Model Predicts Cost-Efficacy of HPV Vaccination

BY MARY ANN MOON
Contributing Writer

Human papillomavirus vaccination should be targeted at preadolescent girls, with initial "catch-up" programs aimed at women and girls aged younger than 21 years, but should not be directed at older women, according to a report.

The impact of the HPV vaccination will not be "observable for decades," so decisions regarding vaccine policy must rely on estimates and mathematical simulation models, according to Jane J. Kim, Ph.D., and Dr. Sue J. Goldie of Harvard School of Public Health, Boston.

They devised such a model to examine possible outcomes of current HPV vaccination programs.

In creating this simulation model, the investigators took into consideration the cost-effectiveness of vaccinating various age groups as well as "the dynamics of HPV transmission, the duration of vaccine efficacy, the potential benefits of preventing noncervical HPV-related conditions, the anticipated changes in screening practice, and potential disparities in access to care."

If it is assumed that the HPV vaccine confers lifelong immunity, the simulation model showed that routine vaccination of 12-year-old girls had a cost-effectiveness ratio of $43,600 per quality-adjusted life year gained.

This is well within the commonly cited threshold of good value for resources spent, which is $50,000-$100,000 per quality-adjusted life year gained, the investigators said (N. Engl. J. Med. 2008;359:821-32).

Adding a "catch-up" program to vaccinate girls aged 13-21 years also was found to be reasonably cost-effective, especially when the benefits of averting genital warts and of cross-protection against other high-risk types of HPV were added into the model.

However, extending such a catch-up program to women older than 21 was not found to be a good value, the investigators said.

Both the routine vaccination of 12-year-olds and the "catch-up" vaccination of adolescents remained cost-effective only at high levels of vaccine coverage, Dr. Kim and Dr. Goldie noted.

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The model predicted less success for HPV vaccination programs if it turns out that immunity is not lifelong but lasts only 10 years.

In that case, continued screening and booster vaccines will be necessary and will add substantially to costs, Dr. Kim and Dr. Goldie commented.

In an editorial comment accompanying this report, Dr. Charlotte J. Haug, editor-in-chief of the Journal of the Norwegian Medical Association, Oslo, called the Harvard researchers' model "well done and ambitious."

"There has been pressure on policy makers worldwide to introduce the HPV vaccine in national or statewide vaccination programs.

"How can policy makers make rational choices about the introduction of medical interventions that might do good in the future, but for which evidence is insufficient, especially since we will not know for many years whether the intervention will work or—in the worst case—do harm?" she asked (N. Engl. J. Med. 2008; 359:861-2).

One answer is to "develop mathematical models of the natural history of the disease in question, introduce various intervention strategies, and use cost-effectiveness analysis to estimate the costs and health benefits associated with each clinical intervention," as Dr. Kim and Dr. Goldie have done.

However, their model and its predictions are only as accurate as the assumptions on which the model is based, Dr. Haug noted.

If any of these assumptions turn out to be overly optimistic, then HPV vaccination will not turn out to be as successful as the model predicts.

The researchers cited other limitations in their analysis, saying that data on sexual behavior were primarily based on population averages from large surveys.

Also, data are limited on several factors: incidence; mortality and quality of life associated with noncervical HPV-related cancers; the long-term efficacy of the vaccine; and the efficacy of the vaccine against noncervical cancers.

The researchers stated that they did not have any potential conflicts of interest to report with regard to this study. ■

An Expert Makes the Case for Universal HPV Vaccination

BY DOUG BRUNK
San Diego Bureau

CALGARY, ALTA. — As an epidemiologist whose research focuses on the prevention of cervical cancer, Dr. Eduardo L. Franco spends a lot of his time dispelling arguments and protests from other health care professionals and patients that more research is needed before universal human papillomavirus vaccination can be recommended worldwide.

"Although clinical experience has just passed 6 years, the evidence base is one of the strongest in disease prevention," Dr. Franco said at the annual meeting of the Society of Obstetricians and Gynaecologists of Canada.

"The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past. It may be the most scrutinized vaccine by the public and the media concerning need and safety," he said.

Prophylactic HPV vaccines include a quadrivalent form manufactured by Merck & Co. that was licensed in the United States in June 2006 and a bivalent form manufactured by GlaxoSmithKline Inc. that was submitted to the Food and Drug Administration in March 2007.

Dr. Franco, director of the division of cancer epidemiology at McGill University, Montreal, shared several examples of arguments against HPV vaccination that he encounters, followed by his counterargument for each.

One chief argument he hears is that the vaccine is too costly and unaffordable where it's most needed.

However, he said, procurement programs such as the Centers for Disease Control and Prevention's Vaccines for Children Program, the Global Alliance for Vaccines and Immunization, and the Pan American Health Organization's revolving fund should help to lower the cost.

'It may be the most scrutinized vaccine by the public and the media concerning need and safety.'

DR. FRANCO

"Historically," he added, "prices decline with time since deployment. Competition among manufacturers should force a reduction in prices."

In addition, ongoing studies of more simplified schedules—such as administering two doses instead of three—may affect price.

Other common arguments against HPV vaccination include the following:

► **There are no data on long-term duration of protection.** In fact, to date, studies demonstrate a sustained antibody response with no indication that humoral immunity will wane before 10 years.

"Even with lowered antibody titres, postvaccination protection has continued unabated," said Dr. Franco, who also is a professor of epidemiology and oncology at McGill.

"We did not wait for such proof before deploying other vaccines."

► **Protection is limited; vaccines cover only two oncogenic types.** In fact, protection is against the two most important types (HPV 16 and 18), which translates into a protective fraction of 70% of all cervical cancers. That protection "is likely to be expanded via cross-protection," he said. "In combination with tailored screening strategies, it may achieve unprecedented lifelong protection."

► **Screening will continue to be needed.** True, Dr. Franco said, but recent progress on new technologies such as HPV testing with Pap triage "will permit extending screening intervals safely and cost effectively. Proper integration of primary and secondary prevention strategies is likely to reduce costs and improve cervical cancer control."

► **There is a risk of type replacement, which occurred with the pneumococcal vaccine**. In fact, Dr. Franco said, type replacement is unlikely to occur because there is no epidemiologic proof that HPV types compete for specific niches. "Several studies have tested this hypothesis," he noted. "The fraction of the population not exposed to HPV 16 or 18 is always high; exposure to HPV 16 or 18 does not constrain the pool of susceptible individuals who could acquire other HPVs."

► **We should not vaccinate preteens and teens; there are no efficacy data on patients aged 9-14 years.** This age group is not at risk for lesions and monitoring them "would be unethical and unproductive," Dr. Franco said.

"Immunobridging" studies show that vaccine-induced humoral response in preteens is the highest among all groups, "which is sufficient justification for expectation of benefit," he said.

► **There is no proof yet that vaccination can reduce the risk of invasive cancers.** Dr. Franco counters this notion by pointing out that absence of evidence is not evidence of absence. "Sensible judgment based on understanding of the natural history of HPV infection and cervical cancer indicates that prevention of precancerous lesions is an acceptable end point," he explained.

► **There is no cervical cancer epidemic.** He responds to this argument by emphasizing that the health costs, morbidity, and mortality associated with cervical cancer are sufficiently important to justify action. Moreover, he said, the HPV vaccination is likely to exert protection against other neoplastic diseases such as malignant anogenital and oropharyngeal cancer and benign genital warts and laryngeal papillomatosis.

► **More research is needed on safety.** Dr. Franco responds to this argument by noting that the safety data on the HPV vaccine "are among the most well documented for any new vaccine. There was no waiting period for the adoption of other vaccines with lesser standards of proof. Inaction has a high cost in terms of morbidity and mortality that could have been averted."

Dr. Franco disclosed that his entire research program has been funded by the Canadian Institutes of Health Research (CIHR), the National Cancer Institute of Canada, and the National Institutes of Health. He has received a Distinguished Scientist salary award from the CIHR and has served as an occasional adviser to several companies with products related to cervical cancer prevention. ■

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