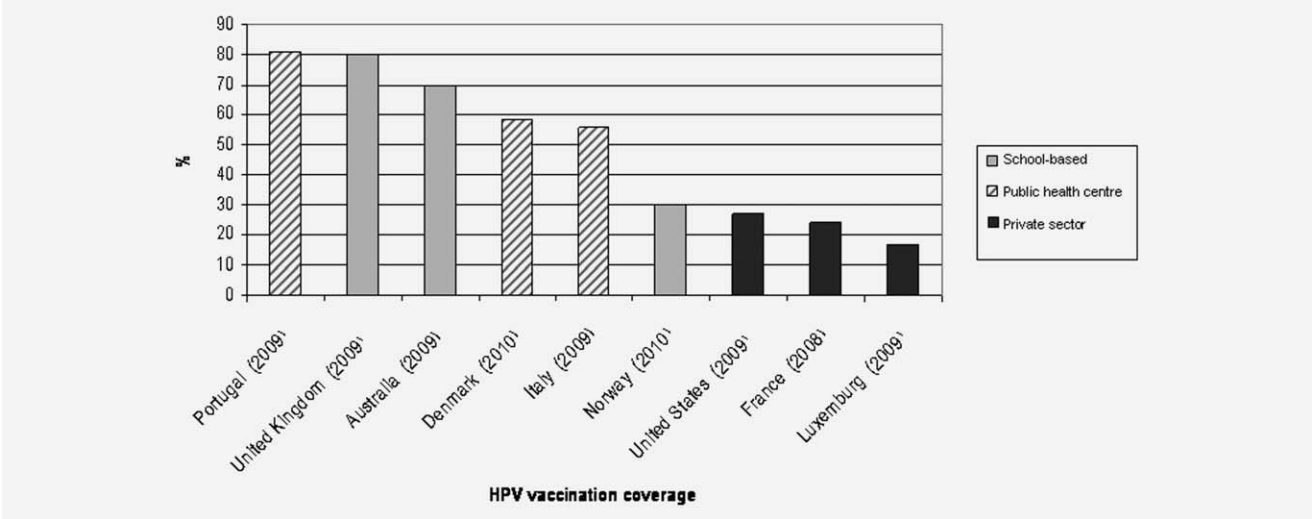

Figure 2. Coverage with the three doses of HPV vaccine among adolescent girls in more developed countries by delivery system.[40,44,46]

vaccines for less developed countries.[52] GAVI (the Global Alliance for Vaccines Immunisation), which subsidizes vaccines for the world's poorest countries, ranked HPV vaccines as a priority in 2009, but implementation will depend on raising additional donor funds. Unfortunately, GAVI is currently undergoing acute funding problems because of the rising demand for children's immunisation programmes and the concurrent economic downturn.[53]

More than 100 countries, including dozens of less developed countries, have approved one or both vaccines.[6] Private-sector prices are lower than in more developed countries, *e.g.*, Cervarix was sold in South Africa at approximately US$44 per dose compared to about US$100 per dose in more developed countries.[54] Both manufacturers have pledged to provide the world's poorest countries with vaccines at either nonprofit or tiered prices.[6]

A few less developed countries have introduced HPV vaccines through public-sector programmes at national or regional levels, nongovernmental organisations or industry donation programmes, including Mexico, Panama, Romania, Micronesia, Palau, Lesotho, Fiji, Nepal and Bhutan.[6,55] Other less developed countries are considering vaccine introduction in the near future through public-sector or industry donations.[55,56] Although some less developed countries are preparing for introduction by evaluating HPV vaccine acceptability, delivery strategies, costs and cost-effectiveness,[57] most are focused on higher priority vaccines for young children that, contrary to HPV vaccination of adolescent girls, do not require new delivery platform.

Demonstration projects in India, Peru, Uganda and Vietnam have shown high acceptability of HPV vaccination of adolescent girls.[58–61] Preliminary data indicate that school- and community-based delivery can achieve coverage of >80%.[62] These projects have tested and developed educational materials for youth, parents, health workers and other stakeholders and have used various methods to mobilise communities, create multisector administrative and financing partnerships, handle controversies and manage mass media.[58–61,63,64] Societal concerns, public emotions and politics can, however, derail programmes in any country, as shown by the prolonged suspension of demonstration projects for HPV vaccination in two Indian States in April 2010.[65]

Recent research indicates that vaccine delivery in less developed countries may be easier than previously expected. For example, both vaccines appear stable outside the cold chain for a week or more.[66,67] Evaluations of multidose vials suitable for large vaccination sessions that would reduce packaging and cold chain volume are underway.[63] Both vaccines are safe and immunogenic when given over a range of dosing intervals within 12–24 months, including intervals that may align better with school calendars and semiannual campaigns like African Child Health Days.[68] A simpler, less costly two-dose series that provides durable protection would be especially attractive to less developed countries. Preliminary data indicate that fewer than three doses may provide comparable immunogenicity[69–71] and degree of protection against incident and persistent HPV16/18 infection.[72] Long-term protection against CIN2+ remains unknown. A large trial in India is evaluating the safety, immunogenicity and efficacy of a two-dose series of the quadrivalent vaccine.[73]

Modelling data from 72 of the poorest countries eligible for GAVI subsidies have shown that if vaccine costs were less than $10–25 per vaccinated girl, vaccination could be cost-effective in many of those countries.[74] HPV vaccines remain, however, expensive compared to other childhood vaccines that cost just a few US dollars or less per dose. Over the last 2 years, experts have explored regional revolving funds and other financing and subsidy mechanisms, as methods to reduce vaccine costs through novel royalty and licensing agreements, and partnerships with low-cost manufacturers in emerging markets.[75–77] Recent advocacy efforts have stressed the need for affordable vaccines in less developed countries.[78]

If high coverage can be achieved, HPV vaccination will especially benefit women in less developed countries who cannot access screening later in life. By raising awareness about cervical cancer, however, vaccination programmes can actually galvanise support for simplified cervical cancer screening programmes for adult women. Modelling demonstrates that combining vaccination of girls and screening of women can reduce cervical cancer mortality faster than programmes resorting to only one strategy.[74]

Affordable Polyvalent HPV Vaccination and HPV Testing: New Possible Scenarios

The implications of the currently available HPV vaccines in future screening programmes were discussed in previous editions of the roadmap.[3,4] If affordable polyvalent HPV vaccines able to prevent the large majority of incident infections with high-risk (HR) HPV types (*e.g.*, HPV L2 vaccines)[79] become available earlier than affordable triage methods able to distinguish the persistent HPV infections, new combinations of vaccination and screening may be considered.

The primary target of HPV16/18 vaccination programmes has been adolescent girls who have not yet been infected by the virus. However, most of the women who will die of cervical cancer over the next 20 years have already been infected with HPV. Consequently, a more urgent public health priority is to develop an effective global intervention strategy for older women. Most HPV infections disappear within a year or two, however, so without an effective triage, a screen-and-treat policy based on a single HPV test would entail substantial overtreatment. The potential value of HPV vaccination in older women should be reconsidered from this perspective.

The simplest intervention would be vaccination against a broad spectrum of HPV types followed at least 2 years later by HPV testing and immediate treatment of all HR HPV infections. Above a certain age (which would need defining), the lifetime risk of cervical cancer in women who do not

Table 2. Main conclusions of the EUROGIN 2010 roadmap on cervical cancer prevention

Cervical cancer screening
• Current evidence from several randomised screening trials supports the use of human papillomavirus (HPV) DNA testing alone as a primary screening test in women aged 30 years or older.
• High-risk HPV-negative women have an extremely low risk of developing cervical cancer in the 5–10 years after screening, hence screening intervals can be substantially longer than in cytology-based programmes.
• HPV testing in less developed countries has shown higher sensitivity than cytology and visual inspection with acetic acid (VIA) and is associated with a greater reduction in cervical cancer incidence and mortality.
• HPV testing is more reproducible and reliable than cytology or VIA.
• Further research is needed to determine the optimal age at which to begin screening, what screening intervals should be applied in HPV-negative women and the optimal management of HPV-positive women (cytology, HPV genotyping or biomarkers that can identify women at risk for progressive disease).
HPV vaccination
• HPV vaccination has been introduced in national immunisation programmes faster than any other new vaccine in the past in more developed countries but not in less developed countries.
• Severe gaps in the access to HPV vaccination exist, notably among less privileged girls, in more developed countries where vaccination is not school-based. Cost-effective screening strategies for partly vaccinated populations have not been well thought through.
• Lessons from successful vaccination programmes can be applied to the design of new programmes, including building political will and partnerships; educating, mobilizing and communicating with communities; delivering vaccines in public-sector programmes; and monitoring coverage and safety.
• Simpler and more effective vaccination schedules are needed, such as delivery of fewer than three doses; cheaper vial formats, packaging and storage; and vaccines that are less costly to manufacture and provide protection against a greater number of high-risk HPV types.
• More effective advocacy for cheaper vaccine prices and subsidised financing through the GAVI Alliance or regional funding mechanisms is necessary. Meanwhile, affordable HPV testing should be implemented to reduce cervical cancer incidence and mortality over the next 2 decades.

already have a persistent HPV infection may be so low that vaccination would not be cost-effective irrespective of vaccine prices. The value of polyvalent vaccination in older women would be, therefore, the possibility of identifying long-duration HPV infections from a single HPV test. Any infection with an HR HPV type included in the polyvalent vaccine that is detected 2 years after vaccination could be considered a persistent infection and would therefore justify immediate treatment.

Ideally, it would be preferable to also offer screening at the time of vaccination and after 2 years to retest only women who were HPV-positive. Repeated HPV testing will, however, be difficult to organise in a less developed country.

If the cost of polyvalent vaccines became low enough, a programme of mass vaccination followed a few years later by mass HPV testing and immediate treatment of all HPV infections might be cheaper and more feasible than HPV testing with subsequent triage and clinical follow-up of HPV-positive women.

Table 2 provides a summary of the main conclusions of our present report, separately by cervical cancer screening and HPV vaccination (Table 2).

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