

From Medscape Medical News

HPV Vaccine: Debate Over Benefits, Marketing, and New Adverse Event Data

Zosia Chustecka



August 18, 2009 — The benefit of vaccinating against human papilloma virus (HPV) to prevent cervical cancer is questioned in an editorial in the *Journal of the American Medical Association*.

"The theory behind the vaccine is sound: if HPV infection can be prevented, cancer will not occur," writes editorialist Charlotte Haug, MD, PhD, from the *Journal of the Norwegian Medical Association*. "But in practice, the issue is more complex."

HPV is the most prevalent sexually transmitted infection, "but the virus does not appear to be very harmful because almost all HPV infections are cleared by the immune system," she explains. In a few women, the HPV infection persists, and some women may develop precancerous cervical lesions and eventually cancer, Dr. Haug writes, "but it is currently impossible to predict in which women this will occur."

"The net benefit of the HPV vaccine to a woman is uncertain," Dr. Haug comments. "Even if persistently infected with HPV, a woman most likely will not develop cancer if she is regularly screened [with cervical smear tests]."

The net benefit of the HPV vaccine to a woman is uncertain.

Dr. Haug has spoken out against HPV vaccination previously. Last year, she urged caution over widespread vaccination programs in an editorial in the *New England Journal of Medicine* (2008;359:861–862), as reported by *Medscape Oncology* at the time.

This latest editorial accompanies 2 articles published in the same issue of *JAMA*. One of the articles is critical of the marketing of the HPV vaccine *Gardasil* (Merck & Co) in the United States, and the other details adverse events that have been reported with the vaccine since it was launched there in 2006.

Dr. Haug comments that, in view of the uncertain benefit from the HPV vaccine, "only a small risk of harmful effects from the vaccine" is acceptable.

The balance between the risks and benefits of HPV vaccination should rest only on medical and scientific evidence, Dr. Haug states.

However, she warns that this balance is "easily skewed" if other matters weigh in; for example, profit for a company or gains for physicians — issues that are explored in the article on marketing.

"The balance will also tilt if adverse events are not calculated correctly," Dr. Haug comments, and her editorial points out limitations of the system used for collecting adverse event reports, detailed in the other article.

Criticism of Gardasil Marketing

The article discussing the marketing of Gardasil in the United States was authored by Sheila Rothman, PhD, from sociomedical sciences and David Rothman, PhD, from social medicine, both at the Columbia College of Physicians and Surgeons, New York City.

Merck & Co promoted Gardasil primarily to "guard" against cervical cancer, rather than promoting it as a vaccine against HPV viruses or sexually transmitted diseases, the authors note. (The vaccine is active against 4 virus subtypes: HPV-6, HPV-11, HPV-16, and HPV-18; HPV-16 and HPV-18 are responsible for about 70% of cervical cancers worldwide and can also cause other anogenital cancers, whereas HPV-6 and HPV-11 are the most common causes of genital warts).

The marketing was so successful that in its first year, Gardasil was named in the industry journal *Pharmaceutical Executive* as the "brand of the year" for building a "market out of thin air," the authors point out.

"By making this vaccine's target disease cervical cancer, the sexual transmission of HPV was minimized, the threat of cervical cancer to all adolescents maximized, and the subpopulations most at risk practically ignored," they write.

"Rather than concentrating on populations in geographical areas with excess cervical cancer mortality, including African Americans in the South, Latinos along the Texas-Mexico border, and whites in Appalachia, the marketing campaign posited that every girl was at equal risk," Dr. Rothman and Dr. Rothman write.

"That these arguments were delivered by professional medical associations (PMAs) is cause for concern," they add. Merck & Co funded activities at the American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology, the Society for Gynecologic Oncologists, and the American College Health Association.

Among the company-funded activities were speaker lecture kits and education resource panels, with sample answers to patient questions, as well sample press releases and sample letters to parents and students explaining why they should have the vaccine. The authors detail specific instances in which the message being promulgated by PMAs was influenced by Merck & Co.

They were overtly exuberant in their hopefulness for vaccination.

Approached for comment, Diane Harper, MD, from the University of Missouri- Kansas City School of Medicine, Kansas City, Missouri, commented to *Medscape Oncology* that the PMAs "must confess to both their memberships and to the women whose health they serve that they were overtly exuberant in their hopefulness for vaccination and are guilty of presenting essentially only the information that Merck wanted presented."

She added, "In order to move on from this mistake, PMAs need to work with researcher clinicians to develop informed consents that include detailed risks and benefits of vaccination and screening." Dr. Harper also said that, now that serious adverse events have been documented, full disclosure of benefits and risks must be presented in all educational lectures.

Dr. Harper is professor and vice-chair, Obstetrics and Gynecology, Community and Family Medicine and Informatics and Personalized Medicine, and she conducted the phase 2 and phase 3 trials for Gardasil, authoring their publications. She has spoken out previously about the HPV vaccine and its marketing, and to *Medscape Oncology*, she expressed her concern over how the message about the need for regular cervical smears was overshadowed by "aggressive and inappropriate promotion of the vaccine."

Dr. Harper also commented that nowhere in any of the information about Gardasil has it been pointed out that in developed countries such as the United States, which have Papanicolaou (Pap) screening programs in place, the HPV vaccine will do little to decrease the already very small cancer rate but mostly will allow screening intervals to be extended safely.

Also approached by *Medscape Oncology* for comment, Maurie Markman, MD, professor of gynecologic medical oncology at the M.D. Anderson Cancer Center, Houston, Texas, questioned the credibility of the article on marketing, which is published as a "special communication." The authors are social scientists, he points out, and they "quote opinions from editorials as if they equate to facts." He emphasized the need to distinguish opinion from data and pointed out that there was no reference to any of the extensive peer-reviewed research articles on the HPV vaccine, which have accumulated data from thousands of patients.

Dr. Markman said he cannot comment directly about the claims made in the article, but added that he would be concerned if there were any truth to the idea that PMAs were not acting appropriately.

However, he strongly disagreed with one of the main points made in the article — the implied criticism of Merck & Co for promoting the vaccine for the prevention of cervical cancer. "I can't say how strongly I disagree with this — in fact, I am appalled," Dr. Markman told *Medscape Oncology*.

This vaccine does prevent cervical cancer, he emphasized, on the basis of all the data that are available, and "you cannot get better studies or a better strategy," he added. He acknowledges that there is no proof, as yet, but "it will take another 30 years or so to have that proof, and in the meantime, thousands of women will have died from cervical cancer."

This paper is opinion masquerading as data.

"This paper is opinion masquerading as data," Dr. Markman said, and he added that it was "potentially harmful, as it may make people who have already received the vaccine think that they made a mistake."

(In fact, Gardasil is licensed for the prevention of cancer and is only the second vaccine to have this indication, point out the authors from the other article, all of who are from either the Centers for Disease Control and Prevention [CDC] or the US Food and Drug Administration. The first was the hepatitis B vaccine against liver cancer, which is also marketed by Merck & Co. Dr. Rothman and Dr. Rothman suggest that the company learned valuable lessons in the marketing of this first vaccine, which helped it make the marketing of Gardasil so successful.)

Dr. Harper says that HPV vaccination has a role to play in the prevention of cervical cancer. However, she emphasizes the need for regular cervical smears and points out that even women who are vaccinated need to have regular smears, as otherwise they are still at risk for developing cancer. In addition, women who do not receive the vaccine can still protect themselves equally well by undergoing regular Pap tests.

HPV vaccination will prevent more cervical cancers in populations that do not have access to cervical cancer screening, she continued. Some developing countries without screening have an incidence of cervical cancer that is 5 to 12 times higher than that seen in the United States. Because the death rate from cervical cancer is so much higher in these populations, they may also tolerate a high rate of serious adverse events, including death, that have been associated with Gardasil, Dr. Harper commented.

However, in the United States, the usefulness of the vaccine is to increase the chance that a woman's next Pap test will be normal, Dr. Harper commented. Women must still have Pap tests after vaccination, and vaccination alone in the United States will only incrementally reduce the rate of cervical cancer, with its greatest benefit being to increase the screening interval between screens, and hence being a cost-saving device, she added. In fact, if women who are vaccinated stop going for Pap smears, the incidence rate for cervical cancer would increase, she said.

In the United States, the death rate from cervical cancer (3/100,000 women by statistics from the CDC) is at present similar to the rate of reported serious adverse events from Gardasil (3.4/100,000 doses distributed), Dr. Harper pointed out. "This is a sobering reality," she commented. "Would a parent accept such a rate of serious adverse events if the same cancer prevention can occur with continued Pap screening? Is there any acceptable level of risk of serious

This is a sobering reality.

adverse events, including death, to prevent genital warts?" she asked, referring to one of the vaccine's other benefits.

Latest Adverse Event Data

The latest data on adverse events with Gardasil, published in the same issue of the journal, comes from the US Vaccine Adverse Event Reporting System (VAERS). In total, 12,424 adverse events after immunization were reported to in United States between June 2006 and December 2008, during which an estimated 23 million doses had been distributed (with a course of 3 doses per person recommended). This represents a reporting rate of 53.9 reports per 100,000 doses distributed.

Of these, 772 reports (6.2% of the total) were described as serious, including 32 reports of death.

The authors, headed by Barbara Slade, MD, from the CDC, comment that most of the rates of adverse events after immunization were "not greater than the background rates compared with other vaccines," with the exception of syncope and venous thromboembolic events, which were higher for the HPV vaccine.

These 2 events, syncope and thromboembolic events, were also reported for the HPV vaccine at a higher rate during this postlicensure period than they had been in clinical trials before marketing, the authors note.

Syncope or syncope vasovagal was mentioned in 1896 reports, and dizziness was mentioned in 1572 and nausea in 1164 reports. The reporting rate was 8.2 cases per 100,000 doses distributed. The majority (>90% – 95%) of these reports were classified as nonserious, the authors note. However, some of the reports mentioned falls, and some of these led to fractures, concussions, hemorrhages, and lacerations.

Venous thromboembolic events were mentioned in 56 reports, giving a reporting rate of 0.2 cases per 100,000 doses distributed. Of these, 19 cases involved pulmonary embolism, and 4 of these resulted in death.

Other adverse events included local site reactions (reporting rate, 7.5 cases per 100,000 doses distributed), headache (4.1 cases per 100,000 doses distributed), hypersensitivity reactions (3.1 cases per 100,000 doses distributed), urticaria (2.6 cases per 100,000 doses distributed), autoimmune reactions (0.2 cases per 100,000 doses distributed), Guillain-Barré syndrome (0.2 cases per 100,000 doses distributed), anaphylaxis (0.1 cases per 100,000 doses distributed), death (0.1 cases per 100,000 doses distributed), transverse myelitis (0.04 cases per 100,000 doses distributed), pancreatitis (0.04 cases per 100,000 doses distributed), and motor neuron disease (0.009).

Dr. Markman commented to *Medscape Oncology* that he saw nothing very new or surprising in this article and said that the surveillance shows that the vaccine is "generally quite safe."

Dr. Harper agreed that "HPV vaccination is generally safe for most girls or women," but she also commented that the adverse events reported are "quite significant."

However, Dr. Harper was critical of the system in which the reports were collected. "VAERS, by all accounts, is an inadequate reporting system whose function in this form is biased towards not showing causality," she said. The definition of the denominator (those exposed to the vaccine) is very broad — if this figure was divided by 3 for women who received all 3 doses, then the reporting rate would be increased, she added.

One cannot conclude that there is no association.

"If a statistical association is shown with this level of inaccuracy, then it is truly there," Dr. Harper commented. "But conversely, if no statistical association is seen, one cannot conclude that there is no association."

This point is also made by Dr. Haug in her editorial. She points out limitations of the VAERS reporting system, which the authors themselves emphasize by saying that the "data must be interpreted cautiously and cannot generally be used to infer causal association." Dr. Haug, however, adds that "these limitations work both ways: it is also difficult to conclude that a serious event is not caused by the vaccine."

Dr. Harper also highlighted another concern about the VAERS data. The majority of the reports (68%) were submitted by the manufacturer (Merck & Co), which the authors say compares with a rate of 40% from manufacturers of other vaccines. But for nearly 90% of these reports, Merck & Co would not provide the CDC with any follow-up information to investigate possible statistical causality link. As the authors pointed out in the article, this is unusual behavior for a pharmaceutical company, Dr. Harper comments. During the same reporting period, manufacturers reported only 14.5% of the adverse events associated with *Menactra* (a meningitis vaccine from sanofi pasteur) and only 7.5% of the adverse events associated with *Adacel* (a polio vaccine from sanofi pasteur), she points out.

"Why would Merck make a concentrated effort at reporting nearly 70% of the adverse events for Gardasil if they did not want to control the information?" Dr. Harper comments. "Legislation needs to be enacted to require adverse events reported to pharma to include medical and contact information for potential follow-up by the CDC."

The editorialist and the authors of both articles have disclosed no relevant financial relationships. Dr. Harper reports having received honoraria from Merck & Co and GlaxoSmithKline, and institutions at which she has worked have received funding from both companies to support clinical trials on HPV vaccines. Dr. Markman reports having received grants for educational activities from Eli Lilly and serving as an advisor or consultant for Genentech, Celgene

Corporation, Tibotec, and Boehringer Ingelheim.

JAMA. 2009;302:750–757, 795–796, 781–786.

Authors and Disclosures

Journalist

Zosia Chustecka

Zosia Chustecka is news editor for Medscape Hematology-Oncology and prior news editor of jointandbone.org, a Web site acquired by WebMD. A veteran medical journalist based in London, UK, she has won a prize from the British Medical Journalists Association and is a pharmacology graduate. She has written for a wide variety of publications aimed at the medical and related health professions. She can be contacted at ZChustecka@webmd.net.

Zosia Chustecka has disclosed no relevant financial relationships.

Medscape Medical News © 2009 Medscape, LLC
Send press releases and comments to news@medscape.net.
