

Caution Urged Over Large-Scale HPV Vaccination Programs

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August 20, 2008 — "There is good reason to be cautious about introducing large-scale vaccination programs" with the human papillomavirus (HPV) vaccines, because many essential questions are still unanswered. This is the conclusion of Charlotte Haug, MD, PhD, from the *Journal of the Norwegian Medical Association*, in Oslo, writing in an editorial in the August 21 issue of the *New England Journal of Medicine*.

"The real impact of HPV vaccination on cervical cancer will not be observable for decades," Dr. Haug comments, but there has been pressure on policy makers worldwide to introduce the HPV vaccine in national or statewide vaccination programs.

Two HPV vaccines are marketed worldwide — the United States and Australia use *Gardasil* (Merck & Co), while the United Kingdom recently announced that it has chosen *Cervarix* (GlaxoSmithKline). A major target of these vaccination programs is girls between 12 and 13 years old, as the vaccine is most effective before the onset of sexual activity.

However, Dr. Haug questions how policy makers can 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?"

Cost-Effectiveness Estimated in a Mathematical Model

The editorial accompanies a study published in the same issue of the journal on the health and economic implications of HPV vaccination in the United States by Jane Kim, PhD, and Sue Goldie, MD, from the Harvard School of Public Health, in Boston, Massachusetts. They use a mathematical model to calculate cost-effectiveness of vaccination in a country where there is already an established cervical cancer–screening program.

The study concludes that vaccination is expected to be economically attractive if high coverage can be achieved in the primary target group of 12-year-old girls and if the vaccine-induced immunity is lifelong. But adding a catch-up program for older girls and women is not cost-effective.

However, these conclusions are based on a mathematical model that makes many assumptions, and these are "quite optimistic," Dr. Haug comments. "Whether these assumptions are reasonable is exactly what needs to be tested in trials and follow-up studies," she maintains.

Dr. Haug discusses several of the assumptions on which the model is based in some detail, pointing out that in many cases there are very little data.

One of the main assumptions is that the effects of vaccination will be lifelong (ie, there will be no need for a booster). But 1 of the main questions still unanswered is how long the protection conferred by the vaccine will last. The researchers themselves point out that if protection wanes after 10 years, vaccination becomes much less cost-effective and screening becomes more effective than catch-up programs. One of the key investigators involved in the HPV-vaccine

clinical trials, Diane Harper, MD, from Dartmouth Medical School, in Hanover, New Hampshire, has said that the evidence so far suggest that protection lasts for 5 years after vaccination, but there are no longer-term data, as previously reported by *Medscape Oncology*.

Another assumption is that the vaccine has the same effect on preadolescent girls as on older women. However, Dr. Haug points out, the only trials that have been carried out on preadolescent girls measured only immune responses, and the trials with clinical end points were conducted in 16- to 24-year olds.

In their model, the researchers also presume that other strains of the HPV virus, which are not targeted by the vaccine, will not take over. However, there is already some evidence suggesting that this may happen, Dr. Haug says. Published reports of trials show an increasing trend of precancerous cervical lesions caused by HPV serotypes other than those targeted by the vaccine (HPV-16 and HPV-18). So far, the results have not been statistically significant, but the numbers involved have been small. If clinical trials continue, data accumulating over the next few years will likely show whether this is a true trend, she says.

In addition, the model presumes that vaccinated women will continue to attend screening programs for cervical cancer and that the vaccine will not affect natural immunity against HPV, Dr. Haug comments. Again, these are assumptions, and it remains to be seen whether they are correct.

In view of all the questions that remain to be answered, Dr. Haug urges more research into HPV vaccination. "We should concentrate on finding more solid answers through research rather than base consequential and costly decisions on yet-unproven assumptions," she concludes.

No conflicts of interests were reported.

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