EDITORIAL

Eradication of cervical cancer in Latin America

Cervical cancer remains within the three most common cancer in women worldwide and is still the commonest female cancer in 41 of 184 countries. Within Latin America, cervical ranks as the most common cancer among women in Bolivia and Peru and the second most frequent in Brazil, Colombia, Ecuador, Mexico, Paraguay, The Guyanas, Surinam and Venezuela. Due to its relatively early age at onset, it ranks among the three most frequent cancers in women aged below 45 years in 82% of all countries in the world irrespective of their screening practices.[1] The annual current burden of human papillomaviruses (HPV)-related diseases has been estimated in 610 000 cancer cases and 320 million cases of anogenital warts worldwide in both genders. Of these 75 000 cancer cases are diagnosed in Central and South America,[2] and another 25 000 in North America. In many developed countries, cervical cancer incidence and mortality has been greatly reduced by screening early diagnosis and surgical treatment of the precursor lesions found in screen positive women. However, these programs are costly and require a high level of social organization, medical development and public financing and control. Globally screening activities have largely failed to reduce mortality in the vast majority of the populations.

Eradication: theoretically feasible, socially difficult

Infectious disease eradication has been considered for a number of conditions but has been achieved only once for small pox, one of the most brilliant examples of success in preventive medicine. Other eradication campaigns are under way for polio DTP and measles and control strategies are well under way for a number of significant viral diseases. Amongst the biological criteria for a disease to be considered for eradication three parameters need to be considered: (i) the infectious agents need to be entirely confined to a human habitat; (ii) there should be a highly effective intervention to interrupt the transmission from one individual to another; and (iii) a non-lethal infection or vaccination must confer life-long immunity.[3]

These three conditions seem to hold in the model of HPV and cervical cancer: (i) there is no known or suspected animal reservoir of HPV neither any other identified way in which HPV could reproduce in nature (ii) the available HPV vaccines achieve efficacy estimates of protection against the HPV vaccine types in the 95%+ range and (iii) current data suggest long term immunity. Further, to monitor disease control and eradication it is necessary to have unequivocal and precise diagnostic and surveillance tools. To this respect molecular HPV testing systems are extremely accurate (95+% sensitivity) in detecting molecular traces of all HPVs types capable of inducing cancer and precisely classify each occurring cancer as to their viral etiology.[4]

Socially the requirements for eradication consideration call for the relevant disease(s) to be recognized as an international public health priority and the existence of a political commitment to eradication efforts. More specifically, it is necessary to define an international strategy agreed and coordinated by essentially all governments and public health institutions. Further the strategy needs to be simple (i.e. generalized HPV vaccination and screening) unify national criteria and mobilize long term investment of very large amounts of resources. Thus, a declaration of the World Health Assembly is required to drive the social and economic resources required over an extended period of time.

At present, even though biologically cervical cancer could be considered eradicable and the HPV-related burden of cancer is numerically and socially significant, its eradication is far from being high in the international agenda and unlikely to be considered

an international public health priority, at least on the short term. Therefore, we are at a stage in which cervical cancer control goals at local and national level need to be demonstrated while consensus and understanding of the opportunities at reach are constructed and digested. This will primarily happen in confined populations adequately served with HPV vaccination and HPV based screening and gradually extend to the developing parts of the world.

The technologically for eradication is now available

HPV testing was first proposed in the late 1990's as a primary screening technology. Results from randomized trials and cohort studies have consistently demonstrated that compared to cytology, HPV tests can achieve a 30 to 40% gain in sensitivity at a cost of a 3 to 5% loss in specificity for detecting the precursor lesions (both CIN2+ and CIN3+). Even larger gains in sensitivity are seen for cervical cancer endpoints. In a recent meta-analysis, the sensitivity of a single HPV DNA test (in this case the most established Hybrid Capture 2 Test (hc2) was 90% for CIN2+ and 95% for CIN3+ as compared to sensitivities of 70% and 74%, respectively for high quality cytology.[5] Randomized controlled trials showed a substantial 70% reduction in subsequent invasive cancer in women screened with an HPV test (hc2 or PCR) as compared to women screened with conventional or liquid based cytology.[6] An important consequence of the higher sensitivity of HPV testing for CIN2+ is the improved negative predictive value of subsequent disease, allowing for a safe extension to longer intervals and a reduced number of lifetime screening episodes. Two additional advantages of HPV testing are the objective, reproducible nature of the test and the availability of novel versions of the technology (i.e. Care-HPV) requiring medium-to-low equipped settings to produce reasonable quality results. Point-of-care detection methods with very short (one hour) time to result delivery, proved to be extremely successful in the context of the diagnosis of infectious diseases (i.e. TBC), are now being tested for HPV screening and may provide additional logistic advantages in the field. As a summary of the developments in the HPV diagnostics, most recent guidelines already recommend HPV testing as a stand-alone test for primary screening and one such technologies has already been approved by the FDA for this purpose.[7]

HPV vaccination should provide the key to cervical cancer eradication. At present, three prophylactic vaccines based on HPV type specific virus-like-particle (VLP) antigens are licensed: Gardasil / Silgard (Merck & Co, Whitehouse Station, USA / Sanofi Pasteur MSD, Lyon France), containing antigens to HPV 6, 11, 16 and 18; Cervarix (GlaxoSmithKline, London UK) containing HPV 16 and 18 antigens; and the recently approved Gardasil 9 (Merck & Co, Whitehouse Station, USA) containing antigens to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Phase III trials of Cervarix and Gardasil have shown essentially full protection against vaccine specific HPV types after up to 9+ years of follow-up, some cross-protection against non-vaccine HPV types, notably of the Cervarix vaccine and an excellent safety profile.[8,9] These vaccines are not therapeutic, and therefore do not protect against progression of infections or diseases related to HPV types present at the time of vaccination. However, vaccination will offer protection against the other HPV types included in the vaccine product.[10]

Following introduction in 2006, population-based post-marketing studies have confirmed that within five years of introduction, the population shows significant reductions of the prevalence of (i) cervical, vulvar, vaginal, anal and oral infections by the HPV types included in the vaccines; (ii) precancerous cervical lesions; and (iii) genital warts if Gardasil is used.[8,11-16] In addition, a significant 'herd protection effect' has been observed, by means of infection and disease reduction, among non-vaccinated girls and boys in populations with high background HPV vaccination rates.[12,17]

The potential for prevention of HPV vaccination is underused by initial recommendations

In 2005 and 2006, HPV vaccine indications were based on a set of very restrictive group of terms of reference: (i) the target disease was cervical cancer and therefore vaccination was only indicated for women; (ii) the focus for HPV vaccination were adolescents before sexual initiation to avoid vaccinating women previously exposed to the virus. These criteria, albeit sound, prompted the misinterpretation that sexually active women would not benefit from vaccination irrespective of her previous exposure to the virus; and (iii) prevention was restricted to HPV 16 and 18 related disease, creating the notion of a partial (thus less attractive) vaccine against cancer. In addition, the initial cost of the vaccine was very high and most national indications were strongly influenced by local budgetary constraints. Models of cost effectiveness and early regulations were all based on these principles and as a consequence, very limited indications of vaccine use were recommended and adopted. Many countries initiated vaccination of single cohorts of girls in the range 11 to 14 years of age and only a few programs extended the catch up age range up to age 25-26, notably in Australia and Denmark.

The limited implementation of catch up programs was further explained by the costs, logistics and necessary efforts required to extend the age range and the gender-neutral indications for vaccination.

Since their initial introduction in 2006, a wealth of information has been generated by trials and epidemiological studies. Relevant to his discussion is i) the recognition that HPV induces a non-negligible burden of cancer in both genders ii) the burden and costs of dealing with genital warts iii) the reduction in the required number of doses and the calibrated costs of the vaccine in regional tenders and developing countries and most importantly that iv) adult women up to age 55 are equally protected by vaccination as adolescents are provided they are HPV negative at the time of vaccination.

The HPV-FASTER protocol: an interesting alternative for Latin America

HPV screening and vaccination are complementary preventive options that are often implemented as separate and non-coordinated programs aiming at preventing the same disease. The HPV-FASTER protocol aims to address this gap by strategically combining both strategies with the end-purpose of accelerating the reduction of cervical cancer incidence and mortality.

The HPV FASTER protocol builds on the results from two Phase III trials comparing HPV vaccination against placebo among adult women (to age 45y for the quadrivalent vaccine and to age 55y for the bivalent vaccine)[18,19] and on the consistent results of the HPV screening trials. The two vaccination trials reported results in different cohorts of women whose HPV and cytology status were measured at the time of vaccination. In these cohorts of adult women, those HPV DNA negative at baseline and receiving 3 doses ("per protocol" group) showed vaccine efficacy (VE) estimates of protection against HPV vaccine types in the range of 85 to 90% depending on the trial's endpoint (infection, persistent infection or cervical, vulvar or vaginal lesions). In all vaccinated women, irrespective of HPV baseline status, who received at least one dose ("intention to treat" cohort), reduced but still important VE of approximately 50% were seen.

The HPV-FASTER protocol proposes to offer HPV vaccination to women in a broad age range 9 to 45/50y irrespective of HPV infection status. Women at any age above 30 would in addition, be screened with a validated HPV test as part of their first vaccination visit. HPV positive women would be offered triage and diagnostic / treatment follow up in accordance with recommended guidelines. Increasing the number of vaccinated cohorts would have a net result in accelerating the reduction in cervical cancer incidence (and likely mortality). HPV screen-negative women at baseline, once vaccinated would have a very low risk of subsequent cervical cancer and little requirements of further HPV screening.

Under these premises, the scenario for cervical cancer prevention would change from the traditional proposal of repeated screening requirement (an alternative that has proven very difficult to follow in most Latin American countries) to a vaccination campaign approach paired with at least one HPV screening and eventual triage / diagnostic episode among women screening HPV positive. The HPV screening episode using a validated HPV test, should clear the vast majority of prevalent cases requiring treatment whereas the vaccination should ensure long term protection against incident HPV infections. After completion of the vaccination campaign in a given population, vaccination would remain active targeting the new cohorts of girls as they will reach the designated age groups before sexual initiation (i.e. 9 or 10) and some HPV screening activity will remain, focusing on adult women that may have escaped routine vaccination.

Latin America fulfills several of the criteria to consider HPV FASTER as an alternative. The burden of disease is high, with some exceptions the conventional cytology based screening programs have had limited impact in reducing mortality and the manpower and health infrastructures are adequately developed to sustain one-time campaigns of HPV screening and triage. Moreover, the infant vaccination programs are achieving high coverage and the results of the HPV vaccination programs indicate good acceptability and compliance.

To demonstrate the viability of this strategy and to refine the protocols (i.e. to determine the age at fist HPV screen, the upper age limit for HPV vaccination, the number of HPV screening events required in vaccinated women and other), some research projects have been already initiated in different settings. In Latin-America, in two semi-rural areas of Mexico, Tlaxcala and Morelos, the HPV-FASTER protocol (denoted as FRIDA-2) will compare HPV related outcomes in populations that would be allocated to either repeated HPV screening at 3 and 5 years (control arm) or to receive HPV vaccination and repeated HPV screening at 3 and 5 years (intervention arm). The trial is powered to examine the gain in protection afforded by vaccination in these age groups (predicted long term effects) over and above the protective effects of one episode of HPV screening. Other projects are exploring opportunities of implementation of the HPV-FASTER concept in Europe, Latin America and in other populations where repeated screening examinations are problematic.

Conclusions and perspectives

Two important tools are now available for improving cervical cancer prevention: one would boost secondary prevention by testing for the presence of HPV in cervical specimens and treating the HPV induced lesions, the other would introduce primary prevention by immunizing against a selected group of oncogenic HPV types.

Adequately combined, these two options have the potential to dramatically control HPV related cancers. Even after recognizing that some gaps in knowledge require additional research, the time is now right to begin to evaluate strategies that would combine HPV vaccination and HPV screening in the best way possible. Cost benefit analyses should advise the relevant public health institutions and the governments on the most attractive alternatives as well as on the range of prices at which cervical cancer control using HPV technologies would be sustainable.

F Xavier Bosch.[1]
x.bosch@iconcologia.net

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], [accessed March, 2015]. Available at: http://globocan.iarc.fr.
2. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, *et al.* 2012. Global Burden of Human Papillomavirus and Related Diseases'. Vaccine 2012, 30 (suppl 5):F12-F23. doi:10.1016/j.vaccine.2012.07.055.
3. Institute of Medicine/Forum on Emerging Infections. Considerations for viral disease eradication lessons learned and future strategies: workshop summary. In: Knobler S, Lederberg J, Pray LA. Washington, DC: National Academy Press, 2002 [accessed March, 2015]. Available at: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=86910.
4. Arbyn MA, Haelens A, Desomer A, Verdoodt F, Thiry N, Francart J, *et al.* Cervical cancer screening program and Human Papillomavirus (HPV) testing, Part II: Update on HPV primary screening. Health Technology Assessment (HTA) KCE Reports 238Cs. D/2015/10.273/16. Brussels: Belgian Health Care Knowledge Centre (KCE), 2015.
5. Cuzick J, Szarewski A, Mesher D, Cadman L, Austin J, Perryman K, *et al.* Long-term follow-up of cervical abnormalities among women screened by hpv testing and cytology-results from the Hammersmith Study. Int J Cancer 2008;122(10):2294-2300. doi:10.1002/ijc.23339.
6. Ronco G, Dillner J, Miriam-Elfström K, Tunesi S, Snijders PJF, Arbyn M, *et al.* 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383 (9916):524-532. doi:10.1016/S0140-6736(13)62218-7.
7. U.S. Food and Drug Administration. WebContent. 2014. 'News Release - FDA Approves First Human Papillomavirus Test for Primary Cervical Cancer Screening, April 24. FDA, 2014. [accessed March, 2015]. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394773.htm.
8. Lehtinen M, Dillner J. Clinical Trials of Human Papillomavirus Vaccines and beyond. Nat Rev Clin Oncol 2013;10(7):400-410. doi:10.1038/nrclinonc.2013.84.
9. Michela S, Carrillo-Santisteve P, Lopalco PL. Safety of Human Papillomavirus Vaccines: A Review. Expert Opinion on Drug Safety 2015;14(5):697-712. doi:10.1517/14740338.2015.1013532.
10. Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, *et al.* Effect of Human Papillomavirus 16/18 L1 Virus like particle vaccine among young women with preexisting infection: a randomized trial. JAMA 2007;298(7):743-753. doi:10.1001/jama.298.7.743.
11. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, *et al.* Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PloS One 2013;8(7):e68329. doi:10.1371/journal.pone.0068329.
12. Garland SM. The Australian Experience with the Human Papillomavirus Vaccine. Clinical Therapeutics 2014;36(1):17-23. doi:10.1016/j.clinthera.2013.12.005.
13. Hariri S, Bennett NM, Niccolai LM, Schafer S, Park IU, Bloch KC, *et al.* Reduction in HPV 16/18-Associated High Grade Cervical Lesions Following HPV Vaccine Introduction in the United States - 2008-2012. Vaccine 2015;33(13):1608-1613. doi:10.1016/j.vaccine.2015.01.084.
14. 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. doi:10.1093/jnci/djt460.
15. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, *et al.* A 9-Valent HPV Vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372(8):711-723. doi:10.1056/NEJMoa1405044.
16. Drolet M, Bénard E, Boily MC, Ali H, Baandrup L, Bauer H, *et al.* Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infectious Diseases 2015;15(5):565-580. doi:10.1016/S1473-3099(14)71073-4.
17. Tabrizi SN, Brotherton JML, Kaldor JM, Skinner SR, Liu B, Bateson D, *et al.* 2014. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infectious Diseases 2014;14(10):958-966. doi:10.1016/S1473-3099(14)70841-2.
18. Castellsagué X, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, *et al.* End-of-Study Safety, Immunogenicity, and Efficacy of Quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105(1):28-37. doi:10.1038/bjc.2011.185.
19. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce L, Salmerón J, *et al.* Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-Adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the Phase 3, Double-Blind, Randomised Controlled VIVIANE Study. Lancet 2014;384(9961):2213-2227. doi:10.1016/S0140-6736(14)60920-X.

(1) Senior Consultant to the Cancer Epidemiology Research Program, Director of International Affairs, Co-Director of the ICO / IARC HPV Information Centre, Institut Catala d'Oncologia. Barcelona, Spain.