Review Article

Are the Currently Existing Anti-Human Papillomavirus Vaccines Appropriate for the Developing World?

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Abstract

Cervical cancer prevention is expected to be achieved by vaccination of girls 2-3 years before sexual debut, and cervical smear cytology follow-up. The existing human papillomavirus (HPV) vaccines target the low-risk 6 and 11, and the high-risk 16 and 18 subtypes, the most common agents of ano-genital pre-invasive and invasive lesions. We conducted the review by searching PubMed using the terms "HPV," "HPV subtypes," "developing world," and "HPV-vaccine" to retrieve articles published between 2000 and 2011. We focused on studies that were relevant to the developing world. The proposed vaccination policy is currently unachievable in the developing world because of the cost of the vaccine, the lack of adequate cytology and follow-up infrastructures. Moreover, the subtypes of HPV involved in cervical pathology, their associations, and natural history (clearance and persistence rates) differ from the industrialized world. Therefore, the current bivalent and quadrivalent anti-HPV vaccines are unlikely to achieve their target in the developing world. It follows from published data that there is an obligation of the pharmaceutical industry and of the public-health policy makers not to embark on mass vaccination campaigns without thorough information and investigation of the local relevance.

Keywords: Cervical cancer, Developing world, Human papillomavirus, Vaccine

Introduction

Cervical cancer is the third most common cancer worldwide, and 80% occur in the developing world where it causes about 190,000 deaths per annum.[1] In the US, approximately 4000 women die annually from cervical cancer.[2] In the developing world, the peak age-specific mortality rate from cervical cancer is in the 55-64 age groups; in the developed world the peak occurs 10 years later.[3] Globally, close to half a million women are diagnosed with cervical cancer annually.[4] Cervical cancer ranks first or second (before or after breast cancer) among female cancers depending on whether a woman lives in the developing or developed part of the world.

Cervical cancer screening has been a major contributor to the decrease in the incidence of the disease in the industrialized world. One of the main reasons for the still high incidence of cervical cancer in the developing world is the low screening coverage (± 5.0%), as compared with the developed world (± 50.0%).[5] A South African survey showed that 80% of unscreened participants had never had a Pap smear.[6] Another research indicated a concerning lack of understanding of Pap reports' recommendations by primary health workers.[7] A Tanzanian survey showed that less than half of the nurses had adequate knowledge of cervical cancer.[8] Additional factors such as shortage of health professionals and facilities, as well as poor referral systems compound the situation.

Cervical cancer and its precursors are caused by various strains of the human papillomavirus (HPV).[9] The HPV family comprises more than 90 subtypes that are classified as low-risk (LR), high-risk (HR), and potentially/probably HR in terms of their oncogenic potential REF. Around 30 of them are involved in ano-genital pre-invasive and invasive lesions, and are transmitted during sexual activity (oro-genital, ano-genital, penile-vaginal intercourse, and digital intimate contact).[10,11]

Two HPV vaccines are currently available. The bivalent vaccine immunizes against the two HR-HPV 16 and 18; the

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quadrivalent targets the LR 6/11 and the HR 16/18 subtypes. The prerequisites of successful vaccination are age, gender, sexual naïveté, and magnitude of coverage. The possible limitations are cost and socio-cultural factors and the spectrum of non-16/18 subtypes involved but not covered by the currently existing vaccines. More and more potentially/probable HR HPV are being found in ano-genital lesions, especially in human immunodeficiency virus (HIV) infected subjects.[12] So far, HIV-infected persons have been mostly excluded from participating in HPV vaccine trials; therefore, it is currently unknown if the vaccines would provide the same prevention from HPV acquisition as in uninfected individuals.[13] Currently, however, some trials are in progress.[14] Both HIV and cervical cancer are leading causes of morbidity and mortality in the developing world in general and sub-Saharan Africa (SSA) in particular. There is a hitherto unconfirmed possibility that HIV and HR-HPV-infection work in synergy: One might facilitate infection by the other.[15] Furthermore, HIV-infected women may be affected by HPV-associated malignancies caused by viral subtypes that differ from HIV-naïve malignancies.[12] These factors are especially relevant in the developing world. Although, cervical cancer is a global public-health issue, one may wonder whether there is a global solution.

Methods of literature search

We conducted a systematic review by searching PubMed using the terms "HPV," "HPV subtypes," "developing world," and "HPV-vaccine" to retrieve articles published between 2000 and 2011. We focused on studies that were relevant to the developing world.

The Natural History of HPV Infection in Females

The HPV virus "hits and runs." The life-time risk of cervical HPV infection can be as high as 80%; up to 90% are cleared within 2 years, and only 5-10% persist (not clear).[11,16] The global estimate of HPV infection in asymptomatic women in the general population is around 10%, with continental variants between 8% in Asia, and 22.1% in SSA.[17-20] Although, the main route of infection is by sexual contact (i.e., horizontally), newborns may be infected during labor, delivery, and breastfeeding (i.e., vertically).[21] In a Finish study, 15% of genital samples from and 10% of oral samples infants after delivery (not clear) were positive for HR-HPV; at the age of 12 months, the carrier rate had dropped to 7%. Of note is that one third of the viruses were 16, 18, 31, and 33 (i.e., oncogenic and probably oncogenic subtypes).[21]

Thirty-nine percent of women acquire HPV infection within 24 months after the onset of sexual debut; the highest rate of infection is reached 2-3 years later.[22] This is followed by a decline over the years and an upsurge in the early fifties. In SSA, however, the ratio of infection remains constant over the years.[10] In young women, if the interval between menarche and coitarche is shorter, the risk of acquisition of HPV is higher. It has been speculated that early sexual debut might be a marker of sexual behavior such as a greater lifetime number of partners.[23,24] Even if HPV is a sexually transmitted infection (STI), it does not denote *per se* sexual promiscuity or a specific sexual life pattern. None the less, the risk-factors of infection and transmission are those of STIs: Unprotected sex, multiple partners, recent or present number of partners, frequency of sex or intimate skin-to-skin contact, and sexual histories and behaviors of sexual partners.[11,22-24]

Anti-HPV Vaccination of Females

In order to reach its optimal target, vaccination is recommended in the early teens and before sexual debut.[25] It is estimated that in the developed world, 20% of adolescent girls are sexually active by the age of 14 years.[26-28] Seven percent of high-school students, male and female, report having initiated sexual debut before the age of 13.[22] In the developing world, there is considerable variation in the prevalence of virginity and age at marriage, and premarital sex. Premarital sex is more common in SSA than in Latin America and the Caribbean.[17] In Nigeria, the mean age at sexual debut is 16.8 years in the less than 25 age group, and 20.3 in the 45 and older.[10] In South Africa, the median age at coitarche among women 25-49 years was reported to be 18.4.[19] Accordingly, the age at vaccination may have to vary according to local circumstances and customs.

Early age vaccination against a STI may cause socio-cultural concerns that may affect the magnitude of required coverage to reach herd immunity. Regardless of these considerations, from a strictly public-health viewpoint, the advocates of the vaccine consider that at least 70-80% of pre-pubertal or teenage girls need to be vaccinated to reach herd immunity. Therefore, there is concern about the possible high-rate of parental and cultural objections to vaccinate young girls against a STI-(REF). In order to overcome this hurdle, some public-health policy makers and legislators support the concept of making it mandatory, as it is the case with air-borne induced illnesses such as measles, small pox, and pneumococcal diseases. In the US, vaccination against air-borne viral infections is mandatory for school entry because the mere presence of a carrier is a risk for those present in the classroom. At variance with air-borne diseases, hepatitis B virus (HBV) and HPV are transmitted from person to person mainly through sexual contact and blood (IV substance users). This means that HBV and HPV (as well as HIV) infection denotes a life style and that prevention of transmission implies life style changes, and a risk of discrimination.[28]

Around 90% of cervical cancers result from the HR-HPV 16 and 18.[9] In most pre-invasive and invasive cervical cancers more than one subtype coexists.[29] Since more than one type is usually associated, it is difficult to determine, which one is actually causative. In addition, the types associated with

pre-cancerous lesions, differ from those associated with invasive cancer; HPV types 16, 18, and 45 are significantly over represented in cervical cancer compared to pre-invasive lesions.[30-32] Over the last 20 years, the proportion of the HR-HPV 16 involved in pre-invasive and invasive cervical cancer has declined, and the proportion of oncogenic HPV-other than 18 has increased.[33] High levels of HPV 52 and 58 are prevalent in pre-invasive lesions in Japan.[34] The 16 subtype is more prevalent in European than sub-Saharan African women.[26] Although the 16 and 18 subtypes are found worldwide to be associated with cervical cancer, a higher than average presence of subtypes 45 and 31 is found in the developing world.[26,35] For instance, in South Africa, antibodies to HPV virus-like particles 16, 18, 31, 33, and 45 were detected in all women with cervical pre-invasive lesions, as well as in asymptomatic blood donors and children.[36] The prevalence of HPV 16 and/or 18 was reported to be 62.8% in cervical cancer in South Africa (as opposed to 90% in early studies).[9,20] Studies from Thailand found a high prevalence of HPV 58, 33, and 68 among women with cervical pre-invasive lesions.[37,38] Similar findings were reported from Uganda.[39] In Zambia, HPV 52, 53, and 58 were more common overall than 16 and 18.[40] In Cameroon, the most common potentially/probably HR was the 45 and 58 subtypes.[12] In Mozambique, HPV 16 and 18 were found in 47.0 and 31.3% respectively of cervical cancers.[41] Nevertheless, since 71% of African cervical cancers, and 68% Central and South American carry HPV 16/18, two-thirds of cervical cancers could be prevented if the local conditions for vaccination are met.[26,42] 6/18 emphasized by Clifford *et al*.,[26] HPV-positive women in Europe are significantly more likely to be infected with HPV16 than those in SSA. Muñoz *et al*.[35] emphasized that a higher than average proportion of HPV 45 was found in SSA. The quadrivalent vaccine prevents HPV 6, 11, 16, and 18 infections; the bivalent vaccine is geared at the 16 and 18 subtypes. It appears thus that they could not be as beneficial as anticipated in the prevention of cervical cancer in the developing world, and perhaps elsewhere.[42-44] For these reasons, researchers have investigated the possibility of cross-reactivity of the existing vaccines, namely the appearance of immunity against non-16/18 subtypes.[31,45] Although, there appears to be some degree of cross-reactivity against non-16/18 subtypes, the protection of the vaccine against infection is mainly type-specific.[35,46,47] Although, some cross-protection (measured by the level of antibodies) does appear, especially, against subtypes 31, 33, and 45, it happens only in around half of the vaccinated subjects and more with the bivalent than the quadrivalent vaccine.[48] This remains speculative since the minimum protective threshold of antibodies for disease protection is still unknown.[49]

Natural History of HPV Infection in Males

Like in women, most infections in males are asymptomatic, and the most commonly found subtypes are the HR-HPV 16, and the LR-HPV 6 and 11.[50-55] In heterosexual asymptomatic sexually active men, the prevalence of HR-HPV, mainly the 16 subtype, vary between 2.3 and 72.9%, with an estimated average of 20%.[52] A recent study reported that 30% of men carry HR-HPV, and 38 LR-HPV. The median duration of any HPV infection was 7.5 months, and 12.2 months for HPV 16. The clearance of oncogenic HPV was inversely proportional to the number of life-time female partners; as opposed to women, the clearance was faster with increasing age.[50]

Penile HPV infection increases with the increasing number of sexual partners and with the number of sex workers partners.[16] The risk of cervical cancer in the female partner of men positive for HPV is increased as compared with women without cervical cancer.[52] More than half of husbands of women with pre-invasive and invasive cervical cancer are carriers of HPV.[56] Of concern is the fact that, in one study, the quadrivalent vaccine targeted-HPVs 6, 11, 16, and 18 constituted only 10% of the transmitted types in heterosexual monogamous couples.[50-55] Another study of genital HPV infection in men found that half carried one or more HPV subtypes, mainly 16, 51, 52, and 59.[53] The latest centers for disease control/American college for immunization recommendation is the routine use of quadrivalent vaccine in males aged 11 or 12 years.[56]

Anti-HPV Vaccination of Males

It has been claimed that since the distribution of HPV subtypes is similar in both sexes, the same vaccine should achieve the same prevention in both sexes.[51] None the less, although some vaccine trials in boys are under way, there seems to be little enthusiasm to promote vaccination of those who play a significant role in the transmission of the virus to their male or female sexual partners. The arguments raised against the vaccination of boys vary from waste of resources to "boys have no uterus." The counter-arguments would be that if boys had no penis women would not suffer from cervical cancer, and that it makes equal sense to mass vaccinate boys rather than girls.

Limits of Anti-HPV Vaccination

The primary endpoint of the HPV vaccine trials is to determine the combined incidence of HPV infection and the occurrence of a pre-invasive lesion in HPV-naive young female participants of less than 27 years of age; the secondary end-point (also called intention-to-treat population) is to assess the occurrence of such lesions in participants already infected at the time of vaccination but who have no history of genital warts, and to measure vaccine-induced antibody titres and the reduced incidence of persistent infection.[57] Follow-up studies claim an efficacy in excess of 90%. It remains unknown for how long the effect will last or whether boosters will be necessary. What is surprising is that, despite the well-known fact that ano-genital wart and cervical pre-invasive lesions may take many years to develop, currently available and reported follow-up times after vaccination vary between two and a maximum of 8 years (i.e., the time of first approval in 2006). It is well-known

that the average time from infection with a carcinogenic HPV to invasive cancer, if it occurs, is 25-30 years or more.[58] By the time a HR-HPV infection has persisted for approximately two or more years, an associated risk (not an actual lesion) is noted.[59] It takes 5-7 years between the infection and the first occurrence of a pre-invasive lesion.[59] It would be reasonable to conclude only on the appearance and levels of antibodies; and even that neither is no prove of a protective effect since the minimum threshold of immunity from disease is unknown.[20,60] To claim that the vaccine prevented the occurrence of lesions after follow-up of only a few years seems misleading at best. If that were the case, there would be no need to pursue cytological screening as widely advocated.[61]

It is important to bear in mind that all the studies are sponsored and run under the auspices of the vaccines' manufacturers. Another concern is the possibility of the emergence of serotypes not contained in the bivalent and quadrivalent vaccines. This is already the case with invasive pneumococcal non-vaccine serotypes.[62,63] What happens if other strains of HPV replace strains 16 or 18 after vaccination by the current vaccines? Will the replacement viruses cause less or more disease?[64] In addition, it has been suggested that if a woman who has previously contracted HPV 6, 11, 16, and/or 18 is vaccinated against them, her chances of getting cervical cancer might increase.[65]

Challenges for the Developing World

Systematic Papanicolaou cytological (Pap smear) population screening to detect pre-invasive lesions has drastically reduced the incidence of cervical cancer in the developed world. Screening can only be effective if there is a well-organized system of follow-up, diagnosis and treatment.[66] For many reasons, such as insufficient education, availability of trained personnel, follow-up and referral systems, and cost, the burden of cervical cancer has not decreased in the developing world. This explains the huge discrepancy in the incidence of cervical cancer between the two worlds. In addition, health-care budget allocation in the developing world has to make difficult choices between competing priorities, mainly infectious diseases like malaria, tuberculosis, HIV/AIDS, air-borne, and water-borne infections.

At the current cost of US$ 360 for a course of vaccine (bi- or quadrivalent), mass vaccination is unaffordable in the developing world, and raises questions even in the developed world. Efforts to decrease the cost for the developing world are laudable, but they miss the point. The real point concerning the developing world is that the existing vaccines aimed at HPV subtypes that are less prevalent in the developing than in the developed world would not reduce the cervical cancer related morbidity and mortality to expectation. Ample evidence shows that the spectrum of HPV subtypes involved in the genesis of pre-invasive and invasive cervical lesions differs between the developing and the developed world. In addition, nothing is known about the risks and benefits of the vaccine for HIV-infected women who represent a significant proportion of subjects at cervical cancer risk. Furthermore, in view of the relatively short follow-ups, the duration of immunity is unknown. The risk of the emergence of non-vaccine subtypes responsible for cervical lesions is well documented (68). To engage in mass vaccination campaigns with limited budgets, problematic sufficient coverage and follow-up could be unwarranted. Furthermore, it is widely accepted that any cervical cancer prevention program requires: (1) To achieve high coverage of the population at risk; (2) to screen with an accurate test as part of high-quality services; and (3) proper management of positive findings. Unfortunately, none of these are met in the developing world. The challenges to ensuring the successful control of cervical cancer include affordable prices, education at all levels, and adherence to screening programs.[64] The worldwide coverage of the six key childhood vaccinations is around 75%; in some developing countries it may be as little as 30%.[64]

Although, the implementation of the HPV program in the developing world has increased the awareness about HPV and cervical cancer, knowledge continues to be limited.[66,67] HPV vaccine would be the primary prevention; secondary prevention through properly organized screening programs, is a pre-requisite of national immunization programs.[66] This also requires sufficient public awareness and understanding of what the vaccine is aimed at.[69-71] Further, as recommended by the WHO, the implementation should be tailor-made. Finally, many questions remain unanswered in the developing world, especially where HIV/AIDS is highly prevalent, such as the vaccine safety and efficacy.

Conclusion

It is our view that pharmaceutical companies have a moral duty to be honest and transparent. The promotion of anti-HPV vaccines is largely based on surveys sponsored by the manufacturers. To claim that the occurrence of HPV-induced ano-genital lesions decreased significantly after a vaccination time of a few years is scientifically unsound. The only justifiable claim would be that the antibody titres rose significantly after a given period of time. However, still we are talking about antibodies against the specific HPV subtypes of the vaccines, and not those involved in ano-genital lesions in the developing world. It is commendable to develop a vaccine that would prevent morbidity and mortality in the developed world. Although, this paper is not aiming at an ethical analysis of HPV vaccine marketing, potentially or actually misleading incentives are to be avoided. It is quite clear that a large proportion of the clinical trials were sponsored by the manufacturers. What is wrong is to market it for a part of the world where it would be of limited benefit, if any at all, and hard to implement in view of the local financial and programmatic constraints. Many queries such as the duration of protection, the

possible need for booster injection, the spectrum of subtype cross-protection, the emergence of non-16/18 oncogenic subtypes, and vaccine-resistance remain unanswered. The intention of this paper was to provide a note of caution with regard to the appropriateness of HPV vaccine campaigns in settings that differ in many aspects from the developing world.

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