Hi. My name is Kathleen Schmeler. I'm an Associate Professor in the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. And today I'm going to talk --- give a lecture on the Human Papillomavirus Vaccination and Cervical Cancer Prevention.

The objectives of the study are to discuss the epidemiology of cervical cancer; describe HPV vaccination; and explain current cervical cancer screening recommendations.

Worldwide, there are about 500,000 new cases of cervical cancer and 275,000 deaths annually. In developing countries cervical cancer --- 85% of cases and deaths related to cervical cancer occur in developing countries where it's the first or second leading cause of cancer and related deaths. In the United States, however, cervical cancer is the 14th most frequent cancer among women. There are approximately 12,000 new cases and 4,000 deaths per year. Cervical cancer rates have decreased by approximately 70% over the last 40 years in the United States and other developed countries due to screening with a Pap test.

As you can see from this map, 85% of cervical cancer cases occur in developing countries, primarily in Latin America and Central America and South America as well as in Africa.

Cervical cancer is completely preventable. It has a known etiology, the human papillomavirus. We have great prevention with the HPV vaccination. There are good screening tests including the Pap test, HPV DNA testing as well as visual inspection with acetic acid or VIA. In addition, cervical cancer has a treatable pre-invasive phase known as CIN or cervical intraepithelial neoplasia. CIN can be treated with a cervical cone, LEEP, or cryotherapy, which are procedures that I will describe in a little more detail later in the talk. In addition, it takes several years, up to a decade, to progress from cervical dysplasia or pre-cancer CIN to cancer.

As I said, the etiology of cervical cancer is known. It's caused by the human papillomavirus which is present in over 99% of cervical cancers. High-risk types of HPV cause cancer and those include 16, 18, 31, 33 and several others. However, HPV has -- also has low-risk types, such as 6 and 11 that don't cause cancer, but do cause genital warts or condyloma. In addition, there are several other HPV-associated cancers. These include vulvar cancer, vaginal cancer, anal cancer, penile cancer as well as oropharyngeal cancer.

HPV is the most common sexually transmitted disease. The initial infection usually occurs during adolescence. The estimated sexual debut in the U.S. is that 25% of people by the age of 15 are --- have had sexual intercourse, 38% by the age of 16, and 62% by the age of 18. 80% of women will have HPV in their lifetime, but less than 5% will have significant pre-invasive disease and less than 1% will develop invasive cancer. So the large majority of women will clear the HPV infection and not develop pre-invasive
disease or cancer. So HPV is necessary but is not sufficient for cervical cancer development.

So for cervical cancer prevention, we have primary prevention with HPV vaccination. And then we also have secondary prevention with screening. And as I said earlier different options for screening include cytology or the Pap test, HPV DNA testing or visual inspection with acetic acid or VIA.

There are currently two commercially available HPV preventive vaccines. One is the quadrivalent HPV vaccine that covers HPV 6 and 11, the HPV types that cause genital warts or condyloma as well as HPV 16 and 18 that cause the majority of invasive cervical cancers. The quadrivalent vaccine was FDA-approved in 2006. And it’s given in --- with three injections that are administered at 0, 2 and 6 months. So the three injections are given within a 6-month time period. There is also a bivalent vaccine that covers HPV 16 and 18, the two types that cause the majority of cervical cancers. The bivalent vaccine was FDA-approved in 2010. And that one is administered at 0, 1 and 6 months. So again, three injections over a 6 month period. And the cost of the vaccination series is approximately $300 for all three injections.

The HPV vaccines have been shown to have a 93-98% efficacy in the prevention of cervical dysplasia or cancer in people who have not previously been infected with HPV 16 and 18, so patients who are HPV naïve. Vaccines do not affect disease or infection that was present prior to the vaccination. In addition, we believe that the vaccines provide 20-50% efficacy against other high-risk HPV types, such as 31, 33 and 45.

The vaccines have also been shown to be very safe. Adverse events that have been reported are headache, fatigue, dizziness, and syncope. There has been a slight increased rate of VTE noted in some studies. However, most VTE or venothromboembolism or blood clots. But studies have shown that 90% of these are associated with oral contraceptive use which is known to increase the rate of VTE. In addition, recent studies have shown that there is no increased risk of VTE associated with HPV vaccine. HPV vaccine is also shown to have an increased rate of syncopal events. But there is no increased risk of Guillain-Barre syndrome or other significant adverse effects associated with the HPV vaccine.

The Advisory Committee on Immunization Practices or the ACIP from the Center for Disease Control recommends that girls be vaccinated with the HPV vaccine between 11 and 12 years of age. And that catch-up vaccination is done for girls who did not receive the vaccines between the age of --- between --- at 11 and 12 and that’s given between the ages of 13 and 26. There’s no preference between the bivalent and the quadrivalent vaccine as both cover HPV 16 and 18 types which are the main causes of cervical cancer. And the HPV vaccine ideally should be administered before the onset of sexual activity because once people have been exposed to the HPV virus, the vaccine will no longer work. And then in 2011 the CDC expanded their recommendation to include boys. So currently we recommend that all boys and girls be vaccinated between the ages of 11 and 12.
People often ask, “Why immunize boys or males?” One reason is if the quadrivalent vaccine is used it will prevent genital warts. It also will likely prevent anal, penile and oropharyngeal cancer, the HPV-related types of each of those cancers. And very importantly it will decrease HPV transmission to female partners with the idea of herd immunity. So greater protection of the general public decreases infection in those who do not get vaccinated. So currently we recommend vaccinating both boys and girls.

Several studies have shown the HPV vaccine to be cost-effective. The cost-effectiveness ratio is 40 --- has been shown to be $43,600 per quality-adjusted life-year gained when vaccinating 12-year-old girls. And one of the studies showed that if we vaccinated the entire U.S. population of 12-year-old girls, annually we would prevent about 200,000 HPV infections, 100,000 abnormal Paps and all the followup required for an abnormal Pap and 3,300 cases of cervical cancer. So we would decrease almost all our cervical cancer cases in the United States if we were able to vaccinate all 12-year-old girls.

However, the vaccination rates in the U.S. have not been terrific. So for females receiving one dose is approximately 54%, but the three dose completion is 33%. So a little more than half of the girls who are recommended to get the vaccine are getting it and only about a third are completing the three dose series. For males, one dose is about 21% and the three dose series is 7%. So these rates are much poorer than other countries that are similar economically to the U.S. such as Australia, Canada, and the United Kingdom where their vaccination rates exceed 70%. And interestingly, in the U.S. the hepatitis vaccine rates are greater than 90%. And I'll talk a little bit more about that in a minute.

So here you can see on this map the HPV vaccination rates by state in the United States. The yellow states are vaccinating approximately 17-25% of girls receiving all three doses so those are the lowest states and the dark red or brown are the ones --- some of the highest states. So again you can see the majority of states are well below the 50% vaccination level.

When we look at HPV vaccination rates and ethnicity, interestingly Hispanic women have higher rates of HPV vaccination despite lower rates of health insurance compared with white women. So from this table you can see that Hispanic women approximately 63% received one dose and 36% received all three doses compared with white women where 51% received one dose and 34% completed all three doses. And then black --- the rates in black women were slightly less with 50% receiving one dose and 29% receiving all three doses. And there’s been a lot of suggestions of why this is the case and it --- one of the reasons often when we talk to Hispanic women who have come from other countries where cervical cancer rates are higher is that they actually have friends and family who have died of cervical cancer. So they consider this a very important vaccine. And also they often look to vaccines as being life-saving for their children, especially those who have lived in places where vaccines are not universally
available. So it’s been very different than other vaccines where underserved populations tend to have higher vaccination rates.

This is a great quote from Dr. Harold Varmus, the Director of the National Cancer Institute. And he states that “The investments we have made in HPV research to establish these relationships and to develop effective, safe vaccines against HPV will have the expected payoffs only if vaccination rates for girls and boys improve markedly.” So again cervical cancer is one of the cancers that we have figured out the cause and a way to prevent it and treat it pre-invasive --- the pre-invasive phase but we really need to get more people vaccinated and in for screening to really be able to --- to decrease our cervical cancer rates both here in the U.S. and abroad.

So why is vaccine uptake so low in the United States? One is inadequate provider recommendations. Often patient --- or children --- or adolescents and parents don’t necessarily feel like they get the right --- get a strong recommendation from their provider to have the HPV vaccination. There are some concerns both from providers and the patients about reimbursement and the cost of the vaccine. As you saw, about half of girls are getting the vaccine. But only a third are returning for all three doses. So there’s infrequent use of a reminder or recall system that would foster completion of all three dose series. In addition, we don’t have school-based vaccination programs in this country. Many of the other countries that have very high vaccination rates have a vaccination program in the school where the girls and boys are actually vaccinated in school so that there’s no need to take them to the pediatrician or to the doctor. The vaccinations are given by the school nurse. But we don’t have that system here in the United States. Then there are several political reasons why the vaccination rate uptake has been so low in the United States.

This is a great quote by Dr. Chou who says, “If prophylactic HPV vaccines were presented as a means to prevent cancer, instead of a means to prevent infection associated with sexual contact, uptake would increase.” So there’s been a lot of controversy in the United States about people not wanting to get their 11 and 12-year-olds vaccinated against a virus that’s caused by sexual contact. So instead of looking at the vaccine as a cancer prevention vaccine, it’s looked at as a vaccine that prevents an infection associated with sexual contact.

So the HPV vaccine has been politicized by its association with a sexually transmitted disease. And there’s a false belief that giving the vaccine actually condones sex and this has been disproven in several studies where they’ve not seen higher rates of --- of initiating sexual contact at an earlier age in girls and boy who have undergone the HPV vaccine. The HPV --- The hepatitis B vaccine avoided this controversy. The hepatitis B vaccine also protects against an STD that causes cirrhosis and potentially liver cancer. But for some reason it has never been viewed as protecting against an STD by the general public and, therefore, has had very little controversy. And as I showed earlier over 90% of eligible babies are vaccinated with the hepatitis B vaccine. The other reason that hepatitis B vaccine has much higher uptake is that it’s given to babies
instead of pre-pubescent girls and boys. So it --- the vaccine series falls at the same time as other childhood vaccines.

So when we look at HPV vaccination by state, there are about 24-25 states that have tried to mandate the HPV vaccine. And what that means is that it’s a requirement for school. So for a child to attend school, they have to show that they’ve been vacc --- had you know a series of required vaccines. Currently HPV --- the --- what several states tried to do was to mandate that HPV vaccine be part of that list. What that would mean is that patient --- that parents would need to either have their child vaccinated or sign a form that they did not want to have their child vaccinated in order to go to school. Of the 24+ states that have tried to mandate the vaccine, only Virginia and Washington, D.C. have been successful where there is a mandate for the HPV vaccine. And again parents can opt out in both those areas. In Texas, the HPV vaccine is covered at no cost if you qualify for Medicaid. And the HPV vaccine is also covered at no cost under the Affordable Care Act or ACA or Obamacare.

So the good news is that among females --- a recent study showed that among females age 14-19 the HPV prevalence decreased from 11.5% in 2003 to 2006 so prior to the HPV vaccine being available to 5.1% in 2007 to 2010. So they looked at females age 14-19 pre-vaccine and post-vaccine and they’ve seen a significant drop in the rates of HPV. So this is a decline of 56%. So within four years of vaccine introduction, the HPV prevalence has decreased significantly despite such a low vaccine uptake. So even with a low uptake that we have of 33% completing all three doses 50 --- there’s a decline of 56% in HPV prevalence which we believe will translate into a decrease in cervical dysplasia and eventually a decrease in cervical cancer rates.

So there are several areas --- current areas of study. One very important area is trying to determine whether one or two doses are as good as three. Obviously from a cost standpoint and also a convenience standpoint of having the girls and boys come back in, there are several studies looking to see if one or two doses are as good as three with some early promising results. The other question that’s not known is will booster shots be needed. We are giving --- we’re --- The vaccine is recommended at ages 11 to 12 so before the start of sexual activity. But the question is it’s still unknown how long the --- the vaccine will last so there are several studies going on to determine that. And then very exciting is that there’s a new HPV vaccine that’s under development and this will cover 9 different HPV types so it will cover the existing types of 6 and 11 which cause genital warts, 16 and 18 that cause about 75 --- 70% of cervical cancers. But it will now add on these other HPV types that also are related to cervical cancer, so 31, 33, 45, 52 and 58. We believe that together this will result in a 96.7% reduction in cervical, vaginal, and vulvar pre-cancers. So this new vaccine really shows some promise to really cover pretty much all the primary HPV types that cause cervical cancer and pre-cancer. And FDA approval for this new vaccine is pending.

So now I would like to talk a little bit about cervical cancer screening.
And people often ask, “Why do we still need screening if we have these excellent preventive vaccines?” And the first reason primarily—especially in this country—is that we have very poor vaccine uptake with so few girls and boys getting the recommended vaccine. In addition, the existing vaccines don’t cover all the high-risk HPV types. As I said, the existing vaccines cover 16 and 18 that cause 70% of cervical cancer but they don’t cover all the types. When the 9-valent vaccine becomes available then that will---will help improve this. But very importantly is that vaccines don’t treat pre-existing HPV infections and we have one to two generations of women that were already exposed to HPV prior to the vaccines becoming available. So we believe that screening will be necessary for the foreseeable future. And currently we still recommend cervical cancer screening after vaccination. This may change in the future. But for now we recommend that even if someone has had the HPV vaccine series that they continue to have cervical cancer screening.

So the U.S. Guidelines for cervical cancer screening are that we begin Pap testing at age 21. We don’t do any cervical cancer screening before the age of 21 regardless of sexual activity. And it’s important to remember that most HPV infections in young women are transient and that 70% of infections regress within two years. So screening before age 21 is avoided because it may lead to unnecessary and harmful testing and treatment.

For women age 21-29 years, we do a Pap test every three years. We do not do HPV testing in women under 30. Essentially, as I said, you know 80% of women are exposed to HPV at some point in their lifetime. So we assume when women are in their 20s that many, many will be HPV-positive. So we don’t even test for it. It only becomes a problem if the HPV infection persists. So for women over 30 and over we do Pap and HPV testing every three to five years depending on the algorithm. But in general we can do Pap and HPV every five years if they are both negative. We stop screening at age 65 but that is only if a woman has had a normal screening history. So if someone comes in at age 70 and has never had any cervical cancer screening, we would screen that woman or if someone’s had abnormal Paps in the past or cervical dysplasia, we would not necessarily stop at age 65. But if someone’s had normal screening, then we can stop screening at age 65. And for women who’ve had a hysterectomy for benign indications meaning non-cancerous indications or non-pre-cancer of the cervix then no Pap is needed after they’ve had the hysterectomy.

So in the United States, there are usually three clinical visits required for cervical cancer prevention if a patient has abnormalities. So the first test is a Pap test and if they’re over 30, we also do HPV testing. If that comes back abnormal the patient is called back and undergoes colposcopy where we look at the cervix put vi---acetic acid or vinegar on the cervix and look at the cervix with a colposcope, a special microscope. And then if there are any abnormalities we do cervical biopsies. And then if significant pre-cancerous lesions are noted which is less than 5%, then we do a treatment with either a conization, a LEEP, or cryotherapy and essentially that’s removal or ablation or freezing of the pre-cancerous lesions. One of the problems is that this system is not feasible in
low-resource settings. It’s expensive and requires pathology at each step and also it’s very difficult for a woman to return for three separate visits.

And when you look at where most of the cervical cancer cases are occurring, it’s in low and middle income countries. So it’s even more difficult in these low-resource settings to use the system that we currently use in the U.S. for cervical cancer prevention which is very effective, just expensive and requires the three separate visits.

Furthermore, if you look at the availability of a pathologist in different countries, low resource settings have very few pathologists making it very difficult for that --- those pathologists to spend their time reviewing all these cervical biopsies. So if you look at this map of Africa, you can see that many countries have one pathologist for two to five million people. Even South Africa, which is the most developed, has one pathologist for every 200 to 5 --- 200,000 to 500,000 people. This is in comparison to the United Kingdom where there is one pathologist per 15,000 patie --- people and in the United States where there is one pathologist per 19,000 people. So we have far more pathologists and pathology services available for our system. But in Africa and very similarly in Latin America, it’s very difficult to be able to use our current system.

So in many low and middle income countries, visual inspection with acetic acid is used or VIA. And this is a very simple procedure where vinegar or 5% --- 3-5% acetic acid is placed on the cervix and abnormal areas will actually turn white and look very different. And then at that time cryotherapy can be performed where you freeze the lesions. The equipment is very low cost and requires only one visit. So it’s what we call “see and treat” where you do the VIA with --- by placing the vinegar on the cervix and then treat immediately with cryotherapy if it’s abnormal. A recent study from India showed that they had a 30% decrease in cervical cancer mortality using this system of VIA.

So in summary 85% of cervical cancers and related deaths occur in developing countries. HPV vaccination has been shown to be safe and very effective. Unfortunately, there’s poor uptake of HPV vaccination in the United States with only about a third of boys and girls between the ages of 11 and 12 receiving the HPV vacc -- - the entire HPV vaccination series. And vaccine mandates and school-based programs have resulted in high vaccination rates in other countries and hopefully will one day be able to be adopted in the United States. So thank you and we would welcome any feedback about this lecture or other lectures in the series.