Introduction of HPV prophylactic vaccines: A new challenge for Public Health in the 21st century

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Cervical cancer affects almost half million women each year worldwide, 70% of them living in developing countries. If current trends continue, this number will almost double in 2,020 (Parkin & Bray, 2006). Primary prevention with a very effective vaccine could change this scenario dramatically. However, the present cost of the vaccines as well as the lack of information, policies and implementation strategies may hinder its broad application, particularly in low-resource settings where it is most needed.

Current evidence-based medicine

Several clinical trials of two prophylactic HPV vaccines have been conducted in different countries including about 50,000 individuals. The per-protocol populations included women who were naïve at baseline to HPV 16 and 18, or to HPV 6, 11, 16, and 18, as determined by serology testing for the presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA (Harper *et al.*, 2004; Villa *et al.*, 2005). For both the bivalent and quadrivalent vaccines, results of different trials allow for the examination of broad trends in efficacy in preventing HPV 6/11/16/18-related disease in several groups of patients classified according to their HPV status at baseline. The quadrivalent vaccine was 100% effective in reducing the incidence of HPV 6/11/16/18-related disease in women who were serologically and DNA PCR negative at baseline to the relevant HPV type, as well as in women who had been previously exposed to at least 1 HPV type vaccine at enrollment, but had no ongoing HPV infection (i.e., seropositive but HPV DNA negative by PCR) (Future II study group, 2007; Garland *et al.*, 2007). However, there was no clear evidence of protection from disease caused by HPV types for subjects that were HPV DNA positive by PCR and/or seropositive at baseline (Ault *et al.*, 2007; Joura *et al.*, 2007). Similar results were obtained for the bivalent vaccine (Harper *et al.*, 2005 and 2006). In fact, vaccination of HPV16/18 DNA positive women does not enhance clearance of the viral infection (Hildesheim *et al.*, 2007). In a recent publication of a phase III trial, this bivalent vaccine showed 90% prophylactic efficacy against CIN2+ associated with HPV 16 or HPV 18 (Paavonen *et al.*, 2007).

Challenges for HPV vaccine introduction

Based on its demonstrated clinical efficacy and favorable safety profile, HPV prophylactic vaccines are being introduced in many countries around the World. In several developing countries, including among others, Brazil, Chile, Mexico, Peru, the Quadrivalent HPV 6, 11, 16, 18 vaccine has been in use for more than 1 year. The rapid approval and launch of such vaccines provide a clear indication that governments and policy makers are aware of the expected impact on the prevention of one of the most common causes of female mortality worldwide. However, incorporation of HPV vaccination in the public health sector is

still to be seen in the developing World, mostly due to vaccine cost. HPV vaccine implementation will also depend on local infrastructure for vaccine delivery to the initial target population during the window of highest vaccine efficacy, i.e. prior to sexual exposure. Furthermore, introducing HPV vaccines in the present cervical cancer control system is hampered by the fact that secondary screening with Pap tests (or HPV DNA testing) will still be required to detect cervical cancers and pre-cancers caused by non-vaccine HPV types. Ongoing cost-benefit studies and negotiations between governments, the private sector, and non-governmental organizations may enable some of the developing countries, where the vaccine is most needed, to implement the necessary programs. Education of physicians, policy makers, parents, and adolescents will be crucial for delivering HPV vaccines, which ultimately will result in the reduction of cervical cancer rates and other HPV-related diseases worldwide. Vaccine acceptance is largely determined by health beliefs, such as the individual's perceived susceptibility to the disease; vaccine characteristics, such as cost and efficacy; and obstacles to obtain the vaccine. Health perceptions are expected to play a major role in the acceptance of HPV vaccine, as is the fact that the vaccine raises the morally and politically charged issue of adolescent sexual behavior. Physicians' attitudes are extremely influential to both parents and adolescents, and physicians' perception regarding the HPV vaccine as important and recommended will be a critical step towards vaccine acceptance. Altogether, education of physicians, parents, and adolescents will be crucial for delivering HPV vaccines to target populations during the window of highest vaccine efficacy, prior to sexual debut.

Despite these excellent efficacy results, it may take some time before these vaccines are administered to the general population worldwide. Moreover, women will still be at risk for developing cancers caused by other HPV types not included in the vaccine and hence screening and monitoring strategies will be required. Finally, since at present the durability of these vaccines has been evaluated only for up to 5 years (Harper *et al.*, 2006, Villa *et al.*, 2006), monitoring of antibody levels and high grade disease caused by the HPV vaccine types in sentinel groups of immunized individuals will be required over the next decades (Lehtinen *et al.*, 2006). It is important to stress that disease outcomes should be recorded since at present there is no immune correlate and the importance of serum antibody levels is simply not known. To achieve this, standardized methodologies that measure total serum antibody, neutralizing antibody and type specific antibody concentrations will be necessary. However, at present neither HPV serological assays nor HPV DNA tests can be used as clinically relevant tools for individual patients. These assays will require the establishment of International Standard(s) with an arbitrarily assigned unit measure or International Units (http://www.who.int/biologicals/areas/vaccines/hpv_labnet/en/index.html and Ferguson *et al.*, 2006).

The availability of two prophylactic HPV vaccines will require thorough considerations on monitoring and surveillance of those vaccinated and of the general population, respectively (Stanley & Villa, 2008). Vaccinated populations should be followed-up for long-term safety, sustained immune responses and vaccine disease efficacy (Dillner *et al.*, 2007). Effective monitoring will benefit from linkage of vaccination history and screening history, as well as precise measurement of HPV infection, plus both DNA and serological testing. Lack of record linkage in many settings is one of the main obstacles for an effective surveillance program, though other surveillance activities can contribute to assessing HPV vaccine efficacy, including information from organized screening programs and phase IV studies. Importantly, loss of screening performance may occur because of the expected reduction in cervical abnormalities in vaccinated populations. In this scenario, HPV testing has the potential to perform better as a primary screening test, followed by cytology for triage of HPV-positive cases (Franco *et al.*, 2006).

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