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**Summary**

- High risk types of human papillomavirus (HPV) are the causal agents of cervical cancer. The prevention of HPV infection can reduce the incidence of this cancer.
- Five phase II clinical trials have been published, and several large phase III trials are underway.
- Trials have shown marked reductions in HPV infection. Most studies did not evaluate the effect of the vaccines on cancer because of lengthy time spans between HPV infection and the development of cancer.
- Injection site pain, headache, and fatigue are the most common adverse events reported.
- Important considerations include vaccine efficacy; acceptability; integration into existing vaccine schedules; cost; role of cervical screening programs; and access, particularly for people in the developing world.

**The Technology**

HPV is the cause of more than 99% of cervical cancer cases. The concept of prevention through vaccination is compelling, but vaccine development has been a challenge, as there are more than 100 HPV types, of which 13 to 18 are linked to cervical cancer. HPV types 16 and 18 occur in 70% of cervical cancer cases worldwide. Primary prevention is being addressed through prophylactic vaccines that are administered before potential exposure to HPV. For those infected with HPV, secondary prevention is being explored through therapeutic vaccines. This bulletin focuses on primary prevention.

HPV is a non-enveloped, encapsulated, double-stranded DNA virus. One of its coat proteins, L1, can be produced to generate non-infectious, virus-like particles that can stimulate significant antibody responses in hosts. Two prophylactic HPV vaccines have undergone phase II clinical trials, with phase III trials underway: Cervarix™ (GlaxoSmithKline Biologics, Rixensart, Belgium) and Gardasil™ (Merck & Co., Inc., Whitehouse Station, NJ).

**Regulatory Status**

No HPV vaccines have been submitted for approval, or licensed for use in any country. Filing for approval of Gardasil could occur before the end of 2005 in the United States, and in Europe in 2006 for Cervarix.

**Patient Group**

Worldwide, more than 250,000 women die of cervical cancer annually; 80% of these deaths occur in the developing world, where cervical cancer is the most common cause of cancer-related mortality. More than 500,000 women are affected and require treatment. Estimates in Canada indicate that 1,350 new cervical cancer cases and 400 deaths are expected in 2005.

Globally, the prevalence of genital HPV infection among women ranges from 2% to 44%. Depending on setting and testing technology, Canadian prevalence estimates range from 12% to 50% for women younger than 25, and less than 10% for women age 40 and older. Most
HPV infections occur soon after the initiation of sexual behaviour and are transient, resulting in a peak prevalence in young women and decreasing prevalence after age 30. The main risk factor is the number of sexual partners. A second HPV infection peak in Canadian women older than 60 could be due to virus reactivation. The body can clear most HPV infections in six to 12 months, although HPV type 16 may take longer than average to clear. Infection with HPV is common; researchers in Belgium have estimated a cumulative incidence of 75%.

Current Practice

Cervical cancer screening using Papanicolaou tests, often through established programs in the developed world, is used to detect pre-cancerous cervical lesions. This is followed by the use of colposcopy and biopsy to investigate women who tested positive. Screening programs are effective, but they are resource-intensive, and cases of cervical cancer still occur, often in women who are inadequately screened. Screening programs are less common in the developing world.

The Evidence

We identified phase II clinical trials that investigated vaccines for HPV type 16 alone, HPV types 16 and 18 combined, and an HPV 6, 11, 16, and 18 quadrivalent vaccine. Four were randomized controlled trials (RCTs). The main efficacy outcome measures were HPV acquisition and persistence rates. As viral culture is not possible and serology testing cannot distinguish between present and past infections, the identification of HPV is based on the detection of HPV DNA. This surrogate outcome measure is used in most studies, as lengthy time spans between HPV infection and the development of cancer prevent the use of cervical cancer incidence as an outcome.

Koutsky et al. investigated an HPV type 16 vaccine (n=2,392). Results showed that the vaccinated group demonstrated no cases of persistent HPV infection versus 3.8 per 100 women-years for the placebo group, and no cases of HPV-related cervical intraepithelial neoplasia versus nine for the placebo group. Two years later, Harper et al. reported the results of a bivalent vaccine trial against HPV types 16 and 18 (n=1,113). Vaccine efficacy in the intention-to-treat analysis was calculated as 95% against persistent HPV infection and 93% against cytological abnormalities associated with the HPV types. Shortly afterwards, Villa et al. published the quadrivalent vaccine findings of their trial (n=552), which reported a 90% reduction in persistent infection or disease due to one of four HPV types, as compared with placebo. The two remaining studies included an RCT and an observational study reported in an abstract. The study by Poland et al. was a dose-ranging RCT of HPV type 16 vaccine (n=480). All four vaccine doses used in the study produced statistically significant antibody responses to HPV type 16, which persisted for at least 1.5 years. Nolan et al. enrolled sexually naïve boys and girls, and HPV type 16 naïve young women, immunizing them with the quadrivalent vaccine. Overall seroconversion rates were 96% to 100%.

Phase III efficacy trials are underway, with more than 50,000 people enrolled. Initial data are available from a two-year Gardasil study in young women from 13 countries (the FUTURE II study). No cases of cancer occurred in the intervention group (n=5,301) versus 21 in the placebo group (n=5,258) after 17 months of follow-up. More ground-breaking work will be published from 2005 to 2007.

Adverse Effects

The four RCTs available in full text presented data on overall adverse events (AEs) and specific short-term, vaccine-related AEs (which occurred within seven to 14 days of vaccination or were deemed to be vaccine-related). Injection site pain was common, ranging from 85% to 94% for vaccine recipients, and 82% to 88% for placebo recipients. The comparable ranges for systemic vaccine-related symptoms, (e.g., headache and fatigue) were 38% to 86% and 33% to 86% in vaccine and
placebo recipients respectively. There were few trial withdrawals due to AEs and no reported serious vaccine-related AEs.

**Administration and Cost**

The vaccine is given as a 0.5 mL intramuscular dose on three occasions: the first day of treatment, at month one or two (varies by vaccine), and at month six. Three studies that addressed cost-effectiveness were identified. All were complex decision models using hypothetical cohorts to compare current screening practices with vaccination alone, or with combinations of vaccination and cytologic screening. There were divergent assumptions about vaccine coverage, efficacy, duration, cost, and screening practices. Extensive sensitivity analyses were performed. All authors concluded that base case results suggest HPV vaccination in combination with a cytologic screening program is, or can be, cost-effective. The incremental cost-effectiveness ratios presented in these studies range from $22,755 to $58,500 per quality adjusted life-year (2001 and 2002 US dollars respectively).

**Concurrent Developments**

Most HPV infections and HPV-positive pre-malignant lesions resolve without treatment, but some do not, inspiring the search for therapeutic HPV vaccines for secondary prevention. There are also vaccines under development that combine prophylactic and therapeutic functions.

**Rate of Technology Diffusion**

For primary prevention, people must be immunized before active sexual behaviour begins; this means targeting adolescents who are under about age 12. Most literature focuses on the immunization of females. The nature of HPV infection and the use of HPV vaccine in males are also being studied. It is possible that males can act as viral vectors, with their immunization enhancing herd immunity and reducing cervical cancer incidence. Further research is required to determine whether males should be vaccinated.

The role of cervical cancer screening will require examination. Cervical cancer generally does not develop until decades after the initial HPV infection. Although an HPV vaccine could reduce the number of new HPV cases, the need for cytological screening may continue beyond the introduction of HPV vaccination programs, perhaps in combination with HPV testing. This long period indicates that assessment of the vaccine’s long-term effectiveness and adverse events will be impossible until a full generation of patients is vaccinated. According to current models, maximal benefits in disease reduction will be achieved by combinations of vaccination and cervical screening programs. Therapeutic vaccines may bridge the gap, because people who are already infected with HPV may be treated.

**Implementation Issues**

A 2003 expert panel assembled by the World Health Organization suggested that, beyond the efficacy of a vaccine, potentially important considerations include its affordability, suitability for mass immunization, and potential impact on cervical screening programs. Attention must also be paid to building awareness about HPV and its sequelae in the community and among health care providers, assessing the acceptability of vaccination programs, and considering the practical issues of vaccine availability and cost-benefit. The tracking of disease-causing types of HPV will be important. Developing countries face challenges that are related to a lack of resources, including poor access to cervical cancer screening programs. There may also be problems in achieving high coverage among those pre-adolescent girls who are most at risk of cervical cancer, traditionally a group that is difficult to reach.

In the US, the experience with vaccines for adolescents has led to opposition on moral and ethical grounds for vaccination programs that are linked to sexual activity. This attitude...
may be less prevalent in Canada. One US study analyzed survey responses from 506 parents of adolescents as to the acceptability of HPV vaccination and the impact of education. Initially, a 30-question survey revealed that 55% (278 of 506) of subjects were supportive, 22% (111 of 506) undecided, and 23% (117 of 506) opposed. After reading a one-page HPV information sheet, 65% (72 of 111) of the undecided moved to the supportive group, as did 37% (43 of 117) of those opposed. A survey of young adult women in Ohio (n=52, mean age 25) revealed a high level of knowledge about HPV and a high level of support for HPV vaccination for themselves (89%) and their daughters (81%).

References


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