



Human papilloma virus vaccines: ethical issues

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Resumen

Los autores discuten sobre los principales aspectos y temas éticos acerca de la vacunación contra el HPV, una de las más difusas ETS causante del cáncer cérvico-uterino y otras severas patologías. Esta vacunación se ha propuesto recientemente para mujeres jóvenes (cerca de los 12 años de edad), antes del llamado “debut sexual”. Incluso si se está consciente de los múltiples beneficios de esta propuesta, los autores subrayan que ésta no puede ser considerada únicamente, desde la perspectiva médica, sino a través de un acercamiento al “bien total” de la persona.

Summary

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The authors discuss on the principal scientific aspects and ethical issues about the vaccination against HPV, one of the most diffuse STI and cause of the cervix cancer and other severe pathologies. This vaccination has been recently proposed to young

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women (around 12 years), before their, so-called, “sexual debut”. Even if aware of the many benefits of this proposal, the Authors underline that it cannot be considered from the only medical aspects connected to it, but through an approach to the “global good” of the person

Palabras clave: Virus del papiloma humano, vacunas, conducta de riesgo, enfermedades de transmisión sexual.

Key words: Human papillomavirus, vaccines, risk behaviours, sexually transmitted infections.

Introduction

Human papillomavirus (HPV) is the most prevalent infection of reproductive system organs, which causes cervical cancer and other less severe diseases (Le., genital warts). Cancer of the cervix uteri is the second most common cancer among women worldwide. 470.000 cases are diagnosed each year, resulting in approximately 233.000 deaths. Some 83% of the cases occur in developing countries, where cervical cancer accounts for 15% of female cancers, with a risk before age 65 of 1.5%. The highest incidence rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia, and South-East Asia. In developed countries the estimated lifetime cervical cancer risk is 3,67% and cervical cancer mortality risk is 1,26%, with a peak incidence of 81/100.000 at age 50 years.²

The most effective prophylaxis against viral infections is the vaccination. Very recently a new vaccine against HPV passed the phase-III of clinical trials and became commercially available after *Food and Drug Administration's* (FDA) approval in the USA. This event was announced as the next great victory in the war against cancer. The point is that the general vaccination of women can protect them from cervical cancer, but this brilliant proposal contains some serious ethical concerns.



HPV is a Sexually Transmitted Infection (STI). It is acquired primarily by sexual intercourse with an infected person and the risk of contamination is strongly related with sexual behaviour. An important aspect is that the group of most risk consists of very young females: adolescents have been identified as risk group for STI because of high rates of disordered sexual intercourses, inconsistent condom use and several sexual partners. To be effective, vaccination should be done before infection, which means before the “sexual debut”: for that reason, researchers have suggested that girls between the ages of 10 and 13 be vaccinated. In Italy the vaccination of 12 years-old-girls was proposed after AIFA’S (*Agenzia Italiana per il Farmaco*) approval. In this paper we will reflect on ethical problems which appear, especially when the vaccination against STI is applied for adolescent groups.

Scientific data

Human papillomavirus

HPV particles consist of 8.000 base-pairs (bp) long circular DNA molecules wrapped into a protein shell that is composed of two molecules (L1 and L2). The genome has the coding capacity for these two proteins and at least six so-called early proteins (E1, E2, E4-E7) that are necessary for the replication of the viral DNA and for the assembly of newly produced virus particles within the infected cells.³

Papillomaviruses are perfectly adapted to their natural host tissue, the differentiating epithelial cell of skin or mucosa, and exploit the cellular machinery for their own purposes. HPV infects the mucosal areas of the cervix, vagina, vulva, and anus. The cycle is initiated when infectious particles reach the basal layer of the epithelium, where they bind to and enter into cells, through small breaks. It has been suggested that for maintenance of the infection, the virus has to infect epithelial stem cells.⁴ The critical molecules in the process of virus replication are the viral proteins E6 and E7, which interact with a number of cellular proteins. In experimental systems these interactions have shown to induce proliferation and sometimes even immor-



talization and malignant transformation of cells.⁵ Molecular studies actually show HPV-DNA in all (i.e., 99,7%) cervical cancers.⁶

Over 100 HPV types have been characterized molecularly and about 40 of them are able to infect the genital tract. Most HPV infections are asymptomatic and transient. About 70% of new HPV infections clear within 1 year and about 91% clear within 2 years.⁷

The eight most common HPV types, in descending order of frequency, HPV-16, -18, -45, -31, -33, -52, -58, and -35, are more persistent and - over a gap of time ranging between a few years and some decades - may lead to grade 2 or 3 of cervical intraepithelial neoplasia (CIN) or cervical cancer. They are responsible for about 90% of all cervical cancers worldwide.⁸

Mechanisms of transmission

Genital HPV infection is the most common STI among women. Sexual intercourse is the primary route of genital HPV infection. Data supporting this include documented transmission of genital warts between sexual partners, concordance in sexual partners for type specific and HPV-16 variant-specific HPV-DNA, the rarity of genital HPV infection in women who have not had vaginal intercourse, the strong and consistent associations between lifetime numbers of sexual partners and HPV prevalence in women and men (albeit less consistently), and increased risk of HPV acquisition from new and recent sexual partners. Although plausible, mechanisms other than sexual intercourse are less common routes of genital HPV infection. While oral and digital infection with genital HPV types clearly occurs, the risk of transmission by digital-genital or oral-genital contact appears to be minimal.⁹

Estimated exposure is within a few years of sexual debut. In one study, 39% of female college students are infected with HPV within 24 months after sexual debut, rising to about 54% by 48 months.¹⁰ Two other studies found a 43-44% cumulative HPV incidence by 36 months in women who were HPV-negative at baseline.¹¹

Several cross-sectional studies have reported that earlier sexual debut or shorter intervals between menarche and sexual debut are risk



factors for prevalent HPV infection.¹² The highest prevalence of HPV is in 14-19-year olds. This is probably because of very high sexual activity of young adults. The percentage of females reporting ever being sexually active are 29% for 9th graders, 39% for 10th graders, 50% for 11th graders, and 60% for 12th graders.¹³ Oral contraceptive use, high number of sexual partners, male partners with several sexual partners, and knowing a partner for less than 8 months before intercourse can all be predictors of HPV infection.¹⁴

The associations between numbers of new and recent sexual partners and likelihood of detecting HPV-DNA in female genital tract specimens are strong and consistent. The characteristics of male partners are critical for female HPV acquisition. In case-control studies of cervical cancer, male partners of cases report higher numbers of partners than those of controls.¹⁵ Female HPV prevalence and acquisition have been positively associated with women's estimates of their male partners' lifetime number of partners or not knowing a male partner's prior sexual history.¹⁶

HPV vaccines

A successful immune response to genital HPV infections is characterised by strong, local cell-mediated immunity (CMI) that is associated with lesion regression and protection against a further infection with the same genotype of HPV. Humoral immunity (antibody) is directed against conformational epitope(s) on the major coat or capsid protein L1 displayed on the outer surface of the intact virus particle. Serum-neutralising antibody levels in natural HPV infections, even at peak titres just after seroconversion, are low.¹⁷ This low response probably reflects the exclusively intra-epithelial infectious cycle of the Papillomaviruses and the consequent absence of a viraemia.¹⁸ Two HPV L1 Virus-Like particles (VLPS) vaccines have been developed commercially and are, at present, in phase-III trials. Cervarix™ is a bivalent HPV-16/18 L1 VLPS vaccine developed by *GlaxoSmithKline* (GlaxoSmithKline Biologicals, Rixensart, Belgium). The product consists of purified L1 VLPS of HPV types 16/18 at 20/20 mcg per



dose. The product is delivered by intra-muscular injection in a three-shot immunisation protocol at 0, 1 and 6 months as a 0.5-rnL dose.

Gardasil is a quadrivalent HPV-16/18/6/11 LI VLPS vaccine developed by *Merek and Co.* (West Point, Pennsylvania, USA). The product consists of purified LI VLPS of HPV types 6/11/16/18 at 20/40/40/20 mcg per dose and is delivered by intra-muscular injection as a 0.5-rnL dose in a three-shot immunisation protocol at 0, 2 and 6 months.

Efficacy Gardasil was assessed in 4 placebo-controlled, double-blind randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of Gardasil (N=2391) and the second evaluated all components (N=551). The Phase III studies evaluated Gardasil in groups of 5.442 and 12.157 subjects. Together these four studies evaluated 20.541 women 16 to 26 years of age at enrolment.

The average duration of follow-up was 4.0, 3.0, 2.4 and 2 years. Gardasil was administrated without pre-screening for presence of HPV infection and the efficacy trials allowed enrolment of subjects regardless of baseline HPV status. A total of 27% of subjects had evidence of prior exposure to ongoing infection with at least 1 of the 4 vaccine types.

Contraindications are for hypersensitivity to the active substances or to any of the excipients of the vaccine. The vaccine-related adverse experiences that were observed among female recipients of Gardasil at a frequency of at least 1,0% and also at a greater frequency than that observed among placebo recipients.¹⁹

Data from the published phase-II and phase-III trials of HPV LI VLPS vaccines demonstrate clearly that both the bivalent and quadrivalent vaccines protect women from persistent cervical HPV-16/18 infection and cervical HPV-16/18-induced disease; the quadrivalent vaccine also protects women against HPV-6/11-induced mucosal and cutaneous genital disease. Duration of protection is a key issue that will influence vaccine implementation: how long will protection last and will booster immunisation be necessary? There are both theoretical and evidence-based reasons for some optimism on this issue. The available data from the HPV vaccine trials indicate that antibody levels fall from the peak levels after immunisation to a plateau level



that is at least higher than those detected in natural infections and that persists for at least 48 months post-vaccination.²⁰

However, HPV infections may occur repeatedly over a number of years and the risk of acquiring new infections is closely linked to the sexual behaviour of the individual. This raises the possibility that vaccinated individuals may change their behaviour and increase the risk of acquisition of new infections. The data from the vaccine trials cover a relatively short time-span (4,5-5 years) therefore there is no hard data that antibody persistence relates with protection and, in reality, we do not know how long the protection induced by LI VLPS will be.²¹

Gardasil is indicated for 16-26 years old women. Besides the high risk related to a high sexual activity they highlight some immunological reasons to immunise before puberty: antibody responses induced by these (and other) vaccines are higher in pre-puberty than in post-puberty in both males and females.

Ethical issues

The availability of vaccines for this diffuse infection, responsible for serious pathologies, seems to suggest its big distribution, especially among women with greater risk of infection. But we have to make some considerations.

Potential benefits and risks of HPV vaccination

First of all, in a corrected medical approach, the use of HPV vaccines should be preceded by the appraisal of the benefits/risks report. The principal benefit of this vaccination is reduced frequency of HPV infection and associated lesions. Potential harm includes adverse reactions: although HPV vaccine has a low level of local reactions, widespread use might uncover a rare adverse reaction not previously seen.

The particularity, which differ HPV from many other vaccination, is that HPV infection is an STI and is strongly associated with lifestyle choices. Although the majority of authors do not take into account the option of moral values, they speak out the concern of adver-



se vaccination outcomes due to existing potential for increased sexual activity among partners, increased numbers of partners, and decreased use of barrier protection methods because of perceived protection from vaccination. The possible results of such actions include increased unplanned pregnancies, increased abortions, increased rates of other types of HPV, and increased rates of other STIS including HIV. A modelling analysis by S.M. Blower and A.R. McLean based on data from *San Francisco Young Men's Health Study* about HIV vaccine use found out that if risk behaviours increase as the result of an HIV vaccination campaign, then "vaccination could result in a perverse outcome by increasing the severity of the epidemic".²² Of course, there are many differences between these HIV analyses in men and HPV in women.

Among other risks of vaccination, we remember the following two: *a)* the concern that some women may mistakenly assume that HPV vaccine protects against other STIS. Such overgeneralization has been noted before by health services researchers for routine childhood vaccines: there is a tendency for some parents to lump, that is thinking of "shots" in general, instead of the particular antigens.²³ *b)* Another hypothetical but non improbable risk of HPV vaccination, is an inappropriately decreased use of cytology screening for cervical cancer due to the mistaken belief that screening is no longer needed or to confusion about new screening schedules introduced after widespread use of the vaccine.

Parents' opinion

E. Olshen *et al.* write: "To be most effective, the HPV vaccine should be given to children before they become sexually active. Thus, it would be prudent to administer the HPV vaccine to preteens".²⁴ Because the teen- and preteen-age vaccination has been put into discussion, the informed consent of both parents is a necessary option. Parents' reasons for acceptance or declination of vaccines against STIS include protection of their children, vaccine efficacy, concern about diseases/severity of infection, patients' attitude to vaccinations, previous experiences with the infections, perception that their children



would be at low risk for infection and lack of concern about the diseases in question.

Not always the information is given in the right way. In the set of questions dedicated to parent's opinion about HPV vaccination provided by Olshen et al., they use the comparison with other vaccines given to children, in particular, tetanus vaccine: "Tell me about some of your experiences with vaccines and your children; a vaccine to prevent tetanus is often given to children between the ages of 10-15. Have any of your children gotten the tetanus vaccine recently? How do you feel about your child getting the tetanus vaccine? What things about tetanus vaccine did you like?". And so on. Nothing of HPV infection specificity due to its strong relation to disordered sexual behaviour was declared to be included in this questionnaire. Although majority of parents concerns were about the HPV vaccine safety for child health, nevertheless, some parents from the study group wondered how to explain the HPV vaccine to a child and some worried that giving the HPV vaccine would encourage "unsafe" sexual activity: "I can't imagine how I would explain to this kid what this vaccination is (...) and why you have to get it...if you were ten years old"; "It's scary telling a child that they are protected by certain sexual transmitted disease". A few parents believed the HPV vaccine should be offered to adolescents when they can take part in the decision whether to be immunized. In another study some parents feared that an adolescent would interpret a parent's approval of STI immunization as condoning sexual behaviour.²⁵

Risk behaviours and prevention

The only medical approach, already inadequate for adults, seems limited when we refers to people under age. In fact, we know that the target of this vaccination –in Italy as somewhere else– could be 12: years-old-girls. The reason –as said– is epidemiologic: the widest spread of HPV infection is in the years of the "sexual debut" that often occurs in the school age. This approach is often justified through two moral reasoning: the "lesser evil" and the "double effect" principles.²⁶



The principle of the “lesser evil” is also used for spreading condom as a mean against STI. It has led to further values failure, reinforcement of public belief to acceptance of disordered sexual behaviour and probably to growth of disease. Advocates of condom spreading state that these unwanted consequences are of lesser “evil” than the good of eventual protection from HIV infection. Yet, there is no statistical data which could confirm that the condom use really protect society from AIDS.

But even if it is so, we need to look at the prevalent good, especially when life and health are involved. Health defence, no doubt, is a serious responsibility for everybody and for society, but it cannot be reduced to the only medical action of intervention. In fact, a medically correct sexual act is not, in itself humanly significant. So, when girls under age are involved we deal with people whose moral values are still in the stage of formation, and who do not have yet own legal responsibilities.

According to the principle of “double effect”,²⁷ there are some efforts to justify the HPV vaccination of minors: “To apply these criteria to vaccination of a person today: 1. the act of vaccination is good, as it results preventing disease in the recipient and may contribute to herd immunity. 2. The theoretical possibility of decreased safer sex practices or confusion about cervical cancer screening is not the means by which HPV vaccine works. 3. The motive for vaccination is protection of the vaccinee and, secondarily, potential protection of their contacts and the community by herd immunity; thus, the motives are good. 4. If vaccine advertising and counselling are done in a manner that promotes sexual responsibility, then the good effect, in this circumstance, seems clearly greater than the bad effect. The decrease in cervical cancer and HPV transmission, given that HPV is the most common STI, is likely to outweigh the negatives and I believe that the criteria for the Principle of Double Effect will be met”.²⁸

We make this objection: first of all, HPV infections is not a social emergency because it is not transmitted for mere exposition (e.g. in a classroom), ‘but it’s the result of a risk behaviour, a early and promiscuous sexual activity. So the issue concerns not only medical aspects (Le. to reduce harm associated with cancer), but also the more complex problem of the prevention for risk behaviours.



In this sense, it seems that the approach of the “lesser evil” and of the “double effect”, as presented, involve a prevention finalized to only reduction of harms without considering the globality of the human persona. In fact, these systems of moral evaluation include some mistakes which lead then to definitive confusion. First of all, when we talk about the actions touching very intimate personal components, like sexual activity, we may not operate with numbers, percents of population as criterions. The proposal of HPV vaccination for adolescent would contain *in se* the justification for a disordered sexual activity and provokes young person into choosing a life style which otherwise would never been chosen. Moreover, the result should be considered morally unacceptable, if only one single person will initiated disordered sexual life because of HPV vaccine popularization. With other words, using the language of “double effect”, the bad effect of disordered sexual life is significant and may not be covered by medical benefit of vaccine. Zimmerman wishes that “vaccine advertising and counselling are done in a manner that promotes sexual responsibility”: it sounds as nonsense because, if “sexual responsibility” doesn’t mean only to avoid STI or unplanned pregnancies, the fact of vaccination proposal itself includes the option of free sex.

A prevention, that pays attention to the globality of the person, must take into consideration the psychological and existential impact of the vaccination for 12 years old girls. The educative project in which the vaccination is proposed cannot be leaving out. The sexual activity of an adolescent, in fact, cannot be object of a simple information about medical aspects (e.g. risks of STI or unplanned pregnancies), but must be object of formative processes to build and promote the personal identity of the adolescent. This does not mean to deny or underrate the medical validity of the vaccine, but rather to not forget the “global good” of young girls, who are in a very delicate phase of their existence. In this sense we disagree on mandatory HPV vaccinations. But also a proposal of vaccination, without adequate information about behaviours already outside of the abilities and decisional responsibilities of many adolescents, is highly problematic and risks putting in background also the educational engagement of the parents.



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²⁷ The Principle of Double Effect is used to evaluate moral conflicts when an action could produce both good and bad effects. HPV vaccine should lead to a number of benefits including reduced cervical cancer and reduced genital warts. On the other hand, adverse effects need to be considered, including adverse vaccine reactions, the hypothetical possibilities of decreases in safer sex practices, increases in other STIS, and confusion about cervical cancer screening. The criteria for the Principle of Double Effect follow: 1. the action itself must be morally indifferent or good; 2. the bad effect must not be the means by which the good effect is achieved; 3. the motive must be the achievement of the good effect only; 4. the good effect must be at least equivalent in importance to the bad effect.

²⁸ ZIMMERMAN. Ethical analysis...



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