

A Vaccine for Genital HPV: A Time to Rejoice!

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In this issue of the journal, Dr. Steven Cline discusses in his Issue Brief the newly licensed and approved vaccine “Gardasil” for human genital papilloma viruses (HPV) types 16, 18, 6 and 11, produced and marketed by Merck.¹ The vaccine requires three parenteral injections over six months, and is expensive (\$360). It is approved by the FDA for use in females ages 9-26. A similar vaccine is in development by GlaxoSmithKline, and may be presented for approval in a year. This is an exciting development because HPV types 16 and 18 are the principal causes of cancer of the cervix, accounting for about 70% of such cancers in the developed world and about 60% in less well developed areas of the world. HPV types 6 and 11 are responsible for about 90% of benign genital warts. Clinical studies of the Merck vaccine were about two years in duration, long enough to document remarkable protection against persistent infection and the early cytological changes (cervical intraepithelial neoplasia, or CIN-II and III) that are the prelude to cancer.² The clinical studies were limited to women ages 15-26 but studies of immunogenicity in girls 9-15 show the vaccine is equally immunogenic in children. It is extremely likely that the vaccine will prevent HPV 16 and 18 associated cancers that typically follow persistent HPV infection by many years. The Glaxo vaccine consists of only HPV types 16 and 18 only, but appears equally efficacious in preventing incident HPV infection by the type strains in the vaccine, and seems to provide durable immunity at least up to five years.³

It has been clear for decades that cervical cancer is associated with sexually transmitted diseases. Extensive basic and clinical research finally narrowed the cause down to the minority of HPV infections in which HPV DNA integrates into host

DNA, persisting for years, down-regulating two important tumor suppressor genes, and eventually leading to cancer. Most incident HPV infections clear due to immune responses in less than two years, but persistent infection is dangerous.

How the Vaccine Works

The vaccine is composed of a combination of viral-like particles (VLPs), made up from recombinant HPV protein L1 prepared from each of types 6, 11, 16 and 18. Protein L1 self-assembles into an empty viral capsid (VLP), and lacking any other viral proteins or DNA, is entirely safe. Conformational

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L1 epitopes are expressed in the VLPs, undoubtedly important to the vaccine's efficacy. The vaccine is quite immunogenic, and stimulates an antibody response that blocks initiation of infection. Remarkably, the vaccine was almost 100% effective in the clinical trials in prevention of infection by the covered types of HPV,

but has little effect against most other HPV types. It also has no effect on already established infection. The Glaxo vaccine, which uses a different adjuvant, also results in a cellular immune response against the vaccine strains and a few very closely related HPV types, and may have limited effects against a few other HPV types.⁴

When Must Vaccination Take Place?

The question is, will the HPV vaccines be accepted and widely used? For them to be effective, they must be used before women acquire HPV, which happens soon after onset of sexual activity. Sexual activity often commences in adolescence,

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whether parents approve or not. Some have worried that a vaccine for a sexually transmitted disease will only serve to promote sexual activity among the young and susceptible. A recent meeting of the Centers for Disease Control and Prevention's (CDC's) Advisory Committee for Immunization Practices (ACIP) recommended widespread deployment of the vaccine in school aged girls 12 and older, and noted that it may be used in girls as young as nine, so as to prevent acquisition of HPV before onset of sexual activity. Clearly this is crucial, since the vaccine has no therapeutic activity for established infection, and must be used before exposure to the virus. This recommendation was hailed by most public health authorities, and the stage is set to find out just how well the public accepts this new vaccine.

Remaining Questions

Many questions about the HPV vaccine remain, including how it can be deployed in populations in the United States, and especially abroad, who are unable to afford its cost. How durable is the immune response? Will booster immunization prove necessary? Will women continue to undergo regular Pap smear testing, which will be necessary because all HPV types associated with cancer are not included in the vaccine? Although the vaccines appear very safe, will large scale use reveal rare and unanticipated side effects? Will use of a vaccine that includes HPV types 6 and 11 lead to use in men, to prevent socially unacceptable, visible genital warts? Will use in men have an impact on their female sexual partner's risk of acquiring genital HPV? On the longer range horizon, can other vaccines be developed that are effective against established HPV infection?

What about the Prospects for Vaccines to Prevent Other STDs?

The triumph of this development effort, culminating a huge effort by scientists across the globe for well over 20 years, raises the question of whether other vaccines for STDs are imminent. Unfortunately, the answer is "no" with perhaps one exception. A huge effort to discover a vaccine for HIV has been entirely

fruitless to date. Although there is a bit of experimental evidence that a vaccine for syphilis might be possible, basic research demonstrating antigenic variation of a key surface protein is one of many arguments that a vaccine will be difficult to discover and even more difficult to develop. Gonorrhea and genital chlamydia have stirred only a modicum of vaccine interest, and the results have not been encouraging. The gonococcus is a master at immune evasion and perhaps also immune suppression, and a few small efforts to develop a vaccine have failed completely. There is no enthusiasm among pharmaceutical companies for development of such vaccines, in part because of their difficulty and expense of development, and also undoubtedly because of market considerations. That is unfortunate, because gonorrhea and chlamydia are common diseases in much of the world, with significant sequelae, and in the case of the gonococcus at least, resistance to antibiotics is spreading rapidly.

The one bright spot on the horizon is herpes simplex virus (HSV). This common and debilitating disease, the cause of so much angst in the pre-HIV era, is still very common. It is one of the major causes of genital ulcers that promote the sexual transmission of HIV. A recombinant surface glycoprotein D is undergoing an extensive phase III trial against genital HSV. Early results showed promise in prevention of disease in women who were seronegative for both HSV-1 and HSV-2, although there was little or no effect in women previously exposed to the virus, or in men.⁵

Challenges Ahead

We should rejoice in the advent of a vaccine for HPV. One hopes that concerns of social conservatives about the possible effects of a vaccine for a sexually transmitted disease on sexual behaviors will not limit use of the vaccine, and that means to pay for the vaccine in those who most need it will be found. Recent evidence suggests both the HPV vaccine and a potential HSV vaccine will be widely acceptable to adolescents and their parents.⁶ Public acceptance of this vaccine should help pave the way for acceptance of other STD vaccines, when they become available. The HPV vaccine is the second vaccine to enter clinical use that prevents an important human cancer, joining the hepatitis B vaccine. **NCMedJ**

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