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Eurogin Roadmap 2015: How has HPV knowledge changed our practice: vaccines

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Abbreviations used:

HPV human papillomavirus
PIN – penile intraepithelial neoplasia
AIN – anal intraepithelial neoplasia
WHO – World Health Organization
CIN – cervical intraepithelial neoplasia
HIC – high income country
MIC – middle income country
LIC – low income country
VIA – visual inspection with acetic acid
SEER – Surveillance Epidemiology and End Result Program
NPCR – National Program of Cancer Registries
OPCs – oropharyngeal cancers
HNSCC – head neck squamous cell cancer
PD1 – programmed cell death-1
EU – European union

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What's new: Ten years since the licensing of HPV vaccines, evidence of their efficacy, safety, and potential cost-effectiveness has continued to grow; we have also seen the fruit of efforts to develop vaccines that target a broader number of HPV types. Despite efforts to decrease vaccine price, the implementation of HPV vaccination worldwide remains a considerable challenge on account of insufficient political commitment, competing priorities in poor countries, and remaining problems with vaccine hesitancy.

This review is one of two complementary reviews that have been prepared in the framework of the Eurogin Roadmap 2015 to evaluate how knowledge about HPV is changing practices in HPV infection and disease control through vaccination and screening. In this review of HPV vaccine knowledge, we present the most significant findings of the past year which have contributed to our knowledge of the two HPV prophylactic vaccines currently in widespread use and about the recently licensed nonavalent HPV vaccine. Whereas anal cancer is dealt with in the companion mini-review on screening, we also review here the rapidly evolving evidence regarding HPV-associated head and neck cancer and priority research areas.

Current knowledge about the efficacy and safety of prophylactic HPV vaccines

It is now ten years since the first prophylactic HPV vaccine was licensed for use following extensive clinical trials. At the time of licensing, the vaccines were known to be highly efficacious in HPV-naïve individuals at preventing vaccine-type HPV infection and type specific cervical disease and, for the quadrivalent vaccine, genital warts and vulvar/vaginal intraepithelial lesions. We have now direct evidence that both vaccines provide protection for close to a decade, if not longer. Large sentinel cohorts of young Nordic women and smaller cohorts from the original trials are being closely monitored to detect any loss of protection over time.[1-3] Antibody levels elicited after vaccination peak after the third dose and decline (to levels still well above those seen following natural infection) by 24 months and are relatively stable thereafter.[4] Bivalent HPV vaccination produces higher levels of both vaccine-type antibodies and antibodies that have some cross-protective efficacy against high risk HPV types related to HPV16 and 18 (specifically, types 31, 33, 45, and 51[5]) as compared with the quadrivalent HPV vaccine although long term protection is unknown.[6] The utilization of differing serological assays complicates the interpretation of 'seropositivity'[7] and there is as yet no established immune correlate of protection. Since initial licensure, trials of the quadrivalent vaccine in men have also established efficacy against genital warts, penile intraepithelial neoplasia (PIN) and anal intraepithelial neoplasia (AIN)[8,9] leading to registration and use of the vaccine in males in some countries.

The safety of the vaccines has continued to be monitored through population-based vaccine safety surveillance systems, studies and follow up of trial participants.[10-18] The WHO Global Advisory Committee for Vaccine Safety continues to regularly review these data and confirm safety.[19] Failure to achieve high population coverage limits the full potential benefits gained from vaccination, which are observed in countries with successfully implemented vaccine programs.[20] A 2015 meta-analysis by Drolet and colleagues of multi-country HPV vaccine effectiveness data demonstrates that significant reductions in HPV infection, genital warts and cervical intraepithelial neoplasia (CIN) are being achieved and that herd protection of males and unvaccinated women is occurring in populations with sufficient coverage of females, e.g., Australia.[20] A recent modelling study indicates that including males accelerates the reduction in HPV prevalence and improves the resilience of vaccination programs.[21]

A potentially significant development to improve population coverage was WHO's 2014 endorsement of two dose HPV vaccination schedules for young adolescents, using an interval of at least 6 months.[22] This endorsement was partly based on trials comparing immunogenicity in young adolescents of two doses with three doses given to adult women in whom efficacy was established.[23,24] These studies established non-inferiority of antibody titres out to 36 months (quadrivalent) and 48 months (bivalent) induced by a two dose extended schedule in females aged up to 15 years at first dose. Two dose schedules should reduce costs and may improve coverage depending upon how effectively delivery systems are able to ensure receipt of the second dose given the wider dose spacing. Surveillance of cohorts vaccinated with two doses will be required to ensure protection is maintained.[25] Duration of protection is clearly critical to the effectiveness and cost-effectiveness of a two-dose versus three-dose schedule.[26] The most recent data available demonstrate non-inferiority of antibody titres induced by bivalent vaccine for young two dose recipients compared with older women out to 5 years.[27] In addition, efficacy of not only two doses of bivalent vaccine, but also a single dose, against persistent HPV infection has recently been shown in

an analysis of clinical trial data from women intended to receive the three dose schedule.[28] This analysis extends the findings from the Costa Rica HPV Vaccine Trial[29] which suggested that even one dose of the bivalent HPV vaccine had similarly high efficacy against targeted infections compared to two- or three-doses over the four-year follow-up period. Parallel data on the efficacy and immunogenicity for a single dose of the quadrivalent vaccine are starting to emerge.[30] However, two dose schedules are not recommended for those with immune compromising conditions. Recent trials indicate that HPV vaccines are safe and immunogenic in those with HIV using a three dose schedule.[31-37]

Clinical trials have now established the safety, efficacy and immunogenicity of a three dose schedule of a nonavalent HPV vaccine, whose composition is based on the VLP and vaccine production methods underpinning the quadrivalent vaccine with higher HPV16/18/6 VLP concentrations, more adjuvant and inclusion of the next five most commonly detected oncogenic HPV types in cervical cancers (types 31, 33, 45, 52, 58).[38-40] For ethical reasons, the control group in the vaccine trial was given the quadrivalent vaccine rather than a placebo. The nonavalent vaccine provided equivalent antibody titres against HPV16/18/6/11 as the quadrivalent vaccine at month 7 and recipients had an equivalent incidence of 6/11/16/18-related infection and high grade cervical disease (CIN2+) rates. In the per-protocol efficacy population (uninfected at baseline), the vaccine provided significant efficacy against persistent infection (risk reduction 96.0% (95%CI 94.4-97.2%) and high grade cervical disease (96.3% (95%CI 79.5-99.8%) due to the added protection against HPV31/33/45/52/58. Injection site reactions were more frequent in nonavalent vaccine recipients (90.7% vs 80.9%).[38]

Positioning the value of new HPV vaccines: the nonavalent vaccine and beyond

Now that the nonavalent vaccine is licensed, vaccine purchasers are faced with a choice of three vaccines: bivalent, quadrivalent and nonavalent, each with different price points. Understanding their relative value is vital for optimal national recommendations and procurement decisions. Economic models of HPV vaccination are needed to inform this process, but published cost-effectiveness evaluations of the nonavalent vaccine are currently limited to Canada[41], US[42], Kenya and Uganda [43] and vaccine costs can rapidly change.

A key determinant of the incremental value of the nonavalent vaccine compared with previous HPV vaccines is the relative contribution of high-risk HPV types besides HPV 16 and 18 to HPV-related cancers and cancer precursors. These HPV types contribute little to anal, oropharyngeal, penile, vulvar and vaginal cancer,[44] so protection against cervical cancer and its precursors is by far the most important incremental benefit of nonavalent vaccination. A large meta-analysis of HPV-type distribution in HPV-positive women across the spectrum of cervical disease showed that high-risk types other than HPV16 and 18 account for important proportions of HPV-positive CIN2 and CIN3, but their contribution dropped in invasive cervical cancer.[45] Another study suggests that HPV types in the nonavalent vaccine together account for 89.4% of cervical cancers worldwide, compared with 70.8% for HPV 16 and 18 alone.[46] Analysis of the placebo arms of the quadrivalent HPV vaccine trial suggests that over 85% of CIN3 lesions, 70-80% of CIN2 lesions and about half of CIN1 are caused by the types included in the nonavalent vaccine.[47]

Yet a trial of the bivalent vaccine in 14 countries demonstrated 93.2% reduction of CIN3+ lesions irrespective of HPV type, which could be attributed to strong vaccine cross-protection against high-risk HPV types not in the vaccine.[48] However, the study only showed results for trial participants followed up for four years, which complicates interpretation of potential cancer prevention. First, it is unclear if cross-protective immunity will last.[49] Second, non-vaccine high-risk HPV types take longer to progress to CIN3+ lesions compared with HPV 16 and 18[50] and the majority of CIN3+ lesions prevented were 16 or 18 related.

An alternative approach to project potential vaccine impact against cervical cancer is to apply vaccine efficacy against persistent infection to estimate cancer reduction. This approach has been used by several modelling studies [51,52] and using this approach the nonavalent vaccine is projected to prevent a much greater proportion of cervical cancers than the bivalent or quadrivalent vaccines. A Canadian study suggested that the nonavalent vaccine could be priced about $CAN11 ($CAN4-$18) higher (about 10% higher per dose) than the quadrivalent vaccine and still be considered more cost effective.[41] A similar study, predicted that, at a price of $13 more than the quadrivalent (9% more) per dose, the nonavalent would be cost-saving in the U.S.[42]

Several countries have adopted two-dose vaccine schedules using bivalent or quadrivalent vaccine. The nonavalent vaccine is currently licensed only with a three-dose schedule, although two dose immunogenicity studies are in progress.[53]

Utility of screening in the new era of vaccines

In most of the developed world, cervical cancer screening by routine cytology has proven effective in reducing cervical cancer burden.[54] The availability of prophylactic HPV vaccines will challenge many countries to revise their cervical cancer prevention programs to integrate screening and vaccination. Similar to the considerations raised above, the utility of screening vaccinated populations is directly related to the proportion of cancers predicted to be prevented by the vaccination program, which are dictated by the type of vaccine used and the population level vaccine coverage over time. Because these factors will vary over time and between countries, we discuss the utility of screening under four general scenarios: (1) high income country (HIC) with organized national HPV immunization (high coverage) and screening programs, (2) HIC with opportunistic immunization (variable coverage) and screening, (3) middle income country (MIC) with national immunization program and ineffective national screening program, and (4) low income country (LIC) with no immunization or screening program.

In the two HIC scenarios, there are challenges inherent in making a single integrated screening recommendation based on vaccination, since the screen-eligible populations will have a significant mix of both vaccinated and unvaccinated women. For example, in Denmark (a country representative of scenario 1), no more than half of the screen-eligible population (ages 21-65 year) will have been vaccinated by 2029, and a fully vaccinated cohort would not occur until around 2060.[55] The situation will only be exacerbated in the second HIC scenario, which is typified by the United States with a relatively low (<40% female three dose)[16] and variable vaccine coverage. [56,57] Therefore, while screening cannot be discontinued in the foreseeable future in these scenarios, the epidemiology of cervical cancer

and pre-cancer will evolve in an age-dependent manner as the vaccination populations mature. The impact will be most profound on the incidence of CIN3, the primary target of screening. Based on the attributable fractions of CIN3 caused by HPV16/18, in cohorts vaccinated with bivalent or quadrivalent vaccine, CIN3 rates could be reduced up to 70% in women under age 30 years.[58-60] The degree of overall reduction is expected to be lower (~50%) in women aged 30 and older, as other less-oncogenic types cause a larger proportion of the disease burden at older ages.[61] In Australia, rates of CIN3 are already declining in young women, halving in those under 20 and falling by 21% in those 20- 24 years by 2012, 5 years after HPV vaccine implementation.[62]

Thus, when considering bivalent or quadrivalent vaccinated populations, the residual risk of cancer remains sufficiently high to make elimination of screening undesirable. The primary goal of integrated vaccination and screening in these scenarios is to implement changes to screening programs which increase the efficiency and cost-effectiveness without a significant detriment to sensitivity. Options include increasing the age to initiate screening, given the extremely low rate of non-HPV16/18 positive CIN3 lesions in younger women, and increasing the interval between normal screens in vaccinated cohorts.[63,64] Primary screening with HPV DNA testing followed by appropriate triage (e.g., cytology or molecular markers such as HPV genotyping, p16/Ki67, or methylation[65]) offer potential alternatives to current screening algorithms to meet these requirements. When considering nonavalent vaccinated populations, the residual CIN3 and cancer risk will be low (~10% of unvaccinated populations).[61] Further work is needed to evaluate the balance of costs of continued screening in a population vaccinated with nonavalent vaccine at high coverage against an increasingly low risk of cervical cancer.

More practical considerations prevail when considering the utility of screening in the MIC and LIC settings. The costs of current combinations of HPV vaccination and screening in the HIC scenarios are very high, e.g., around $10 billion per year in the US.[66] In MIC and LIC settings, this high cost is simply not feasible. In LMIC with national immunization programs and ineffective national screening programs, the near term decision is whether and how much to invest in improvements in screening. The transition time to a fully vaccinated screening population is similar in these countries, and thus it is reasonable to try to identify an affordable and effective screening strategy to avoid continued high rates of cervical cancer for another half century. As recommended by the WHO, screening using HPV-based tests is preferred to a more subjective morphology-based screen (eg, VIA or cytology). At the present time, costs of HPV assays remain prohibitively expensive in many LMICs, though with expiring patents and competition this may represent only a temporary barrier to implementation.[67] If the countries with national immunization programs with high coverage (e.g., Bhutan, Malaysia, Rwanda) were to transition to nonavalent vaccination, it may be feasible to phase out screening in vaccinated cohorts altogether in the future. In LIC with no screening or immunization program and extremely limited financial resources, integrated screening and vaccination programs will likely be unaffordable. More work on the cost-effectiveness of once or twice in a lifetime screening using screen-and-treat strategies versus vaccination in these scenarios will be important[43,68], but will most likely be driven by costs of screening tests and vaccine, as well as the infrastructural requirements and costs for each program.[68]

Impact of HPV vaccine on cancers other than cervical cancer

Research in the field of HPV has traditionally been focused on cervical infection and related cancers, mainly because cervical cancers account for an estimated 87% of all HPV-attributable cancers worldwide (92% in Low to Middle Income Countries and 64% in High Income Countries (HIC)).[69] Reasons for shifting attention to HPV-attributable non-cervical cancers include the reported increase in the incidence of oropharyngeal and anal cancers in the US and some other HIC[69,70], and recent results showing that HPV vaccines are highly effective at preventing persistent HPV infection and pre-cancerous lesions in sites other than the cervix.[8,,71-75] HIV-infected people are a population especially vulnerable to HPV-induced cancers. Among people living with HIV in the US, 10% of incident cancers are caused by HPV infection, with two thirds of these cases being anal cancer in men.[76]

Examining the potential population-level impact of current prophylactic HPV vaccination on non-cervical cancers is particularly important given the absence of evidence-based screening programs for these cancers. Key research questions include: 1) what will be the impact of HPV vaccination on non-cervical cancers and 2) when will these benefits occur? Epidemiological and economic models are increasingly being used to examine such questions as clinical efficacy trials are often limited in duration and scope (e.g., they do not capture herd effects).[77]

A recent transmission-dynamic modelling analysis predicted that prophylactic HPV vaccination can substantially reduce the burden of non-cervical HPV-related cancers in HIC.[42] Assuming lifelong vaccine efficacy, the model predicted that vaccination with the nonavalent vaccine can reduce non-cervical HPV-attributable cancers in the U.S. by 80-84% over 70 years, which would lead to about 300,000 cancers averted and $12,000 million in healthcare costs saved in this timeframe.[42] The model estimated that one non-cervical HPV-related cancer would be prevented for every 420 vaccinated individuals. Modeling analysis from the U.S., Canada and U.K., also suggest that the prevention of non-cervical cancers would represent about 30-40% of health gains from prophylactic HPV vaccination.[26,42,77-79] However, given the older median age at cancer diagnosis (58-68 years for non-cervical cancers vs. 48 years for cervical cancers[80], the benefits of HPV vaccination on non-cervical sites will take significantly longer to realize. Finally, there is expected to be very little difference between the bivalent, quadrivalent and nonavalent HPV vaccines in non-cervical cancer prevention, given that HPV-16 is present in more than 85% of these cancers.[69]

HPV and head and neck cancer, work in progress

HPV is responsible for a rising incidence of oropharyngeal cancers (OPCs) in the US and in other HIC.[81,82] These incidence trends are most notable in younger age cohorts and men.[81,83] In the US, approximately 70-80% of OPCs, which include base of tongue and tonsil cancers, are attributed to HPV infection and the incidence of OPC is projected to exceed the incidence of cervical cancer by 2025.[82]

Given the increase in HPV-driven OPCs, primary prevention is ideal. Prophylactic HPV vaccines are expected to protect against the majority of biologically-relevant oral HPV infections (mainly HPV16) that could lead to HPV-driven OPC.[74] Yet, an important public health question is whether the current vaccine strategies, which aim to vaccinate adolescents with the goal of protecting against anogenital HPV

infection and its associated diseases acquired after sexual debut[84], will have the necessary duration of protection to provide lifelong protection against oral HPV infections. Understanding when the infections that lead to HPV-driven OPC are acquired is now a critical question.[85]

For currently unvaccinated cohorts, early detection of HPV-driven OPC is an appealing strategy, if key requirements for evidence-based screening can be met: 1) a highly sensitive and specific screening tool; 2) diagnostic measures to identify precancerous and/or early staged cancers; 3) less intensive treatment for the early-stage cancer; 4) evidence that early detection and treatment reduces cancer-specific mortality; and 5) confirmation that the benefits of screening outweigh the risks. To that end, scientists have investigated an 'oral Pap smear', but with little success.[86] A candidate biomarker is the HPV16 E6 antibody assay. In a prospective cohort study, HPV16 E6 seropositivity increased risk of OPC >100-fold with notably high specificity (0.5% seroprevalence in controls); the marker was present among OPC cases up to 10 years prior to diagnosis[87]. HPV16 E6 seroprevalence among OPC was similar to published estimates based on tumor DNA at that time[88] suggesting that HPV16 E6 seropositivity has a very high sensitivity, approaching 100%, in diagnosing HPV-driven OPCs. This biomarker does not identify the majority of HPV-driven cancers at non-OPC sites, including oral cavity, larynx, cervix, vagina, vulva and penis, although results related to anal cancer may be promising.[89] However, even with such promising estimates of sensitivity and specificity of HPV16 E6 seropositivity for OPC, these still may not be sufficiently stringent for a rare cancer. Further work on this marker, in parallel with improved diagnostics of early stage cancers, identification of oropharyngeal precancers, and understanding the risks and benefits of a screening approach for a relatively rare disease, is warranted.[73]

The presence of HPV in OPC confers a distinct clinical profile from HPV-negative patients.[90,91] For example, such patients have improved performance status with fewer co-morbidities, small primary tumors and larger lymph nodes.[92] HPV-positive tumor status confers a significant improvement in survival for patients with OPC at primary diagnosis and recurrence.[92-94] Long-term survival, up to 15 years, has been reported in population-based studies in the US.[83] Given the increasing incidence of OPCs in younger individuals with expected long-term survival, current clinical trials have been designed to reduce the long-term sequelae of therapy. These are investigating whether reduced doses of radiation therapy, sparing select patients with chemotherapy or alternate chemotherapeutic choices, and the integration of surgery into the primary treatment algorithm, will improve the quality of life of patients while maintaining the improved survival benefit presently observed in patients with HPV-associated OPC.

In addition, therapeutic HPV vaccines, which elicit cytotoxic T cell responses in order to eliminate virally-infected cells, are being investigated. If successful, therapeutic vaccines may be of relevance not just for primary treatment, but in the context of secondary prevention. Furthermore, topical delivery of small molecule therapeutic agents for HPV-associated genital infections and precancers have demonstrated efficacy in phase I/II clinical trials and has yet to be explored in head and neck cancers.[95,96]

Immune checkpoint blockade is a promising, novel treatment which is being explored and growing in popularity in the field of oncology. One immunomodulatory therapy which is actively being evaluated in cancer patients, including HPV-OPC, is immune checkpoint blockade, specifically blockade of the

Programmed Cell Death-1 (PD-1) and Programmed Death Ligand-1 (PD-L1) pathway.[97,98] This therapy focuses on re-activating host immune responses against the cancer cells. Preliminary studies demonstrate its safety and efficacy to reduce tumor burden in head and neck cancer patients with locally recurrent and/or metastatic disease.[98]

With the impetus to design new therapeutic trials, there is controversy regarding the implications of nodal staging, and extracapsular extension, in HPV-OPC[99] and whether surveillance guidelines and methods should differ by HPV-tumor status.[100-105]

In summary, the understanding of HPV infection as a cause of OPC, and its implications for prevention and clinical therapy is rapidly evolving. Significant knowledge gaps remain, which provide compelling justification to further study the natural history of oral HPV infection and OPC, vaccine efficacy, prevention and therapeutics.

Future opportunities and challenges

Consistent evidence supports the efficacy, effectiveness, and safety of HPV vaccines. However, optimal implementation of HPV vaccines remains a considerable challenge. Decreases in vaccination coverage have occurred as a result of targeted anti-vaccination campaigns or trends in social preferences toward vaccination, despite efforts to decrease vaccine prices.

HPV vaccination is perceived by many countries, including HIC, as too expensive and providing delayed benefits. For instance, several countries in the European Union (EU), mainly Eastern European countries, have not yet initiated HPV vaccination programs[106] and, although in most of the EU Member States the vaccine is offered free of charge or reimbursed, the success in terms of coverage of the target groups has been highly variable, ranging from <30% to 80% and over.[107] The determinants of a high uptake of HPV vaccination programs are multi-factorial but organized school-based programs[108]usually provide the best coverage and more equitable access to HPV vaccines, followed by organized programs through health-care centres and through general practitioners. Opportunistic programs usually achieve low or ill-defined levels of coverage.

Fortunately, encouraging progress has been made in lowering the vaccine price. Through public/private negotiations, Gavi has achieved a US $4.50-$4.60 per dose price, and more than 20 Gavi-eligible countries have started vaccinating adolescent girls. The model that has been developed to ensure success is generally a demonstration project prior to full nationwide implementation. High national coverage has been achieved in such programs in Rwanda and Bhutan.[109,110] Since the cost of delivering the vaccine is estimated to be around US$5 a course in these setting, the overall cost of vaccinating a girl is probably below US$15, of which only a fraction is paid by country governments themselves. At these costs, HPV vaccination is potentially affordable in the poorest countries and has been shown to be a cost-effective intervention to introduce. [111,112]

In non-Gavi eligible countries, the sustainability of the health budget required for HPV vaccination may depend on collective negotiations with vaccine manufacturers.[113] Decision-makers, policy-makers and

programme managers should therefore be aware of the wide range of prices (currently $8.50-100 per dose) for HPV vaccines and the potential to reduce costs by appropriate tendering.

Finally, policy-makers are understandably afraid of investments that take decades to produce fully accountable results. However, the implementation of HPV vaccination programmes is highly feasible compared with that of other cancer prevention strategies, especially in LIC.[110,114] Cervical cancer screening, for instance, is a more logistically demanding program to implement. It can save individual lives immediately, but in a country starting with no organized cervical cancer prevention programs in place, it can take decades to achieve high coverage and high quality of the entire screening, diagnostic and treatment process.

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