Vaccine Strategies against Human Papillomavirus: A Discussion Focused on Developing Countries

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Abstract

Cervical cancer is the second most common form of cancer among women, and responsible for 274,000 deaths each year, most of which occur in developing countries. Persistent infection with high-risk human papillomavirus (HR-HPV) is an essential factor in the development of cervical cancer and also a contributory factor in other types of cancer. The current prophylactic HPV vaccines provide protection against the -16 and -18 genotypes which are most commonly associated with cervical cancer worldwide. However, the increased costs of these vaccines inhibit their implementation in developing countries, affecting their viability. Moreover, a therapeutic vaccine is needed for women who are already infected by HPV and/or affected by HPV-related cancer. A number of innovative approaches to combat and treat HPV infection are currently being studied and some of these will be considered in this work, together with the development of new vaccines, especially in seriously affected areas located in developing countries. At the same time, there will be a discussion of the issues involved in carrying out effective HPV vaccination programs; these will take account of financial constraints, the lack of adequate infrastructure and the competing priorities, that are found in the surrounding social context of the developing countries.

Keywords: Human papillomavirus; Cervical cancer; Prophylactic vaccines; Therapeutic vaccines; HPV vaccination

Introduction

Every year about 500,000 women develop cervical cancer and 274,000 die from this disease throughout the world, resulting in a mortality rate of approximately 35% [1-4]. Over 80% of these deaths occur in developing countries [4,5]. Worldwide, cervical cancer affects around 1.4 million women, and the highest incidence rates are found in Africa and Latin America, while India has the largest number of cases (20%) [4]. While among developed countries the 5-years patient survival rate ranges from 51% to 66%, in developing countries, where cases only tend to be diagnosed in a relatively advanced stage, this survival rate is about 40%. The world average is estimated as being 49% [3].

According to World Health Organization (WHO), persistent infection by Human Papillomavirus (HPV) is the main risk factor for developing cervical cancer [6]. The relationship between cervical cancer and HPV infection has been established by epidemiological and functional studies [7,8], in which the virus was detected in more than 99.7% of squamous cell carcinoma [9,10] and in 94-100% of cervical adenocarcinoma and adenosquamous carcinoma [11,12]. However, it takes several years for the cervical cancer to become established. At least 15 oncogenic HPV types have been identified as high-risk (HR-HPV), among which -16 and -18 genotypes are detected in more than 70% of all cases of cervical cancer [13]. The monitoring of the uterine cervix and removal of premalignant lesions can result in significant decline in the mortality rates reported worldwide. Apart from skin cancer, cervical cancer shows the greatest scope for prevention and cure when diagnosed early [3].

It should be mentioned here that screening programs are necessary to ensure that cervical cancer is prevented to a satisfactory degree, but in developing countries these programs are performed in precarious manner. Prophylactic vaccination is a potential means of supplementing the screening programs, and helping to reduce the burden of cervical cancer by preventing HPV infection [14]. The search for preventive vaccines against HPV infection has been the object of studies for several decades [15]. Although the production of inactivated or attenuated HPV virions on a large scale is difficult to reproduce in vitro, because the productive life-cycle is dependent on epithelial differentiation [16,17], the emergence of new technologies has intensified the development of these vaccines [18]. The HPV prophylactic vaccines already licensed are based on these methodologies.

Since a large number of people are already infected with HPV, and current treatments have a low rate of effectiveness, a therapeutic approach is needed to treat patients with advanced lesions. Therapeutic HPV vaccines form a part of more recent studies, and are still undergoing preclinical testing and clinical studies [19].

The aim of this paper is to review the current status of vaccines that are being evaluated for HPV infection and hence for cervical cancer. These innovative technologies to combat infection are argued, especially given the challenges posed to its availability in developing countries. Finally, we focus on the need to discuss the importance of implementing an effective program involving currently licensed vaccines against HPV for the control of cervical cancer and other HPV-related cancers in developing countries and the poorest regions of the world.

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The Current Situation with Regard to Prophylactic HPV Vaccines

Principles and current formulations

About 120 HPV genotypes have been identified and more than 15 have been shown to induce tumors that can progress to carcinomas [20]. In particular, 53.5%, 17.2% and 6.7% of cervical cancer cases worldwide are attributed to HPV -16, -18 and -45 respectively. The remaining 12 oncogenic genotypes (31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73 and -82, in descending order of importance) cause 30% of all the cases of cervical cancer [18].

At present, there are two licensed preventive vaccines against HPV, both composed of macromolecular structures formed by the L1 subunits, called virus-like particles (VLPs), which are morphologically similar to the virion. These current HPV vaccines comprise Gardasil® from Merck & Co., Inc. [21], composed of four VLP types (HPV-6, -11, -16, and -18), and Cervarix® from GlaxoSmithKline, UK. [22], which is bivalent and combines two VLP types (HPV-16 and -18). The need to produce multivalent vaccines is attributed to type-specific conformational (nonlinear) epitopes, which result in a greater binding immune response, which is due to the L1 immunodominant epitopes that are located in the hypervariable regions of the loops that compose the protein [23]. In addition, neutralizing antibodies recognize conformational (nonlinear) epitopes, which result in a greater binding specificity [24]. Nevertheless, weak cross-reactivity is observed with other HPV types, leading to certain protective effects [25,26].

According to reports from the major phase III trials, the vaccines prevent from 97 to 98% of infections caused by HPV-16 and -18 [27]. Investigators from the FUTURE (Females United to Unilaterally Reduce Ecto/Endocervical Disease) II study found a 98% protection rate after a 3-year follow-up period. Gardasil® is recommended for 11-12 year old girls (who are expected not to have been sexually exposed) [28]. Females in the age range of 9-26 years may also be vaccinated and, recently, vaccination has been shown to be efficacious in women in the age range of 24-45 years who have not already been infected with the relevant HPV types. Cervarix®, on the other hand, is licensed for use among women up to 45 years old in Australia and an immunogenicity study showed 100% seroconversion in women up to the age of 55 [28]. Despite the efficacy that has been observed, the exact duration of antibody protection is unknown, although the longest follow up study so far has shown high antibody levels up to 7.3 years after vaccination with Cervarix® [28].

Attempts to develop alternatives for prophylactic HPV vaccines

Perhaps, the most serious concern about the licensed prophylactic vaccines is their high cost (up to $120 per dose, and 3 doses are required), which makes it difficult for them to be widely available in developing countries, where the vast majority of cervical cancer cases occur [29]. In view of this, several attempts have been made to establish other biotechnological HPV VLP production platforms that can fill the gap that exists in the demand and supply [30]. These measures can reduce the price of currently licensed vaccines, and increase their global penetration [30].

The VLPs can be obtained through the production of L1 protein in heterologous expression systems using mammalian cells [31], plants [32], bacteria [33], insects [34] and yeasts [24]. Both the bivalent and quadrivalent HPV vaccines contain VLPs produced from insect cells (Trichoplusia ni Hi5 infected with recombinant baculovirus) or Saccharomyces cerevisiae yeast, respectively. Since 2007, several investigators have reported the expression and purification of HPV L1 protein in Pichia pastoris, and characterized the system as a potential vaccine platform in view of its low cost and the high levels of recombinant protein expression reported in the last 15 years [35]. In a similar way, our research group has been working with the HPV -16, -18 and -33 L1 expression in P. pastoris [36,37].

All these studies in the Pichia system employ commercial vectors and exploit the potential of the AOX1 inducible promoter, with a wide range of expression results. In 2005, de Almeida and colleagues [38] isolated and characterized the P. pastoris constitutive PGK1 promoter, which showed higher expression levels than the AOX1 promoter. Currently, our group has been working on the expression of HPV proteins by employing a non-commercial vector based on this constitutive promoter and the partial results are promising (unpublished data). The main distinguishing feature of this work involves the use of a non-commercial vector and an alternative expression system to those already being employed or that adopted by Merck and GlaxoSmithKline. This avoids the payment of royalties tied to the use of commercial vectors and allows the possibility of making a patent application and thus, having exclusive rights for use in the future production of HPV vaccines.

The role of universities is essential in the production of medicines and vaccines and their participation has been critical in providing the basis for the creation of HPV vaccines [39-41]. The main problem is that, in the past, every public research entity involved in the initial development of these vaccines obtained licenses for the exclusive commercial use of this technology, and this has created a major obstacle to laboratories in developing countries that seek to draw on the new technology. Additionally, all of the business partners involved were based in the developed world [42]. This meant that there was little incentive to develop vaccine for low-cost sale in developing countries.

Technology transfer mechanisms are essential to ensure low-cost access to these new vaccines in developing countries, as well as for the funding of research by foundations with adequate resources. One study of manufacturers in developing country found that there were various arrangements between multi-national corporations (MNCs) and academic research institutions [42]. In the case of Indian and Brazilian vaccine manufacturers, this reliance on technology transfer allows a greater freedom to operate and more equitable benefits. These Indian and Brazilian vaccine manufacturers found that, on average 28 percent of new antigens were being produced, either by in-house research activities or by technology transfer [42].

With regard to this, the financial support by the Bill & Melinda Gates Foundation for the development of a new generation of HPV vaccines is also very important. Public institutions are taking the lead in developing these vaccines and among the participating research institutes is the Ludwig Cancer Center in Brazil [43].

A Pan-HPV vaccine

Another drawback of the available vaccines against HPV is their failure to provide protection against other carcinogenic genotypes which account for about 30% of cervical cancer cases reported worldwide. In addition, the prevalence of HR-HPV [44] is subject to geographical variation, which is the case, for example, in Brazil. Although there are no clear statistics on the prevalence of HPV infection in the sexually-active population in various states and regions, several studies confirm the high prevalence of HPV-16 in all Brazilian regions,
whereas in the case of the second most relevant HPV type, the degree of incidence differs in each region. For example, HPV-31 and -33 are more commonly found than -18 in the Northeast and Midwest regions, while in the North, South and Southeast regions, HPV-18 appears as the second most prevalent type [45-48]. This clearly shows that there is a need to develop a second generation of prophylactic vaccines against HPV, with a larger spectrum of action [49].

As well as the L1 protein, which is the main structural unit of the viral capsid, the PVs have another capsid protein called L2. This contains an N-terminal region that was found to be conserved among the HPV genotypes, and suggests that there is a potential peptide that can cause a cross-immune reaction. In confirmation of this, animals immunized with the HPV L2 protein produced neutralizing antibodies for a broad HPV spectrum [50,51]. This observation contrasts sharply with the type-specific protection induced by L1 and suggests the possibility of a simple pan-HPV prophylactic vaccine, based on the L2 protein [49,52,53].

However, some caveats must be noted. The neutralizing antibody titers produced by vaccination with L2 are much lower than those produced by vaccination with L1 VLPs. Since VLPs, as well as natural immunogens, have proved to be efficient carriers of peptides, DNA and small molecules to dendritic cells [52], some researchers have produced VLPs based on both L1 and L2 proteins to increase the immunogenicity of L2 and extend protection to more genotypes. Unfortunately, the immunogenicity of L2 is subdominant to L1 and, in the context of an L1/L2 VLP or even in serological studies of natural infection; the neutralizing antibodies are produced almost exclusively against the L1 protein [54].

In 2010, Jagu and colleagues [53] evaluated different vaccine formulations with L2 polyepitides (different HPV fused neutralizing epitopes) in animals. In accordance with the findings of the authors, the formulations containing L2 polyepitides with L1 capsomeres were found to be the vaccine with the highest potential. This may be an inexpensive strategy, because lowered the production costs of the vaccine by employing a system based on Escherichia coli, to expand the immunity against HPV. However, the L2-based prophylactic vaccines have not been tested on patients and when providing protection, it was unclear how long this immunity would last [53].

**Therapeutic Vaccine Against Cervical Cancer**

A vaccine for the prevention of cervical cancer is very important in public health. However, women (an estimated figure of 5 million) are already infected by HPV and several of them will develop invasive cervical cancer [54]. The two HPV vaccines currently in use cannot be effective if a patient has been infected by the virus. Therefore, there have been a large number of studies aimed at enhancing the DNA vaccine by using a non-specific immune response. The results of the tests carried out with patients who had high-grade CIN-2 lesions were successful in young women (under 25) than in those who received placebo doses [79,80]. Another example of DNA vaccine, called Sig/E7detox/HSP70, was administered in Phase I clinical trials. This vaccine encodes a signal sequence, fused to an E7 mutated form (E7detox) for loss of affinity for pRB, which in turn is fused to heat shock protein (HSP70). The results of the tests carried out with patients who had high-grade CIN-2 lesions showed an E7-specific immune response of cytotoxic cells (CD8+ T), with no adverse effects. A lesion regression was observed in 3 of the 9 vaccinated patients [81].

The E5-based therapeutic vaccines also hold out good prospects. An adenovirus vector (AdV) carrying an E5 gene has been tested in mice with an E5-expressing tumoral cell line (TC-1/E5) and showed a reduction of the tumor [82]. Another vaccine, which comprises a potential Db-restricted CTL peptide of the HPV-16 E5 gene fused to CpG motifs (DNA sequences found in bacteria and used as vaccine adjuvant) showed better results than the previous recombinant adenovirus vaccine (rAd-E5) [83,84]. These studies show that E5 is recognized by the immune system as a tumor antigen and supports the hypothesis that this oncogene is a good candidate for the eradication
of premalignant lesions, since this viral protein is more active in the early stages of cervical cancer [85,86]. Following this line of argument, our group has been working on a therapeutic strategy based on genetic immunization with the HPV-16 E5 gene (unpublished data).

The Impact of HPV Vaccination on Developing Countries

Over 80% of new cases of cervical cancer diagnosed each year occur in developing countries and it is estimated that this percentage will rise to 90% by 2020 [4]. In developing world, cervical cancer is the biggest single cause of years of life lost from cancer, because affects relatively young women. The 5-year survival rate of patients observed in these countries is less than 50%, while in developed countries it reaches 66% [87].

According to the American Cancer Society, the introduction of Pap smear screening in prevention programs in the United States reduced deaths from cervical cancer by almost 75% between 1955 and 1992 [88]. Similarly, the incidence of cervical cancer and mortality rates sharply declined in Europe (particularly in Nordic countries) and Canada due to the implementation of cervical cytology in health care, most notably in population-based screening programs [27]. The establishment of cervical cancer trial programs requires a large number of well-trained professionals and persistent public funding to support the requisite infrastructure [30,89]. The cytology-based cervical screening needs to be conducted regularly and systematically using an organized approach, with quality systems ensuring sufficient uptake, laboratory services and continuous improvement, in order to have substantial impact [90]. Unfortunately, the developing countries have experienced great difficulty in doing this in a satisfactory manner.

In the developing countries (and even in some developed or middle-income countries), the situation in rural areas can cause people great difficulty in gaining access to the health services. The accessibility of health services in these areas is far too low to guarantee desired impact overall [27]. At the same time, it should be noted that the conventional methods of detection, such as Pap smears and liquid based cytology, have been found to yield contradictory results. In a clinically-controlled study, Clavel and colleagues [91] conducted tests based cytology, have been found to yield contradictory results. In a clinically-controlled study, Clavel and colleagues [91] conducted tests that showed sensitivity of 68% and 88%, respectively, for HSIL. In view of this, it is essential to test for DNA hybridization of HR-HPV, as a supplementary test for women over 30 years old and in cases of dubious Papanicolaous test (atypical squamous cells of undetermined significance, ASCUS) [92], although this inflate even more the cost of the procedure.

The HPV vaccines provide different means of prevention, and theoretically, they are more practical in the poorest areas, because they make it easier to control cervical cancer [90]. Since 2007, there have been two prophylactic vaccines against HPV. Both have the potential to prevent 70% of cases of cervical cancer and 90% of genital warts in the next 10-20 years [93]. In a shorter period (5-10 years), it is estimated that the implementation of an effective HR-HPV vaccination program can prevent 30% of the infections caused by these virus types, as well as 40-50% of cytological abnormalities and 50-60% of HSIL [93]. Some mathematical models suggest that it would take 40-60 years of vaccination to see significant reductions in all HPV-related diseases worldwide, including non-genital disease [94]. However, the introduction of prophylactic vaccines in mass vaccination programs by developing countries is impracticable due to their high cost. As a result, the expected impact of these vaccines on the reduction of cervical cancer will not be achieved if current economic conditions persist.

Another key issue is the choice of a target group for vaccination. First, it should be noted that the success of vaccination (or even a screening program) partly depends on the decision made by the objects of the intervention or other parties (such as parents, other family members, leaders of communities). In particular cases of HPV, attitudes toward vaccination tend to be more positive among people who have more information about the vaccine, and the causal link between HPV and cancer. People with a low social status in developing countries, living in the rural regions, are the least well off in the case of HPV-related diseases [27]. Although some experts regard HPV vaccination as a prevention strategy in low-income areas, a campaign to heighten awareness among the people is needed by the authorities to ensure it is provides effective coverage.

With regard to the specific case of HPV vaccination, with a strait window of applicability (before sexual debut), it is advisable to decide early on if the vaccine will be offered only to females or to both sexes. Additionally, delivering HPV vaccines effectively in primary prevention programs raises various issues and challenges, ranging from financial constraints regarding access to questions of cultural or religious acceptability, unlike those faced by other routine childhood vaccination programs [27,90].

While the average age of “sexual debut” differs across populations, most countries recommend primary HPV vaccination between the ages of 10 and 14. Several studies have shown that there is an increased immune response with high antibody titers during pre-puberty, compared to post-puberty [90]. Nevertheless, the vaccination of adolescents in some regions of the world raises moral, social, religious and ethical questions, such as in India, where pre-marital sex is socially unacceptable [95]. In that country, cervical cancer cases comprise 25% of cases worldwide and the implementation of these vaccines against HPV could reduce the incidence of cervical cancer by 60-100% [92]. However, a preliminary survey carried out with the parents of 9-16 year old girls showed that most of them believe that these vaccines could encourage early sex and promiscuity, which is disapproved in India. This could cause social stigmatizing and undermine the family’s prestige [95].

Other fundamental questions about the provision of vaccines to pre-adolescent/adolescent girls entail concerns about how best to access this group. Since routine vaccination of pre-adolescents and adolescents is less common than infant vaccination in developing countries, the health care provision of this group is generally less structured. While the delivery of public health interventions (including immunization) to this age group in many developed countries occurs most effectively through school-based services, developing countries often lacks any infrastructure or experience in school-based delivery vaccine [90]. Possible strategies to reach adolescent girls in school-based approaches are contracting out non-government organizations or the inclusion of the private sector. PATH (Program for Appropriate Technology in Health) is leading HPV vaccine implementation schemes in four countries – India, Vietnam, Uganda and Peru – and shows that a high coverage has been achieved, between 80 and 95% [90,96].
On the other hand, although boys cannot develop cervical cancer, they can be infected by HPV and suffer from other diseases related to the virus, such as anogenital and oropharyngeal cancers. Vaccinating males is currently not recommended by the WHO, but some experts believe that the impact of herd immunity on female cancers and other HPV-related cancers may need to be reconsidered. The cost benefits of vaccinating both sexes are still under investigation and there is evidence that the vaccination of males with the quadrivalent vaccine reduces the risk of HPV transmission to their partners, as well as the HPV-6/11-associated disease burden [27,97,98].

**Type replacement**

There has also been much discussion about the potential risk of new oncogenic genotypes emerging from the introduction of vaccination programs based on currently licensed vaccines. Previously work reported the increased risk of acquiring co-infections over time [99]. The herd immunity and resulting reduction in the prevalence of HPV-16 and -18 could create the required ecological niche for type replacement, and give to the HR-HPV non-targeted by the vaccines a competitive advantage over those two types [99]. Women who are vaccinated, in the belief that they are protected against all types of HPV, could adopt a high-risk sexual behavior and be at risk of infection by oncogenic genotypes, besides the HPV-16 and -18.

Data recently published by our group [48] suggest that, in Pernambuco (Brazil), while HPV-31 (15.49%) shows a much higher incidence than HPV-18 (2.82%), which has the same incidence as HPV-33, there was also a high percentage of concurrent infections between HPV-16/-31 (70.67%) and between HPV-16/-33 (18.66%). In addition, among women infected with HPV-31, there was a greater frequency of HSIL when compared with low-grade lesions, contrary to what was observed in women infected with HPV-16. Finally, it was observed that when the HPV-16 infection was combined with HPV-31, the lesions tended to be more severe. Thus, these results suggest that the vaccines currently available cannot meet the requirements of different populations such as those of Pernambuco (Brazil). Some studies have found that the bivalent vaccine provides little protection against HPV-31 and -33, but nothing can be inferred about its effectiveness when it is observed that these genotypes are, at least, as prevalent as those that it covers [48]. These vaccines could further allow the spread of other oncogenic genotypes, which in certain populations assume a more malignant form, as seems to be the case with HPV-31 in the population of Pernambuco (Brazil).

**Some aspects of the Brazilian experience**

The screening programs for the prevention of cervical cancer are widely available and the self-reported healthcare coverage by the Pap test is generally suited to the conditions in Brazil. The decline in the incidences of mortality attributable to cervical cancer in the last two decades has run parallel with an improvement in the screening practices, which were introduced in the 1980s and has been refined since 1998 [100-102]. From 2003 to 2008, the frequency rate of women between 25 and 59 years old who reported having had at least one Pap test in the previous three years, rose from 25% to 84.6% [101], despite the fact that there are wide variations in levels of income. However, in the rural areas of North and Northeast regions (areas with restricted access to screening programs), mortality rates are still rising. Overall, the incidence of cervical cancer is still very high, with rates close to those countries with the highest incidence, like Peru and some African countries [101,102].

In Brazil, the National Immunization Program has been very successful and achieved the highest immunization coverage rates in the world, without the need to resort to coercive strategies. All the vaccines are offered free of charge at the public health centers. This is largely due to the existence of centenary research centers, such as Adolfo Lutz Institute, Bio-Manguinhos and Butantan Institute, which produce most of the vaccines offered by the SUS (The Brazilian Unified Health System) [103]. The HPV vaccines, in contrast, are only available in private clinics, but recent public-private partnerships have increased the supply by offering large discounts to low-income and middle-income patients, with medical care provided by charity institutions that form part of the Holy House of Mercy Fraternity [103].

Although a constant improvement in screening programs is being made by the Brazilian authorities, in a desire to increase social equity, the number of women infected by HPV and with cervical lesions remains high [102]. Added to this is the fact that Brazil has one of the highest incidences of penile cancer in the world, especially in less developed regions of the country [104]. This situation is untenable and the Brazilian Ministry of Health has fostered the development of therapeutic strategies for HPV vaccines aimed at national needs. Apart from the fact that DNA vaccines have been showing promising results for immunotherapy, their application has an advantage, especially for developing countries, since this approach is cost-effective and simple to produce in large quantities, while at the same time, it can be distributed in poor areas of difficult access, due to the stability of DNA even in high temperatures [66,67]. Running with this, alternative prophylactic vaccines are being undertaken and take account the relevant HPV type that is prevalent in Brazil.

**Conclusion and New Perspectives**

The training of technical and scientific competence in the development of vaccines with the aid of advanced technologies, particularly those involving genetic engineering, is essential for the control of HPV infection and cervical cancer. As a preventive vaccine for cancer, there is community demand for the vaccine in many countries. To what extend decision-makers perceive and are able to respond to this demand will vary depending on competing priorities, available resources and how health-care decisions are made in particular countries [90]. While many governments, together with international health organizations and pharmaceutical companies, are urgently attempting to cooperate and increase the accessibility of the HPV vaccines that are currently available [92], great attempts have been made in many developing countries to establish alternative vaccine platforms, which not only increase competition and help drive down costs, but also enable them to bridge the demand and supply gap [30]. Researchers in South Africa, Brazil, China and India have experienced different expression systems with promising results for a second generation of prophylactic vaccines based on VLPs. The Brazilian Ministry of Health, which has an extensive National Immunization Program [105], estimates that U.S.$ 1.857 billion will be necessary to pay for vaccinating 11-12 year-old girls with the quadrivalent HPV vaccine, in addition to the $750 million currently being invested in the program. For countries with a gross domestic product of less than $1000 per capita, the cost of the HPV vaccine will not be cost-effective unless it is as low as $1 to $2 [106]. Each 5-year delay in establishing a global vaccination program against HPV can lead to the deaths of 1.5 to 2 million people in developing countries due to cervical cancer [107]. In view of this, the search for strategies to reduce the cost of HPV vaccination should become a priority.
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