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THE EVIDENCE GAP

Drug Makers' Push Leads to Cancer Vaccines' Rise

By ELISABETH ROSENTHAL

In two years, cervical cancer has gone from obscure killer confined mostly to poor nations to the West's disease of the moment.

Tens of millions of girls and young women have been vaccinated against the disease in the United States and Europe in the two years since two vaccines were given government approval in many countries and, often, recommended for universal use among females ages 11 to 26.

One of the vaccines, Gardasil, from Merck, is made available to the poorest girls in the country, up to age 18, at a potential cost to the United States government of more than $1 billion; proposals to mandate the vaccine for girls in middle schools have been offered in 24 states, and one will take effect in Virginia this fall. Even the normally stingy British National Health Service will start giving the other vaccine — Cervarix, from GlaxoSmithKline — to all 12-year-old girls at school this September.

The lightning-fast transition from newly minted vaccine to must-have injection in the United States and Europe represents a triumph of what the manufacturers call education and their critics call marketing. The vaccines, which offer some protection against infection from sexually transmitted viruses, are far more expensive than earlier vaccines against other diseases — Gardasil's list price is $360 for the three-dose series, and the total cost is typically $400 to nearly $1,000 with markup and office visits (and often only partially covered by health insurance).

Award-winning advertising has promoted the vaccines. Before the film "Sex and the City," some moviegoers in the United States saw ads for Gardasil. On YouTube and in advertisements on popular shows like "Law and Order," a multiethnic cast of young professionals urges girls to become "one less statistic" by getting vaccinated.

The vaccine makers have also brought attention to cervical cancer by providing money for activities by patients' and women's groups, doctors and medical experts, lobbyists and political organizations interested in the disease, sometimes in ways that skirt disclosure requirements or obscure the companies' involvement.

Even critics of the marketing efforts recognize the benefits of the vaccines. Girls who get the shots are less likely to have Pap tests with worrisome results that would lead to further treatment, saving themselves anxiety and discomfort and, in those cases, saving money. When it occurs, cervical cancer is a dreadful disease; genital warts, partly prevented by the Merck vaccine, can be a painful nuisance.

But some experts worry about the consequences of the rapid rollout of the new vaccines without more medical evidence about how best to deploy them. They say that because of the aggressive marketing, even parents of girls who are far from being sexually active may feel pressured into giving them a vaccine that is not yet needed and whose long-term impact is still unclear. Legislative efforts to require girls to have the vaccine only add to the pressure.

In the United States, hundreds of doctors have been recruited and trained to give talks about Gardasil — $4,500

for a lecture — and some have made hundreds of thousands of dollars. Politicians have been lobbied and invited to receptions urging them to legislate against a global killer. And former state officials have been recruited to lobby their former colleagues.

"There was incredible pressure from industry and politics," said Dr. Jon Abramson, a professor of pediatrics at Wake Forest University who was chairman of the committee of the Centers for Disease Control and Prevention that recommended the vaccine for all girls once they reached 11 or 12.

"This big push is making people crazy — thinking they're bad moms if they don't get their kids vaccinated," said Dr. Abby Lippman, a professor at McGill University in Montreal and policy director of the Canadian Women's Health Network. Canada will spend $300 million on a cervical cancer vaccine program.

Merck's vaccine was studied in clinical trials for five years, and Glaxo's for nearly six and a half, so it is not clear how long the protection will last. Some data from the clinical trials indicate immune molecules may wane after three to five years. If a 12-year-old is vaccinated, will she still be protected in college, when her risk of infection is higher? Or will a booster vaccine be necessary?

Some experts are concerned about possible side effects that become apparent only after a vaccine has been more widely tested over longer periods.

And why the sudden alarm in developed countries about cervical cancer, some experts ask. A major killer in the developing world, particularly Africa, where the vaccines are too expensive for use, cervical cancer is classified as very rare in the West because it is almost always preventable through regular Pap smears, which detect precancerous cells early enough for effective treatment. Indeed, because the vaccines prevent only 70 percent of cervical cancers, Pap smear screening must continue anyway.

"Merck lobbied every opinion leader, women's group, medical society, politicians, and went directly to the people — it created a sense of panic that says you have to have this vaccine now," said Dr. Diane Harper, a professor of medicine at Dartmouth Medical School. Dr. Harper was a principal investigator on the clinical trials of both Gardasil and Cervarix, and she spent 2006-7 on sabbatical at the World Health Organization developing plans for cervical cancer vaccine programs around the world.

"Because Merck was so aggressive, it went too fast," Dr. Harper said. "I would have liked to see it go much slower."

In receiving expedited consideration from the Food and Drug Administration, Gardasil took six months from application to approval and was recommended by the C.D.C. weeks later for universal use among girls. Most vaccines take three years to get that sort of endorsement, Dr. Harper said, and then 5 to 10 more for universal acceptance.

"In that time, you learn a lot about safety and side effects and how to use it," Dr. Harper said. "Those getting it early should be the ones who really want it and willing to accept the risk."

Dr. Richard Haupt, medical director at Merck, said the vaccine had not been rushed into use, saying that five years in clinical trails was normal before applying for licensing. He said Merck educated physicians, politicians and the public about the new vaccine to "accelerate and facilitate access."

Spokesmen for Merck and Glaxo say all indications are that their vaccines are safe and effective, and there is no evidence that a booster shot will be needed. A Glaxo spokeswoman, Sarah Alspach, said its formulation produces a "stronger and longer-lasting immune response" than conventional vaccines.

"You can only study a vaccine for so long before you license and use it in a population where it has enormous value," said Dr. Haupt at Merck. "Our hope and belief is that this is a remarkable vaccine that will have huge impact on women."

But with their high price, the vaccines are straining national and state health budgets as well as family pocketbooks. These were the first vaccines approved for universal use in any age group that clearly cost the health system money rather than saved it, in contrast to less expensive shots, against measles and tetanus, for example, that pay for themselves by preventing costly diseases.

Health economists estimate that depending on how they are used, the two cervical cancer vaccines will cost society $30,000 to $70,000, or higher, for each year of life they save in developed countries — a cost commonly seen in treating people already suffering from deadly cancers. That number will be far higher if a booster is needed.

Looked at another way, countries that pay for the vaccines will have less money available for other health needs. "This kind of money could be better used to solve so many other problems in women's health," said Dr. Lippman at McGill. "Some of our provinces are running out of money to provide primary care. I'm not against vaccines, but in Canada and the U.S., women are not dying in the streets of cervical cancer."

By contrast, if the vaccine were to become cheap enough to be used in the developing world, particularly Africa, it would revolutionize women's health. Charities like the Global Alliance for Vaccine and Immunizations, backed by the Bill & Melinda Gates Foundation, are trying to devise a solution.

The vaccines offer partial protection against infection from human papillomavirus, or HPV, a common and generally benign sexually transmitted virus that can in rare cases cause cancer after years of silent infection. The Merck vaccine also prevents some genital warts that are caused by other strains of the virus.

In Britain, "this initiative was seen as a good use of resources that fits with the government's health priorities and political priorities," said Professor David Salisbury, who heads the Department of Health's Vaccine and Immunization Committee.

But critics urge restraint. "There is no need to rush," said Angela Raffle, a specialist in cervical cancer screening with the National Health Service in Britain, where 400 people die of the cancer each year. "If we do this quickly and badly, we could cause more deaths," from side effects, for example, or from giving girls false security that they are protected for life and no longer need to be screened, Ms. Raffle said.

The Campaigns

Stephanie Levi decided to give her two daughters the vaccine in late 2006 after receiving a newsletter from their physician. "When you get a letter saying this is what you need to do to protect your girls, of course you do it," she said, adding that she was curious because she had not realized cervical cancer was a problem.

That week, she noticed articles and advertisements for the vaccine. "I remember thinking I had better do this quickly," said Ms. Levi who lived in New York then and now lives in Rome.

It is not hard to hear about Gardasil.

In television advertisements, a cast of hip people in their 20s — artists, writers and professionals — describe why they got the shots, in the language of liberation, such as, "I chose to get vaccinated because my dreams don't include cervical cancer." The advertisements direct viewers to gardasil.com, which includes patients' stories,

buddy icons and downloads for holding an event at sororities.

Girls of any age who have had one dose of the vaccine can ask for text-message "reminders" from Merck to get the next two shots. The offers come with another reminder: "I understand that the information I provide will be used by Merck or those working on behalf of Merck for market research purposes."

For such efforts, Merck last May swept the 2008 Pharmaceutical Advertising and Marketing Excellence awards, and Gardasil was named Brand of the Year by Pharma Executive Magazine.

The marketing helped make Gardasil one of Merck's best sellers, with a projected sales of $1.4 billion to $1.6 billion outside Europe this year, and more from sales in Europe, where Merck sells the vaccine through a joint venture with Sanofi Aventis.

Aggressive pharmaceutical advertising is nothing new, but the campaign was a revolution for a vaccine. Vaccines were traditionally the orphans of the pharmaceutical world because they were cheap and not particularly profitable. But the two for cervical cancer are the latest in a wave of high-priced vaccines that have come to market since 2001, opening a lucrative new field.

Co-opting Doctors and Nurses

Girls and their families are by no means the only marketing target.

In 2006, hundreds of doctors and nurses were signed up as unofficial spokesmen for Gardasil, trained by Merck, provided with a multimedia presentation and paid $4,500 for each 50-minute talk, delivered over Merck-sponsored meals. Many were paid for attending Merck "advisory board" meetings to discuss the shots.

Merck said it provided assistance to speakers "to make sure they are providing accurate information in accordance with F.D.A.-approved labeling and to make sure dissemination of information is always appropriate," said Amy Rose, a company spokeswoman.

Promotion and marketing for Cervarix, Glaxo's version of the vaccine, has been far less visible, in part because it has not been approved yet for use in the United States, and because consumer advertising of medicines is prohibited in much of Europe. Outstanding data from final clinical trials will probably be submitted to American drug regulators early next year, the company said.

There has also been a proliferation of cervical cancer awareness conferences and campaigns, sponsored by a host of new or newly energized scientific and patient groups financed with the help of Merck and Glaxo. In some cases the financial support has been indirect, so patients are unaware that expert advice has been at last partly paid for by the vaccine makers.

Gregory A. Poland, a vaccine expert at the Mayo Clinic, was a nonvoting member on the C.D.C. panel that recommended Gardasil in 2006 and has publicly defended the panel's decision. Records show he received at least $27,420 in expenses and consulting fees from Merck from 1999 to 2007. Both the C.D.C. and Dr. Michael Camilleri, chairman of the Mayo Clinic Conflict of Interest Review Board, speaking on Dr. Poland's behalf, said the payments complied with institutional requirements.

To encourage vaccination on campus, Merck provided the American College Health Association with an unrestricted grant to train its officers to speak about the new vaccine and to create kits to discuss cervical cancer and promote the vaccine for college health services. The association now recommends the shot for all female college-age students, even though many in that group already have HPV, rendering the vaccine less useful.

Dr. James Turner, president-elect of the association, said it accepted Merck's grant to undertake the campaign because "HPV is a very important health issue for college students," adding that his group was "a very small organization, and we don't have funds."

Small charities have also benefited from Merck's contributions.

At the second annual patient conference of the National Cervical Cancer Coalition, planned for Los Angeles this October, four of the seven scheduled speakers have received money for research or consulting from Merck, Glaxo or other companies involved in HPV screening or detection, though the conference organizers do not mention that. The coalition, which supports widespread use of the cervical cancer vaccines, is headed by a businessman, Alan Kaye, who owns a pathology lab that performs Pap smears and HPV tests, among other services. "We are a poor nonprofit, and I've been working on this issue for years," said Mr. Kaye, who hopes to receive grants from the drug makers to help pay for the conference.

Persuading the Governments

In country after country, Merck and Glaxo also appealed to politicians. Vaccines, unlike antibiotics, tend to be recommended or mandated by governments. "We support policy leaders and try to educate legislators," Dr. Haupt said.

In the United States, 41 states have passed or begun considering legislation on cervical cancer, according to the National Conference of State Legislatures, and 24 have considered proposals to mandate the vaccine for girls, generally in middle school.

Many bills, like ones passed in Colorado, New Jersey and New York, allocate more money for HPV and cervical cancer education or to promote the vaccine. Others, like proposals in Iowa and Louisiana, require insurers to cover it.

The only state to pass a bill requiring the vaccine for school entry is Virginia; it takes effect in October, after school begins, so will first apply in 2009.

Merck has a growing economic interest in Virginia. In December 2006, Merck announced it would invest $57 million to expand its Elkton, Va., plant to make Gardasil, helped by a $700,000 grant from a state economic development agency that is part of the executive branch. Two months later, Gov. Tim Kaine, who has been mentioned as a possible Democratic vice presidential candidate, signed legislation requiring Gardasil for schoolgirls. Four months after that, Merck pledged to invest $193 million more in the plant to make drugs and vaccines, helped by a state grant of $1.5 million.

Delacey Skinner, a spokeswoman for the governor, said the state's vaccination program included an unusually broad freedom to decline the shot. To exempt children from other vaccines, parents must provide a medical reason; for Gardasil, they do not. "It is a very easy step that we can take to prevent a sometimes deadly but certainly serious form of cancer," Ms. Skinner said.

"Without hesitation or question," she added, the decisions about the plant and about the mandate legislation "were completely separate."

But, as in many states where cervical cancer legislation has been considered, there have been ties between drug makers and members of government. In 2006, one of Merck's newly hired Virginia lobbyists was Sandra D. Bowen, who had spent years as Virginia's secretary of administration. And Bill Bolling, the state's lieutenant governor, became an outspoken participant in the "Ending Cervical Cancer in Our Lifetime" campaign, a program

started in 2006 by the National Lieutenant Governors Association and financed largely by Merck and Glaxo.

"This is an important public health issue," said Randy Marcus, Mr. Bolling's spokesman.

In Texas, Merck hired Gov. Rick Perry's former chief of staff as a lobbyist, and contributed $6,000 to the governor and $38,000 to other legislators. Last February, Mr. Perry ordered that all schoolgirls be inoculated with Gardasil, a pronouncement that was overturned by the Texas Legislature, 181 to 3, a few months after the financial conflicts were revealed.

Early last year, Merck announced that it would no longer actively lobby for state mandates. But Dr. Haupt defended the initial impulse, saying that historically such school requirements had been a successful way to increase access to and financing for vaccines.

Other forms of lobbying continue: Merck and Glaxo have both paid into a program run by Cornerstone Government Affairs, a Washington firm, to lobby the C.D.C. and Congress for more federal money for vaccines.

In Britain, drug makers paid for breakfast meetings with politicians and visited the nurses and family practitioners who are the backbone of the National Health Service, urging them to offer the vaccine.

In Belgium, the health minister approved the vaccine before the country's health technology evaluation committee had finished deliberating.

Unanswered Questions

Many questions about the vaccines remain unanswered, including how long immunity will last. Even commercials for Gardasil say — in small print — that "the duration of protection has not been established."

Dr. Harper said that in the data from Merck's clinical trials, which she helped conduct, the vaccine was no longer protective after just three years in some girls. "The immunity of Gardasil will not last — that is dangerous to assume," she said.

She said she believed that at least one booster shot, and probably more, would be needed over a lifetime. Dr. Haupt of Merck said that the "durability of immunity" would ultimately be defined through widespread use of the vaccine, but that the company's research strongly suggested that immunity would be long lasting — far more than five years.

Other independent experts worry that eliminating the two cancer-causing HPV strains covered by Gardasil and Cervarix might allow the other cancer-causing strains of HPV to increase in frequency, reducing the vaccine's effect. But Dr. Haupt said such "theoretical possibilities" should not deter rapid distribution of an important vaccine. "We'll worry about whether boosters are needed down the road," he said.

The question of side effects, however, has nagged the vaccine.

The Centers for Disease Control asks health care centers to report side effects through its Vaccine Adverse Events Reporting System; reporting is voluntary. There have been 9,749 reports, almost all from doctors and nurses, of patients experiencing adverse events after receiving the vaccine, the agency announced in a joint report with the Food and Drug Administration at the end of June. Ninety-four percent of them were not serious, ranging from arm pain to fainting, and 6 percent were classified as serious, including blood clots, paralysis and at least 20 deaths.

But 16 million doses of the drug have been distributed by Merck in the United States, and in a population so large,

"by chance alone some serious adverse effects and deaths" will occur, the F.D.A. and C.D.C. said.

The agencies said there was no indication that the deaths or serious side effects were caused by the shot, concluding that "Gardasil continues to be safe and effective and its benefits continue to outweigh its risks."

Both the agencies and Merck acknowledge that there does appear to be a high rate of fainting, so doctors are now advised to observe patients for 15 minutes after receiving a shot.

For some couples, the vaccine has raised agonizing questions over how to safeguard their children's health. Phillip and Barbara Tetlock, both professors at the University of California at Berkeley, are asking whether Gardasil shots that their daughter, Jenny, received last year contributed to her illness, an extremely rare form of progressive paralysis that has left her bed bound and needing assistance to breathe at age 14.

The Tetlocks, who are not pursuing legal action, are appealing to the C.D.C. and Merck for more data and searching for other girls with similar conditions through their blog (www.jenjensfamily.blogspot.com). "Her parents are scientists — they know better than to assume Gardasil caused her disease," said Terry Murray, a close friend speaking for the family. "But you have to explore the possibility."

Dr. Harper said she believed the vaccine was generally safe. She vaccinated her own children. But with Gardasil's use having grown so fast, she added, "you inevitably find adverse events that you wouldn't have suspected."

"The Tetlocks are right to ask these questions," she added.

Dr. Haupt of Merck said that the company knew of the case but saw no "causal association."

Worth the Cost?

Countries and consumers must decide whether it is worth preventing cervical cancer with a costly vaccine.

Cervical cancer is the second-leading cause of cancer death in women, with 500,000 new cases worldwide each year. But more than 90 percent of them are in developing countries, according to the World Health Organization; 274,000 women died of this cancer in 2006, nearly 95 percent in developing countries.

Where there are Pap smear programs, few women die of cervical cancer. In the United States, it is responsible for 12,000 new cases a year and 3,600 deaths, most in women who did not get Pap smears, said Laurie Markowitz, head of the HPV working group at the C.D.C. (Women with H.I.V. are predisposed to the cancer.)

Pap smears work by detecting abnormal cells that are cancer precursors and that can be destroyed using techniques like lasers and cryotherapy or, rarely, surgery. As with any screening test, and most vaccines, the process is not 100 percent effective, and a small number of women with precancerous cells escape detection with false negative tests, for example. But because the transformation from abnormal cell to cancer normally takes a decade, and frequent Pap smears are recommended, it has been a successful strategy — though the vaccine, used properly, might well prove a useful adjunct.

Indeed, cervical cancer does not even make the American Cancer Society's list of 10 deadliest cancers. Among American women, it causes well under a 10th of the number of deaths caused by lung cancer or breast cancer.

Though classified as a sexually transmitted disease, HPV is nearly universal and generally benign. Eighty percent of people will contract it in their lifetime and most will clear it on their own.

Dr. Haupt of Merck said the vaccines' price was worth it for the deaths prevented and the tests avoided. "Most of

the old vaccines are undervalued," he said.

Dr. Abramson said he thought his C.D.C. advisory committee did the right thing in recommending Gardasil. "Cervical cancer is a worthwhile disease to prevent in a country that has the resources," he said. He believes it should be available to those who want it.

Still, he said he was shocked to hear of proposals to mandate the vaccine for students. "Are you really going to say a girl can't start school because she hasn't had this vaccine?" he said.

Meanwhile, the vaccines' proponents are moving to the next frontier: older women and boys. Merck recently applied for approval to market the vaccine to women 26 to 45 and is conducting studies on vaccinating boys, who can get genital warts from HPV.

One rationale for inoculating boys is that entire populations should be vaccinated to achieve what is called herd immunity. But critics ask whether it is worth conducting a campaign on the scale of the one used against polio to eliminate a generally harmless virus.

Said Dr. Raffle, the British cervical cancer specialist: "Oh, dear. If we give it to boys, then all pretense of scientific worth and cost analysis goes out the window."

Andrew Lehren contributed reporting.