

Flogging Gardasil

In its rush to market its human papillomavirus vaccine, Merck forgot to make a strong and compelling case for compulsory immunization.

Merck's human papillomavirus (HPV) vaccine Gardasil should have been an easy sell. It protects against cervical cancer, the second most common cancer among women. It demonstrates 100% efficacy in preventing infection by the two HPV types most commonly associated with that cancer. And it was endorsed by the World Health Organization and the US Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices. But the company's heavy-handed lobbying of legislators seems now to have soured the reception for this important vaccine and perhaps has sullied the reputation of vaccination in general.

Each year, cervical cancer is diagnosed in ~470,000 women worldwide. Of these, one in two will die, most of them in Latin America, Africa, India and South Asia, where the resources and infrastructure to fully implement Papanicolaou (Pap) smear tests are limited. (In the past four decades, industrialized countries have cut cervical cancer mortality and incidence rates by 74% largely through the use of the Pap smear).

Virtually all (99%) cervical cancers are linked to infection with HPV, and HPV is virtually unavoidable. According to the CDC, almost 80% of US women have acquired one or more genotypes of HPV by the age of 50. Most genital infections are asymptomatic and resolve spontaneously, but the virus can persist and cause precancerous lesions that can become malignant over the subsequent 20–30 years.

Thus, a vaccine like Gardasil has a huge potential market. Based on L1-encoded virus-like particles, it protects against the HPV genotypes 16 and 18 (which account for 70% of cervical cancers) and HPV 6 and 11 (which cause >90% of genital warts and cause abnormalities or dysplasia that can confound Pap test results). And ever since Gardasil gained US Food and Drug Administration (FDA) approval last June, Merck has made no secret of its ambition to make it into a blockbuster product.

In 2005, 1,500 of its sales reps were redeployed to vaccine marketing. It ramped up contributions to political campaigns and to women's health interest groups. And in recent months, it started an unprecedented lobbying blitz, securing in 23 states legislation that would mandate vaccination of pre-teen girls. Unusually, Merck also targeted adolescents directly through television ads in which free-spirited young girls jump rope, pummel punching bags or skateboard, declaiming "one less" cervical cancer case (while mothers gently admonish, "Gardasil may not fully protect everyone" and tenderly list the side effects).

This all seemed to be working very nicely—by October last year the company had already sold ~\$80 million worth of the vaccine. But in the New Year, things began to unravel.

Religious moral crusaders, of course, already opposed the vaccine. But they were joined by an increasingly vocal group of families and consumer advocates who felt that government-mandated HPV vaccination trespassed on the right of parents to make medical decisions for their children (even though most state bills had an opt-out provision). In January, the medics joined in: the American Academy of Pediatrics and the Association

of American Physicians and Surgeons, among others, voiced concerns over patchy reimbursement, absence of safety data in the target population and the wisdom of immunizing girls against a disease that is now less prevalent in the US and that, in any case, doesn't develop until later in life (prompting the question, "Will immunity last?").

Things came to a head, though, early last month when Texas governor Rick Perry circumvented his state legislature and signed an executive order making HPV vaccination compulsory for 11- to 12-year-old girls. Adding fuel to the resulting outcry, it was revealed that Merck had contributed \$6,000 to Perry in the past and now employed Mike Toomey, a former Perry chief of staff, as its lobbyist.

Surrounded by a chorus of disapproval, Merck cracked. As *Nature Biotechnology* went to press, the company announced a cessation of all efforts to lobby for US state laws requiring compulsory vaccination.

There are several lessons from all this. First of all, make the clinical case fully. Preteens are the preferred demographic for vaccination (Gardasil is ineffective in HPV-infected subjects, so sexually inactive girls are the ideal immunization population), but only 1,184 (5%) of the 25,000 people participating in Gardasil's clinical trials were from this group. Critics could, therefore, claim that an "untested" product was being foisted onto America's children, and Merck didn't have a strong enough data-based case to allay parents' fears concerning vaccine safety. Merck's quest for compulsory immunization so soon after approval also broke with precedent for vaccines, which are usually in use for years before being mandated.

Second, if you're going to introduce the most expensive vaccine in history (\$360 for three doses) as a government-mandated prophylactic, you'd better make a solid economic case. A back-of-the-envelope calculation shows that an immunization program in 11- to 12-year-olds would cost \$30 billion (4 million children per year \times \$360 \times 20) in the first 20 years before Gardasil would save a single life. This is a huge initial outlay, even when the net present value of the long-term savings in reduced screening and treatment in an HPV-immune population are considered.

Finally, present the product in its full context. Gardasil is an important part of the cervical cancer management picture, but not the whole solution. Greater awareness of disease risks, safe sex, condom use and improved 'opt-in' cervical cancer screening should also have been promoted. If Merck had run a public health education campaign rather than simply plugging its product, Gardasil might have had a better reception.

It's telling that Peter Loescher, Merck's president of global human health, emphasized to Wall Street in January the need for "speed, speed, speed" in a product launch. But amid its overblown marketing blitz, the company lost sight of another important goal: full engagement with stakeholders, whether they be the media, opinion leaders, physicians, pharmacists, health workers or the general population (which ultimately pays for it all). Only after this has been accomplished should the marketers be unleashed.

