

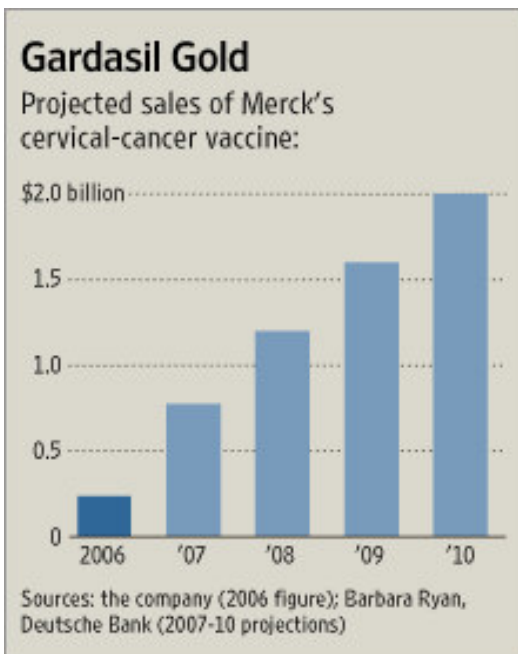
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VIRAL MARKETING

Questions on Efficacy Cloud a Cancer Vaccine

**Merck Predicts Big Fall
In Cervical Lesions,
But Data Are Complex**
By JOHN CARREYROU



When **Merck** & Co. introduced its new vaccine against cervical cancer last June, it gave it one of the biggest pushes any new medicine has received. The company lobbied dozens of states to make the vaccine mandatory for 11- and 12-year-old girls. It aired TV ads featuring young girls skipping rope while reciting the slogan, "I want to be one less" woman to battle the disease.

The campaign scored some big victories. The Centers for Disease Control and Prevention declared all women age 11 to 26 should get the vaccine, called Gardasil. Texas and Virginia passed mandatory-vaccination laws for girls entering the sixth grade. Even after Merck halted its lobbying in February amid criticism, an organization backed by the company continues

to push for similar laws, and about 20 states are considering them. The vaccine costs \$360 for a three-shot regimen. ([See the full CDC recommendations.](#)¹)

But behind the scenes, Gardasil has been dogged by uncertainty about how effective it really is. Merck won approval for the vaccine based on research that showed it protected against two strains of the human papillomavirus, known as HPV 16 and 18, that are thought to cause 70% of cervical-cancer cases. The Food and Drug Administration didn't ask its panel of experts advising on Gardasil to rule on whether the vaccine specifically prevented the cancer itself. In clinical trials, 361 of 8,817 women who received at least one shot of Gardasil went on to develop precancerous lesions on their cervixes within three years of vaccination, just 14% fewer than in a placebo control group.

Scott Emerson, a professor of biostatistics at the University of Washington who sat on the FDA advisory committee, says he's not persuaded the vaccine is worth the billions of dollars likely to be spent on it in coming years. "I do believe that Gardasil protects against HPV 16 and 18, but the effect it will have on cervical-cancer rates in this country is another question entirely," says Dr. Emerson. "There is a leap of faith involved."

Merck says the 14% figure is misleading because more than a quarter of the women in the study were already infected with HPV before receiving the vaccine, blunting its effect. Gardasil isn't designed to treat those with pre-existing infection. The company prefers to point to a subset of 4,616 trial participants who were mostly free of HPV when they were vaccinated. Only 52 of these women went on to develop precancerous lesions on their cervixes over the next three years, 46% fewer than among the placebo group. Merck says this smaller group of women is the one most representative of the 11- and 12-year-old girls for whom Texas and Virginia have required vaccination. (See a [recent presentation by Merck's Eliav Barr](#)⁷ giving the latest data on Gardasil's efficacy.)

Safety is another issue. Merck tested the vaccine in only a few hundred 11- and 12-year-old girls. Some doctors consider that number too small to declare the vaccine safe for preteen girls, given the big changes their bodies undergo.

In its approval letter, the FDA ordered Merck to follow "a sufficient number of children 11-12 years of age" in a large postmarketing study to further establish the vaccine's safety. That study won't be completed until 2009. Norman Baylor, the director of the Office of Vaccines Research and Review at the FDA, says it's common for the agency to recommend postmarketing studies for vaccines, and the FDA considers Gardasil safe.

The company says it complied with the FDA's request that the clinical trials include more than 3,000 9- to 17-year-olds. It adds that it didn't test Gardasil more widely on girls because it wanted to focus on sexually active women to demonstrate the vaccine's efficacy. So far, Merck has distributed more than four million doses of the vaccine in the U.S., and the CDC says adverse events have been mostly minor and within the normal range.

Eliav Barr, the head of Merck's HPV vaccine program, says Gardasil is a "lifesaving" vaccine and its widespread adoption will result in "a substantial decline in the rate of cervical cancer." Dr. Barr says Merck provided "an extremely strong dossier" on Gardasil that both the FDA and the CDC have deemed satisfactory.

Merck has a lot riding on Gardasil. It faces patent expirations on other best sellers and legal costs related to Vioxx, the withdrawn painkiller linked to heart attacks and strokes. Some analysts believe Gardasil's annual sales could reach \$2 billion or more by 2010.

Work on a cervical-cancer vaccine goes back nearly two decades, after scientists discovered that HPV infection can trigger lesions of the cervix that eventually turn into cancer. In the early-to-mid-1990s, Merck licensed patents held by the National Cancer Institute and CSL Ltd. of Australia, and began work on commercializing the vaccine.

From the start, Merck faced a challenge in winning acceptance of the vaccine as a universal necessity for American women. Though common in developing nations, cervical cancer is a relatively rare disease in the U.S., accounting for about 0.7% of cancer diagnoses and deaths each year. Women already have a highly effective method of prevention: visiting a gynecologist for regular Pap tests. The low-tech exam has contributed to an 80% reduction in cervical-cancer deaths in the U.S. over the past 50 years.

Human studies of the present version of the vaccine, which also targets two HPV strains that cause genital warts, began in 2000. The vaccine was administered to more than 20,000

women. It is delivered in three injections over six months. Merck submitted Gardasil to the FDA for approval in 2005.

Hints of Trouble

A meeting of the FDA advisory panel that reviewed Gardasil in May 2006 gave the first hint of Merck's troubles in persuading doctors of Gardasil's real-world efficacy. In its presentation, Merck stressed the vaccine's nearly 100% effectiveness in blocking infection by HPV 16 and 18 and in preventing precancerous lesions caused by those two strains. But a document prepared for the committee by an FDA reviewer noted the vaccine's limited overall efficacy against precancerous lesions in the broader group of nearly 9,000 trial participants. ([Read the FDA reviewer's document.](#)⁸)

Dr. Emerson, the University of Washington professor, expressed concern that Merck wasn't putting enough emphasis on the question of whether the vaccine prevented cervical cancer. "It's almost the treating the symptom but not the disease sort of idea," he said, according to a transcript of the meeting. ([Read the transcript.](#)⁹)

Merck pointed to the confounding factors behind the lower efficacy rates, including the problem of women who came into the trial already infected. In an interview, Merck's Dr. Barr says Gardasil's true efficacy will become more apparent with time, particularly in the group that includes women with a pre-existing infection.

While Merck often states that Gardasil prevents infection with viruses that account for 70% of cervical-cancer cases, Dr. Barr concedes that the vaccine is less than 70% effective against precancerous lesions. Merck says this is because the HPV strains not covered by Gardasil cause disproportionately more precancerous lesions that don't end up turning into cancer.

Efficacy against lesions is a significant issue because after a Pap test, doctors generally remove any lesions that reach a certain grade of seriousness, even though some might not turn into cancer. The surgery involves cutting out part of the cervix and can cost several hundred to several thousand dollars. Dr. Barr predicts Gardasil will eventually be shown to prevent nearly 60% of precancerous lesions that doctors would want to remove among women who were free of HPV infection when they were vaccinated.

Ultimately Gardasil received the panel's unanimous approval, and the FDA approved the vaccine in June 2006. The agency reasoned that waiting for more data would prevent some women who needed the vaccine from getting it.

With the FDA's approval, Merck faced a new challenge: persuading the public to take its vaccine. It got a quick boost from the CDC, which issued guidance in late June recommending that all girls receive the vaccine at age 11 or 12. The CDC said women age 13 to 26 should also get the vaccine. Gardasil was also endorsed by the American Academy of Pediatrics.

Merck crafted its advertising and public relations to avoid some of the less-favorable numbers surrounding Gardasil. The TV commercial says the vaccine "may help protect you" from HPV strains "that may cause 70% of cervical cancer." The company doesn't often discuss the lower efficacy against precancerous lesions or in populations where some women are already infected. The "one less" slogan avoids the question of how many lives will be saved.

Some Gardasil supporters funded by Merck are less careful about qualifying their claims. At the FDA advisory committee hearing, Martha Nolan, vice president of a women's health group that receives funds from Merck, said that by approving Gardasil, the agency had "the opportunity to eradicate this terrible disease."

After the FDA approval, a group of female state legislators called Women in Government started a campaign to get states to mandate vaccinations. The group receives money from Merck but won't say how much. Many of the pending bills would allow parents to keep their children out of the vaccination program, but only after submitting proof that they have received information about cervical cancer and the vaccine.

In early January, Women in Government held a conference for some 60 state legislators in Marco Island, Fla., paying for their airfare and hotel rooms. One of the speakers was Christine Baze, a pop singer and cervical-cancer survivor. As she performed songs on the piano, Ms. Baze told the story of her battle with the disease and said she wished a vaccine had been available to her. Ms. Baze says Women in Government paid her a \$2,500 fee and covered her travel and lodging. She says she didn't receive any money from Merck for the appearance, but the company has paid her \$7,500 to speak at three other events.

Marilyn Canavan, a representative in the Maine assembly who attended the conference, says she was bothered by the large number of drug-industry lobbyists she saw. A list of conference participants shows that 30 pharmaceutical-industry representatives were present -- one for every two state legislators. Merck had two representatives there. Ms. Canavan has since resigned her post as Women in Government's director in Maine over concerns that the group's agenda is being dictated by drug companies. Susan Crosby, Women in Government's president, says those concerns are unfounded.

Other state lawmakers came away from the conference inspired. Upon returning home, Jessica Sibley Upshaw, a representative in the Mississippi assembly, drafted a bill that would make vaccination a school requirement. "For me, it's a common-sense thing to do if we can eradicate a disease," she says. Ms. Upshaw's bill has since died, but she plans to reintroduce it.

Sparking an Uproar

In February, Texas Gov. Rick Perry bypassed the state legislature and issued an executive order mandating that all girls entering the sixth grade be vaccinated as of September 2008. One of Merck's lobbyists in Texas is Mike Toomey, Gov. Perry's former chief of staff, and Merck contributed \$6,000 to the governor's re-election campaign. Mr. Toomey didn't return calls and emails seeking comment. A spokeswoman for the governor says he acted to protect the public's health, not because of the contribution or the lobbying of his former aide.

Gov. Perry's order sparked an uproar. Among the opponents are religious conservatives who say receiving the vaccine conflicts with their message of abstinence. Other opponents say Gardasil isn't worth the cost, which includes \$360 for the vaccine and up to several hundred dollars more for three doctors' appointments to get the shots. The money would be better spent, these people say, in pushing Pap tests for women who aren't getting them now.

John Schiller, one of the National Cancer Institute scientists whose vaccine work was licensed by Merck, believes Gardasil is an important advance that should receive wide use, but he has mixed feelings about the way the company has promoted it. He hopes it won't divert public-health dollars away from regular Pap screening, which he says remains the most important weapon against cervical cancer. Merck "is a heavy-handed company," Dr. Schiller says. "When they do something, they spare no energy. It's the Merck way or the highway."

Merck says cost-effectiveness studies suggest the vaccine could deliver its life-saving benefits at a reasonable cost, in part by reducing the need for frequent Pap tests. Most of these studies have been funded by Merck and **GlaxoSmithKline** PLC, maker of another HPV vaccine, Cervarix. Glaxo applied for FDA approval of Cervarix last month.

One skeptic is Diane Harper, a longtime HPV researcher and professor at Dartmouth Medical School, who was involved in Gardasil's clinical trials and has received speaker and consulting fees from Merck and Glaxo. She says as many as 10% of 11- and 12-year-old girls may already have HPV, either from sexual activity, sexual abuse or transmission through nonsexual skin-to-skin contact. That could reduce the vaccine's efficacy, she says.

Dr. Harper also suspects the vaccine may require booster shots after 10 years. Merck says it's not sure how long the vaccine's protection will last and is monitoring women over the long term to find out.

The American Cancer Society, while agreeing with the CDC that girls should be vaccinated, said in January there is "insufficient evidence" that women age 19 to 26 will benefit from the vaccine because many have already been exposed to HPV.

Worried about the backlash that emerged in February in Texas and other states, Merck shifted into damage control. Richard Haupt, Merck's executive director of medical affairs, placed calls to respected figures in the vaccine field, including Jon Abramson, the chairman of the CDC's advisory committee on immunization practices, and Joseph Bocchini, chairman of the committee on infectious diseases at the American Academy of Pediatrics. Both men and others told Dr. Haupt they supported the vaccine, but it was too early and counterproductive to push for school requirements.

On Feb. 20, Merck announced that it was suspending its lobbying push, but Women in Government continues to lobby for school requirements. Virginia's mandate became law two weeks ago.

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