A Case Study: Lessons Learned From Human Papillomavirus Vaccine Development: Approval of a Vaccine for Use in Children and Young Adolescents for Prevention of an Adult Disease

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Abstract: This article presents the adolescent clinical trials program for the quadrivalent HPV vaccine (Merck and Co, Inc, Whitehouse Station, NJ) as a case study of the development of a preventive intervention for use in young adolescents to protect against a future sexually transmitted infection and its associated diseases. In light of similarities in Human Papillomavirus (HPV) and HIV with regard to sexual transmission and the associated social and ethical issues related to prevention trial development, lessons learned from the approach taken to the inclusion of adolescents in the quadrivalent HPV vaccine program have potential relevance to future HIV prevention trials. Epidemiologic support for HPV vaccination in adolescents and a regulatory-approved approach to immunogenicity studies for bridging of efficacy from adults formed the basis for including young adolescents in the HPV program. The successful achievement of regulatory approval for use of this prophylactic intervention in young adolescents for prevention of a sexually transmitted infection that is most frequently not acquired before mid to late adolescence required understanding of the particular challenges of studying the vulnerable adolescent population with respect to issues such as federal regulations, the role of parents, confidentiality, empowerment, and retention, and awareness of the social and political context within which prevention interventions are introduced.

Key Words: adolescents, human papillomavirus, quadrivalent HPV vaccine, vaccine development

INTRODUCTION

Overview of HPV and the Quadrivalent HPV Vaccine Clinical Trials Program

The Human Papillomavirus (HPV) is responsible for virtually all cervical cancers and for a substantial percentage of vulvar and vaginal cancers in women. HPV causes penile cancers in males, and in both sexes is responsible for anal cancers and an increasing proportion of head and neck cancers. HPV is also the cause of genital warts. The HPV family consists of over 90 epitheliotropic viruses, four of which (HPV types 6, 11, 16, and 18) are together responsible for approximately 70% of cervical cancers in women and 90% of genital warts in males and females. The quadrivalent HPV vaccine (qHPV vaccine) is a prophylactic vaccine licensed in 9-year-old to 26-year-old girls and women for the prevention of cervical, vulvar, and vaginal cancers and their precursors, and genital warts. The vaccine was also recently approved in the United States for the prevention of genital warts related to HPV types 6 and 11 in 9-year-old to 26-year-old boys and men.

Unlike other vaccines, which prevent diseases that typically occur at ages more proximal to the vaccinated age group, HPV vaccination prevents disease sequelae that often occur many years later than the target age for vaccination. To study this population in the context of the clinical trials program, a basis for seeking approval for the qHPV vaccine in children as young as 9 years of age needed to be presented to and accepted by regulatory agencies. The rationale that was presented regarding the strategy of the clinical development program for the design of safety and immunogenicity studies in children and adolescents is described here.

First, it was clearly stated that to achieve maximum protection against HPV infection and subsequent disease, the vaccine must be administered to children and young adolescents before the onset of sexual activity. Supportive epidemiologic data were presented including that, in most countries, many young people begin having sexual intercourse at early ages; the median/mean age of sexual debut occurs at ages 15–16 years.1–4 Additionally, natural history studies have suggested that the first 5 years after sexual debut represent the period of highest risk for acquisition of new HPV infection.5,6 Thus, the point was made that virginal adolescents 15 years of age or younger represent the
population group that would derive the greatest benefit from a safe and effective prophylactic vaccine targeting common anogenital HPV types.

It was also explained to regulatory agencies that, although on the basis of the epidemiologic data, virginal male and female adolescents represent the ideal cohort for mass HPV vaccination campaigns, efficacy evaluations of HPV vaccines in such subjects were not feasible due to social, cultural, and legal constraints related to sexual activity among younger adolescents. A bridging approach to licensure in children and young adolescents was therefore proposed and accepted by regulators. The qHPV vaccine efficacy studies were conducted in older female and male adolescents (16 and 17 years of age), young female and male adults (18–26 years of age), and in adult women (24–45 years of age). The efficacy program was supplemented by 2 immunogenicity studies, the first of which was designed to bridge the efficacy findings in this older age group to virginal adolescents 15 years of age or younger by demonstrating that 9-year-old to 15-year-old individuals have immune responses to a 3-dose regimen of the qHPV vaccine that are non-inferior to those observed in 16-year-old to 26-year-old female and male subjects. Based on the demonstration of noninferior immune responses in 9-year to 15-year olds, efficacy in male and female subjects as young as 9 years of age was inferred; this approach formed the basis of licensure of the vaccine in individuals 9–15 years of age. The second study, in addition to gathering additional immunogenicity data, was primarily performed to increase the overall safety database in individuals less than 16 years of age.

The trials in adolescents and children were initiated several years before the first approval of an HPV vaccine in the United States. In total, the clinical trials program for the qHPV vaccine in children and adolescents ultimately comprised 6 immunogenicity and safety studies, with a total sample size of approximately 4000 individuals ranging from 9 to 15 years of age. Ongoing long-term follow-up studies will also provide safety and effectiveness data to support continued use of the vaccine in this age group.

The qHPV Vaccine Case Study

Although the Guidelines for Adolescent Health Research had not yet been published, the conscious application of principles that are presented in that document during the design and conduct of the qHPV vaccine adolescent studies were critical to the success of the program and provide a useful framework for this review. Some of these general principles include the following: (1) there is a critical need for adolescent health research to enhance adolescent health and well-being; (2) adolescent minors should not be excluded solely because of age from participation in research that might benefit them; (3) adolescents are a distinct group, characterized by developing cognitive capacities and judgment, and these emerging abilities directly affect adolescents’ capacity to be involved independently in the research process; and (4) the role of the parents in protecting the adolescent’s interests must be honored and facilitated whenever possible and appropriate.

With regard to principles 1 and 2, the rationale for including adolescents in the qHPV vaccine clinical trials program has already been reviewed. In terms of principles 3 and 4, many arguments have been made for the enrollment of adolescents as independently consenting individuals in clinical trials around sexual health interventions, including treatment of sexually transmitted infections, sexually transmitted infection and pregnancy prevention studies, and sexual behavior research, among others. Regulatory guidelines exist regarding appropriate circumstances in which children may enroll without parental consent. These considerations are the focus of another review in this issue. Given the nature of the HPV vaccine trials in adolescents, parental/guardian consent was necessary. It was also evident that the sexual nature of the target disease meant that special attention needed to be paid throughout the studies to the unique concerns of both parents and their children.

Before potential subjects and their parents were asked to make a decision regarding entry into the trials they were provided with educational materials on HPV infection and HPV-related diseases and were encouraged to ask questions of any nature. Thus, the focus for parents and potential study participants was placed on education around the serious health consequences of HPV-related infection. Although no formal follow-up with parents has been undertaken regarding what motivated them to give permission for their children to participate, anecdotal reports from sites suggest that information on the public health impact of HPV was particularly motivating.

It has been shown that adolescents are more likely to participate in health care if they believe their provider will keep the information discussed during the visit private. Understanding the sensitive nature of information being gathered from study participants, it was recognized that assurance of confidentiality would be critical to successful enrollment. To this end, confidentiality of patient information (within the confines of legal disclosure rules), particularly with regard to sexual history and practices, was stressed to study participants throughout the trials, and the logistics of study procedures were carefully designed to protect patient confidentiality. As a specific example, the qHPV vaccine studies required subjects to be virginal and thus, for a potential subject, concern that refusal of entry into the study might be interpreted by parents as an admission of sexual activity was addressed through a carefully designed “easy out” consent process whereby teens could decline participation without having to provide a basis for refusal. This approach acknowledged and respected the adolescent’s evolving autonomy and decisional capacity by addressing the fact that they need to be active participants in the decision-making process around involvement in research. Also of key importance is that parents/guardians were never to be present during collection of sexual history information.

It has been stated that researchers must be aware of and accountable for the power they hold in influencing adolescents’ decisions to participate in research, and they must keep in mind that voluntary and informed consent principles may be easily and inadvertently violated. The voluntary nature of study enrollment and continued participation was emphasized during the studies. In particular, to provide young subjects with a sense of empowerment, participants were reminded of the voluntary nature of sharing sensitive information.
Given anticipated challenges with loss to follow-up of adolescent participants during the lengthy HPV vaccine trials, retention measures were implemented throughout the studies. Patients were provided with reminder cards, and if Institutional Review Board approved at the given study site could receive gift cards for health-related items. For enrollees who relocated during the study, patient and parent travel to the site was paid for, or if necessary, patients were transferred to an alternate site.

As a result of all the measures described, study investigators reported that enrollment of adolescents was, in general, straightforward. This was specifically attributed to upfront provision of relevant and understandable educational material. Investigators reported that parents, when provided with educational material, in particular, information on the public health impact of HPV, were willing and motivated to have their children participate in the studies. Having been assured of confidentiality and the voluntary nature of information sharing, adolescents seemed to share sensitive information willingly. In addition, retention rates in the young adolescent HPV studies were high, with more than 90% of patients completing the vaccination regimen and completing study follow-up.

The qHPV vaccine experience highlights the need for sensitivity and awareness of the social and political context in which the vaccine was being introduced. Before its approval, there were concerns raised by several groups that the use of an HPV vaccine in adolescents would encourage sexual promiscuity in vaccine recipients.14 In the case of the qHPV vaccine, attention was focused away from the sexual nature of HPV onto cancer prevention, and on the compelling epidemiologic data that show high rates of HPV acquisition in adolescents. Thus the rationale for registration and use of HPV vaccine in adolescents and younger children was disease-driven and data-driven. Given the sexual nature of a significant proportion of new HIV infections in the adolescent population, similar coordinated efforts toward the engagement and education of various stakeholders in academia, primary care medical practice, government, the insurance industry, and the community will be as important during the design of HIV prevention studies and the introduction and implementation of HIV prevention measures.

CONCLUSIONS
As is the case with HIV, in which half of new infections occur in individuals younger than 25 years,15 HPV infections in adolescents represent a significant proportion of new infections. Before undertaking the clinical studies in children and adolescents, the requirements for registration in this age group, including epidemiologic data in the relevant population, demonstration of a noninferior immune response in 9-year to 15-year olds compared with adults, and a robust safety database, were well understood and incorporated into the clinical program.

The lessons learned from the HPV vaccine clinical development program point to the need for information and education during the enrollment process of potential study subjects and their parents and guardians. Application of core principles of confidentiality and participant empowerment were instrumental in the successful enrollment and conduct of the clinical trials and the ultimate registration of the vaccine in the appropriate target population of sexually naive children and adolescents. The qHPV vaccine experience demonstrates that with careful planning and with attention to the specific psychosocial issues of this population, successful prevention studies can be designed and implemented in adolescents.

REFERENCES