INTRODUCTION

The new challenges in the prevention of cervical cancer

In spite of the considerable success registered by the early detection procedures for cervical cancer prevention, the 'smear' did not fulfill all hopes one could expect in reducing cancer incidence at large scale.

Cervical screening seems to benefit a minor part of the world female population, and yet a large proportion of women who benefit from it still prove its weaknesses [1].

At the level of the lower genital tract, infections by human papillomaviruses (HPV) are very frequent, and the most virulent types, 16 and 18, are responsible for two thirds of the cervical cancer cases worldwide. Condyloma acuminata (genital warts) induced by HPV 6 and 11 affect nearly 2–4% of boys and girls younger than age 25 years, and their clinical management is generally long and difficult. The burden and the weight of papillomavirus associated diseases are significant [2]. The psychological and emotional impact is also an important issue.

The fact that these genital lesions are the consequence of a chronic genital infection with HPV opens new and extraordinary opportunities for prevention through vaccination. The HPV vaccines are the first vaccines presented as an anti-cancer immunization. Indeed, these prophylactic vaccines, to protect against precancerous and cancerous lesions associated with HPV, shall save lives, reduce costly treatment interventions, and have an individual and collective benefit that should not be neglected.

The clinical studies of vaccines against papillomavirus based on the use of viral like particles (VLPs), constituted of the major protein L1 of the capsid of the virus, without any viral genetic material — immunogenic while not infectious and non-transforming — demonstrated their remarkable efficacy in preventing cervical precancers and cancers, as proven for the quadrivalent [against HPV types 6,11,16,18] and the bivalent [against HPV types 16, 18] vaccines. Their level of clinical efficacy in the "per-protocol" analysis (consisting of women who were naive to vaccine targeted HPV types at baseline 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) is unprecedented in the history of vaccination: close to 100% [3–7].

The highest efficacy is demonstrated in young women naive to the virus types associated to the vaccines. The vaccines seem to have no therapeutic effect on existing lesions or on the course of viral infections already carried by healthy individuals [3,4,8,9,10]. The impact of vaccination is also relevant in vaginal and vulvar lesions [4] that, somewhat less frequent than cervical lesions, however cannot benefit from early detection programs and treatment, can be scattered and relapsing, and hence traumatizing. Data supporting additional cross protection vaccine efficacy have been reported in the conference and are expected to be published in short [5,8,11].

Four large trials of either a HPV 16 monovalent vaccine or the quadrivalent HPV vaccine demonstrated a vaccine efficacy of 44% for preventing HPV 16/18 associated CIN 2,3 or AIS in the "intent-to-treat" population (consisting of all women who were enrolled into the trial) after a mean follow-up of 3 years [8]. Results with a limited benefit have been reported for the bivalent HPV 16 and 18 vaccine [7].

The vaccines also have been shown to not accelerate clearance of infections in women already infected with HPV 16 and 18 [12].

In practice the effectiveness of HPV vaccines are limited by two factors: all genital cancers and precancerous lesions are not induced exclusively by HPV types 16 or 18, and the optimal benefit is demonstrated in adolescents and young women before they have encountered these viruses.

In fact, delaying the period of vaccination could imply loosing its maximal valuable protective effects. Nevertheless, in clinical practice it is necessary to interpret the trials' results with a critical view. For instance, it is unlikely that a person has been exposed to all types of viruses included in the vaccines, and therefore a protective effect might be expected against the HPV types that have not been encountered [13]. In the clinical trials, about 70% of girls and young sexually active women under 26 years with
an average of two lifetime sexual partners were HPV DNA and serology negative (naives) for HPV 16 and 18 vaccine types. Because approximately half of all individuals exposed to genital HPV infections never develop antibodies, 70% is an obvious underestimation of the actual cumulative HPV exposures in these populations. Thus although a reasonable proportion of women with few lifetime sex partners might be expected to benefit from HPV vaccines, the benefit will certainly decline as HPV exposures increase. Finally, among young women aged 14–25 years, the clearance rate of genital HPV infections is high, and disease occurs in a minority of women who can decrease their risk for cancer in settings where organized screening programs are available (REF)[1]. The question of vaccination before or after sexual debut is controversial, and depends on the concept of individual or collective benefits and arguments of effectiveness over efficacy. Regardless, continued cervical cancer screening is necessary in both vaccinated and unvaccinated populations.

The reported adverse effects of vaccination are generally minor. National and international plans for monitoring and evaluating risks linked to HPV vaccination are already in place, and will allow to measure within a few years the benefits of vaccination by age group.

Practical questions will need to be addressed, such as the potential for disease replacement through unmasking of oncogenic HPV types not included in current HPV vaccines, if effective, the need and cost-effectiveness of vaccinating boys, the duration of vaccine protection, the extent and longer term benefit of cross protection against HPV types not targeted by current vaccines, and most important access to vaccines in poor countries. In developed countries, possible negative effects of vaccination programs must be considered such as a decreased participation in cervical cancer screening programs by vaccinated women [14] and changes in the performance of screening methods [15].

If vaccination would be left to individual choice and initiative, the coverage would be low, and the benefit in reducing the frequency of this cancer would be barely perceived. We need to keep in mind that, in the context of public health, it may take several years to observe the benefits of preventing cervical cancer cases following vaccination of cohorts of adolescents with high coverage. Reductions in precancerous lesions could be significantly reduced within much shorter time period when vaccination is extended to broader age cohorts of women, consistent with clinical trial benefits observed over 2–4 years.

Thus, there is a need for vaccination policy, which is likely to differ in poor countries where the magnitude of disease represents a larger toll of disease and mortality, and in wealthy countries where screening programs have significantly reduced the frequency and mortality of this cancer.

The adoption of systematic or routine vaccination of girls aged 9–15 years, with a catch-up of cohorts of young women aged 16–26 years, correspond to date to the indication of the product as defined in the marketing authorization by the European Medicines Agency (EMA).

The success of vaccination as a public health intervention, will depend on its acceptability and on the degree of engagement of health professionals. A vast educational program for the general population, for patients and for health professionals is needed. As vaccines will not protect from all possible HPV types associated to cervical cancer, the screening programs shall be maintained at current intervals and conditions. Vaccination and screening act complementary and synergistically, and constitute to date the new standards of disease prevention.

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References


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