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REVIEW ARTICLE

Human papilloma virus (HPV) vaccination in childhood: challenges and perspectives

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Abstract
Vaccination against human papilloma virus (HPV) in childhood is a significant step forward in the reduction of HPV-associated morbidity and mortality and a considerable scientific achievement. However, many challenges remain to be overcome if an effective HPV vaccine programme is to be successfully introduced worldwide. The aim of this review is to identify and summarize the new issues concerning HPV vaccination that have emerged since its introduction into clinical practice in school-aged girls. According to the literature, the overall impact of HPV vaccination on cervical cancer is unlikely to be apparent for the next decade. Cost-effectiveness is of particular importance, particularly in developing countries. Determining the age at which the vaccine should be administered, whether to include boys in addition to girls, the costs and the implications for cervical screening are issues that need to be addressed by conducting further research. Hippokratia 2011; 15 (4): 299-303

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Human papilloma viruses (HPVs) are small double-stranded DNA viruses that comprise a remarkably heterogeneous family of more than 130 types[1]. Different HPV types can cause a wide range of infections, including common warts, genital warts, recurrent respiratory papillomatosis, low- and high-grade squamous intraepithelial lesions (SILs) and cervical cancer. 'High-risk' HPV types (Table 1) have been implicated in the development of intraepithelial lesions (SILs) and the progression to cervical cancer[1-3]. HPV types 16 and 18 are considered to be the most common 'high-risk' HPV types worldwide, and are responsible for approximately 70% of all cervical cancer cases[4-6]. 'Low-risk' HPV types have been associated with benign warts of urogenital epithelium in adults and children and are rarely found in malignant tumours. Different HPV types vary in tissue distribution, oncogenic potential and association with anatomically and histologically distinct diseases.

HPV vaccines are bioengineered, component vaccines comprising virus-like particles produced from the surface proteins of HPVs. Two vaccines have been recently evaluated in randomized controlled trials: the bivalent vaccine for HPV 16 and 18 (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) and the quadrivalent vaccine for HPV 6, 11, 16, and 18 (Gardasil; Merck and Co, Inc, Whitehouse Station, NJ). Currently, these two HPV vaccines have been approved by the US Food and Drug Administration as well as by the European Union, and several countries have already introduced vaccination programmes to school-aged girls[7,8]. For example, in the United Kingdom, vaccination against HPV was introduced in September 2008 and included girls aged 12-13 years. A catch-up programme was initiated in Autumn 2009 and ran for two years. According to this programme, girls aged 16-18 years were offered the vaccine from Autumn 2009, while girls aged 15-17 years were offered the vaccine from Autumn 2010. By the end of this catch-up campaign, all girls under the age of 18 years will have been offered the HPV vaccine. In this article, we summarize the new issues (Table 2) concerning HPV vaccination raised since its introduction into clinical practice in childhood.

Prophylactic efficacy

Clinical trials have proven the prophylactic efficacy of the human papillomavirus (HPV) quadrivalent vaccine for HPV types 6, 11, 16 and 18 in preventing low grade cervical intraepithelial neoplasia[9,10]. It has been shown that the quadrivalent vaccine is highly immunogenic, safe and well-tolerated in females aged 9-26 years of age and its efficacy remains high for at least 5 years following vaccination[9]. Similar results have been demonstrated in clinical trials investigating the efficacy and immunogenicity of the bivalent vaccine[11, 12]. However, the evaluation of the efficacy of both HPV vaccines did not considered cervical cancer as the end-point. Persistent HPV infection can cause cervical squamous intraepithelial lesions (SILs) which in turn, serve as a forerunner of invasive squamous cervical carcinoma (SCC). This progression to cancer is a relatively rare consequence of infec-

tion and may take up to 20 years. Recent data indicate that persistent 'high-risk' HPV infection represents a significantly increased risk of developing high-grade SIL and may be used as a surrogate endpoint of progressive SILs[13]. However, this means that ongoing clinical trials need more time to prove beyond doubt that the HPV vaccines actually prevent cervical cancer. Moreover, the duration of protection that can be achieved with the current vaccines remains to be elucidated. Protection needs to be long-lived to have a significant impact on cervical cancer prevention in the population. The overall impact of HPV vaccination on cervical cancer will, however, not be noted during this decade[14].

Therapeutic efficacy

Current HPV vaccines have demonstrated efficacy in prophylaxis but suffer from a lack of evidence of therapeutic potential in women with high-grade cervical intraepithelial neoplasia[15]. Therapeutic cervical cancer vaccines have been extensively studied and have showed a very good safety profile[16,17]. Strategies used include vaccination with HPV peptides or proteins, alone or in pulsed dendritic cells, DNA vaccines, virus-like particles or viral and bacterial vectors. At the moment, several therapeutic HPV vaccines are in clinical development and in the majority of the studies, specific immunological and clinical responses have been noted.[17] A new generation of efficacious therapeutic vaccines for the treatment of SILs and cervical cancer should be expected in the near future.

Geographic variations

Local prevalence of specific HPV types can play an important role in the effectiveness of HPV vaccination and thus needs to be considered in the design of policies to combat HPV. Several researchers have demonstrated that the distribution of different HPV types in women with cervical neoplasia varies according to geographic region[6,18-20]. HPV 16 and 18 are considered to be the most common HPV types and are responsible for approximately 70% of all cervical cancer cases[6,19]. However, a recent meta-analysis of low-grade SILs by Clifford et al revealed that the prevalence of HPV 16 ranges from 9% in Africa to 21% in Asia, while in Europe the prevalence is 19%[18]. A similar meta-analysis of high-grade SILs showed HPV 16 to be 32% in Africa, 37% in South America, 46% in North America and 53% in Europe[19]. Among cases with cervical cancer, the prevalence of HPV 16 varies consistently with the majority of cases being found in Europe and the lowest in Africa[6]. Among low-grade SILs, the prevalence of HPV 18 has been shown to be 5.3% in Africa, 7.1% in Asia, 9.2% in North America, 3.6% in South/Central America and 5.2% in Europe[18]. Among high-grade SILs, the respective prevalences range from 6.5% in Europe to 10% in North America, while the pattern is consistent among patients with cervical cancer[19]. Among women with SILs, the frequency of non-16/18 HPV types ranges from 34% to 68%. Large meta-analyses have demonstrated considerable geographical variation in the frequency of HPV sub-types associated with both low- and high-grade SILs. A high prevalence of non-16/18 HPV types is of great importance since no vaccines are currently available for these types.

Cross-protection

Taxonomically, the distinction between the 130 subtypes of this heterogenous virus is based on differences in the nucleotide sequences of three open reading frames (E6, E7 and L1). A difference of at least 10% is required to delineate a distinct subtype[21]. Both current and future HPV vaccine candidates are HPV type-specific, conferring immunity specifically against 'high-risk' types HPV 16 and 18[22-24]. It has been shown that prophylactic use of the quadrivalent HPV virus-like particle vaccine results in a neutralizing antibody response that is HPV type-specific against types HPV 6, 11, 16 and 18[22]. However, data strongly suggest that both vaccines can have a variable level of cross-protection against HPV types, which are genetically and antigenically closely related to the vaccine types[25,26]. Notably, cross-protection following vaccination by the bivalent HPV vaccine has been extended to 'high-risk' types HPV 45, 31 and 52[23,26]. Further research on cross-protection of the current HPV L1 virus-like particle vaccines against other HPV types and long-term follow-up studies are expected to clarify the role of HPV vaccination against non-16/18 HPV types.

Cervical screening

Since HPV vaccines are not expected to prevent infection attributable to all 'high-risk' HPV types, cervical cancer-screening recommendations should continue to be followed for patients who have received the HPV vaccine[27]. Ensuring that women do not assume 'resistance' to cervical cancer once vaccinated, presents another challenge to the introduction of HPV vaccination[28]. This also implies that the cost of the HPV vaccination programme is additional to the existing costs of cervical screening[29]. Moreover, modifications to the current screening programme will have to consider the vaccination programme as well as emerging evidence regarding the impact of vaccination on cervical disease. The post-vaccination period may also present a challenge to the maintenance of skills in cytological screening incorporated in primary prevention programmes.

Age target group

To optimize the efficacy of the vaccination, it is necessary for it to be administered at an age when the greatest possible proportion of vaccinated individuals is not yet exposed to HPV. Consequently, pre-adolescent girls have thus far been considered as the primary target population for vaccination against HPV. The United States as well as several European countries have already decided to introduce vaccination programmes to girls aged 12[8]. This age has been selected since fewer adolescents of this age are likely to have been infected with HPV compared with older adolescents. However, the recent UNICEF In-

Table 1: 'High-risk' HPV types implicated in the development of cervical cancer and 'high-risk' HPV types covered by the bivalent and the quadrivalent vaccines against HPV.

'High-risk' HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
'High-risk' HPVs covered by the bivalent HPV vaccine 16, 18
'High-risk' HPVs covered by the quadrivalent HPV vaccine 16, 18

ocenti Report has highlighted different rates of sexual activity and age of first sexual contact in teenagers under the age of 15 in different countries[30]. This observation should be taken into account in the planning of vaccination programmes, perhaps necessitating the targeting of younger aged children in countries where sexual activity starts in younger age groups.

Vaccinating adolescents versus neonates

Compared to infants and young children, adolescents are less likely to obtain preventative care. Poor participation of adolescents in the vaccination programmes may lead to their under-immunization against HPV. To date, low rates of coverage have been observed both in the target and catch-up groups in several countries indicating that the cost-effectiveness of vaccination in combination with opportunistic screening or organized screening needs to be re-evaluated[31]. In contrast, introducing vaccination against HPV into neonatal schedules would assure high participation rates. It has been well demonstrated in clinical trials that vaccine administration is safe and effective in children as young as nine years of age[32]. However, no data are available for younger age groups. This limitation needs to be overcome before pre-adolescents or neonates can be considered as possible candidates for HPV vaccination.

Vaccinating both boys and girls

Many studies have highlighted the potential benefits of vaccinating males as well as females[33-36]. Genital warts caused by 'low-risk' HPV 6 and 11 infection are a very common sexually transmitted disease[33]. In contrast with 'low-risk' HPVs, infection from 'high-risk' HPV 16 and 18 is largely asymptomatic in males[34]. It has been demonstrated that in populations of a similar age, the prevalence of specific HPV types and the seroprevalence of specific anti-HPV antibodies are usually lower in men than women[34]. Whether these observations relate to lower viral load, duration or antibody responses in men compared with women has yet to be determined. The presence of HPV in men highlights their role in transmitting HPV to their sexual partners[35]. Including men in the vaccination programme against HPV can reduce the probability that a susceptible individual will come into contact with an infected partner[36]. This can suppress HPV transmission and reduce the overall burden of cervical disease in females. The current high cost of HPV vaccine, however, remains a very real obstacle to including both boys and girls in the vaccination programme.

Table 2: Challenges involving HPV vaccination since its introduction into clinical practice.

Prophylactic efficacy
Therapeutic efficacy
Geographic variations
Cross-protection
Cervical screening
Age target group
Vaccinating adolescents versus neonates
Vaccinating both boys and girls
High cost
The three doses scheme
Parental and adolescent acceptance
Developing countries

High cost

The cost of HPV vaccines is of particular importance in introducing vaccination programmes in high as well as in low-income countries[37,38]. The present cost of the HPV vaccine is approximately US$360 in the United States and 500 Euro in European countries. In countries such as the UK, with tax-funded health-care systems, HPV vaccination programmes must prove their effectiveness and efficiency if they are to receive adequate funding. Thus, the issue raised is whether insurance companies will cover the costs of vaccination in countries with insurance-based health care, and whether patients without private insurance will be able to rely on state funded programmes. Possible solutions identified include mobilizing patient demand for increased public financing of HPV vaccines. We expect future analyses of cost-effectiveness to be more instrumental in policy-making regarding vaccines covering additional HPV types, therapeutic HPV vaccines, and novel diagnostic tests for biomarkers of HPV infection and disease integrated with cervical screening programmes[39]. The new generation of HPV vaccines is expected to cost less and this may contribute to greater financial coverage of HPV vaccines by governments, particularly in developing countries.

The three doses scheme

Three doses of the HPV vaccine over a six-month period have been recommended[7]. However, the challenges of incorporating a three-dose vaccine schedule into clinical practice cannot be underestimated. Research suggests that uptake of the first dose of HPV vaccine appears to be satisfactory[9]. However, second and third doses must be administered for the vaccine to be successful in generating an adequate immune response[40]. This necessitates that adequate consideration is given to political commitment, availability of staff, access to electronic databases and that adequate funding be made available for training and education.

Parental and adolescent acceptance

Acceptance of HPV vaccination for adolescents by parents and health care providers is an important determinant of success of any HPV vaccination programme[41-43]. However, obstacles to HPV vaccine acceptance need to be overcome. These obstacles have been attributed to misunderstandings about HPV infection, cervical cancer screening and the sequelae of HPV infection[41]. The ethnic composition of the population, economic deprivation, the effectiveness of primary care and the acceptability of childhood vaccinations have been proposed as salient factors in explaining HPV vaccine uptake[42]. Education of adolescents and their parents about HPV infection and prevention of cervical cancer has to be provided by health care workers. Vaccination programmes carried out jointly in primary care and school settings would increase vaccine coverage[43]. Although it has been demonstrated that young women and parents are interested in HPV vaccines and they value the information and recommendations offered by health care providers, further effort is required.

Developing countries

HPV-related disease is very widespread and represents a vital clinical issue, particularly in developing countries[8]. However, vaccination against HPV in these countries remains a major challenge due to the high cost of the vaccines and the lack of effective vaccine delivery platforms for children and adolescents[44]. Local production options in developing countries leading to reduced prices and cheaper alternative technologies for HPV vaccine production will prove critical for their rapid introduction in developing countries.

Conclusions

The recent introduction of HPV vaccines into clinical practice in school-aged girls is definitely a significant preventative step and a considerable scientific achievement. However, many challenges and uncertainties (Table 2) have yet to be overcome and clarified if an effective HPV vaccine programme is to be successfully introduced worldwide. The overall impact of HPV vaccination on cervical cancer will not be observable for at least a decade. New therapeutic vaccines for the treatment of SILs and cervical cancer should be expected in the near future. Cost-effectiveness is of particular importance especially in developing countries. Determining the age at which the vaccine is administered, the possibility of including boys in addition to girls, as well as the integration into and maintenance of cervical screening uptake remain issues that need to be investigated; thus, more research on HPV and HPV vaccines is required.

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