International Journal of Gynecology and Obstetrics 131 (2015) S33–S35

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

REPRODUCTIVE HEALTH

HPV vaccination: The most pragmatic cervical cancer primary prevention strategy

Rengaswamy Sankaranarayanan *

International Agency for Research on Cancer, Lyon, France

ARTICLE INFO

Keywords:
Cervical cancer
HPV vaccination
National programs
Prevention
Screening

ABSTRACT

The evidence that high-risk HPV infections cause cervical cancers has led to two new approaches for cervical cancer control: vaccination to prevent HPV infections, and HPV screening to detect and treat cervical precancerous lesions. Two vaccines are currently available: quadrivalent vaccine targeting oncogenic HPV types 16, 18, 6, and 11, and bivalent vaccine targeting HPV 16 and 18. Both vaccines have demonstrated remarkable immunogenicity and substantial protection against persistent infection and high-grade cervical cancer precursors caused by HPV 16 and 18 in HPV-naïve women, and have the potential to prevent 70% of cervical cancers in adequately vaccinated populations. HPV vaccination is now implemented in national programs in 62 countries, including some low- and middle-income countries. The early findings from routine national programs in high-income countries are instructive to encourage low- and middle-income countries with a high risk of cervical cancer to roll out HPV vaccination programs and to introduce resource-appropriate cervical screening programs.

1. Introduction

Cervical cancer is the fourth most common cancer in the world with an estimated 528 000 new cases and 267 000 cervical cancer deaths annually, of which 445 000 new cases and 230 000 deaths occur low- and middle-income countries (LMICs) in Sub-Saharan Africa, Central and South America, Asia, and Oceania [1]. Lack of screening programs and high prevalence of HPV infection in the population are the major factors responsible for the high risk observed in LMICs. The knowledge that persistent infection with one of the oncogenic HPV types is the necessary cause for cervical cancer has led to HPV vaccination and HPV testing as emerging strategies for prevention and early detection of cervical cancer. However, these are yet to be implemented in national programs in many LMICs, where they are most needed. The overarching role of HPV vaccination as the most pragmatic and feasible primary prevention strategy for cervical cancer is briefly discussed here.

2. HPV infection and cervical cancer

Cervical cancer is a rare long-term outcome of infection with a high-risk HPV type (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), particularly HPV 16. Peak frequency of HPV infection occurs in adolescence and early adulthood, with a life-time probability of infection of approximately 80% — 90%. The frequency of incident HPV infections declines steadily with age. HPV infection persists in 5% — 15% of the infected women, while 85% — 90% of the infections become undetectable within two years. Those with persistent HPV infection are at high risk for cervical cancer and HPV 16 and 18 cause 70% — 75% of the cervical cancer cases across the world [2,3]. HIV-infected women are at higher risk of HPV infection despite the advent of antiretroviral therapy (ART) and are, therefore, at high risk for cervical neoplasia.

The natural history of cervical cancer involves four stages, namely HPV infection of the transformation zone (TZ), HPV infection persistence, clonal expansion of HPV infected cells to high-grade cervical intraepithelial neoplasia (CIN 3) or adenocarcinoma in situ (AIS), and their progression to invasive cancer [2]. Minor cellular abnormalities, such as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or atypical glandular cells of undetermined significance (AGUS), on cytology or low-grade CIN (CIN1) on histology may be observed within months following incident and transient HPV infections. With the clearance of infection in the vast majority (>80%), the low-grade lesions resolve [2]. CIN 3 and AIS are considered to be the real precursors of cervical cancer and 40% — 50% of untreated lesions may progress to cancer over a 5 — 30-year period [4–6]. The duration between HPV infection and developing CIN 3 is shorter than the time between CIN 3 developing into invasive cancer. Although healthy lifestyles, improved socioeconomic status, awareness, empowerment of women with education and better social status, male circumcision, and improved hygiene contribute to reducing risk of cervical cancer, prophylactic HPV vaccination of pre-adolescent/adolescent girls before

* International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372, Lyon Cedex 08, France. Tel.: +33 472 73 85 99; fax: +33 472 73 85 18.
E-mail address: sankarr@iarc.fr.

http://dx.doi.org/10.1016/j.ijgo.2015.02.014

sexual debut is singularly the most cost-effective and efficient primary prevention strategy [7,8].

3. Prevention

The fact that high-risk HPV infections cause almost all cervical cancers has led to two new approaches for cervical cancer control: primary prevention by vaccination to prevent HPV infections in pre-adolescents and adolescents (9 — 18-year-old girls) and early detection of cervical precancerous lesions such as CIN 3 and AIS by HPV screening in women aged 30 years and older. Two recombinant HPV vaccines containing viral-like particles (VLP) are currently available: quadrivalent vaccine targeting oncogenic HPV types 16, 18, 6, and 11, and bivalent vaccine targeting HPV 16 and 18. Both vaccines have demonstrated remarkable immunogenicity and substantial protection against persistent infection, CIN 3, and anal intraepithelial neoplasia caused by the vaccine-targeted HPV types in women aged 15–26 years naïve to the corresponding type at the time of vaccination. Both vaccines have the potential to prevent 70% of cervical cancers in adequately vaccinated populations [9]. Efficacy against persistent infection with vaccine-targeted HPV types and related CIN 3 frequency in HPV-naïve populations in Phase III clinical trials exceeded 99% [9]. Immunogenicity bridging studies demonstrated strong immunogenicity and excellent safety in pre-adolescence, although clinical trials did not include pre-adolescent girls who are the primary target populations for current national immunization programs. The evidence on safety and efficacy of the vaccines in clinical trials, demonstration projects, and routine public health settings all strongly support the introduction of HPV vaccination in national immunization programs. Mild to moderate injection-site pain, headache, and fatigue were the most common adverse events following HPV vaccination.

HPV vaccination is currently part of the national immunization program in 62 countries targeting pre-adolescent and adolescent girls and "catch-up" immunization of older cohorts with upper age limits up to 26 years. Cost-effectiveness studies support the implementation of HPV vaccination of pre-adolescent/adolescent girls before sexual onset including LMICs provided the vaccines are affordable; the cost-effectiveness in LMICs is heavily influenced by the unit cost of the vaccine [7,8,10–12]. Difficulty in procuring vaccines due to high costs is a major challenge, although in recent years vaccine costs have been coming down. From a realistic implementation perspective, government commitment, procuring HPV vaccines at affordable prices (through tiered pricing or negotiated pricing, or through the Gavi vaccine alliance or the PAHO revolving fund), using the recently recommended two dose schedules as well as education of the community at large to create awareness about the safety and efficacy are critical to introduce HPV vaccination in national immunization programs in LMICs.

It is estimated that full vaccination of a cohort of 58 million 12-year-old girls in 179 countries for which UN population estimates are available will prevent 690 000 cervical cancer cases and 420 000 deaths at a net cost of US $4 billion; HPV vaccination was cost-effective (with every disability-adjusted life-year averted costing less than the per capita gross domestic product of the country) in 156 (87%) of the 179 countries [8]. Although studies differ in their conclusions about the optimal age for catch-up vaccination, a catch-up round for young adolescent girls (12–15 years), whose future access to screening is uncertain in LMICs, is worth considering and 16% — 20% of HPV 16/18 protection from vaccination is attributed to catch-up vaccination strategy [13]. Only a few cost-effectiveness studies indicate that including boys in HPV vaccination programs would be a cost-effective strategy [7,14].

Vaccinating with fewer than three doses will lower costs, ease logistics of vaccine delivery, increase accessibility, and improve adherence to vaccination. Immunogenicity following two doses in adolescent girls has been shown to be non-inferior to that of a three-dose course in the age group where efficacy against persistent infection and pre-cancerous lesions has been demonstrated [15–19]. Protection in terms of persistent infection of vaccine-targeted HPV types among a small sample of women who received two doses, or a single dose only by default, has been reported [20]. Based on findings that immunogenicity of two doses is comparable to three doses in 9 — 14-year-old girls, the European Medical Agency and 10 countries in Central and North America, Africa, and Asia have licensed the use of two-dose regimens. Whereas most countries continue to use the three-dose schedule in their national immunization programs, based on the recent research evidence, a two-dose regimen is being used in some countries such as Canada, Chile, Colombia, Mexico, South Africa, and Switzerland, and England will switch over to a two-dose schedule from September 2014 onward. The guidelines in England for switching over to two-dose regimen suggest that the first dose can be given at any time during school year 8 (12 — 13-year-old girls) followed by a minimum of six months and a maximum of 24 months between doses; for operational purposes a 12-month gap between the first and second doses has been recommended.

Among LMICs, Bhutan, Malaysia, Uzbekistan, Fiji, Rwanda [21], South Africa, Zambia, Uganda, Panama, Mexico, Brazil, Chile, Argentina, Colombia, Peru, Uruguay, and Paraguay have implemented HPV vaccination as part of a national immunization program. High coverage of the target populations (>90% third dose or second dose) and excellent safety profile have been observed in Bhutan, Malaysia, Rwanda, Brazil, and South Africa among others. Ten LMICs (nine in Sub-Saharan Africa, i.e. Ghana, Kenya, Madagascar, Malawi, Mozambique, Niger, Sierra Leone, Tanzania, and Zimbabwe, as well as Laos in Asia) have introduced HPV vaccination demonstration projects supported by GAVI. Uganda, Rwanda, and Uzbekistan are currently receiving support from GAVI alliance for HPV vaccination in their wider national immunization programs. The introduction of HPV vaccination as part of national immunization programs in some LMICs has happened in spite of anti-vaccination campaigns in different countries. Indeed, one of the real challenges at present seems to be the significant anti-vaccine propaganda, political and media frenzies spreading misinformation, and exaggerated and erroneous adverse event coverage in many countries.

Preliminary evaluation of HPV vaccination programs, in some high-income countries where vaccination was introduced 4 or 5 years ago, has shown that the frequency of vaccine-targeted HPV infections, precancerous lesions, and genital warts associated with vaccine- included HPV types among vaccinated cohorts is declining [22–24]. In April 2007, Australia introduced quadrivalent HPV vaccination for 12 — 13-year-old girls through a school-based program followed by a catch-up vaccination for 13 — 26-year-olds via schools, community-based programs, and general practices during July to December 2009. Third-dose coverage among the primary target group exceeded a modest 70%. A significant decline in the prevalence of HPV types 16/18/6/11 after introduction of a national HPV vaccination program such as a 77% fall in prevalence of HPV vaccine-related infections, 90% reduction in genital warts, and 48% reduction in CIN3/AIS lesions in the vaccine-targeted age group has been reported in Australia [22], corresponding to model-based projections made in 2007 [25]. In Scotland, a significant decline in HPV 16 and 18 prevalence was demonstrated among HPV-vaccinated women (prevalence = 150/1100 [13.6%]) compared with unvaccinated women (prevalence = 1018/3418 [29.5%]) in a cross-sectional study involving 1000 women aged 20–21 years recruited annually during 2009 — 2012 [24]. Six years from the introduction of HPV vaccination in Denmark in 2006, the risk of atypia or worse lesions and CIN2 and 3 lesions have significantly declined among vaccinated women; there is a 44% reduction in CIN2 — 3 lesions among vaccinated cohorts of women born during 1991 and 1992 and a 73% reduction in CIN2 — 3 lesions in the 1993–1994 birth cohorts [23].

4. Conclusion

After reviewing the evidence, WHO currently recommends a two-dose HPV vaccination schedule for girls with a minimal interval of six months between the doses, if vaccination is initiated prior to 15 years of age; this interval may be extended to 12 months if this facilitates vaccination [26]. This new recommendation on two doses makes

implementation of HPV vaccination programs more feasible and affordable than a three-dose schedule. A three-dose schedule at 0, 1–2, and 6 months remains necessary if immunization is initiated after the girls' 15th birthday and for immunocompromised individuals, including those known to be HIV infected.

The early findings on safety and intermediate endpoints from routine national programs in high-income countries are instructive to encourage LMICs with a high risk of cervical cancer to roll out HPV vaccination programs to prevent cervical cancer and to introduce resource appropriate cervical screening programs taking into account the post vaccination scenario of successive cohorts of women at low risk for HPV infection and CIN as vaccination proceeds. High-income countries eventually need to reorganize their existing screening programs to balance the overall costs of both vaccination and screening taking into account the challenges for cytology screening and colposcopy triage in view of the anticipated low frequency of HPV infection and dysplastic changes due to both post vaccination immunogenicity and herd immunity. Based on the anticipated impact of vaccination on the performance of cytology, a changeover to HPV testing as the primary screening test followed by cytology triage (in view of the already built-up cytology infrastructure in high- and in some middle-income countries), later initiation of screening (at 30 or 35 years), and less frequent screening (e.g. one in 10 years or even a single round of screening in low- and low-middle-income countries) is inevitable in due course. While HPV vaccination will result in successive cohorts of women at low risk of HPV infection and cervical neoplasia as vaccination progresses, screening will reduce the risk of cervical cancer deaths among targeted women not yet protected by HPV vaccination or in women in whom vaccination has failed. The timing of the effect of vaccination on cervical screening will be country-specific and will depend on any catch-up vaccination, variation in coverage, the impact of herd immunity, and the age at which screening started.

Conflict of interest

The author has no conflicts of interest to declare.

References

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon: IARC; 2013http://globocan.iarc.fr. Accessed October 29, 2014.

[2] Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine 2012;30(Suppl. 5):F24–33.

[3] International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Human Papillomavirus, vol. 90. Lyon, France: IARC; 2007.

[4] Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12(2):186–92.

[5] McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008;9(5):425–34.

[6] Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol 2009;200(2):182.e1–5.

[7] Natunen K, Lehtinen TA, Torvinen S, Lehtinen M. Cost-effectiveness of HPV-vaccination in medium or low income countries with high cervical incidence - A systematic review. J Vaccines Vaccin 2013;4:172.

[8] Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health 2014;2(7):e406–14.

[9] Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30(Suppl. 5):F123–38.

[10] Diaz M, Kim JJ, Albero G, de Sanjosé S, Clifford G, Bosch FX, et al. Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India. Br J Cancer 2008;99(2):230–8.

[11] Reynales-Shigematsu LM, Rodrigues ER, Lazcano-Ponce E. Cost-effectiveness analysis of a quadrivalent human papilloma virus vaccine in Mexico. Arch Med Res 2009;40(6):503–13.

[12] Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. Vaccine 2013;31(37):3786–804.

[13] Baussano I, Lazzarato F, Ronco G, Dillner J, Franceschi S. Benefits of catch-up in vaccination against human papillomavirus in medium- and low-income countries. Int J Cancer 2013;133(8):1876–81.

[14] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13(1):28–41.

[15] Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin 2011;7(12):1374–86.

[16] Safaeian M, Porras C, Pan Y, Kreimer A, Schiller JT, Gonzalez P, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res (Phila) 2013;6(11):1242–50.

[17] Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309(17):1793–802.

[18] Romanowski B, Schwarz TF, Ferguson LM, Ferguson M, Peters K, Dionne M, et al. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Hum Vaccin Immunother 2014;10(5):1155–65.

[19] Lazcano-Ponce E, Stanley M, Munoz N, Torres L, Cruz-Valdez A, Salmerón J, et al. Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose vs. a three-dose schedule at 21 months. Vaccine 2014;32(6):725–32.

[20] Kreimer AR, Rodriguez AC, Hildesheim A, Herrero R, Porras C, Schiffman M, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst 2011;103(19):1444–51.

[21] Binagwaho A, Ngabo F, Wagner CM, Mugeni C, Gatera M, Nutt CT, et al. Integration of comprehensive women's health programmes into health systems: cervical cancer prevention, care and control in Rwanda. Bull World Health Organ 2013;91(9):697–703.

[22] Garland SM. The Australian experience with the human papillomavirus vaccine. Clin Ther 2014;36(1):17–23.

[23] Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early impact of human papillomavirus vaccination on cervical neoplasia–nationwide follow-up of young Danish women. J Natl Cancer Inst 2014;106(3):djt460.

[24] Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer 2014;110(11):2804–11.

[25] Smith MA, Canfell K. Testing previous model predictions against new data on human papillomavirus vaccination program outcomes. BMC Res Notes 2014;7:109.

[26] Meeting of the Strategic Advisory Group of Experts on immunization, April 2014–conclusions and recommendations. Wkly Epidemiol Rec 2014;89(21):221–36.