

People In Life Sciences (P.I.L.S.)

New report on cervical cancer vaccine gets media jumping

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Mark Terry



A media and industry buzz was created with the publication of a paper in *The Lancet Oncology* by researchers at Merck & Company, Inc., about results from a Phase II clinical study comparing their new human papillomavirus (HPV) vaccine, Gardasil, against a placebo. There are currently two major clinical trials underway for an HPV vaccine, the other for a vaccine called Cervarix by GlaxoSmithKline.

The media jumped on the news with both feet in a way that seems somewhat premature for the results of a Phase II clinical trial and a Phase III clinical trial that is just beginning. Gregory Zimet, PhD., a psychologist and professor in the Department of Pediatrics at the University of Indiana School of Medicine whose research interest is vaccine acceptance, says, “For some reason there has been a bit of a whirlwind of stories about HPV vaccination, and a lot of reaction. I don’t know if it’s premature—I know there’s this new paper—but it’s not as if the vaccines are coming out in a month or two months.”

The interest is possibly two-fold. One, it’s the first vaccine that has the potential to eliminate a form of cancer. And two, because the human papillomavirus is transmitted sexually, there is both a political and religious component to the story, with expected controversy.

HPV and Cervical Cancer

Human papillomaviruses (HPVs) as a group consists of more than 100 different viruses. More than 30 of those viruses are transmitted sexually, infecting both men and women. Some cause genital warts. Others can develop into cervical cancer. HPV infections are common. The Centers for Disease Control and Prevention (CDC) estimate that each year 6.2 million people in the United States get a new genital HPV infection. About 14 strains or subtypes of HPV are associated with a high-risk of cervical cancer development. Of those 14 subtypes, two--16 and 18--are responsible for about 70 percent of cervical cancers worldwide. Some reports say that by 50 years of age, 80 percent of women will have acquired genital HPV infection. Pamela Duncan, company spokesperson for GlaxoSmithKline Biologicals, says, “It is important to remember that the predominant disease burden of high-risk HPV types 16 and 18 is related to cervical cancer and associated pre-cancers in women. This is a devastating disease, the second most commonly diagnosed cancer in women worldwide. Each year approximately 500,000 women are diagnosed with cervical cancer and an estimated 270,000 women die from the disease.”

Dr. Mack T. Ruffin IV, MD, MPH, Associate Professor of Family Medicine at the University of Michigan's Comprehensive Cancer Center says that cervical cancer is relatively uncommon in the United States. "It's been almost eliminated with the introduction of Pap smears. The burden we're going to be eliminating with the vaccine is not so much cervical cancer, but the huge burden that relates to having an abnormal Pap smear and the intermediate steps that would lead to cancer. Now, clearly, the 4,000 or 5,000 women a year who get cervical cancer, if the vaccine prevents getting cervical cancer, that would be a huge impact."

The Vaccine Clinical Trials

Merck and GlaxoSmithKline's HPV vaccine trials take slightly different approaches. GSK's vaccine, Cervarix, uses only two strains of HPV, types 16 and 18. Says Duncan, "In a Phase II trial, Cervarix was shown to protect women 100 percent against persistent infection and against early pre-cancer lesions caused by HPV 16 and 18. GSK's candidate HPV vaccine contains an innovative adjuvant. It has been shown in several studies that using this adjuvant in the HPV vaccine, compared to using a conventional alum adjuvant, resulted in higher, stronger and longer antibody response."

Representatives of Merck did not respond to repeated interview requests for this article. However, their product, Gardasil, is slightly different from Cervarix. Says Ruffin, "There's a little nuance about the Merck vaccine, because the Merck vaccine is a quadrivalent vaccine—it goes after four different HPV types—and they include (in addition to subtypes 16 and 18) 6 and 11, not because they play a big role in cervical cancer, but because they play a big role in genital warts."

The Merck Gardasil clinical trial is in the Phase II and Phase III phases. The GSK Cervarix trials is beginning a large Phase III trial, which will involve over 30,000 women worldwide. "These large-scale trials with long-term follow-up are being carried out to extend the observations made in the pivotal proof of efficacy study, published in the *Lancet*, November 19, 2004, which were the first demonstration by a cervical cancer vaccine of complete protection against two high-risk HPV types," says GSK's Duncan. "The Phase III trials are also designed to confirm that vaccination impacts cervical lesions and further document the safety of GSK's HPV vaccine. These trials will report at various times between 2005 and 2009."

Although these vaccines stop the HPV virus, and the HPV virus can lead to cervical cancer, it's difficult for scientists to then definitively conclude that the vaccines prevent cervical cancer. "One interesting aspect that neither company has addressed that I've seen in public forums or their writings," says Ruffin, "is the fact that we still do not know the immune reaction that needs to take place to prevent HPV from developing in the lymph or prevent the development into cervical cancer. So we don't know the correct immune response that needs to take place and we're just assuming that, based on a significant antibody response present, it will prevent that. We don't know. Neither has shown that they prevent cancer. Both have shown that people vaccinated had significantly lower rates of precursor lesions, but neither one has shown that they prevent

cancer.”

Controversies?

Sexual Behaviors

Some of the furor over these vaccines has to do with the fact that HPV is sexually transmitted. Dr. Louis Cooper, MD, who is on the Steering Committee of the National Network for Immunization Information (NNii), says, “We are such a heterogeneous world with such diverse opinions about sexuality, for example, that it’s hard at the moment for me to have a feeling about how mom and pop, taking their 11-year-old in, what their views are going to be in regards to giving a vaccine that is heavily focused on sexual transmission. So public acceptance, best times to distribute, how much it’s going to cost, who’s going to pay for it, should it be routine, does it fall into being desirable for all kids, will you just give it to kids who are ‘high risk.’ These are all the kinds of questions that I know will go on. And they’re discussions for which I don’t think the answers are in, but bottom line, my sense of it is that this will be another valuable tool in preventing a serious cancer.”

Interestingly, Zimet recently published a study on this subject, “Parental Attitudes About Sexually Transmitted Infection Vaccination for Their Adolescent Children.” [Zimet GD et al. Archives of Adolescent Medicine. 2005;159:132-137]. “What I found,” says Zimet, “and this is relatively consistent across the research, not just mine but other people’s, is that the large majority of parents are really interested in vaccinating their kids against HPV and other STDs. Our expectations, actually, were that there would be more resistance than we found.”

For this particular study, Zimet says, “I think there may be parents who may be a little uncomfortable with the whole issue, but I think for the vast majority of parents, the desire to better protect their children is really the overriding moral and ethical belief. They may be uncomfortable with the idea of their adolescents having sex, but they want to protect them.”

Dr. Michael Caldwell, MD, MPH, is one of the principle investigators for the HPV study with GSK and the Commissioner of Health for Dutchess County, New York. “I think this is predominantly a vaccine that’s geared to reducing the burden of cervical cancer in our society, and that we know the causative agent happens to be a particular virus, and that virus is connected to being transmitted through sexual activity,” says Caldwell. “I don’t think anybody’s going to dare say that if you get this vaccine you don’t have to worry about sexually transmitted disease, because there’s plenty to go around. It’s still a problem. But this one is very closely linked to cervical cancer.”

Who and When to Vaccinate

Assuming the vaccines get FDA approval, who do you vaccinate and when? GSK’s Duncan says, “It will ultimately be up to the independent advisory committees on immunization practices in each country to make recommendations on the most effective vaccination policy from a public health perspective. HPV infection is a normal part of

women's life regardless of the age at which they start a sexual relationship or partnership. Up to 70 percent of women contract HPV at some point during life. GSK believes that it would be appropriate if its candidate HPV vaccine targeting cervical cancer were available for all women and adolescent girls (10 years and older) worldwide to protect them from cervical cancer."

The issues here have to do with vaccination prior to sexual activity. "Right now they're studying women 18 and older who have less than four lifetime sexual partners. So they're really trying to find women who haven't been exposed to HPV and vaccinating them only," Ruffin says. "This is a sexually transmitted infection, so does it make sense to only vaccinate half of the partnership that's causing the infection? And then, the question of when to vaccinate them--do you wait until they're 18 or do you vaccinate under 18? I've actually heard both companies suggesting you just vaccinate infants, and that's really based on the idea that they're the easiest population to grab."

Caldwell has a slightly different take on the situation, noting that the GSK study focuses on women 15 to 25 years old. The Merck study, according to their guidelines on the National Institutes of Health clinical trials website (<http://www.cancer.gov/clinicaltrials/>), is on women 24 to 45 years of age. "My experience," says Caldwell, "is that the FDA will look to approve an age range based upon what was tested. So, should—at least for this product—it be found to be safe and effective for this age group because we tested on this age group, my experience tells me that they will only be approved for this age group. Now, subsequent to that, I would imagine there would be spin-off trials where we use expanded age groups or whether we need booster shots or things like that. I think initially you would probably only see FDA approval for whatever we have data for."

Marketing Considerations

Clearly, when and if either of the vaccines gets approved by the FDA, many issues will have to be decided. The topic is already a little bit of a political hot potato, with some conservative religious groups arguing that there already is a way to prevent HPV—abstinence, and conservative politicians and lobbyists going after research and funding that might be construed as promoting sexual promiscuity.

The two companies involved may, oddly enough, find themselves on different sides of the issue. Says Zimet, "They've taken a slightly different tack. GSK's taken the two types, about 70 percent associated with cervical cancers and no types associated with genital warts, whereas Merck has gone with the quadrivalent one that includes the two types associated with about 90 percent of (genital) warts. Once you have a vaccine that includes genital warts prevention, it's pretty hard to pretend that it's not a sexually transmitted infection (STI) vaccine. In both cases it's pretty clear that you would want to market it as a cervical cancer vaccine. The issue is, what else do you say?"

As mentioned earlier, the vaccines seem to prevent the virus, but the actual prevention of cervical cancer remains—at this time, anyway—unproven. "I think," says Zimet, "that with the HPV vaccine there are some things they don't know about. They obviously

haven't been able to test it for the ultimate end state of cervical cancer. They're ultimately open to criticism. Is the FDA going to say, 'You can't say that this prevents cervical cancer because we don't know that yet?'"

On the other hand, who's going to intelligently argue against a vaccine against cancer? "I think it will be interesting to see how this plays out," says Zimet. "For instance, to be able to say to these [conservative] groups, 'Are you saying you're pro-cancer?' I'm just not sure that's a position that they're ultimately going to want to take."

270,000 A Year

With all the attention sometimes focused on the political issues and whether or not it should be done, and when, and who pays, it's sometimes possible to lose track of what the HPV vaccine is all about—the potential elimination of a type of cancer that kills over a quarter of a million women a year worldwide. Maybe everybody should just take a breath and think about that number for a moment. "I think at this point we need to complete the studies," says Caldwell. "We need to present the results to the FDA advisory panels so that they can decide, based on their criteria, whether it meets (necessary) safety and effectiveness. And hopefully they will and we'll have another tool to provide reduction of cancer in our community. So we're really very excited about it. It seems very positive and we just want to keep moving forward."