

HPV & CERVICAL SCREENING 2007

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EXPERT PANEL

The new HPV vaccine: What the ObGyn needs to know

Who should be immunized? Who pays? Should women over 26 be vaccinated? Is cervical screening on its way out?

What once seemed far in the future is now a reality: the human papillomavirus (HPV) vaccine. The quadrivalent vaccine (Gardasil) that prevents the development of lesions caused by HPV types 6, 11, 16, and 18 was approved last June by the US Food and Drug Administration (FDA) for clinical use in females 9 to 26 years old. Shortly after its approval, the Advisory Committee on Immunization Practices (ACIP) issued guidelines on who should be vaccinated.

In light of these developments, OBG MANAGEMENT invited Dr. Tom Wright to convene an expert panel to discuss the ACIP recommendations and ways of introducing the vaccine into practice.

ACIP recommends vaccination at age 11 or 12

WRIGHT: Dr. DeFrancesco, would you review the ACIP recommendations for us?

DEFRANCESCO: Shortly after the FDA approved Gardasil, the quadrivalent vaccine (Merck, Whitehouse Station, NJ), the ACIP recommended routine vaccination with 3 doses for girls aged 11 or 12 years,

but noted that vaccination is also acceptable for girls as young as 9 at the discretion of the physician or health-care provider. The new 2006–2007 Recommended Adult Immunization Schedule states that the HPV vaccine is “recommended for all women aged ≤ 26 years of age” (available at www.cdc.gov/nip/recs/adult-schedule).

Ideally, the vaccine should be given before the onset of sexual activity (ie, before a woman is exposed to the virus), but sexually active girls and women through 26 years should still be vaccinated, as they are not likely to have been exposed to all 4 HPV types covered by the vaccine.

ACOG recommendations mirror those of ACIP

WRIGHT: Dr. Gall, are ACOG’s recommendations similar to the ACIP’s?

GALL: Yes. They mirror those of the ACIP, as they recommend that:

- All females aged 9 to 26 years receive the vaccine. For the ObGyn, that will usually mean adolescent females and young women through 26 years.
- In the target population, the vaccine is warranted if the patient has a history of abnormal cytology, HPV DNA positivity, or genital warts.
- There is no need to assess whether the patient is positive for any of the vaccine

Dr. Wright is an author of the 2001 Consensus Guidelines on Managing Women with Cytological and Histological Abnormalities, the 2004 Interim Guidance for Use of HPV DNA testing for Primary Screening, and the 2001 Bethesda System. He is Professor of Pathology, Columbia University, New York.

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HPV types before giving the vaccine.

- There is no reason to expect a negative immune effect when the HPV vaccine is given with other vaccines. For example, when the HPV and hepatitis B vaccines were given together, no negative effect on immune responses (eg, “non-inferiority”) was observed with either vaccine, according to a randomized study of more than 1,100 patients.¹ Although we lack data on coadministration of the HPV vaccine with the meningococcal conjugate vaccine (MCV4) or the tetanus, diphtheria, and pertussis (Tdap) vaccine, there is no reason to think non-inferiority will exist.
- Because the HPV vaccine is a non-live virus vaccine, it can be given to immunosuppressed women. However, the immune response in these patients may not be as robust as in women with normal immune systems.

■ Should sexually active women be vaccinated?

WRIGHT: Both the ACIP and ACOG suggest that we encourage “catch-up” vaccination of sexually active women through 26 years. However, many experts disagree, arguing that vaccination of this population may not be worth the effort.

Dr. Gall, why does ACOG recommend that sexually active women get vaccinated?

GALL: Data from the Merck Phase III trials indicate that only 25% of women at age 23 are either serologically or DNA positive for 1 of the 4 HPV types included in the quadrivalent vaccine and that only 0.1% of women are positive for all 4 vaccine HPV types. Data on HPV 16 from the National Health and Nutrition Examination Surveys (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), are in line with this estimate. It is pretty clear that most sexually active women aged 26 or younger will benefit from vaccination.

Vaccine may benefit even women with high-risk sexual practices

WRIGHT: OK, Dr. Levy, you heard Dr. Gall

say we should vaccinate sexually active women. Are you convinced? What are you going to tell a 24-year-old single woman who has had 12 lifetime sexual partners?

LEVY: I would tell her that she is extremely likely to have been infected with 1 or more HPV strains—but unlikely to have been exposed to all 4 types present in the vaccine. I would also explain that the vaccine is almost 100% effective at preventing genital warts caused by HPV 6 and 11 and will prevent both infections and lesions with HPV types 16 and/or 18 if the patient has not been exposed to them.

The benefit for this 24-year-old may not be as great as it is for our primary target population of preteens not yet exposed to HPV, but vaccination can reduce the disease burden—even in a woman who has had multiple sexual partners.

If this patient has already had genital warts and an abnormal Pap smear, or is positive for high-risk HPV DNA, the benefit would be even lower. Ultimately, she will have to decide whether the cost is worth the lessened benefit in her situation.

Lessons learned from the hepatitis B experience

WRIGHT: One of the things we learned 20 years ago when we introduced the hepatitis B vaccine is that limiting vaccination to

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“Vaccination can reduce the disease burden—even in a woman who has had multiple sexual partners”

—Barbara S. Levy, MD

groups expected to gain the most benefit doesn't work very well. With hepatitis B, we initially targeted only high-risk groups such as intravenous drug users, men who have sex with men, and health-care workers—but this strategy didn't reduce the rate of hepatitis to the extent expected. Once we recommended universal vaccination of the general population, however, a rapid reduction in hepatitis B occurred.

In many respects HPV is like hepatitis B. I have heard some experts say that we may eventually vaccinate all at-risk women—essentially, all sexually active women.

■ Vaccinate women over age 26?

WRIGHT: Women older than 26 are already asking whether they should be vaccinated. What do we know about the safety and efficacy of the vaccine in these women?

GALL: Even though the number of women infected with at least 1 HPV type, or who have evidence of such infection, exceeds 60% by age 50, only a small number of women will have been exposed to all 4 HPV types covered by the vaccine. Thus, it seems likely that sexually active women over age 26 will benefit from vaccination.

The safety data on the vaccine are excellent. In our experience, the quadrivalent vaccine has been less reactogenic than the influenza vaccine. There is no reason to suspect that the HPV vaccine will be less safe in women over age 26.

Recently, immunogenicity data for the bivalent vaccine—not yet approved by the FDA—were presented to the American Society of Clinical Oncology for women aged 26 to 55 years, and excellent immune responses were observed. All we need to recommend vaccination of sexually active women over age 26 is the efficacy data, and I see no reason to think that the HPV vaccine will not be effective.

■ Counsel older women about off-label use

WRIGHT: What would you tell a recently

divorced 32-year-old who got married in college, has had only a couple of partners, and is beginning to date again?

DEFRANCESCO: The vaccine is approved and recommended only for females aged 9 to 26, so vaccinating an older woman would be off-label—or “off-recommendation,” as those who specialize in vaccination say.

We also know that the immune system is generally more responsive in younger people, although the immunogenicity data that Dr. Gall just mentioned indicate that the bivalent HPV vaccine is highly immunogenic in older women. I would be hard-pressed to deny the apparent protection of the vaccine to a 32-year-old woman simply because she is over age 26.

However, given the medicolegal climate, I would ensure that informed consent includes a caveat about use of the vaccine in someone outside the approved age range and makes it clear that the patient has acknowledged being informed about the “off-recommendation” use.

Readers will want to know that Phase III trials are now assessing the safety and efficacy of the quadrivalent and bivalent vaccines in women over 26; data should be available in the next couple of years.

WRIGHT: I agree completely. In today's litigious world, it is vital to counsel women appropriately and obtain informed consent prior to any vaccination. One way to educate the patient about potential benefits and risks is by providing her with a Vaccine Information Sheet, available for download from the CDC's Web site (www.cdc.gov/nip/publications/VIS/default.htm#hpv).

■ Can an adolescent give her own consent?

WRIGHT: It has not yet been fully clarified whether a sexually active adolescent can provide consent on her own, or whether a parent must sign the consent form. Most states have laws that allow at least some adolescents to seek reproductive services, as well as screening and treatment for sexually transmitted diseases, without

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parental notification. However, at several meetings I attended recently, lawyers specializing in the legal rights of adolescents said it remains unclear which of these state laws extend to the HPV vaccine.

DEFRANCESCO: I've been told the same thing by our legal advisors. Pending clarification, it is important to emphasize to our patients that the vaccine is a cancer vaccine, not a drug to prevent sexually transmitted infection. The vaccine does not give young people "permission" to have sex, but helps prevent them from ever developing cervical cancer. Young people should not have to sneak around to get this protection.

■ Who will pay for it?

WRIGHT: One of the really big issues is how we are going to pay for the HPV vaccine, which has a list price of \$120 per dose and requires 3 injections. If you add the cost of 3 office visits, that's almost \$500.

LEVY: Most insurance companies in our area have already determined that they will cover the HPV vaccine. Even carriers that are usually slow to make coverage decisions added the HPV vaccine to their list of covered services fairly promptly.

WRIGHT: That's good news for people who have health insurance. What about women who don't, or who have high deductibles or carve-outs for "preventive services"?

Patients may be willing to foot the bill

LEVY: I have been discussing the vaccine with eligible women and mothers of young girls for several months. Even before payers stepped up with coverage, no patient was seriously concerned about the cost. Clearly, this will not be true for everyone, but when offered an opportunity to avoid cancer, my patients have been happy to pay for it. In addition, many offices now accept credit cards, which may make it possible for patients to make payments over time.

I think success will depend in large part on how we educate our patients. I frequently discuss preventive care in the context of other things we do in our lives for

"maintenance." For example, none of us would expect our automobile insurance to cover the cost of changing the oil or buying new tires. The HPV vaccine is comparable: The costs incurred now may prevent significant health risks in the near future.

Further, the price of the vaccine series is quite low relative to the potential costs of office visits for follow-up of abnormal Pap smears or treatment of genital warts.

We must stress to our patients that Pap smears aid in the *detection* of cervical cancer precursors, but the vaccine is an opportunity to *prevent* cervical cancer.

The poor and uninsured have several alternatives

WRIGHT: In the predominantly Latin American neighborhood where I am located, there are many uninsured who simply cannot afford \$500 for the full course of 3 vaccinations. For uninsured children and adolescents, or those on Medicaid up to age 19, the federally funded Vaccines for Children program will cover the cost. However, for women aged 19 and older, vaccinations are considered an "optional" benefit under Medicaid, which means that individual states must decide whether the HPV vaccine will be a covered service.

One bit of good news: Merck plans to provide free vaccines, including the HPV vaccine, to low-income and uninsured adults 19 years and older who visit private clinicians who already provide Merck vaccines. Although the details of this initiative have not been finalized, the program may help individuals in states that decide not to cover the HPV vaccine with Medicaid.

■ Vaccine appears safe near time of conception

WRIGHT: I have heard varying opinions about the level of risk vaccination poses if a woman becomes pregnant shortly afterward. What do the data show?

GALL: It is inevitable that this vaccine will be administered to some women who are not yet aware they are pregnant. In the



"Young people should not have to sneak around to get this protection"

—Mark DeFrancesco, MD, MBA

Merck trials, more than 1,000 pregnancies occurred in both the vaccine and placebo groups. There were 15 abnormal infants in the vaccine group and 16 in the placebo group. The abnormalities were nonrepetitive and did not raise concern at the FDA.

Among the women who received an injection within 30 days of conception, there were 5 abnormalities, compared with none in the placebo group—but none of the abnormalities were repetitive and some involved such things as an extra digit.

The vaccine was accorded a pregnancy category B. This is a landmark for the FDA because no other vaccine has this designation, even those used extensively during pregnancy, such as the trivalent inactivated influenza vaccine (TIV) and hepatitis B.

At present, clinicians are asked to report any women who receive the quadrivalent vaccine and become pregnant, but I can foresee a time when we will administer this vaccine during pregnancy.



“The HPV vaccine is an ObGyn vaccine, and we should embrace it with vigor”

—Stanley Gall, MD

■ How ObGyns are reacting

WRIGHT: Dr. DeFrancesco, you are involved in managing almost 200 ObGyns. How do you expect the specialty to respond to the new vaccine?

DEFRANCESCO: Vaccination is not a traditional ObGyn responsibility, but I think most of us are comfortable administering other injections, such as Rho(D) immune globulin, leuprolide acetate, and depot medroxyprogesterone acetate, or even hepatitis B vaccines for our staff. The HPV vaccine is a different injection with a different purpose, but well within our expertise to administer. I am pleased to report that—in record time!—all our practices are offering the vaccine and implementing this new service. It clearly is the right thing to do.

ObGyns need to build a vaccination infrastructure

WRIGHT: There are related issues: maintaining stocks of vaccine in ObGyn offices, developing and using consent forms, and implementing a tracking system to make

sure patients get all 3 injections of the vaccine. How are you addressing these issues?

DEFRANCESCO: We have implemented a clinical guideline consistent with the ACIP and ACOG policy statements, along with a model informed consent and insurance waiver within our large group practice. This helps us ensure that providers are up-to-date on the latest recommendations and are ready to provide this service.

If patients are concerned about the potential cost, we advise them to check with their carriers. We also ask them to sign a waiver that will permit us to bill the patient herself if she is not covered.

In addition, we have set up an account for each of our practices with the vaccine manufacturer so we can order vaccine on fairly short notice. We have recommended that our divisions each stock a reasonable number of doses to ensure enough supply to meet the demand expected in the very near future. We have also recommended that our practices go ahead and schedule the 2- and 6-month booster visits at the time of the patient's first vaccination and counsel the patient about the importance of receiving all 3 doses.

ACOG hopes to create better (and bigger) vaccinators

GALL: In general, ObGyns don't do a very good job at vaccinating. The last CDC survey I saw indicated that less than 60% of ObGyns collect immunization and infection histories from their patients, and only two thirds offer even a single vaccine.

WRIGHT: You have been working for several years to help the ObGyn community with vaccine implementation. What is ACOG doing to help physicians in private practice?

GALL: ACOG has promoted the concept that ObGyns should, and need to, become better vaccinators. A working committee on immunization has developed a program for practicing ObGyns. The concept is simple: The HPV vaccine is an ObGyn vaccine, and we should embrace it with vigor. If the ObGyn office gets set up to administer the HPV vaccine, why not administer other important vaccines such as TIV, hep-

atitis B, Tdap, MCV4, and herpes zoster?

This working committee has prepared a number of materials that should be available by the next annual clinical meeting:

- A **monograph** of information on vaccines, basic science of vaccines, international travel and immunization, bioterrorism, medicolegal aspects, coding for reimbursement, and more.
- A short form of **outlines of each vaccine**.
- A **tool kit** that tells how to set up a vaccine program in the ObGyn office.
- A **vaccine wheel**, similar to the estimated-gestational-age wheel.
- An outline of the **adolescent consultation** visit.

We also plan presentations for the district and annual clinical meetings.

■ Is there a future for cervical cancer screening?

WRIGHT: Dr. Levy, can you explain why we are going to need to continue screening once the vaccine becomes widely used?

LEVY: For the next 30 to 40 years we will have a large population of women—already over age 26—who have not received the vaccine. These women will require ongoing screening for cervical cancer precursors throughout their lives.

Although the vaccine protects against HPV types 16 and 18, which cause 70% of cancer cases, and types 6 and 11, which cause 90% of genital warts, immunity to these HPV types will not protect a woman against the other 11 high-risk HPV types. These 11 types are not as commonly associated with cervical cancer or its precursors, but they do lead to cancer in some women and can still infect the cervix in women who have received the vaccine. Even if we reach all at-risk young women with our vaccine program, they will still be at risk—albeit lower risk—for cervical cancer due to infection with other high-risk HPV types.

One other point: We do not yet know how long the immunity from these vaccines will last. So it seems clear that screening will still be required to detect cervical cancer

precursors and prevent cervical cancer from developing—even in women who have received the HPV vaccine.

■ Do we risk increasing the cancer rate?

WRIGHT: I worry about vaccination coverage. In the absence of state school requirements for the HPV vaccine, we are unlikely to get a high coverage rate among adolescents in the US. In several European countries, such as Germany, that have both recommendations and funding for universal hepatitis B vaccination of adolescents, only about 30% of adolescents have been vaccinated. The reason? These countries lack school requirements for the vaccination and have no school-based vaccination program. With the high prevalence of HPV infections in young, sexually active women in the US, we could actually increase our cervical cancer rate if we recommend reduced screening without ensuring high levels of vaccination coverage.

Dr. Gall, what do you predict for the next decade?

GALL: The future looks bright. A bipartisan bill was just introduced in the Michigan state legislature to add the HPV vaccine as a requirement for entry into junior high school. I expect more states to follow.

In general, adolescents are a poorly served group when it comes to health care because many fall out of the system. The HPV vaccine provides a great opportunity for us to encourage patients to bring their adolescent daughters to the office for a consultation. During this visit, we will conduct an “about the umbilicus” (ie, non-pelvic) physical exam, provide immunization, and discuss a number of topics such as contraception, menstruation, nutrition, etc. A critical step is to get state health departments and Medicaid officials off the dime and supporting the HPV vaccine. ■

REFERENCE

1. Gardasil [package insert]. Whitehouse Station, NJ: Merck.

Drs. Wright, DeFrancesco, Gall, and Levy report no financial relationships relevant to this article



“Even if we reach all at-risk young women with our vaccine program, they will still be at risk for infection with other high-risk HPV types”

—Barbara S. Levy, MD