HPV Vaccine Policy: At Odds With Evidence-Based Medicine?

Roxanne Nelson | Jan 31, 2012

January 31, 2012 — Is the policy for the human papillomavirus (HPV) vaccine at odds with evidence-based medicine?

Yes, according to an essay published online December 22, 2011, in the *Annals of Medicine*.

Canadian researchers Lucija Tomljenovic, PhD, and Christopher Shaw, PhD, from the Neural Dynamics Research Group, University of British Columbia, in Vancouver, point out that there is a major discrepancy in claims regarding the safety and efficacy of *Gardasil* (Merck & Co) and *Cervarix* (GlaxoSmithKline) — the 2 HPV vaccines that are currently on the market.

The vaccines have been heavily promoted in the United States by their respective manufacturers, the essayists report. In addition, the vaccines are backed by government agencies in the United States, including the Center for Disease Control and Prevention and the US Food and Drug Administration, and by medical authorities in a number of other countries.

HPV vaccination has been mired in controversy since the first vaccine was approved in the United States in 2006. There have been clashes among politicians, parents, professional and advocacy organizations, and public health officials, with heated exchanges over issues ranging from safety, the premise that vaccination will promote sexual activity in teens, cost, and concerns about aggressive lobbying by Merck to make the vaccine mandator for girls.

Drs. Tomljenovic and Shaw note that skepticism about the vaccine has been increasing for a number of reasons, despite reassurances from the public-health sector. In their essay, they examine the current evidence to answer a key question: "Is it possible that HPV vaccines have been promoted to women based on inaccurate information?"

Does it Prevent Cancer?

One major issue is the claim made by medical authorities that HPV vaccines are an important tool in preventing cervical cancer. The efficacy of the vaccines in preventing cervical cancer has not been demonstrated because the study periods have been too short, say the essayists.

The longest follow-up from phase 2 trials for Gardasil is 5 years and for Cervarix is 8.4 years, but invasive cervical cancer can take 20 to 40 years to develop from the time of HPV infection.

"We don't know the duration of the immune response of the vaccines," Dr. Tomljenovic told *Medscape Medical News*, "so we don't know if they are actually preventing cervical cancer or simply postponing it."

Both vaccines very effectively prevent persistent infections with high-risk HPV types 16 and 18 and the associated cervical intraepithelial neoplasia (CIN) 2/3 lesions in HPV-naïve young women. However, note the essayists, even persistent HPV infections caused by high-risk strains generally do not lead to precursor lesions in the short term or to cervical cancer in the long term.

The reason for this is that up to 90% of HPV infections resolve spontaneously within 2 years; even among those that remain, only a small proportion progress to a malignancy. Research shows that high-grade CIN can resolve or stabilize over time, the essayists explain, adding that neither vaccine is able to clear existing HPV16/18 infections or to prevent the progression of existing infections to high-grade lesions.

True Value of Vaccines

The essayists "have clearly and succinctly shown that the true value of HPV vaccines is not necessarily in the number or oncogenicity of HPV types included in the vaccine, but in how long the immunogenicity and efficacy of the vaccine is to this epithelial immune-system-avoidant HPV virus," said Diane Harper, MD, professor of medicine at the University of Missouri in Kansas City, who was approached by *Medscape Medical News* for independent comment.

HPV vaccines must maintain a near 100% efficacy for a full 15 years, at a minimum, for cervical cancer to be prevented, she explained. "If we vaccinate 11- and 12-year olds and Gardasil only lasts 10 years, then 21- and 22-year-old women are no longer protected," explained Dr. Harper, who was involved in clinical trials for both vaccines.

So far, Merck has not conducted any studies, nor are any planned, to evaluate the long-term immunogenicity and efficacy of needed booster shots, she continued. "Merck stopped their immune memory challenge study 1 month after the booster shot was provided, so that long-term immunokinetics and efficacy could not be evaluated. The cost-effectiveness models, which include a sensitivity analysis of finite duration, show that Gardasil is no longer cost effective if it requires a booster shot."

Can it Reduce the Cancer Rate?

An important question is whether the HPV vaccines can lower the rate of cervical cancer to below what has been achieved with Pap test screening. In industrialized nations, where screening is common, there has been a 70% reduction in the incidence of cervical cancer during the past 50 years, write the essayists. So even though cervical cancer is cited as the second most common cancer in women worldwide, existing data show that this only applies to developing countries.

Rachel Winer, PhD, assistant professor in the Department of Epidemiology at the University of Washington, Seattle, agrees that the vaccine can have the greatest impact in developing countries that lack adequate screening programs.

Although "it's true that Pap screening has been instrumental in reducing rates of cervical cancer in developed countries, over half of cervical cancers in the United States occur in women who are underscreened," said Dr. Winer. "Therefore, interventions such as vaccines are still important to further reduce rates of cervical cancer in developed countries."

In addition, she explained, vaccination can reduce rates of precancerous lesions, which place a tremendous burden on women and the healthcare system.

Charlotte Haug, MD, PhD, editor-in-chief of the *Journal of the Norwegian Medical Association*, pointed out that one of the problems in discussions of the HPV vaccine is that the risks, benefits, and cost effectiveness are very different, depending on whether you are in industrialized or developing countries. "The risk of cervical cancer is high in many developing countries, and women in these countries hardly have access to healthcare at all," said Dr. Haug, who was approached for independent comment.

Precursor lesions will not be easily detected without access to regular care, she noted. "Reducing the prevalence of cervical cancers in these countries can be done easily, and most cost effectively, by offering women a minimum of standard gynecological follow-up."

Even though cervical cancer does not have the same impact in industrialized nations as it does in the developing world, it still does occur. "This is where the HPV vaccine comes in," said Dr. Haug. "The studies show that, hypothetically, there might be a chance that we could lower the prevalence of cervical cancer even more."

However, she noted that the potential benefit is currently unclear and the cost is high. "So if you look only at

prevent a disease that may or may not develop until decades later, and which can be easily prevented in another, safer way."

But Dr. Winer pointed out that some of the information regarding adverse events is misleading. "For example, comparing the serious adverse event rate from VAERS to the cervical cancer rate is misleading; there is currently no indication that any of the serious adverse events reported to VAERS were caused by the HPV vaccine," she said, noting that as the essayists themselves indicate, "a report to any passive vaccine surveillance system does not by itself prove that the vaccine caused an adverse drug reaction.'"

More Rigorous Assessment Needed

Since 2006, when Gardasil was approved in the United States, there have been 18,727 adverse reactions reported to VAERS — 1498 (8%) of which were serious (68 of which were deaths). Passive vaccine surveillance systems are inadequate in proving cause and effect, the essayists note.

They add that active surveillance needs to replace passive surveillance, and that systematic prospective controlled trials are needed to accurately establish or reject causal relations for drug-related adverse reactions of any type. Currently, many medical authorities have dismissed potential links between HPV vaccination and serious adverse events too quickly, they note.

The unusually high frequency of reported adverse events related to the HPV vaccines, along with their consistent patterns, indicates that "the risks of HPV vaccination may not have been fully evaluated in clinical trials," they write.

In addition, independent scientific reports have linked HPV vaccination to a number of serious adverse events.

They also note that the aggressive marketing strategies by the manufacturers have been questionable in some cases. More disturbingly, the "aggressive marketing strategies employed by the vaccine manufacturers is the practice by which the medical profession has presented partial information to the public."

Better surveillance is needed for adverse-event reporting, more independent research is needed, and long-term data are needed to evaluate the true duration of the vaccines. "Independent evaluation of HPV vaccine safety is urgently needed and should be a priority for government-sponsored research programs," Drs. Tomljenovic and Shaw conclude. "Physicians should adopt a more rigorous evidence-based medicine approach in order to provide a balanced and objective evaluation of vaccine risks and benefits to their patients."

Drs. Tomljenovic and Shaw "have succinctly and accurately portrayed the significant unknowns of Gardasil and the complicit interaction of the public-health system to politely not ask the embarrassing questions about true long-term efficacy and true cost effectiveness," said Dr. Harper.

This study was supported by the Dwoskin, Lotus, and Katlyn Fox Family Foundations. Dr. Tomljenovic and Dr. Shaw have disclosed no relevant financial relationships.

Ann Med. Published online December 22, 2011. Abstract

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Cite this article: HPV Vaccine Policy: At Odds With Evidence-Based Medicine? *Medscape*. Jan 31, 2012.

industrialized countries, there may be no rational justification for introducing the vaccine," she said.

With the cervical cancer screening that is already in place in the United States, 8.0 in 100,000 women develop the disease every year, according to a study coauthored by Dr. Harper (*Discov Med.* 2010;10:7-17). Estimates of the impact of HPV vaccination in the absence of screening, based on modeling and the assumptions that efficacy will last a lifetime and that all women will be vaccinated, predict that 9.5 in 100,000 women will develop cervical cancer annually with Cervarix, as will 14 in 100,000 women with Gardasil.

The combination of screening and vaccination would not be expected to significantly reduce these numbers.

"The incidence of cervical cancer in the United States in 1999 was 9.7 in 100,000 women; in 2000, it was 9.6 in 100,000 and in 2001 it was 9.1 in 100,000," said Dr. Harper, noting that the year-by-year numbers vary quite a bit, so a 5-year weighted average is used to get an idea of trends.

There is a lot of variability in the number of women who get cervical cancer, Dr. Harper explained. "The American Cancer Society has varied its estimates of cervical cancer anywhere from 10,000 a couple of years ago to 12,200 most recently, so there is inherent variation in the success rate of Pap screening," she said.

"Under the modeling assumptions of lifetime immunity (without the need for boosters), 100% efficacy against the HPV types, and 100% population uptake of the vaccine, the number of women who would not get cervical cancer, outside of those whose cervical cancer is detected by Pap screening, is very, very small," she added.

However, the vaccine might be beneficial in other ways. "Using the vaccines will decrease the number of abnormal Pap screens, the number of colposcopies, and the number of excisional procedures," Dr. Harper pointed out. "This is the true benefit of HPV vaccines in the United States."

Risk vs Benefit

Health agencies and regulatory bodies worldwide have stated that the HPV vaccines are safe and effective, and that the benefits outweigh the risks, note the essayists. "However, the rationale behind these statements is unclear, given that the primary claim that HPV vaccination prevents cervical cancer remains unproven," they write.

According to data from the World Health Organization, the current age-standardized death rate from cervical cancer is 1.7 in 100,000, they note.

This is 2.5 times lower than the rate of serious adverse reactions from Gardasil that have been reported to the Vaccine Adverse Event Reporting System (VAERS) (4.3 in 100,000 doses distributed). In the Netherlands, the reported rate of serious events from Cervarix is 5.7 in 100,000 doses administered, which is nearly 4 times higher than the age-standardized death rate from cervical cancer (1.5 in 100,000).

"It may not be fair to compare serious adverse events with death from cervical cancer, but we really have to look at the whole picture," explained Dr. Tomljenovic. "Cervical cancer is not a disease that affects teenagers and it can be prevented with regular Pap screening, which carries no risk."

Reported serious adverse reactions associated with HPV vaccination from Australia, France, Ireland, the Netherlands, the United Kingdom, and the United States include death, convulsions, paraesthesia, paralysis, Guillain–Barrel syndrome, transverse myelitis, facial palsy, chronic fatigue syndrome, anaphylaxis, autoimmune disorders, deep vein thrombosis, pancreatitis, and pulmonary embolism.

"We have to ask if it's worth receiving a vaccine that has been associated with a permanent debilitating disease, or death, in young girls, said Dr. Tomljenovic, emphasizing that these vaccines only have "a theoretical potential to